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A single reference measurement can predict liver tumor motion during respiration

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ABSTRACT

Aim: To evaluate liver tumor motion and how well reference measurement predicts motion during treatment.

Material and methods: This retrospective study included 20 patients with colorectal cancer that had metastasized to the liver who were treated with stereotactic ablative radiotherapy. An online respiratory tumor tracking system was used. Tumor motion amplitudes in the superior-inferior (SI), latero-lateral (LL), and anterior-posterior (AP) directions were collected to generate patient-specific margins. Reference margins were generated as the mean motion and 95th percentile of motion from measurements recorded for different lengths of time (1, 3, and 5 min). We analyzed the predictability of tumor motion in each axis, based on the reference measurement and intra-/interfraction motions.

Results: About 96,000 amplitudes were analyzed. The mean tumor motions were 9.9 ± 4.2 mm, 2.6 ± 0.8 mm, and 4.5 ± 1.8 mm in the SI, LL, and AP directions, respectively. The intrafraction variations were 3.5 ± 1.8 mm, 0.63 ± 0.35 mm, and 1.4 ± 0.65 mm for the SI, LL, and AP directions, respectively. The interfraction motion variations were 1.32 ± 0.79 mm, 0.31 ± 0.23 mm, and 0.68 ± 0.62 mm for the SI, LL, and AP directions, respectively. The Pearson's correlation coefficients for margins based on the reference measurement (mean motion or 95th percentile) and margins covering 95% of the motion during the whole treatment were 0.8–0.91, 0.57–0.7, and 0.77–0.82 in the SI, LL, and AP directions, respectively.

Conclusion: Liver tumor motion in the SI direction can be adequately represented by the mean tumor motion amplitude generated from a single 1 min reference measurement. Longer reference measurements did not improve results for patients who were well-educated about the importance of regular breathing. Although the study was based on tumor tracking data, the results are useful for ITV delineation when tumor tracking is not available.

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1. Background

Liver oligometastases of solid tumors are potentially curable. The most effective therapeutic option is surgery; however, not all patients have resectable disease due to anatomical conditions or comorbidities.[1,2] In these patients, stereotactic ablative radiosurgery (SABR) has been very effective in terms of local control and survival, with only mild toxicity.[3,4] This effect is dose-dependent[5,6] so the appropriate conditions must be met for safe delivery of radiation (especially high dose per fraction).

The liver moves a lot with respiration[7]; therefore, the internal margin (IM) and setup margin (SM) must be added to the clinical target volume (CTV) for proper definition of the planning target volume (PTV).[8] Yet these margins cannot be too generous to avoid exposing the healthy liver parenchyma, which leads to radiation-induced liver disease (RILD). Although it is possible to determine the range of motion in pre-treatment imaging to create an internal target volume (ITV), there is still uncertainty regarding how exactly a reference measurement can describe the tumor motion for the entire course of treatment. In this study, authors analyzed intrafraction and interfraction movements of liver metastases in 3 or 5 fractions over 1 or 2 weeks for 20 patients. The main objective was to evaluate whether one reference measurement is a good predictor of tumor motion in each axis during the entire treatment session and if the length of the reference measurement can affect the predictability of the tumor movement.

2. Aim

To evaluate liver tumor motion and how well reference measurement predicted motion during treatment.

3. Material and methods

3.1. Patients

From January 2013 to July 2014, 20 consecutive patients (12 males, 8 females) with liver metastases of colorectal cancer were treated with SABR. The CyberKnife® Robotic Radiosurgery System was used with the Synchrony respiratory tracking system (Accuray Inc., Sunnyvale, CA). Twelve patients were treated with 45 Gy in 3 fractions every other day, and eight patients with 50 Gy in 5 fractions every other day. A total of 76 fractions were analyzed.

3.2. Motion assessment

Four gold markers (fiducials) were implanted percutaneously, under CT control (each fiducial was within 30 mm from the tumor center and the fiducial constellation centroid was within 10 mm from the tumor center). It was assumed that the motion of the fiducial's center of mass (COM) closely approximated the motion of the tumor's COM if placement guidelines were met. The motion of the tumor was monitored with the Synchrony system that allows real-time tumor tracking and recording of the tumor position. The positions of the implanted fiducials were extracted from the treatment X-ray images and correlated with the breathing light signal from external markers on the patient's chest. The correlation model must be done before the start of the treatment; in addition, it was updated after each x-ray acquisition and adapted continuously during the treatment. The tumor position was predicted between two x-ray acquisitions. This method has a high accuracy in evaluating the tumor motion.[9] The user was informed about correlation precision through the correlation error parameter. If the correlation error exceeded 3 mm, the entire model was rebuilt.

3.3. Motion data collection

During monitoring with the Synchrony tracking system, tumor location coordinates were saved in log files. An in-house program was developed for determining amplitudes of motion in the superior-inferior (SI), latero-lateral (LL), and anterior-posterior (AP) directions (rotation motion was not evaluated). All treatments included an initial intrafraction alignment step (checking position of both spine structures and fiducial markers). A precise patient setup (spine alignment with error lower than 1 mm) ensured the same patient position at the start of each fraction.

The day of the planning CT, we used the Synchrony system to test the tracking conditions and tumor motion was monitored for 5 min. These data were used as the "reference measurement". The reference margins for the SI, LL, and AP directions were set as the mean motion in 1, 3, and 5 min (mean of all peak to peak amplitudes), and as margins which cover 95% of tumor motion amplitudes (95th percentiles) in 1, 3, and 5 min. The amplitudes of tumor motion from all treatment fractions were analyzed and margins for the SI, LL, and AP directions, which cover 95% of tumor motion amplitudes, were delineated.

To evaluate possible margin under- or overestimation of the tumor motion based on the reference measurement, we derived the following formulas:

$$\mathrm{TAU} = \frac{\sum_{j-1}^{u}(x_j - x_{\mathrm{margin}}) \cdot t_j}{t_1 + t_2 + \cdots + t_n} \quad \mathrm{TAO} = \frac{\sum_{j=1}^{o}(x_{\mathrm{mragin}} - x_j) \cdot t_j}{t_1 + t_2 + \cdots + t_n}$$

where TAU is the time averaged margin underestimation (mm), TAO the time averaged margin overestimation (mm), x_{margin} the margin (mm) used for ITV determination (value from the reference measurement), x_j the periodical tumor motion amplitude (mm) during the jth portion of treatment (1 breathing cycle), t_j the duration (s) of the jth portion of treatment (1 breathing cycle), $t_1 + t_2 + \cdots + t_n$ the duration of the whole treatment (n is the number of breathing cycles), u the number of portions of the treatment with underestimated margins, and o is the number of portions of the treatment with overestimated margins.

3.4. Statistical analysis

Statistical analysis was performed using STATISTICA 10 software (Statsoft, Tulsa, OK). We used a regression analysis to evaluate the length of monitoring needed and whether one reference measurement of tumor motion could adequately

represent the daily motion of liver tumors. We used the linear regression function to model the correlation between tumor motion during the reference measurement and during treatment fractions. The test for differences between the two regression coefficients was used. The intrafraction variability was defined as the standard deviation of the tumor motion amplitude during one treatment fraction. The interfraction variability was defined as the standard deviation of the mean daily tumor motion amplitude from the whole treatment session.

4. Results

Approximately 96,000 tumor motion amplitudes were analyzed from 76 fractions. The median duration of one fraction was 81 min (range 38–184 min). The mean correlation errors during treatment were 0.9 mm (range 0.1–3.0; SD 0.70), 0.6 mm (range 0.1–3.1; SD 0.47), and 0.6 mm (range 0.1–3.1; SD 0.50) for the SI, LL, and AP directions, respectively. The gross tumor volumes (GTVs) and the mean tumor motion amplitudes from all fractions in the SI, LL, and AP directions are shown in Table 1.

4.1. *Reference measurement analysis*

The Pearson's correlation coefficient for margins based on the reference measurement (mean motion or 95th percentile) and margins that covered 95% of motion during the whole treatment indicated that there was a high correlation in the SI and AP directions and a medium correlation in the LL direction which had the smallest amplitude of motion (Fig. 1). The Pearson's correlation coefficients were within the range 0.906–0.811 ($p = 0.000$), 0.701–0.654 ($p = 0.002$), and 0.822–0.802 ($p = 0.000$) for the SI, LL and AP directions, respectively. There was no statistically significant difference between the Pearson's correlation coefficients for reference measurements recorded for different lengths of time (1, 3, and 5 min), except between the 1 and 5 min 95th percentiles in the SI direction ($p = 0.0096$). We used the test for differences between two Pearson's correlation coefficients to compare mean tumor motion and 95th percentile reference measurement sand there was no statistically significant difference (for the 1, 3, and 5 min long reference measurements).

4.2. *TAU and TAO*

The formula to determine the TAU and TAO estimations calculates how the tumor irradiation could be under- or overestimated if different margins from the reference measurements were used related to the total time of each fraction. The TAO was decreased if the mean value from the reference measurement was used, while the TAU did not increase significantly (Table 2).

4.3. *Intrafraction and interfraction motion variability*

The intrafraction variations were 3.5 ± 1.8 mm, 0.63 ± 0.35 mm, and 1.4 ± 0.65 mm for the SI, LL, and AP directions, respectively. The interfraction motion variations were 1.32 ± 0.79 mm (range 0.37–3.77), 0.31 ± 0.23 mm (range 0.02–0.92), and 0.68 ± 0.62 mm (range 0.10–2.88) for the SI, LL, and AP directions, respectively.

5. Discussion

For liver metastases, SABR is an effective treatment if an adequate dose can be safely administered. Liver motion secondary to breathing is one of the largest sources of internal organ motion.[10] It is necessary to understand the tumor range of motion during the treatment planning to create a patient-specific margin, instead of a conventional constant margin. A planning 4D-CT can help determine margins to cover the target throughout the breathing cycle.[11] Nevertheless, there is still uncertainty regarding how exactly a reference measurement can describe the tumor motion for the entire course of treatment. Our data provide new insights on this topic because they were acquired from online tracking and this long monitoring of the target creates a bright picture of real organ motion. Twenty patients in our study were treated with 3 fractions over 1 week (12 patients) or 5 fractions over 2 weeks (8 patients). The total time of tumor tracking for the entire group was approximately 6000 min.

In this study, the mean tumor motions were 9.9 ± 4.2 mm, 2.6 ± 0.8 mm, and 4.5 ± 1.8 mm in the SI, LL, and AP directions, respectively. The mean margins covering 95% of tumor motion amplitudes were 15.5 mm, 3.4 mm, and 6.8 mm in the SI, LL and AP directions, respectively (Table 1). Xi et al. obtained their data using 4D-CTin 10 patients. They observed a mean SI motion of 11 ± 5.4 mm (range 7.5–23.6 mm) and smaller mobility in the LL and AP directions.[12] Xi et al. also analyzed the abdominal organ mobility with 4D-CT in 13 patients and found the predominant SI movement of the liver was 10.1 ± 3.9 mm.[13] Analysis of the COM of hepatocellular GTVs showed the mean SI motion was 8.5 ± 4.3 mm and the amplitudes were much smaller in the LL and AP directions.[14] Hallman et al. reported a mean motion of 9.7 ± 5 mm (range 3–18 mm) in the SI direction after analyzing the 4D-CTof 11 patients.[15] These results are in agreement with our findings.

To deliver a safe and accurate treatment, we must account for internal organ motion as well as patient motion. A planning 4D-CT is commonly used to generate the patient-specific internal margin for abdominal tumors.[16] If 4D-CT is used for margin delineation, the mean tumor motion during this examination usually represents the margin for the whole treatment. The online tumor tracking can describe the tumor motion very precisely, if the strict criteria for implantation of fiducials are met. The tumor motion prediction based on COM displacement is a validated method.[17] Our results demonstrated that the motion of liver tumors was highly predicable in the SI and AP directions and slightly less in the LL direction when derived from both types of reference measurements. Different results have been reported by Ge et al. who analyzed only 6 patients with liver tumors and used one single fiducial closest to the tumor as a surrogate. Their results showed that the motion measured with 4D-CT was not able to adequately represent actual motion during radiation therapy for 92% of fractions. The disagreement between 4D-CT motion and daily motion was also fraction-specific.[18] Case et al. evaluated the correlation between motion amplitude from 4D-CT and mean liver

Table 1 – Summary of the values from 1 min long reference measurement (95th percentile and mean), mean tumor respiratory motion during treatment generated from all amplitudes of motion separately from all treatment fractions, standard deviations and margins covering 95% of the tumor respiratory motion over the whole treatment session. Reference measurement mentioned only for the highest motion in the SI direction.

Patient	Reference measurement SI		SI			LL			AP		
	95th percentile (mm)	Mean (mm)	Mean motion (mm)	SD	Mean 95th percentile margin	Mean motion (mm)	SD	Mean 95th percentile margin	Mean motion (mm)	SD	Mean 95th percentile margin
1	16	14	10.25	4.59	17	2.45	1.35	3	3.09	1.50	5
2	11	9	9.31	3.54	15	2.08	0.28	3	4.40	1.15	6
3	15	9	16.60	5.04	24	5.81	1.49	8	6.99	1.63	9
4	9	4	5.45	1.95	9	2.52	0.68	4	4.60	1.51	6
5	29	15	11.12	4.33	18	2.64	1.44	5	4.45	1.77	10
6	14	10	8.86	3.64	14	2.20	0.44	3	5.54	1.56	8
7	12	9	8.95	2.60	13	2.70	1.06	4	4.25	1.09	6
8	40	29	22.06	8.50	32	3.33	0.99	4	7.74	2.11	11
9	20	13	7.18	2.41	11	2.54	1.98	2	2.68	0.80	4
10	18	17	11.73	5.26	18	2.40	0.99	3	4.11	1.67	6
11	22	15	10.40	3.47	16	2.23	0.78	3	4.55	1.40	7
12	12	10	10.21	2.84	14	2.12	0.44	2	5.97	1.68	8
13	27	21	15.40	4.25	23	2.15	0.50	3	8.83	2.64	14
14	12	6	6.72	2.90	11	2.26	0.60	3	4.36	1.75	7
15	12	10	5.48	2.93	10	2.48	0.87	4	3.24	1.56	6
16	14	6	6.02	1.78	8	2.79	2.58	2	3.15	0.92	4
17	14	9	6.68	2.43	11	2.24	0.53	3	2.83	0.89	4
18	8	8	11.08	2.53	15	2.35	0.63	3	2.31	0.57	3
19	19	12	9.37	3.44	15	3.10	1.15	5	4.28	1.68	7
20	8	5	5.31	1.89	8	2.07	0.33	2	2.21	0.50	3
Mean	16.6	11.5	9.9		15	2.6		3	4.5		7

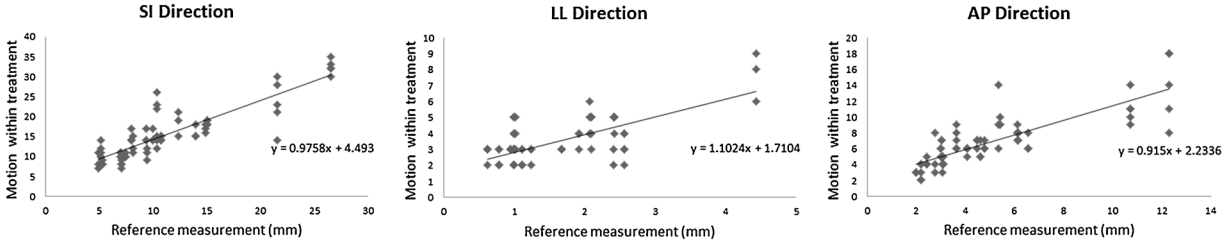

Fig. 1 – Example of regression analysis with equations for the SI, LL, and AP directions. The reference measurement was the mean tumor motion over 5 min. Motion during the treatment is represented by the 95th percentile of tumor motion during all fractions.

Table 2 – Mean anisotropic margins generated from reference measurements of different time lengths and presented as the mean motion or 95th percentile of motion and relevant mean time averaged under/over estimation (TAU/TAO) values for each margin in the SI, LL, and AP directions.

	95th percentile 1 min	Mean 1 min	95th percentile 3 min	Mean 3 min	95th percentile 5 min	Mean 5 min
Average Margin SI (mm)	**16.6**	**11.5**	**15.3**	**11.1**	**15.0**	**10.9**
Mean TAU	0.47 ± 0.98	1.22 ± 1.69	0.45 ± 0.86	1.18 ± 1.43	0.35 ± 0.52	1.31 ± 1.54
Mean TAO	7.00 ± 5.09	2.81 ± 2.51	5.58 ± 4.43	2.46 ± 2.22	5.39 ± 4.35	2.22 ± 2.19
Average Margin LL (mm)	**2.6**	**1.6**	**2.7**	**1.7**	**2.6**	**1.6**
Mean TAU	0.48 ± 0.54	0.91 ± 0.64	0.47 ± 0.56	0.93 ± 0.57	0.39 ± 0.49	0.99 ± 0.59
Mean TAO	0.53 ± 0.91	0.18 ± 0.59	0.64 ± 1.03	0.10 ± 0.24	0.37 ± 0.59	0.13 ± 0.41
Average Margin AP (mm)	**7.3**	**5.1**	**6.8**	**4.9**	**6.7**	**4.8**
Mean TAU	0.18 ± 0.34	0.50 ± 0.70	0.18 ± 0.29	0.53 ± 0.61	0.17 ± 0.26	0.59 ± 0.62
Mean TAO	2.79 ± 2.59	1.08 ± 1.21	2.46 ± 2.42	0.95 ± 1.32	2.24 ± 1.97	0.85 ± 1.20

motion during treatment for 29 patients and also reported a good correlation in the SI and AP directions ($R^2 = 0.8$).[10] These results are in agreement with our findings.

Commonly used margin delineation from the mean tumor motion during the reference measurement was analyzed to show possible margin under/overestimation compared with the margin from 95th percentile (Table 2). The 95th percentile margin led to very low TAU values, independent of the time length of measurement (1, 3, or 5 min), compared with the mean motion margin (Table 2). The test for differences between two regression coefficients was used to compare correlation based on different types of reference measurements and there was no significant difference between coefficients except when comparing the 95th percentile reference measurements monitored for 1 vs. 5 min ($p = 0.0096$) in the SI direction. This showed that a very strict margin delineation and a reference measurement monitored for a short time could significantly decrease correlation.

The mean standard deviations of the amplitudes during the reference measurements were similar for the three time lengths and similar to the mean intrafraction variations (3.6, 3.5, and 3.5 mm for 1, 3, and 5 min, respectively, in the SI direction; 1.6, 1.6, and 0.6 mm for 1, 3, and 5 min, respectively, in the LL direction; and 1.4, 1.3, and 1.3 mm for 1, 3, and 5 min, respectively, in the AP direction). We found that using the mean value of tumor motion from reference measurements could eliminate higher amplitudes that might occur during the treatment; thus, the breathing pattern from the reference measurement should be verified during the treatment. We also used the mean tumor motion values from the reference measurement to determine the TAU and TAO. We found that there was only a small increase in the TAU and a higher decrease in the TAO compared with the 95th percentile margin. These results indicate that the use of mean motion during the reference measurement reduces the margin and significantly decreases the TAO (Table 2). Admittedly, this is only true in patients with regular breathing patterns and all our patients were educated on the importance of regular breathing. If a patient's breathing is not regular, a longer reference measurement will probably be useful.

The mean intrafraction tumor motion variations were 3.5 ± 1.8 mm, 0.63 ± 0.35 mm, and 1.4 ± 0.65 mm for the SI, LL, and AP directions, respectively. Despite the intrafraction variability, the TAU and TAO values confirmed sufficient margin delineation. Our liver lesions were characterized by a high range of motion, but the frequency of the highest amplitudes was minimal; thus, the TAU and TAO values were not significantly influenced by these amplitudes. A high range of motion could also be related to the length of tumor tracking. The TAU and TAO concepts are time averaged, which should describe the risk of under/overestimation more realistically. Ge et al. found that the intrafractional changes of breathing motion were 2.2, 1.5, and 1.0 mm in the SI, LL, and AP directions, respectively.[18] Case et al. reported mean absolute intrafraction changes of 1.6, 1.3, and 1.9 mm for the SI, LL, and AP directions, respectively.[10]

The mean interfraction variations were 1.32 ± 0.79 mm, 0.31 ± 0.23 mm, and 0.68 ± 0.62 mm for the SI, LL, and AP directions, respectively. Only one patient from our group exceeded 3 mm and 2 mm in the SI and LL directions, respectively. Ge et al. found that the interfractional changes in breathing motion were 2.9, 1.6, and 4.8 mm in the SI, LL, and AP directions, respectively.[18] Case et al. reported mean absolute interfraction changes of 1.7, 1.0, and 1.6 mm for SI, LL, and AP directions, respectively.[10] In our study, the intrafractional change of tumor movement was more important than the interfraction variation.

6. Conclusion

Liver tumor motion in the SI direction can be adequately represented by the mean tumor motion amplitude generated from a single 1 min reference measurement. Longer reference measurements did not improve results for patients who were well educated about the importance of regular breathing. Although the study was based on tumor tracking data, the results are useful for ITV delineation when tumor tracking is not available.

Conflict of interest

None declared.

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