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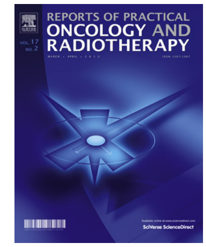

Original research article

A single reference measurement can predict liver tumor motion during respiration

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ARTICLE INFO

Article history:
Received 22 July 2015
Accepted 30 November 2015
Available online 29 December 2015

Keywords:
Liver cancer
Tumor motion
Internal target volume

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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http://dx.doi.org/10.1016/j.rpor.2015.11.003
1507-1367/

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