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Research article

Breath-hold versus mid-ventilation in SBRT of adrenal metastases

Melissa de Kuijer [a], Jaap van Egmond [b], E. Kouwenhoven [b], Dieke Bruijn-Krist [a], Heleen Ceha [a], Mirjam Mast [a,*]

[a] Haaglanden Medical Center, Department of Radiotherapy, Leidschendam, the Netherlands
[b] Haaglanden Medical Center, Department of Medical Physics, Leidschendam, the Netherlands

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ABSTRACT

Purpose: To improve local control in radiotherapy of adrenal metastases precise dose delivery without increasing toxicity is vital. Decreasing the Clinical Target Volume (CTV) – Planning Target Volume (PTV) margins by reducing breathing movement can achieve this. Few data were published concerning the effect of a breath-hold technique. This study investigates the potential of Active Breathing Control (ABC) to limit adrenal breathing movement and reduce CTV-PTV margins.
Methods: We compared adrenal gland movement in free-breathing, making use of the Mid-ventilation (MidV) technique, and with ABC. The coordinates of the adrenal glands obtained on ten phases of a free breathing 4D-CT and on several repeat inspiration ABC CT-scans were measured. Separate coordinates, the random margin component and the margin vector norm were computed and compared between the two techniques.
Results: We compared the two techniques in 11 patients (21 adrenal glands) and found the largest movement in the Z-direction, with values of 8.7 ± 4.2 mm for MidV and 2.4 ± 1.5 mm for ABC. In 71% of the cases ABC resulted in a smaller margin component than MidV, although non-significant ($p \geq 0.4$).
Conclusion: Movement of the adrenal gland is largest in the Z-direction. The mean difference in the margin vector norm between both techniques was small with large variations over the patient group, the clinical effect of these differences is unknown. Applying an individualised motion management strategy could be beneficial. If a peak-to-peak amplitude above 15 mm in the Z-direction is observed in the MidV scan we advise to examine if a breath-hold technique could reduce margins.

Introduction

Although cancer treatment is improving, distant metastases still occur. This is mostly related to a poor prognosis. However, this does not apply to a subgroup of patients with a limited burden of disease, i.e., with fewer than five distant metastases. The latter is described as "oligometastases" [1].

Studies show that patients with adrenal oligometastases may benefit from metastasis-directed therapy [2,3].

With more extensive imaging in diagnosis and follow-up of malignancies, adrenal metastases are more frequently identified [4]. Surgical resection can be considered in selected cases. However, this technically challenging operation may result in considerable morbidity [5]. Stereotactic body radiotherapy (SBRT) has been suggested as an alternative, non-invasive ablative treatment by several authors [3,6,7]. One and three year local rates are reported of more than 80% [8]. Furthermore, SBRT resulted in low rates of toxicity, mostly grade 2 acute toxicity was found [6,7]. Although SBRT appears to be effective, longer follow-up is needed to achieve more solid outcome results. Also, radiation techniques still require refinement. To obtain higher local control rates it is crucial that the prescribed dose is delivered without increasing toxicity. Therefore, special efforts should be made to improve the SBRT treatment by reducing the Clinical Target Volume (CTV) – Planning Target Volume (PTV) margins. A way to achieve this is by reducing the movement of the patient's specific breathing cycle [9]. In our department we apply individual CTV-PTV margins for SBRT of liver metastases with use of a breath-hold technique, Active Breathing Control (ABC) [10]. Therefore, it was questioned if this individualised strategy could be adopted for SBRT of adrenal metastases. In literature sparse data are found concerning the effect of a breath-hold technique on the CTV-PTV margins in SBRT of adrenal metastases. The purpose of this study is to investigate whether ABC

* Corresponding author at: Dept. of Radiotherapy, Burgemeester Banninglaan 1, 2262 BA, Leidschendam, PO Box 432, 2501 CK, The Hague, the Netherlands
E-mail address: m.mast@haaglandenmc.nl (M. Mast).

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could be applied to limit adrenal breathing movement and thereby reducing the CTV-PTV margins.

Materials and Methods

Until now we performed SBRT of adrenal metastases with an Internal Target Volume (ITV) technique based on a free breathing 4D-CT-scan. Using this approach the motion of the tumour is accounted for by creation of an envelope structure that contains the GTV during every phase of the breathing cycle. An improvement of this technique is the mid-ventilation (MidV) technique. Using MidV the CT selected for planning is the one out of all phases that corresponds to the time-weighted average of the tumour position (GTV). Research showed that when applying the MidV technique the PTV's can be reduced [11]. To investigate whether our breath-hold technique (Active Breathing Coordinator™, ABC, Elekta, UK) could reduce CTV-PTV margins, we compared the movement of the adrenal glands both in free-breathing, making use of the MidV technique, and in breath-hold. The breath-hold technique we apply was extensively described earlier [10]. Despite the fact that breathing motion is absent during ABC, a variation in tumour position between consecutive breath-holds should be accounted for in the calculation of margins. For this purpose, we measured the coordinates of the adrenal glands obtained on ten phases of a free breathing 4D-CT, and the coordinates of the adrenal glands obtained on several repeat ABC CT-scans. Data were used from a cohort of patients with liver metastases treated with SBRT in breath-hold between January 2016 and May 2017 (liver group). In this group of patients with liver metastases we determined for each patient whether ABC or ITV resulted in the smallest margins [10]. The liver group consisted of patients with a 4D-CT and repeat ABC CT-scans of which at least one adrenal gland was visible on both scans. As a second patient cohort, we selected patients with adrenal metastases and one patient with a primary adrenal tumour (adrenal group) earlier treated applying ITV. We studied if the movement in patients with adrenal metastases was comparable to the adrenal movement in the liver group. The adrenal group consisted of patients treated between January 2017 and August 2018.

Regardless of the differences in technique, the amount of movement is one of the determinants in the CTV - PTV margin recipe [12]. Concerning the strategy using the 4D-CT-scan, motion is one of the components in calculating the random error. We used 0.36 times the peak-to-peak amplitude to obtain the standard deviation, required for the calculation of the margin [11]. For the ABC strategy several breath-holds are required during CT-scanning, during treatment and during cone beam imaging. The reproducibility of a breath-hold is of relevance as it has the potential to increase the treatment error. The random margin component was obtained from the variation in target position (standard deviation) of 10 consecutive ABC CT-scans.

The adrenal breathing movement (MidV) and breath-hold variation (ABC) was measured by a manual 3D-match of the contour of the delineated adrenal gland on all separate phases of the 4D-CT-scan and the repeat ABC CT-scans. The coordinates of the centre of mass of the delineated adrenal gland were obtained for further processing, with the aid of in house developed software (Pinnacle 3 v.9.10 scripts combined with a post processing utility). From the relative displacements between phases we calculated the peak-to-peak displacement for the 4D-CT-scans, from which the CTV-PTV margin could be obtained [13]. For the consecutive repeat ABC CT-scans the variability in the positioning of the adrenal gland was obtained by calculating the standard deviation in all three directions; the standard deviation could then be converted to a random margin component [14]. Besides these separate 3D-components a vector norm (the square root of the quadratic sum of the separate 3D-components yielding the margin magnitude) of the margin was calculated for further analysis.

Inter- and intra-observer variability

The process for calculating the movement of delineated structures is based on a manual match of the structures on the CT-scans. This procedure has an inherent accuracy that is determined by several factors, such as image contrast and visibility of the structures of interest, and the operator's experience. To assess the accuracy of the method we compared the analyses of two observers (RTT MK, RTT DK), but also repeated the analysis of a single observer (RTT MK). To quantify the accuracy we computed the root mean square (RMS) of the differences of the coordinates of the centre of mass of two delineations:

$$\mathrm{RMS} = \sqrt{\sum_{i=1}^{N} \frac{\left(\Delta x_i^2 + \Delta y_i^2 + \Delta z_i^2\right)}{N}}$$

N is the number of phases of the CT-scans (4D) or the number of repeat CT-scans (ABC).

An RMS of ≤ 2 mm was defined as appropriate, considering the accuracy of the process.

Statistics

Descriptive statistics were performed, describing the mean and standard deviation (SD) of the data. Normality tests were executed and when the data were skewed a log transformation was performed. Depending on the data a paired or an unpaired T-test was used. Statistical analysis was performed using IBM SPSS version 22 (IBM Corp, Armonk, NY, USA). A two-sided p-value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

The liver group consisted of 11 patients treated with SBRT for liver metastases between January 2016 and May 2017. On the repeated ABC CT-scans 21 adrenal glands were visible and contoured. The average age was 66, and 82% of these patients had a primary colorectal carcinoma (CRC). The adrenal group consisted of 12 patients treated with SBRT between January 2017 and August 2018. In this group we were able to delineate 21 adrenal glands. The average age was 62, 58% of the patients had non-small cell lung cancer (NSCLC). In Table 1 the patient characteristics are described.

Inter- and intra-observer variability

The accuracy of the method to determine the peak-to-peak and standard deviation values was tested by calculating the RMS for the two different observers. Concerning the intra-and inter-observer variabilities determined on the 4D-CT for both the liver group and the adrenal group, no significant differences were found ($p = 0.2$ and $p = 0.5$ respectively). For this reason, we decided that we could use the data of RTT MK for the analysis.

When comparing the intra- and inter-observer variabilities for the ABC technique to the MidV technique significant differences were found ($p < 0.001$ and $p = 0.007$ respectively). For the inter-observer variability it appeared that in 71% of the cases ABC had a lower RMS value than MidV. Furthermore, in 47.6% of the cases ABC resulted in RMS values higher than the desired 2 mm. Our study showed that ABC scans were of higher quality (Fig. 1). The

Table 1
Patient characteristics adrenal group A (n = 12) and liver group L (n = 11). Non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), colorectal carcinoma (CRC).

Liver group (n = 11)			Adrenal group (n = 12)		
Age	Sex	Primary tumour	Age	Sex	Primary tumour
80	Female	CRC	48	Male	NSCLC
74	Female	CRC	54	Male	NSCLC
81	Male	CRC	55	Female	Ovarian carcinoma
38	Male	CRC	74	Female	Breast carcinoma
65	Male	CRC	58	Male	NSCLC
57	Male	Pancreatic carcinoma	71	Male	NSCLC
63	Male	CRC	73	Male	Adrenal gland carcinoma
66	Male	CRC	54	Male	Renal carcinoma
72	Male	CRC	68	Female	NSCLC
65	Male	CRC	74	Female	NSCLC
69	Male	NSCLC	69	Female	NSCLC
			49	Female	SCLC

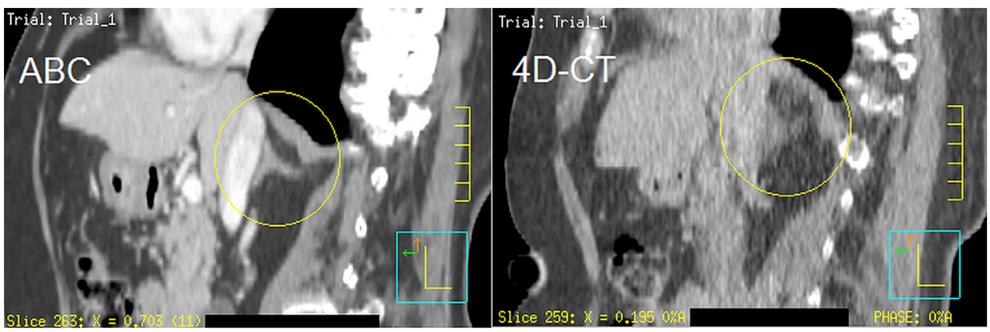

Fig. 1. The ABC-technique (left) versus the 4D-CT-technique (right).

adrenal gland is more clearly visible on the ABC CT compared to the 4D-CT.

Adrenal movement

For the adrenal movement based on the 4D-CT the largest movement of the adrenal gland was noted in the cranial-caudal direction (Z-direction), and the left-right movement (X-direction) was smallest in both groups. No significant differences were found between the adrenal group and the liver group ($p \geq 0.2$). Fig. 2 shows the peak-to-peak values of the adrenal gland in X, Y and Z-direction on the 4D-CT for both groups. Although there is considerable variation of breathing motion, in some cases large amplitudes are found, being responsible for the major part of the margin.

When investigating the peak-to-peak values and the standard deviations the movement in the Z-direction was the largest, supplementary Table 1. With the data the random component of the margin recipe was computed, using 0.7 times the standard deviation. This was done for both MidV and ABC, using the procedure for calculating the standard deviation as described in the Methods section. The results are given in Table 2. In 71% of the cases ABC resulted in a smaller margin component than MidV, although

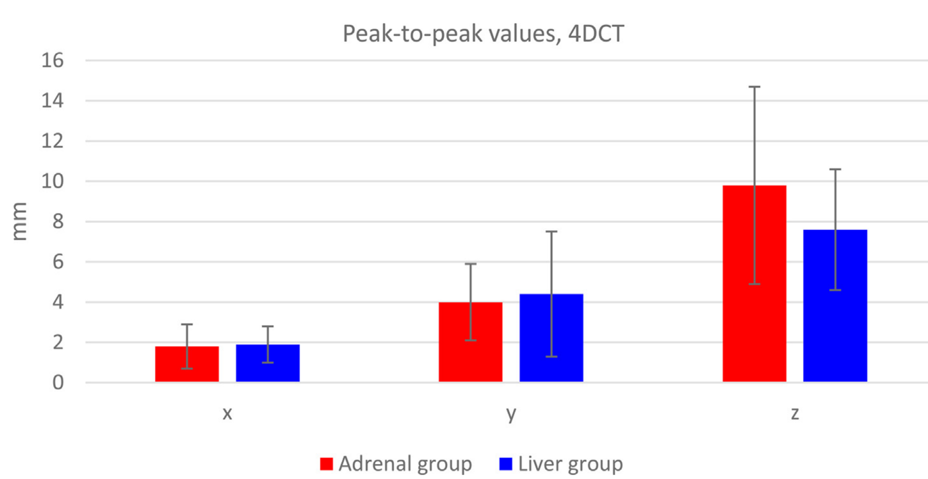

Fig. 2. Peak-to-peak values obtained on a 4D-CT represented in mm.

Table 2
Random component calculated as a margin in mm.

Random component	MidV				ABC			
	X	Y	Z	Vector norm	X	Y	Z	Vector norm
Mean	0.5	1.1	1.9	2.3	0.6	1.3	1.7	2.3
Standard deviation	0.2	0.8	0.8	0.9	0.3	0.9	1.1	1.3
Minimal	0.2	0.4	0.5	1.0	0.2	0.4	0.7	0.8
Maximal	0.9	3.2	3.2	4.4	1.4	3.7	4.2	5.7

non-significant ($p \geq 0.4$). The range of the differences between ABC and MidV is −3.5 mm and −3.2 mm in favour of the ABC technique, supplementary Table 2.

Since we did not find a significant difference between the two observers we chose to use the data of observer 2 (RTT MK). To find out if the outcome was reliable the T-tests were performed with data obtained by observer 3 (RTT DK) as well, comparable results were found ($p \geq 0.3$).

Discussion

We found that in most cases the ABC-technique resulted in smaller margins compared to the MidV-technique. However, the differences in the margins between both techniques were small ($p \geq 0.4$) and the clinical relevance of these non-significant differences is unknown. Furthermore, also in 71% of the cases smaller RMS values were found on the repeated ABC CT compared to MidV ($p = 0.007$). This is likely caused by the fact that the 4D-CT on which the MidV technique was applied is noisier than the ABC CT and in addition may have movement artefacts between different breaths of the same phase.

Another disadvantage of the 4D-CT was described by Lens et al., they found that tumour motion at treatment planning was not representative for the tumour motion during a fractionated treatment [15]. This could be reduced by using (audio or visual) coaching during 4D-CT acquisition and treatment. Application of 4D-ConeBeam CT (4D-CBCT) might be beneficial when applying MidV, for better estimation of the MidV-phase and evaluation of tumour motion.

We found, in our group of 23 patients with 42 delineated adrenal glands, mean peak-to-peak (based on the 4D-CT-scans) X, Y, Z values of 1.9, 4.2, 8.7 mm. Chen et al. found an average peak to peak of 3.4, 3.8, 9.5 mm [16]. These values are in line with our data. However, their study group was smaller, 12 patients. Another study found the largest adrenal movement in the Z direction as well, based on fiducial gold marker match in combination with the Cyberknife. The motion distances were 0.5–1.2 cm (0.87 ± 0.21 cm) respectively along the Z-axis [17].

In addition, we showed that the ABC-technique resulted in non-significantly smaller margins compared to the MidV technique in 71% of the cases. With the smaller margins, less healthy tissue is irradiated and less toxicity may be expected. However, the use of ABC has a considerable impact on the workflow for the CT-scan and the linear accelerator. As an alternative strategy it could be determined in each patient whether ABC would be beneficial, whenever the 4D-CT shows considerable motion. In these cases the (clinical) physicist will firstly have to analyse the peak-to-peak values to assess the movement of the adrenal gland and decide whether ABC has advantage to minimize adrenal movement. As the mechanisms causing the variation in breath-hold position are unknown, we cannot exclude that a large breathing motion is associated with breath-hold reproducibility. The existence of such a correlation would preclude ABC and MidV as competing, complementary techniques. Therefore we calculated the Pearson correlation coefficients. We found no correlation (−0.3 to 0.1, $p \geq 0.6$) between the coordinates determined with ABC and MidV. The latter implies that the standard deviation of the breath-hold technique needs to be computed as well, to be able to determine which technique results in the smallest CTV-PTV margins for the specific patient. A peak-to-peak amplitude above 15 mm in the Z-direction results in a random margin component of 4 mm, which has effect on the CTV-PTV margins.

Up till now we used an ITV-procedure in SBRT of adrenal metastases to account for breathing motion. In this concept an ITV is created, extending the Gross Tumor Volume (GTV) by half the motion amplitude. From the ITV, the PTV is obtained using the regular treatment margins. The MidV concept is based on the motion amplitude, using a factor of 0.36 to convert to standard deviation, and a factor of 0.7 to convert to random margin. Although margin components and ITV extension cannot be compared directly, a difference of about a factor 2 in favor of MidV exists.

A limitation of this study is that the data are calculated from the random error of the margin recipe formula. Not all random components have been included. Moreover, data regarding systematic and random errors (for example delineation uncertainty, matching accuracy, position verification method, inter-fraction movement) in SBRT of the adrenal gland are not available in the literature. Therefore an individual margin cannot be computed. It is recommended that further studies will be performed to define these random and systematic components.

In a sub-analysis, we found no significant difference between the left and the right adrenal motion for 4D-CT ($p \geq 0.2$) and for ABC ($p \geq 0.06$). The average peak-to-peak X, Y, Z values were 1.8, 3.7, 7.7 mm for the left and 2.0, 4.6, 9.8 mm for the right adrenal gland. Chen et al. found comparable non-significant results e.g. for the left X, Y, Z 3.0, 3.6, 7.8 mm and 3.9, 4.0, 11.8 mm for the right adrenal gland. An equivalent method was used. However, it must be noted that it concerned a small group of patients and was not analysed pairwise [16]. Yet, Wang et al. found a significant difference between the movement of the left and the right adrenal gland. These results are also questionable, because it seems that this study compared the movement of the left adrenal tumour with a right adrenal tumour of another patient [17].

In the Haaglanden Medical Center the threshold for a good agreement between observers is a root mean square value of less than 2.0 mm. It was not always possible to meet this requirement. Therefore, it may be more reliable to obtain the data using automated image registration techniques. Still, there is no data in the literature about the quantification of adrenal movement.

Kothari et al. described different local control rates in their review and stated that a higher BED may result in better local control [5]. Along with this requirement, it is a challenge to deliver a high dose to the moving tumour and avoid the critical structures. A literature review shows that there are currently two studies in which ABC is used in SBRT of adrenal metastasis. Gamsiz et al. described encouraging results of SBRT with ABC for local control and toxicity. After 16 months a local control of 86.7% was seen and no toxicity greater or equal to grade 3 [18]. Buergy et al. also report an average local disease-free survival of 18.3 months [19].

At the moment several departments use inserted markers to perform the position verification procedure during SBRT. Since this is an invasive procedure with risk of serious complications [20] we prefer to perform the position verification procedure without making use of fiducial markers. An optimised matching technique has yet to be tested in our clinic. Gamsiz et al. and Buergy et al. only describe that they make use of the kV-CBCT [17,18]. We learned form a personal communication that both authors make use of a mask match (a soft tissue region of interest was defined, the grey values of the CBCT scan and the reference scan were used). This procedure was more extensively described by Sonier et al. for kidney irradiation [21]. They used an automatic grey value match (making use of the grey values in the CBCT scan and the reference scan) to the PTV and adjacent kidney with manual fine-tuning. For all cases, patient positioning was corrected using a robotic couch with a threshold of 1 mm and 1°. Whether this is possible at our institute for adrenal gland SBRT for both the MidV and ABC technique needs to be investigated. It can be expected that the CBCT in breath-hold will show less artefacts but here as well the images are composed of multiple breath-holds.

Finally, from literature it appeared that the expiration breath-hold technique was more stable between breathing cycles as well as between treatment sessions [9]. In contrast, the compliance using an expiration breath-hold technique was 62% [22]. In our department, treating liver metastases with inspiration breath-hold, the compliance was 95% [10]. Because of the latter we decided to use the inspiration breath-hold technique.

Conclusion

In our dataset movement of the adrenal gland is the largest in the Z-axis in ABC and MidV. Applying ABC to SBRT of adrenal metastases resulted in reducing margins in 71% of the patients. However, the differences in the vector norm between both techniques were small and the clinical effect of these differences is unknown. Applying an individualised strategy could be beneficial. Therefore, movement should be measured and accounted for either in margin size or by using motion management techniques. In patients with a peak-to-peak amplitude above 15 mm in the Z-direction we advise to examine if a breath-hold technique would be able to reduce the margins.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tipsro.2019.11.007.

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