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ORIGINAL PAPER

Dynamic MR Based Analysis of Tumor Movement in Upper and Mid Lobe Localized Lung Cancer

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Abstract *Background and purpose*: Tumor motion is a very important factor in the radiotherapy of lung cancer. Uncertainty resulting from tumor movement must be considered in 3D therapy planning especially in case of IMRT or stereotactic therapy. The aim of our dynamic MR based study was to detect tumor movements in upper and mid lobe lung tumors. *Patient and methods*: Twenty-four patients with newly diagnosed stage II-IV lung cancer were enrolled into the study. According to tumor localization in the right S1–S3 segments 9, in the right S4–S6 segments 2, in the left S1–S3 segments 9 and in the left S4–S6 segments 4 lesions were detected. In normal treatment position individual dynamic MR examinations were performed in axial, sagittal and coronal planes (100 slices/30 sec). For tumor motion analysis E-RAD PAC's software was used. *Results*: Movements of the tumor under normal breathing conditions were registered in the three main directions. The mean antero-posterior deviation was 0,109 cm (range: 0,063 cm–0,204 cm), the mean medio-lateral deviation was 0,114 cm (range: 0,06 cm– 0,244 cm). The greatest deviation was measured in cranio–caudal direction (mean: 0,27 cm, range: 0,079 cm– 0,815 cm). The mean direction independent deviation was 0,18 cm (range: 0,09 cm– 0,48 cm). *Conclusion*: Dynamic MR is a sensitive and well tolerated method for tumor motion monitoring in high precision 3D therapy planning of lung cancer patients. Our results demonstrate that tumors located in the upper and mid lobes have moderate breath synchronous movements. The greatest deviation occur in cranio–caudal direction.

Keywords Lung cancer · Dynamic MR · Tumor motion

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Introduction

In the tumor related morbidity lung cancer is the leading death cause, both in the male and female population [1]. In the treatment of lung cancer local control is a crucial question the possibility of tumor recurrence is very high, even in early stage disease [2]. Nowadays CT based 3D radiotherapy is used for the treatment of lung cancer patients. In the 3D conformal radiotherapy for PTV (planning target volume) definition many factors have to be taken in account (e.g.: microscopically spread of the tumor cells, daily set up errors, tumor motions). In the common practice standard safety margins are added to clinical target volumes (CTV) which are derived from a spiral CT scan [3, 4]. These safety margins are estimated arbitrarily, potentially resulting in either excessive exposure of normal tissues (especially in case of combined chemo-radio therapy) or insufficient target volume coverage [5, 6].

With the widespread use of high precision 3D, IMRT and extracranial stereotactic irradiation techniques, in the

Table 1 Patient characteristics

Patient	Gender	Age	Localization	TNM	Tumor size	Hystology
1	Male	59	Right S3	T3N0M0	60×30×15 mm	Planocell.
2	Female	48	Right S3	T4N2M1	38×32×20 mm	Adenocc.
3	Female	48	Rigth S2	T4N2M1	25×10×9 mm	Adenocc.
4	Female	61	Right S2	T4N0M0	43×30×23 mm	Adenocc.
5	Female	54	Rigth S3	T2N2M0	17×12×10 mm	Adenocc.
6	Female	53	Right S6	T2N2M0	35×25×21 mm	Adenocc.
7	Male	50	Right S3	T2N2M0	20×13×7 mm	Adenocc.
8	Male	56	Left S6	T3N2M1	32×25×30 mm	Adenocc.
9	Male	58	Right S6	T2N2M1	35×32×27 mm	Adenocc.
10	Male	58	Left S2	T2N2M1	30×32×24 mm	Adenocc.
11	Female	67	Left S6	T2N1M0	43×25×30 mm	Planocell.
12	Male	54	Right S1	T4N2M1	66×55×42 mm	Adenocc.
13	Female	58	Left S1/2	T3N3M1	76×55×61 mm	Adenocc.
14	Female	57	Left S3	T3N2M1	36×26×26 mm	Planocell.
15	Male	62	Right S1	T2N0M0	43×39×25 mm	Adenocc.
16	Male	57	Left S3	T2N2M0	25×20×20 mm	Adenocc.
17	Male	69	Left S6	T3N2M0	30×30×24 mm	Adenocc.
18	Male	54	Left S1/2	T1N2M1	38×43×21 mm	Microcell.
19	Male	54	Right S1	T1N2M1	22×15×17 mm	Microcell.
20	Male	63	Left S2	T3N0M0	38×43×32 mm	Planocell.
21	Female	60	Left S6	T4N0M0	85×58×42 mm	Adenocc.
22	Male	49	Left S3	T4N2M1	57×37×41 mm	Planocell.
23	Male	49	Left S1/2	T4N2M0	25×18×25 mm	Planocell.
24	Male	49	Left S3	T4N2M0	88×49×34 mm	Planocell.

recent years high interest can be observed in the analysis of breath related tumor motions. For motion monitoring fluoroscopy, marker implantation, CT images have been used but all of these techniques have their limitations [7, 8]. Recently developed fast MR acquisition techniques permit direct dynamic visualization of respiratory motion, including assessment of parenchyma, chest wall and diaphragm, with high spatial and temporal resolution [9–11]. The aim of our dynamic MR based study was to make a high precision characterization of tumor movements in upper and mid-lobe localized tumors, and to calculate numerical data for safety margins to be considered in 3D planning of lung cancer patients.

Patient and Methods

Twenty-four patients with newly diagnosed (no previous surgery, chemo- or radiotherapy) stage II-IV lung cancer patient were enrolled into the study (Table 1) All off the patients were in good general condition (ECOG: 0–1) and were able to breath normally in supine position. According to tumor localization in the right S1–S3 segments 9, in the right S4–S6 segments 2, in the left S1–S3 segments 9 and in the left S4–S6 segments 4 lesions were detected (Fig. 1) After the nature of the procedure had been fully explained, all patients provided written informed consent under an institutionally approved subjects research protocol. The study was performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and 1983.

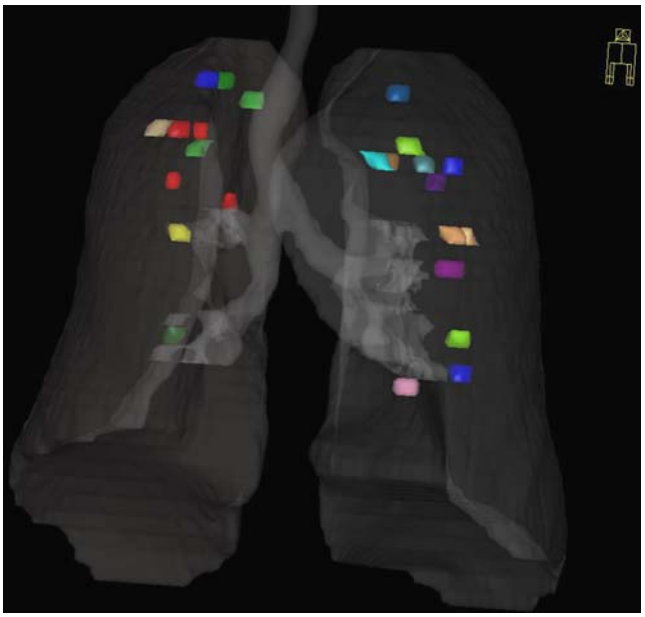


Fig. 1 3D reconstructed, schematic orientation of the investigated tumors

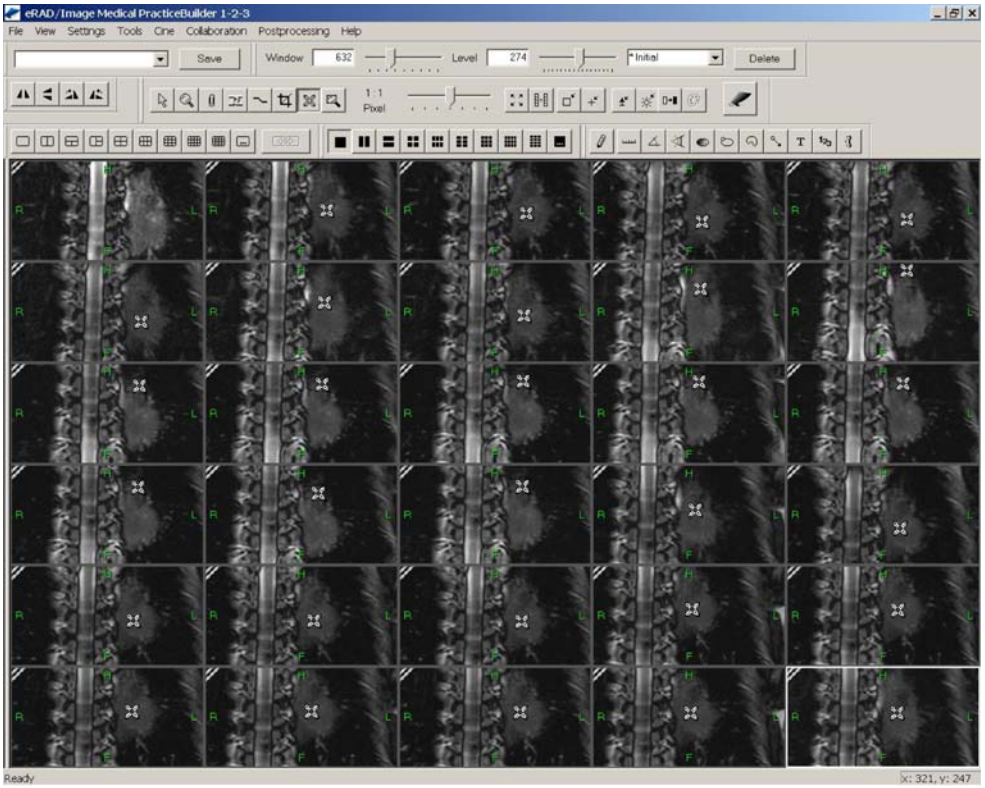


Fig. 2 Registration of the tumor center positions. For all the tumors in all slices in all planes the coordinates of the tumor centers were registered

MRI Examination

All examinations were performed using a clinical 1.5-T whole-body scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) equipped with eight receiver channels and a high performance gradient system (30 mT/m). After the patient preparation (positioning the patient on the MRI cardle, 5 min relaxing time) in the normal treatment position (supine position on the flat cardle, with hands on a hand holder) in coronal, sagittal, and transversal planes

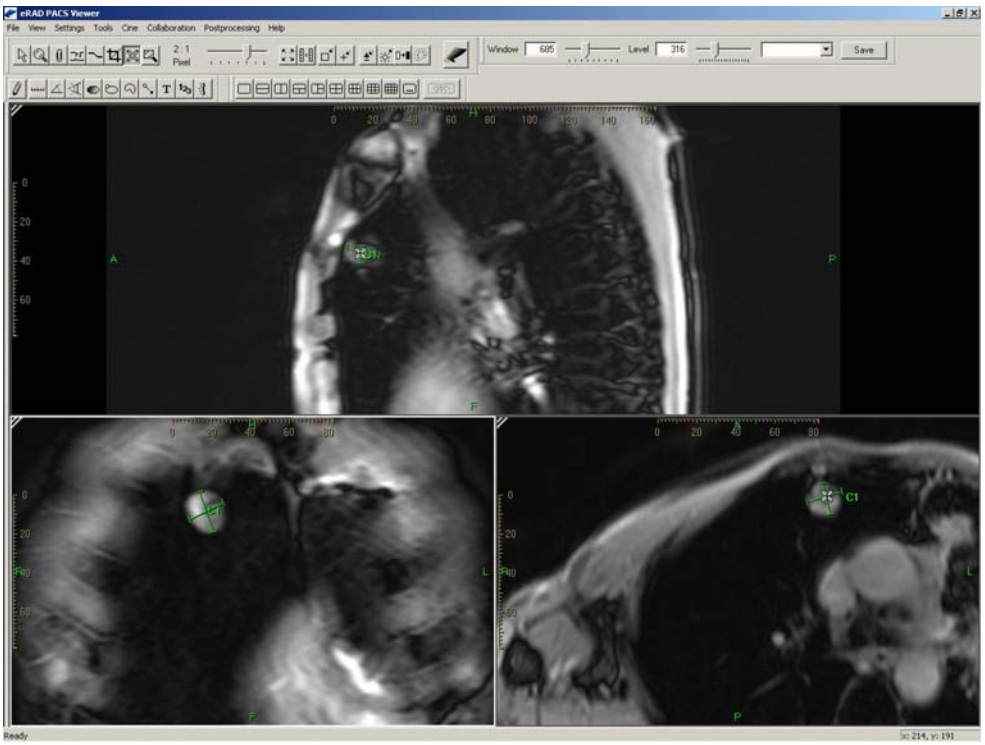


Fig. 3 Orientation of the tumor center in the 3 main planes

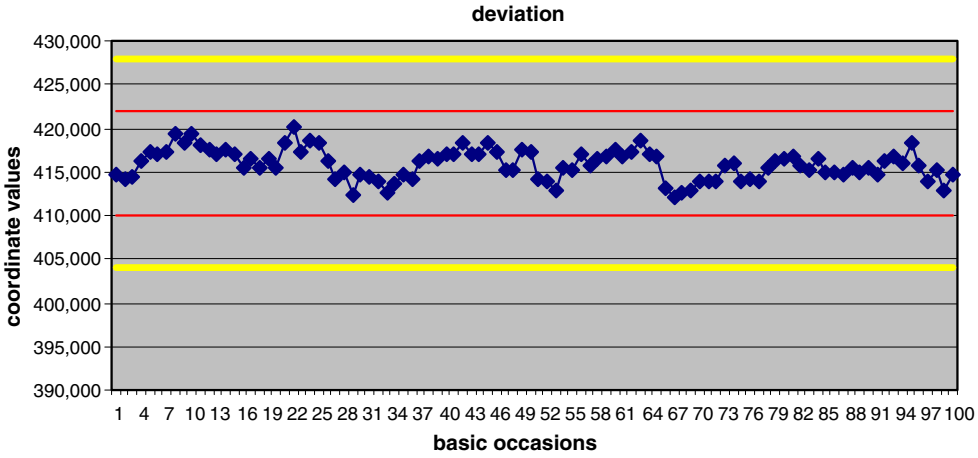


Fig. 4 Visualization of the tumor center coordinates. On the x axis the basic occasions (100/30 sec) on the y axis the basic occasion related coordinate values were registered

through the center of the tumor were acquired in each patient. The total acquisition time was 30 s for each slice, acquiring three frames/s (100 slices/30 sec, TE/TR: 1.81/3.61 ms; flip angle: 71; receiver bandwidth: 501 Hz/pixel; field of view (FOV): 400; matrix 256×256; slice thickness: 10 mm; voxel size: 2.71×1.6×10 mm^3).

Tumor Movement Analysis

All data were studied with E-RAD PAC's software. Tumor displacement was measured in axial, sagittal and coronal plane. To calculate the difference in position primary, the center of the tumor was marked in all slices. By our definition the tumor center was the point of intersection of the tumors greatest diameters on the actual slice. The tumor center definition was carried out manually by two independent physisist (a radiation oncologist and a radiologist) (Fig. 2). For all the tumors in all slices in all planes the coordinates of the tumor centers were registered. Totally $24\times100\times9 = 2{,}16\times10^4$ coordinates were collected, studied, and visualized (Fig. 3, 4).

The tumor deviation was calculated from the coordinates (12 coordinate unit difference equal to 1 cm deviation- defined by E-RAD PAC's measure tool- the difference was measured from the median coordinate values) in the three main planes. For each tumors direction independent deviation was calculated as: $\sqrt{x^2+y^2+z^2}$ (x: cranio–caudal, y: antero-posterior, z: medio-lateral deviation in cm). Finally in all the main directions — and direction independently— the probability of the displacement was visualized (percentage of the basic occasions related to the distance in cm- Fig. 5).

After data collection we investigated possible differences in the following factors:

difference in tumor movements between left–side sided laesions

difference in tumor movements between S1–2 and S3–6 lasions

difference in tumor movements between the patient age under and over 55 year

difference in tumor movements between the maximum diameter under and over 40 mm.

Statistical Analysis

For evaluating the data, paired T-test was used. When comparing the data series, the mean values were confronted in all cases and, during evaluation, a significance level of $p \leq 0.05$ was considered to be a significant difference.

Results

Movements of the tumor under normal breathing conditions were registered in the three main directions. In all patients, dynamic MRI series showed regular synchronous tumor motion with good mobility, displacements were periodic and reproducible. The acquisition of three images per

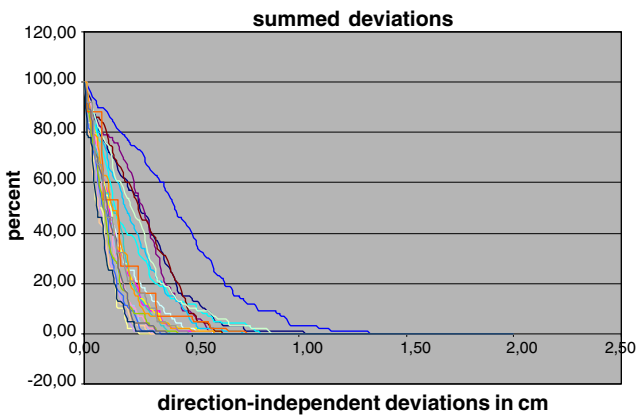
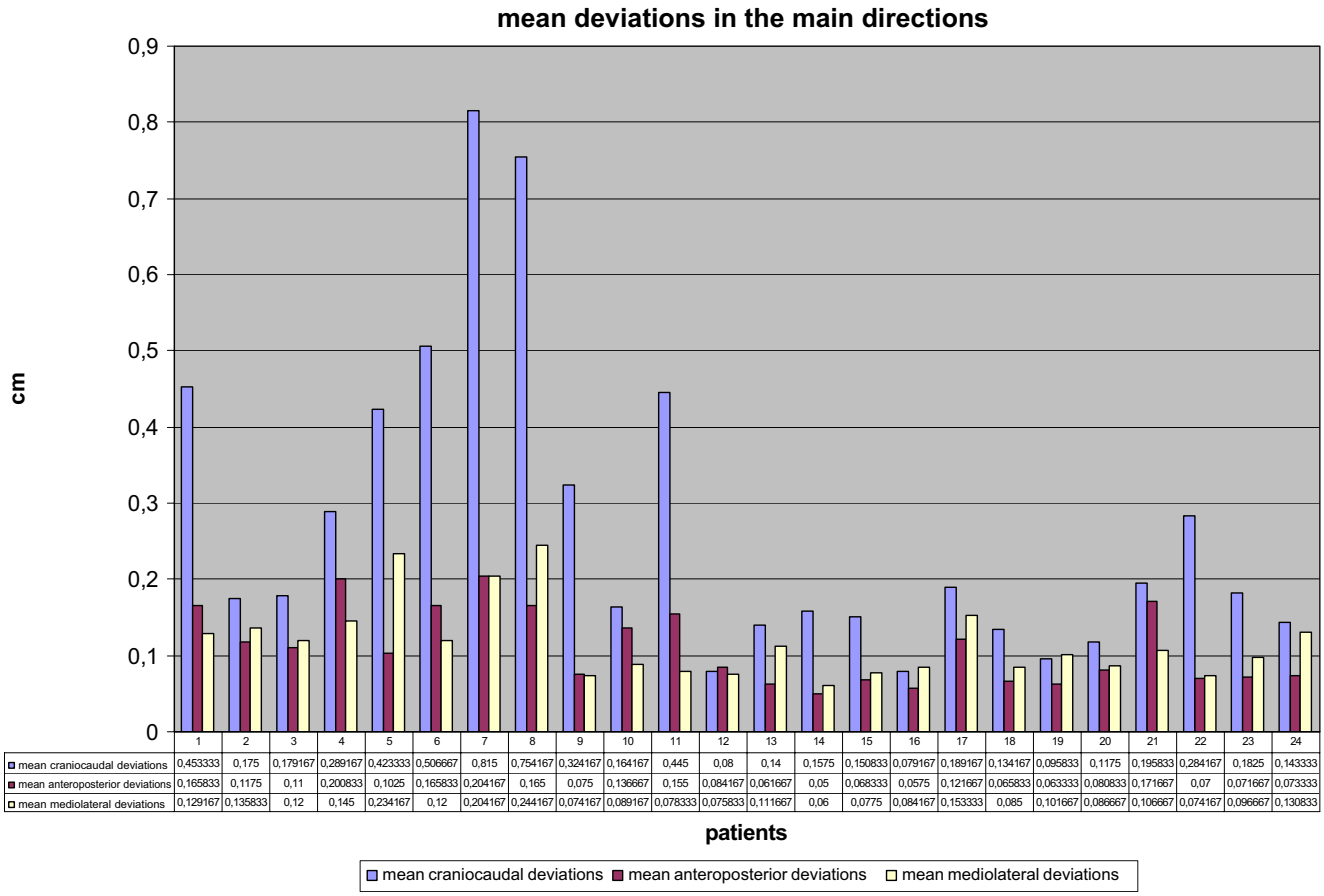


Fig. 5 Direction independent deviations of the tumors. In this figure the distance related Percentages were visualized. As it is shown the possibility of the absolute deviations greater than 1 cm is very low in the upper-and mid lobe located tumors



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
mean craniocaudal deviations	0,453333	0,175	0,179167	0,289167	0,423333	0,506667	0,815	0,754167	0,324167	0,164167	0,445	0,08	0,14	0,1575	0,150833	0,079167	0,189167	0,134167	0,095833	0,1175	0,195833	0,284167	0,1825	0,143333
mean anteroposterior deviations	0,165833	0,1175	0,11	0,200833	0,1025	0,165833	0,204167	0,165	0,075	0,136667	0,155	0,084167	0,061667	0,05	0,068333	0,0575	0,121667	0,065833	0,063333	0,080833	0,171667	0,07	0,071667	0,073333
mean mediolateral deviations	0,129167	0,135833	0,12	0,145	0,234167	0,12	0,204167	0,244167	0,074167	0,089167	0,078333	0,075833	0,111667	0,06	0,0775	0,084167	0,153333	0,085	0,101667	0,086667	0,106667	0,074167	0,096667	0,130833

Fig. 6 Mean deviation of the tumors in the 3 main planes. Distances of the motions were calculated from the coordinate deviations

second allowed for continuous recording during the breathing cycle.

The mean antero-posterior deviation was 0,109 cm (range: 0,063 cm–0,204 cm, SD: 0,04). The greatest AP deviation was 0,204 cm (patient 7.)

The mean medio-lateral deviation was 0,114 cm (range: 0,06 cm– 0,204 cm, SD: 0,05). The greatest medio-lateral deviation was 0,204 cm (patient 7.)

The greatest deviation was measured in cranio-caudal direction (mean: 0,27 cm, range: 0,079 cm– 0,815 cm). The mean direction independent deviation was 0,18 cm (range: 0,09 cm– 0,48 cm). (Fig. 6) On figure the distance related percentages (number of occasions related to the distance-in cm-/100) were visualized (Fig. 5).

In the comparison of the tumor motion (antro-posterior, cranio–caudal, medio-lateral and absolute deviation) between the age groups, the tumor size, the laterality and the sex no significant differences were found (Tables 2, 3, 4). Significant difference (in the level of $p \leq 0.05$) was observed only in case of the laesion localization between

Table 2 Tumor motion differences in the antero-posterior direction (in cm)

Differences in AP Direction (cm)	Mean	SD	Median	P value
Left side (n=11)	0.09	0.04	0.07	
Right side (n=13)	0.12	0.05	0.1	$p \leq 0.2$
Age<55 years (n=12)	0.1	0.04	0.09	
Age>55 years (n=12)	0.11	0.05	0.1	$p \leq 0.5$
Men (n=14)	0.10	0.04	0.07	
Women (n=10)	0.12	0.05	0.11	$p \leq 0.5$
Tumors in S1–S2 (n=10)	0.09	0.04	0.07	
Tumors in S3–S6 (n=14)	0.12	0.05	0.11	$p \leq 0.2$
Tumor maximum diameter <40 mm (n=13)	0.11	0.04	0.11	
Tumor maximum diameter >40 mm (n=11)	0.1	0.05	0.08	$p \leq 0.5$

Table 3 Tumor motion differences in the medi-lateral direction (in cm)

Differences in ML Direction (cm)	Mean	SD	Median	P value
Left side (n=11)	0.10	0.04	0.08	
Right side (n=13)	0.12	0.05	0.12	$p \leq 0.5$
Age<55 years (n=12)	0.12	0.04	0.11	
Age>55 years (n=12)	0.11	0.05	0.08	$p \leq 0.5$
Men (n=14)	0.11	0.05	0.09	
Women (n=10)	0.11	0.04	0.11	$p \leq 0.5$
Tumors in S1–S2 (n=10)	0.09	0.02	0.09	
Tumors in S3–S6 (n=14)	0.13	0.05	0.12	$p \leq 0.2$
Tumor maximum diameter <40 mm(n=13)	0.13	0.06	0.12	
Tumor maximum diameter >40 mm (n=11)	0.1	0.02	0.08	$p \leq 0.2$

the S1–2 and S3–6 segments, in the cranio–caudal direction (Table 5)

Discussion

According to International Commission on Radiation Units and Measurements (ICRU) Report, Recommendation No. 62, in 3D based radiotherapy the planning target volume (PTV) has to include the uncertainties arising from internal organ motion, patient movements and positioning errors [12]. In the modern 3D radiotherapy of lung cancer the question of organ motion is a very important factor. As it described in many studies movements of the tumor during the breathing cycle is a potential cause of RT failure in lung cancer [2, 13–15]. During RT, tumor mobility may be responsible for insufficient coverage of the clinical target volume and delivery of an insufficient total dose to destroy the tumor cells. In particular, high-precision techniques are very sensitive to failures in patient setup and internal motion. Here, the concept of the optimal target volume adoption bears the high risk of field border and out-of-field relapses, if tumor mobility is not sufficiently integrated into treatment planning [16, 17].

Up to now, several authors discussed the monitoring of tumor motions. In the past the respiratory cycle was examined by fluoroscopic measures; however, these techniques include some disadvantages. There is the possibility of an over- or underestimation of the actual movement, if the tumor is not located in a defined distance from focus caused by magnifying and lessening effects, and sometimes (central or small tumors) the exact definition of the tumor may be difficult [8]. Other authors applied beam imaging systems for monitoring tumor motions. A major advantage of this procedure is the real-time imaging, but portal imaging did not become very popular, in addition, visualization qualities need to be improved anyway [18].

CT-based definition of the tumor motion is the most popular and simplest method. According to this most commonly used procedure, the definition of PTV is performed on the basis of CT-images taken under normal breathing conditions. In general, the anatomical position seen on the image taken in normal breathing is considered to be a mid-position between in- and exhalation. However, the examination results showed clearly that the position of diverse thoracic structures during normal breathing can by no means be regarded as interposition between in- and exhalation [3, 11, 19]. Incorrect anatomical definition shall lead to geometric inaccuracy [3]. One study investigated CT to measure tumor mobility in 17 patients at two institutions [20]. It demonstrated that a precise and reproducible documentation of intrathoracic organ motions is possible using CT. In their

Table 4 Direction independent tumor motion differences (in cm)

Direction independent differences (cm)	Mean	SD	Median	P value
Left side (n=11)	0.14	0.1	0.11	
Right side (n=13)	0.2	0.11	0.21	$p \leq 0.2$
Age<55 years (n=12)	0.17	0.11	0.14	
Age>55 years (n=12)	0.16	0.1	0.14	$p \leq 0.5$
Men (n=14)	0.18	0.12	0.14	
Women (n=10)	0.16	0.08	0.14	$p \leq 0.5$
Tumors in S1–S2 (n=10)	0.13	0.03	0.12	
Tumors in S3–S6 (n=14)	0.2	0.13	0.18	$p \leq 0.1$
Tumor maximum diameter <40 mm (n=13)	0.19	0.13	0.14	
Tumor maximum diameter >40 mm (n=11)	0.14	0.06	0.11	$p \leq 0.2$

Table 5 Tumor motion differences in the medio-lateral direction (in cm)

Differences in CC Direction (cm)	Mean	SD	Median	P value
Left side (n=11)	0.22	0.18	0.16	
Right side (n=13)	0.31	0.22	0.28	$p \leq 0.5$
Age<55 years (n=12)	0.26	0.21	0.18	
Age>55 years (n=12)	0.27	0.19	0.17	$p \leq 0.5$
Men (n=14)	0.27	0.24	0.17	
Women (n=10)	0.26	0.141	0.18	$p \leq 0.5$
Tumors in S1–S2 (n=10)	0.15	0.05	0.14	
Tumors in S3–S6 (n=14)	0.35	0.22	0.30	$p \leq 0.05$
Tumor maximum diameter <40 mm (n=13)	0.31	0.24	0.18	
Tumor maximum diameter >40 mm (n=11)	0.22	0.13	0.15	$p \leq 0.5$

study, three CT series were performed, in free-breathing, inspiration, and expiration. The main disadvantage of this technique that only snapshots can be taken from the tumor position and the patient is exposed to additional radiation.

The selection of the comparison points in the motion analysis is a critical question. During respiration almost all parts of the chest are moving, it is difficult to find fixed points of reference. DeNeve et al. defined diaphragms, chest wall, carina and intervertebral discus as bases of comparison [24]. In his study of Plathow et al. cranio–caudal displacement was measured from the T6/T7 disk space to the proximal external tumor edge. Antero-posterior displacement was measured in relation to a line tangential to the anterior edge of the vertebrae. Medio-lateral displacement was measured from the midline through the spinal process. [32]. In our method there is no need to use such comparison points (which are also in motion) the coordinates can be defined easily using the software defining tool and uncertainties arising from this factor can be avoided.

The main goal of our study was to make a precise dynamic MR based analysis for lung cancer patients with upper and mid lobe tumors. In the literature only a few articles can be found using Dynamic MR for tumor and organ motion monitoring in lung cancer patients, and even in the "traditional" fluoroscopy or CT based studies mainly 7–20 patients were investigated. Seppenwoolde et al. described motion with gold implants taken into or near to the tumor, using fluoroscopy [15]. 13 tumors were in the upper and mid lobe region and due to this analysis similar results were found (2±1 mm in AP and medio-lateral direction, 0,7–11,1 mm in cranio–caudal direction) to our data shown in figure. In there CT based study of van Sornsen de Koste JR et al. 14 tumors in the upper localization were studied and a safety margin of 5 mm was proposed in general [21]. Other groups used a safety margin of 1 cm (7 patients) [4]. Shinichiro M et al used a 256 multislice CT for 4D measurement of tumor motion, and in there 14 patient study (upper–mid and lower lobe localization) they recommend in the left, right, superior, anterior and posterior directions the same value of 3.5 mm, and that for inferior direction 21 mm for internal margin [22]. According to dynamic MR based data of Palthow C. and al. taking the most extensive tumor displacement in quiet respiration taken into account, a general safety margin of 3.4 mm for tumors of the upper region (six patients), 4.5 mm for the middle region (four patients) must be considered [23].

In our study 24 tumors were investigated and this is on of the highest number in the context of dynamic MR based tumor motion analysis. This amount of data is comparable to the motion analysis of Plathow et al. (24/35 tumors in the upper and mid lobes [31]). Our numerical data give exact safety margins in all the three main directions and in

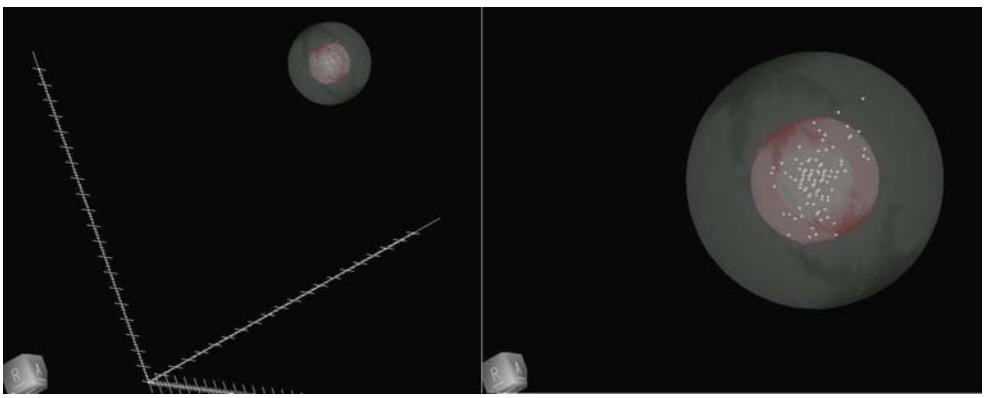


Fig. 7 3 D visualization of the 100 tumor center position in the 30 sec period. Around the median point spheres were generated with 0,5 cm and 1 cm diameter. Using this option tumor center positions moving out from these "barriers" can be visualized

general too (direction independent deviations). According to our results a mean safety margin of 0,25 cm in AP direction, 0,3 cm in medio-lateral direction and 0,85 cm in cranio–caudal direction should be enough in upper and mid lobe lung cancers. Using our method high precision tumor motion definition can be delivered. The tumor center coordinate definition slice by slice in all three directions gives the opportunity of 3D reconstruction and visualization of the tumor center movement. (Fig. 7). The main disadvantage of our method is the time consumption, for each tumor 300 coordinate must be defined to make the analysis. On Fig. 7 we have visualized all the 100 points registered during the 30 sec period in relation to x-y-z coordinates. Around the median point spheres were generated with 0,5 cm and 1 cm diameter. Using this option tumor center positions moving out from these "barriers" can be visualized.

Up to now in the literature, several authors described their investigations relating to respiratory gated techniques and active blocking of patient respiration, and movements. By now, several forms of positioning systems (mask fixation, vacuum systems, arm holders etc) are known [25]. Breathing-synchronized, manually triggered LINAC treatments are also in use, during which the therapy is controlled by respiratory positions transmitted by video equipment, laeser or plethysmograph [13, 26]. Some authors reported on treatments in deep breath-hold with active control allowing a CTV reduction of 0.25 cm, resulting in a decrease of the dosage-induced damage of normal lung tissues [27, 28]. Several papers were published relating to employment of active breath control (ABC) technique [29, 30]. These equipments are not widely used in the daily practice. Tumor motion analysis data can be integrated into the planning process and maybe in the future it can be used for modern tracking systems.

Conclusion

Dynamic MR is a sensitive and well tolerable method for tumor motion monitoring for high precision 3D therapy planning in lung cancer. Our results demonstrate that tumors located in the upper and mid lobes have moderate breath synchronous movements. The greatest deviation should be considered in cranio–caudal direction. In the upper and mid lobe localized tumors the investigated factors (age, sex, tumor size, laterality even the location) showed to be minor factors influencing tumor motions. In the future our analyzing process can be converted into other modalities (CT based motion tracking) and in the future it can be integrated into complex CT-MRI based gating techniques.

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