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Short communications and technical notes

Are liver contour and bone fusion comparable to fiducials for IGRT in liver SBRT?

C. de la Pinta [a,*], D. Sevillano [b,c], R. Colmenares [b], S. Barrio [d], A. Olavarria [e], A. Palomera [e], R. Romera [e], J. Cobos [e], A. Muriel [f], E. Fernández [a], LC. Perna [g], A. Albillos [h], S. Sancho [a]

[a] Radiation Oncology Department. IRYCIS. Ramón y Cajal Hospital. Crta Colmenar Viejo Km 9,100. 28034, Madrid, Spain
[b] Medical Physics Department. Ramón y Cajal Hospital. IRYCIS, Crta Colmenar Viejo Km 9,100 28034, Madrid, Spain
[c] Department of Radiology, Rehabilitation and Physiotherapy, Universidad Complutense de Madrid, Madrid, Spain
[d] Radiation Therapist. Ramón y Cajal Hospital. Crta Colmenar Viejo Km 9,100. 28034, Madrid, Spain
[e] Radiology Department. Ramón y Cajal Hospital. Crta Colmenar Viejo Km 9,100. 28034, Madrid, Spain
[f] Clinical Biostatistics Unit, Ramón y Cajal University Hospital, IRYCIS, CIBERESP. Universidad de Alcalá, Madrid, Spain
[g] Pathology Department. Ramón y Cajal Hospital. Crta Colmenar Viejo Km 9,100. 28034, Madrid, Spain
[h] Dept of Gastroenterology. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. IRYCIS. CIBEREHD., Madrid, Spain

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ABSTRACT

Introduction: Liver stereotactic body radiotherapy (SBRT) is increasingly being used to treat tumours. The purpose of this study was to compare the differences in patient positioning when using implanted fiducials as surrogates compared to alternative methods based on liver contour or bone registration.

Material and methods: Eighteen patients treated with SBRT who underwent a fiducial placement procedure were included. Fiducial guidance was our gold standard to guide treatment in this study. After recording the displacements, when fusing the planning CT and CBCT performed in the treatment unit using fiducials, liver contour and bone reference, the differences between fiducials and liver contour and bone reference were calculated. Data from 88 CBCT were analyzed. The correlation between the displacements found with fiducials and those performed based on the liver contour and the nearest bone structure as references was determined. The mean, median, variance, range and standard deviation of the displacements with each of the fusion methods were obtained. μ, Σ, and σ values and margins were obtained.

Results: Lateral displacements of less than 3 mm with respect to the gold standard in 92% vs. 62.5% of cases using liver contour and bone references, respectively, with 93.2% vs. 65.9% in the AP axis and SI movement in 69.3% vs. 51.1%. The errors μ, σ and Σ of the fusions with hepatic contour and bone reference in SI were 0.26 mm, 4 mm and 3 mm, and 0.8 mm, 5 mm and 3 mm respectively.

Conclusion: Our study showed that displacements were smaller with the use of hepatic contour compared to bone reference and comparable to those obtained with the use of fiducials in the lateral, AP and SI motion axes. This would justify that hepatic contouring can be a guide in the treatment of patients in the absence of fiducials.

Introduction

The development of high conformal techniques in radiotherapy has made it possible to limit the dose to tumors while protecting organs at risk [1,2]. Different strategies have been developed to control hepatic motion during stereotactic body radiotherapy (SBRT) [3]. In addition to motion control, the acquisition of an image prior to each treatment session, IGRT (Image-guided Radiotherapy), is very important and mandatory in SBRT. This image will allow us to locate the tumor at the time of the treatment session and to fuse this image with that of the planning CT (Computed Tomography), thus ensuring that the previously planned treatment is reproduced[4]. The most widely used IGRT system is Conebeam CT (CBCT) [3,4].

In lung SBRT the tumor image on CBCT is defined on a gray scale as a white opacity on a black background derived from the air in the lungs; however, strategies to localize the tumor during treatment in liver SBRT are complex due to the need for high-quality images or the use of intravenous contrast. To overcome this problem, the use of radio-opaque

* Corresponding author.
E-mail address: carolinadela.pinta@salud.madrid.org (C. de la Pinta).

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fiducials in the vicinity of the liver tumor has been proposed. This allows localization of the tumor proximity without the use of intravenous contrast or high-quality imaging.

Despite the theoretical advantages, its benefit in hepatic SBRT has not been demonstrated. This may be due to the fact that placement of the marker in the ideal position is not always possible, as it loses its function if there is too great a distance between the lesion and the marker [5]. In addition, the complication rate of this procedure ranges from 1 to 4% [6]. The risk of tumor dissemination or migration after puncture is 0.76% [7], and hemorrhage or perihepatic bleeding occurs in 0.001%, increasing in anticoagulated patients [8].

This study aims to evaluate the need for the use of fiducials in image-guided radiotherapy by comparing the displacements that would have to be made for correct patient positioning using fiducials, liver contouring and the nearest bone reference, for liver SBRT.

Material and methods

A prospective, open, single-center, non-randomized study was designed.

The study was approved by the ethics committee and patients signed an informed consent form prior to participation.

After evaluation of the patients by the corresponding multidisciplinary committees and establishment of the indication for SBRT, the patient was referred to the Radiology Service for the placement of three radio-opaque markers around the lesion (fibered platinum coil 2x5mm, Boston Scientific). The initial proposal was to place three markers around each lesion; however, by consensus between the radiologist and the oncologist the markers were variable (Table 1), due to each patient's individual tolerance to the procedure or the technical possibilities. In patients with fewer than three markers, at least one was placed within the lesion. One week later, a CT simulation was performed according to the established protocol of the center, using a standard immobilization device by abdominal compression with a thermoplastic mask, taking into account the patient's tolerance to reduction of organ motion related to the respiratory excursion. The oncologist in charge delimited the GTVs (Gross Tumor Volumes) and OARs (Organs At Risk) according to the guidelines. Treatment planning was performed and approved by the radiation oncologist following PTV (Planning Target Volume) coverage criteria and the limitations of OARs established in clinical practice.

Prior to each treatment session, a CBCT was performed and fused with the planning CT manually by the same physician in all cases using fiducials as a guide, which were considered our gold standard for treatment. The CBCT was acquired from 2D projections in a 360° rotation in 60 s.

Additionally, fusions were performed between CBCT and planning CT using the hepatic contour and the nearest bone reference (spine) as guides, recording the displacements found after fusion with each of the guides (example in Fig. 1).

The displacement in mm between the reference CT and the fusion with fiducials in the three axes of space, the displacement in mm between the reference CT and the fusion using hepatic contour and bone references, and the difference in mm between the displacements found with the fusion using hepatic contour and bone references and those observed with fiducials in the three axes of space were analyzed. Displacements were calculated in relation to the fiducial closest to the center of gravity of the lesion.

Statistical analysis

The means, medians, variance, range, and standard deviation in millimeters of the the displacement in all three axes was calculated for the three match methods: fiducials, soft-tissue, and bone matches. Systematic and random errors and the mean for each patient (μ) were analyzed [9].

In addition, the errors and their possible relation to the distance of the fiducials to the tumor were calculated.

With the results obtained, a theoretical calculation was made of the margins that would be necessary to define the PTVs and minimize the effect of these errors, based on the formula developed by Van Herk [9].

Margins $= 2.5\ \Sigma + 0.7\ \sigma$.

All statistical analyses were performed using IBM SPSS V25.

Results

Eighteen patients to be treated with hepatic SBRT were prospectively selected and fiducials were placed on or in the vicinity of the tumor (Boston Scientific®). In five patients, surgical clips derived from previous interventions were used as fiducials.

Thirteen out of the 18 patients included in the studyhad fiducials placed in or near the tumor. One patient suffered migration of the fiducial without clinical repercussions, and another patient presented a perihepatic hematoma that resolved conservatively. Patient characteristics and distance between the center of the tumor and that of the closest fiducial marker are shown in Table 1. A total of 528 displacements values from 88 CBCTs were analyzed. Table 2 shows the means,

Table 1
Characteristics of patients with fiducial markers for liver SBRT.

Patient	Gender	Primary tumor	Number of lesions	Segment	Dose/fractions	Number of fiducial marks	Distance to the nearest fiducial (mm)		
							Lateral	AP	SI
1	Female	Breast cancer	1	II	30 Gy/5	2	0	2	0.9
2	Male	Esophageal cancer	1	VII-VI	50 Gy/5	1	0	3	0.6
3	Male	Liver primary	1	VI	50 Gy/5	1	1	1.2	0.5
4	Male	Colon cancer	2	VII-VIII and IVa	50 Gy/5	> 3*	1	2	0.4
5	Male	Liver primary	1	VI	50 Gy/5	> 3*	2	7.5	3.6
6	Male	Rectal cancer	1	VI	60 Gy/5	1	0	0	0
7	Female	Metastasis of unknown origin	1	VIII	45 Gy/5	3	0.4	2.5	1.2
8	Male	Liver primary	1	VI	50 Gy/5	1	0.3	1.1	0
9	Female	Melanoma	1	I	60 Gy/5	> 3*	0.9	1.1	0.2
10	Female	Carcinoma of the orbit	1	VIII	60 Gy/5	1	0.1	0	0.2
11	Male	Plasmocytoma	1	II	30 Gy/5	2	1.8	0.9	0.8
12	Male	Colon cancer	1	V	60 Gy/5	> 3*	0.5	1	1.8
13	Male	Colon cancer	2	II and VI	50 Gy/5	3	3.3	1.8	1.8
14	Male	Liver primary	1	IV	50 Gy/5	1	0.7	0.4	1.8
15	Male	Cholangiocarcinoma	1	VI	45 Gy/6	Prosthesis and clip	0.4	0	1.5
16	Male	Liver primary	1	IV	50 Gy/5	2	1.5	1.2	1.5
17	Male	Colon cancer	1	V	60 Gy/5	2	0.1	2.6	1.2
18	Male	Rectal cancer	1	I	60 Gy/3	2	2.2	1.3	0.4

mm, millimeters; AP, anteroposterior; SI, superoinferior. * Patients with clips.

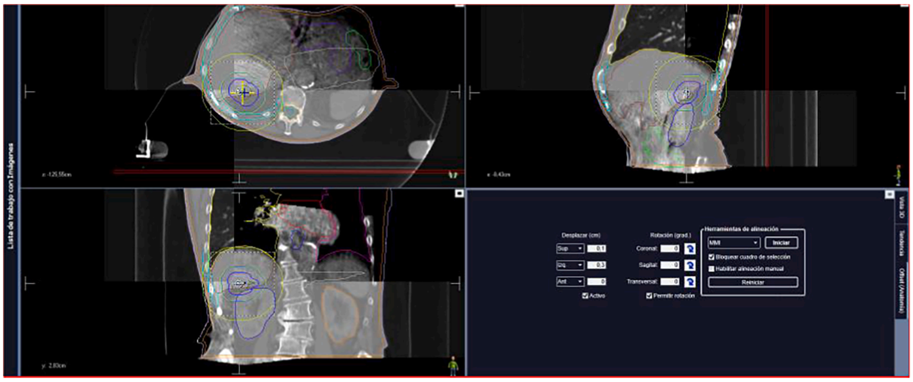

Fig. 1. CBCT showing the displacements with hepatic contour guide.

Table 2
Means, medians, variance, range and standard deviation of the displacement obtained in the treatment sessions with each of the image fusion methods.

	Fiducial markers			Liver contour			Bone reference		
	AP (mm)	Lateral (mm)	SI (mm)	AP (mm)	Lateral (mm)	SI (mm)	AP (mm)	Lateral (mm)	SI (mm)
Mean	0.1	0	−0.2	0.1	0	−0.2	0.1	0	−0.3
Median	0.1	0	−0.1	0.1	0	−0.1	0.1	0	−0.2
Variance	0.1	0.1	0.9	0.2	0.1	1.1	0.2	0.2	1
Range	2	2.3	5.5	2.3	2.5	5.2	2.7	2.1	6.3
Standard Deviation	0.4	0.3	1	0.4	0.4	1.1	0.4	0.4	1

AP, anterior-posterior; SI, superoinferior *All data was in millimiters.

medians, variance, range and standard deviation of the displacement obtained in the treatment sessions with each of the image fusion methods. The correlation between the fiducials and the liver contour and bone reference was determined for every fraction.

The distance between the fiducial marker and the center of the tumor lesion ranged from 0 to 7.55 mm. The median distance between the marker and the tumor center was 0.48 mm, 1.24 mm and 0.9 mm in the lateral, AP and SI axes, respectively.

The errors μ, σ and Σ of the fusions with hepatic contour and bone references were calculated, and the margins were obtained after application of the Van Herks formula [9] (Table 3). The calculation of the errors is the difference in millimeters between the displacements obtained after fusion with liver contour and bone references and those observed with fiducials in the three axes of space.

Differences between CBCT and planning CT registration based on the three methods were calculated. There were 87 values with displacement differences greater than 6 mm in liver contour and bone with lateral displacements of 4.6% vs 23.87%; anteroposterior displacements of 1.1% vs 14.8%, and superoinferior displacements of 22.7% vs 31.9% (Table 4). The uncertainties obtained with fusion using liver contour and bone references are shown in Table 3.

In the analyzed patients analyzed there were no cases of tumor dissemination in the puncture needle trajectory, but one patient suffered migration of the fiducials without clinical repercussions, and another patient presented a small perihepatic hematoma. The local control year at one year was 94.4%.

Table 3
Errors μ, σ and Σ in mm, margins and uncertainly required depending on the reference.

Errors	Liver contour			Bone reference		
	AP	Lateral	SI	AP	Lateral	SI
μ (mm)	**0.3**	0.2	**0.2**	0.5	**−0.1**	0.8
σ (mm)	**1**	**1**	**4**	3	2.4	5
Σ (mm)	**0.9**	**1**	**3**	3.7	2.7	3
Margins*						
Errors	**Liver contour**			**Bone reference**		
	AP	Lateral	SI	AP	Lateral	SI
Margins (mm)	2.9	3.2	10.3	11.3	8.4	11
Uncertainly**						
Errors	**Liver contour**			**Bone reference**		
	AP	Lateral	SI	AP	Lateral	SI
Total	**1.9**	**2**	**7**	6.7	5.1	8

AP, anteroposterior; SI, superioinferior; μ, mu error; Σ, systematic error; σ, random error; mm, millimeters. * In bold the lowest errors in each axis and each type of error. ** In bold lower uncertainty.

Table 4
Displacements less than 3 mm, 4–5 mm or greater than 6 mm, mean, standard deviation, median, variance and range of the displacements obtained from the difference with respect to the gold standard.

Displacements	Liver contour	Bone reference
Lateral		
< 3mm	81 (92%)	55(62,5%)
3–6	3 (3,4%)	12(13,63%)
> 6mm	4 (4,6%)	21(23,87%)
Mean + standard deviation	0.03 + 0.2	−0.1 + 0.8
Median	0	0
Variance	0.04	0.6
Range	−0.9 - +0.8	−6 – +1
AP		
< 3mm	82 (93,2%)	58 (65,9%)
3–6	5 (5,7%)	17 (19,3%)
> 6mm	1 (1,1%)	13 (14,8%)
Mean + standard deviation	0 + 0.17	0 + 0.5
Median	0	0
Variance	0,028	0,25
Range	−1 - +0–5	−1.2 - +2.2
SI		
< 3mm	61 (69,3%)	45(51,1%)
3–6	7 (8%)	15 (17%)
> 6mm	20 (22,7%)	28(31,9%)
Mean + standard deviation	0.05 + 0.6	0.12 + 0.78
Median	0	0.1
Variance	0.3	0.6
Range	−1 - +2.7	−2.8 - +2.5

AP, anteroposterior; SI, supero-inferior; mm, millimeters.

Discussion

The liver is in constant, irregular motion due to respiration. Its motion is irregular. The use of fiducials for the correction of translational errors could be a good option if the liver moves as a rigid body, with rigid motion or without rotation; however, it has been shown that deformations and rotations vary considerably between each session in the same patient and between patients [10].

Fiducials placement is an invasive procedure with a low complication rate, but is not innocuous [6–8]. This procedure has limitations, including incorrect placement, marker migration [11], or tumor dissemination with the puncture needle [9]. In our series, one patient suffered migration of the fiducials without clinical repercussions, and another patient presented a small perihepatic hematoma, but hepatic hemorrhages with significant anemization have been described in the literature [12]. Furthermore, after placement of the fiducials, a waiting period is required so that the hepatic inflammation produced does not alter treatment planning, leading to a delay in definitive treatment. In this regard, there are publications that argue that it would not be necessary to subject patients to this delay, but it is still not completely defined [13]. In our series, the planning CT scan was deferred from 7 to 10 days.

For all these reasons, in the process of implementing hepatic SBRT in our center, one of the questions that we tried to resolve was whether its use was really necessary in SBRT treatments with conventional linear accelerator SBRT with CBCT as IGRT. The placement of fiducials in other units such as Cyberknife® (Accuray, CA) is mandatory; however, in a conventional linear accelerator with CBCT, it is not defined.

As already mentioned, one factor to consider in the placement of fiducials is the distance between the fiducial marker and the tumor [14]. Seppenwoolde's study concluded that if the fiducials were placed in or around the tumor they could reduce lesion localization errors, whereas if they were placed far from the tumor, they would not serve to reduce or correct these errors and could induce errors equal to or greater than those introduced by conventional methods, their usefulness being dependent on the distance to the tumor [5]. Another study confirms this theory, specifying that the distance between the marker and the tumor should not be greater than 5–6 cm [15]. In Lu's study, the distance between the tumor and the marker was between 3.67 and 10.3 cm [10]. In our study the distance between the marker and the lesion had a median of 0.48 mm, 1.24 mm and 0.9 mm along the lateral, AP and SI axes, respectively, being less than in the studies of Lu and Wunderink [10,15], and may be explained by the use of the center of masses.

The tumor could be safely tracked by the fiducial positions, recommending the assessment of the geometric relationship between the marker and the tumor position.

Lu et al. studied liver deformations due to respiratory motion in patients treated for lung (12) and upper abdominal tumors (5) using fiducials and tracking to follow them [10]. In the absence of fiducial mark migration, the only uncertainty regarding correct tumor localization was irregular liver deformation. They concluded that this uncertainty can be solved with a 3–5 mm of margin to set the PTV. The migration of the fiducials can be compensated with an additional 2 mm of margin, and a margin of 5 to 7 mm can be used in that case [16,17]. The largest displacement is on the diaphragm surface (greater than3 mm), and the inter-fraction variations in exhalation are in general 10 times larger than the intra-fraction variations according to the data of the Nottrup study [18]. In our study, the margins were calculated as being larger if fusion was performed with the closest bony reference versus fusion with hepatic contour [19].

In the absence of fiducials, prediction of the liver position has been studied using structures such as the liver contour, diaphragmatic dome, or bone, with a standard deviation between 1.5 and 5 mm [20]. Guckenberger et al. performed a study including 11 patients with 13 intrahepatic lesions who underwent CT4D [21]. The absolute error in liver position and error in relation to bone anatomy were 8+/-4mm and 5+/-2mm, respectively. This study concludes that the use of fusion with liver contouring considering liver motion improves positioning compared to IGRT without consideration of liver motion [22,23]. Case et al. compared the position of the liver before and after treatment with respect to bony structures [24]. They analyzed the motion using CBCT of 29 patients treated with hepatic SBRT, with a total of 314 CBCTs. The mean of displacements was 1 (lateral), 1.7 (SI) and 1.6 (AP) mm, which may explain the correlation between the fiducials and the hepatic registry. In the Wunderik study, 12 patients were included and the fiducial marker was used as a reference standard compared to other methods using fluoroscopy, including the spine and diaphragmatic dome [25]. Regarding the use of the hepatic contour as a reference, Wunderink et al. found larger errors in the SI direction compared to those presented in the current study. Some authors demonstrated that hepatic contouring sometimes does not provide reproducible information on SI motion. Anatomical changes are more striking between the day of the planning CT scan and the start of treatment sessions than between treatment days, so these authors propose a CT scan on the first day of treatment to assess whether re-planning is necessary.

In our data, the error was greater with the use of a bone reference than with liver contouring. In Wunderink's study they concluded that the use of bone anatomy caused more random errors in the lateral axis than the use of fiducials, unlike our study, in which the greatest random errors occurred along the SI axis.

In addition, it has been shown that tumor motion can occur in short periods of time, affecting IGRT. In the previously mentioned studies, in SBRT with compression, Guckenberger et al. found variations of 3.7+/-2.2 mm during the course of treatment [21]. Case et al. evaluated the possible changes in the respiratory pattern during treatment, observing that these movements were small in the majority of the population studied, being less than 3 mm in 80% of cases [24]. They defined more variability in the amplitude of hepatic movement when the treatment was carried out over a total period of more than 2 weeks or if the time per fraction was increased (greater than25 min). In an MRI study, von Siebenthal et al. observed variations of 2.5–5.5 mm over a 10-minute period, increasing from 3.9 to 15.3 mm over 30 min [26]. All these authors found substantial displacements and rotations due to the temporal effect. The results show the importance of decreasing the time between placement and treatment delivery to minimize tumor shifts, which could be achieved with the speed provided by the use of fiducials [21,27–29].

Limitations

The limitations of the study include that the calculation of errors may be affected by the number of patients included, as occurs in other studies of these characteristics. However, the clinical results support the usefulness of liver contouring fusion as an appropriate treatment strategy. Lack of experience in fiducial placement for radiotherapy may have affected the results, especially in the first patients.

Conclusions

Our study showed that lateral displacements of less than 3 mm with respect to the gold standard were 92% vs. 62.5% using hepatic contour and bone as the reference, respectively; 93.2% vs. 65.9% of such displacement was along the AP axis, and SI movement was 69.3% vs. 51.1%. This would justify the use of the diaphragmatic dome as a guide in the treatment of patients in the absence of fiducials in cases where their placement is not indicated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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