Navigated Marker Placement for Motion Compensation in Radiotherapy

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ABSTRACT

Radiotherapy is frequently used to treat unoperated or partially resected tumors. Tumor movement, e.g. caused by respiration, is a major challenge in this context. Markers can be implanted around the tumor prior to radiation therapy for accurate tracking of tumor movement. However, accurate placement of these markers while keeping a secure margin around the target and while taking into account critical structures is a difficult task. Computer-assisted needle insertion has been an active field of research in the past decades. However, the challenge of navigated marker placement for motion compensated radiotherapy has not yet been addressed. This work presents a system to support marker implantation for radiotherapy under consideration of safety margins and optimal marker configuration. It is designed to allow placement of markers both percutaneously and during an open liver surgery. To this end, we adapted the previously proposed *EchoTrack* system which integrates ultrasound (US) imaging and electromagnetic (EM) tracking in a single mobile modality. The potential of our new marker insertion concept was evaluated in a phantom study by inserting sets of three markers around dedicated targets (n=22) simultaneously spacing the markers evenly around the target as well as placing the markers in a defined distance to the target. In all cases the markers were successfully placed in a configuration fulfilling the predefined criteria. This includes a minimum distance of 18.9 ± 2.4 mm between marker and tumor as well as a divergence of 2.1 ± 1.5 mm from the planned marker positions. We conclude that our system has high potential to facilitate the placement of markers in suitable configurations for surgeons without extensive experience in needle punctions as high quality configurations were obtained even by medical non-experts.

Keywords: Computer-assisted Interventions, Marker Placement, Ultrasound, Electromagnetic Tracking, Mobile Field Generator, Liver, Radiotherapy, Radiation Therapy, Calypso

1. INTRODUCTION

Tumor movement during a radiation session is a major challenge in radiotherapy, because it causes dispersion of the dose over a larger area, thus damaging healthy tissue and reducing the dose on the tumor.[1] To alleviate this, systems that track tumor movement have been presented as a solution.[2] These systems either work indirectly e.g. trough a chest belt that tracks breathing, or directly e.g. by inserting markers in the vicinity of the tumor.[2] While indirect means are quick to apply, they only approximate the tumor position. On the other hand, direct means predict the tumor position very well but require more preparation, e.g. a minimally invasive needle punction for each inserted marker. For example, the *Calypso* system for tumor tracking presented by Varian (*Varian Medical Systems Inc., Palo Alto, CA, USA*) requires up to three transponders (so-called *Beacons*^{TM}) to be implanted around the tumor, the position of which can then be inferred in real-time by transponder localization during radiation.[3] Other common methods for tumor tracking use gold markers which are visible under imaging modalities like fluoroscopy or computed tomography (CT).[4] Markers are usually implanted percutaneously under

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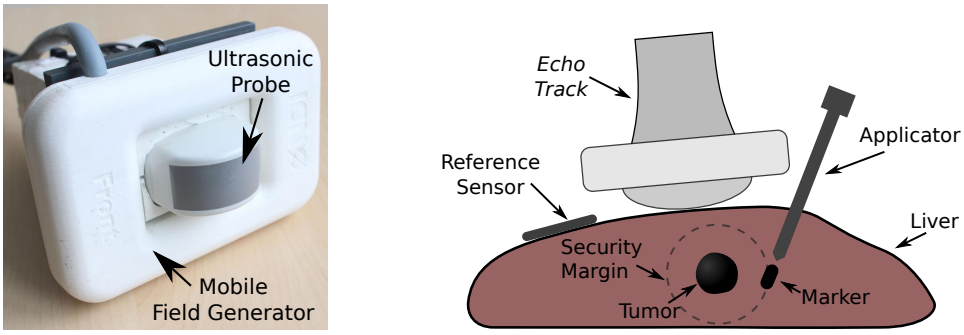


(a) *EchoTrack* prototype. (b) Application scenario.

Figure 1: (a) Concept for navigated marker placement based on *EchoTrack*,[11] which combines an US-Probe with a mobile EMFG. *EchoTrack* is used track Tumor and markers indirectly under a rigid body assumption using a 6Dof reference sensor. The pose of the applicator is determined directly using a tracked needle introduced into the applicator. The system can be used to insert markers percutaneously or during open liver surgery, as shown in (b).

ultrasound (US)[5] or CT guidance.[6] As the markers are used to track the tumor movement in a deforming organ, they should be placed such that they predict tumor movement optimally. For this reason, they are usually placed to encircle the tumor with equal distances to each other while being as close as possible to the tumor surface. On the other hand, a safe distance to the tumor should be kept in order to avoid the displacement of cancer cells that reach into the lesion perimeter. Additionally, the configuration of multiple markers must be planned and an the markers must be placed accordingly which makes the procedure time consuming and requires an experienced interventional radiologist. To complicate the matter, it is difficult to visually track the tumor in three-dimensional space, even with the help of CT or US imaging.

As radiotherapy can succeed open liver surgery, e.g. if additional lesions are found after opening the patient, making resection impossible, markers for radiation therapy may already be implanted during surgery. In this case the easy access to the organ can be leveraged and the patient can be spared the trauma of an additional percutaneous intervention. However, surgeons usually have low experience in marker placement. This can lead to delays while waiting for an interventional radiologist to arrive or to additional procedures being performed at a later point in time.

Although navigation systems for common needle insertions have been proposed,[7,8,9,10] to our knowledge, no system has been presented that allows the physician to plan and execute the insertion of several markers around the tumor. To address this issue we propose a new concept for navigated marker placement in radiation therapy.

2. METHODS

The aim of our new concept for marker placement is to assist the physician in simultaneously reaching the following goals:

1. The markers and the needle must not come into contact with the tumor in order to avoid cancer cell displacement. Therefore a user selectable safety margin has to be kept during the implantation procedure.
2. At the same time the markers should be placed equidistantly on a planning sphere with the tumor at their center, to optimally predict the tumor position. The radius of this sphere has to be large enough to include the necessary safety margin to the tumor.

By fulfilling both criteria, it is assured that the markers are equally distributed around the tumor, i.e. their center of mass lies close to that of the tumor. As a measure of placement accuracy, we take (A) the distances of the markers from the planning sphere and (B) the distances between the center of masses of markers and tumor. These distances should be zero for an optimal marker configuration as shown in Figure 3a.

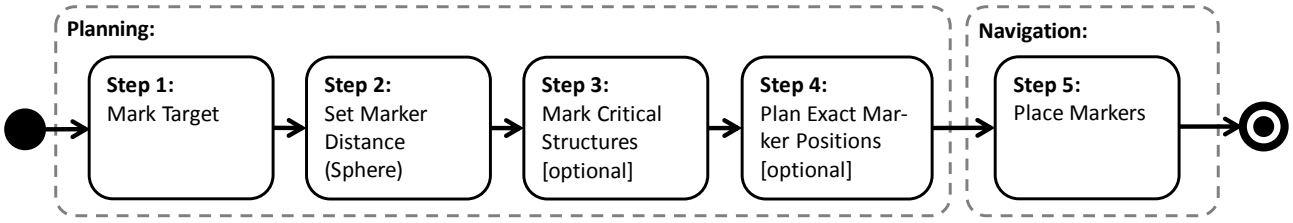


Figure 2: The workflow for *EchoTrack MarkerPlacement*. In the planning phase, the target is marked and the marker distance is set. Optionally, critical structures can be marked and the exact marker positions can be planned. Finally, markers are placed during the navigation phase.

In this section, we present the navigation system, how these criteria are first translated into a treatment plan and then into put into practice (Section 2.1) and the phantom study performed to evaluate its performance (Section 2.2).

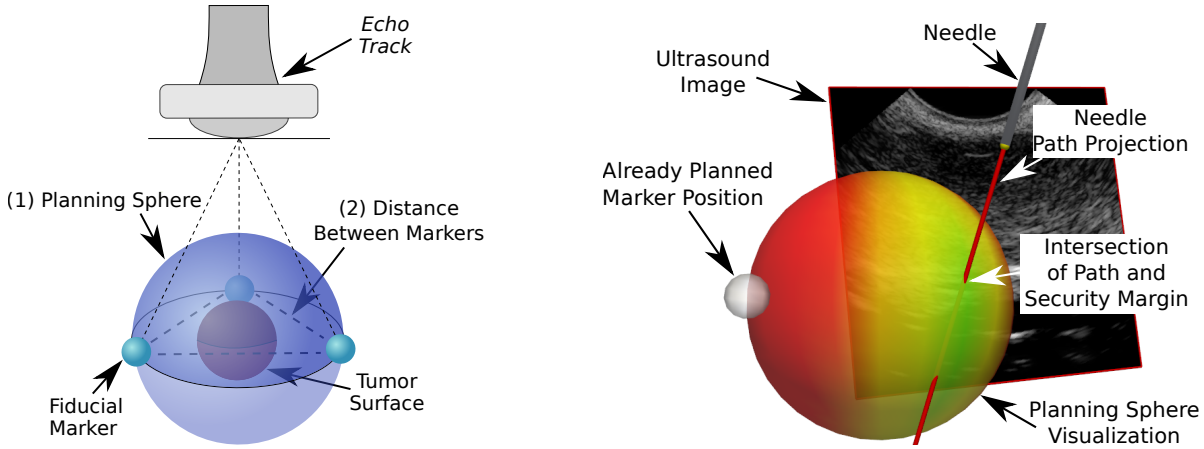
2.1 Navigation Concept

Our system is based on a combined modality of an US probe and a mobile electromagnetic field generator (EMFG) as introduced by März et al.[11] The prototype (see Figure 1a) is called *EchoTrack* and generates a tracking volume around the US probe, allowing instruments to be tracked in relation to the US image by means of an electromagnetic field.[12] *EchoTrack* has been shown to have a high tracking accuracy both in environments of interventional radiology and surgery.[13] Using this modality, the *EchoTrack NeedleGuide*[11] navigation system has been designed to plan and assist percutaneous needle punctions under consideration of critical structures. The same study validated the accuracy and precision of the system in a biopsy scenario in common interventional settings. We adapted the system to allow for planning and placement of markers for motion compensation in radiotherapy (see Figure 1b for the application scenario) under the Name of *EchoTrack MarkerPlacement*. *EchoTrack NeedleGuide* and *EchoTrack MarkerPlacement* differ in two key factors: First, instead of navigating a single needle to the tumor center, several markers need to be inserted around the tumor. It follows, that the target position cannot be seen directly on the US-image and a form of visualization is necessary. Second, the applicator used in this scenario is a relatively thick hollow needle trough which the marker is inserted into the body. Because it cannot be tracked directly, the applicator is tracked by introducing a trackable stylet into it. In principle, any applicator is trackable with this technique, given that a suitable needle can be inserted.

The system allows the physician to perform the intervention in a planning phase and a navigation phase (see Figure 2).

Planning: The physician first marks the tumor by specifying the center and the radius of the tumor using US imaging. An additional sphere then represents the user-defined distance from the tumor, where the markers should be placed. Critical structures may be marked by the physician the same way as the tumor was marked.[11] These structures will then be shown during the intervention.

In the following optional steps, the procedure can be planned in more detail if desired. While holding and orienting the needle on top of the skin or liver surface, the needle path is projected onto the planning sphere and the resulting marker position and orientation is visualized. The physician can then lock the planned position (see Figure 3b). After the first marker position was planned, the system supports the physician of planning optimal positions for the following markers by visualizing the best positions according to the metrics for optimal marker placement as described above. The visualization can be seen in Figure 3b and Figure 4. The suitability of each position on the planning sphere for placing the next marker is shown color coded on the surface. If the physician marked critical structures before, positions unreachable from the current position of the needle without violating a critical structure are shown on the planning sphere visualization like the other unsuitable positions.



(a) Metrics for the marker configuration.

(b) Screenshot of the system.

Figure 3: (a) The marker configuration is optimal according to the metrics we defined for our system. The markers are placed directly onto the planning sphere (1) and they are placed with equal distances (2) to each other. (b) Screenshot of the navigation software showing the needle path and the planning sphere visualization during the planning step. Positions for the markers are planned at the intersection point of the needle path and the planning sphere. The surface is colored from light green to dark red to indicate the best positions for placing a marker.

Navigation: After the planning phase was completed, the system aids the physician in recreating the previously logged insertion trajectories. Deviations from the plan are taken into account and can be compensated during placement of the following markers. This allows the physician to flexibly depart from planning while still being supported by the system. If no plan for the exact marker positions was made because the physician deemed the case simple enough, planned needle poses are not available but optimal marker placement is still facilitated by giving color coded feedback of optimal marker placement on the visualization of the planning sphere and by showing positions blocked by critical structures.

2.2 Phantom Study

The prototype has been implemented using the Medical Imaging and Interaction Toolkit (MITK, *www.mitk.org*),[14] an open-source framework for medical image processing. The tracking functionality was provided by by the module MITK-IGT[15] and for the US imaging the module MITK-US[16] was used. The US probe used in conjunction with the EMFG was the model *C3.5/20/128Z-3* by Telemed (TELEMED, Vilnius, Lithuania). The main frequency of this probe is 3.5 MHz. To asses the measurements outlined above, six identical phantoms were manufactured using ballistic gelatin (Gelita AG, Eberbach, Germany). Four spherical targets with a diameter of 1.6 cm $\pm$ 0.1 cm were placed in each phantom at a depth of approximately 6 cm as shown in Figure 5b. Only 22 interventions were done using the phantoms as two targets were reserved in the event that a target could not be used during the experiments due to errors in manufacturing the phantoms. An opaque layer on top of the phantoms prevented direct sight onto the target structures.

For this study, applicators of the *Calypso* system were used. A physician and a technician performed 11 interventions each at which three markers where placed around each target structure. The physician was experienced in US-based interventions, but had no prior experience with the system, while the technician had deep knowledge about the system but no experience in US-based interventions. Both test persons practiced the procedure on the same conditions as during the experiments a week before the experiments took place. While the physician or the technician performed the actual intervention, an additional technician controlled the software interface. The used markers were custom-designed metal markers with the size and shape of *Beacons* of the *Calypso* system (see Figure 5a). They were planned to be placed in equal distances to each other and on a planning sphere with a distance of 20 mm to the surface of the target. The optional planning of marker positions was always performed during the phantom study. The phantoms did not include critical structures for which reason the marking of critical structures wasn't done.

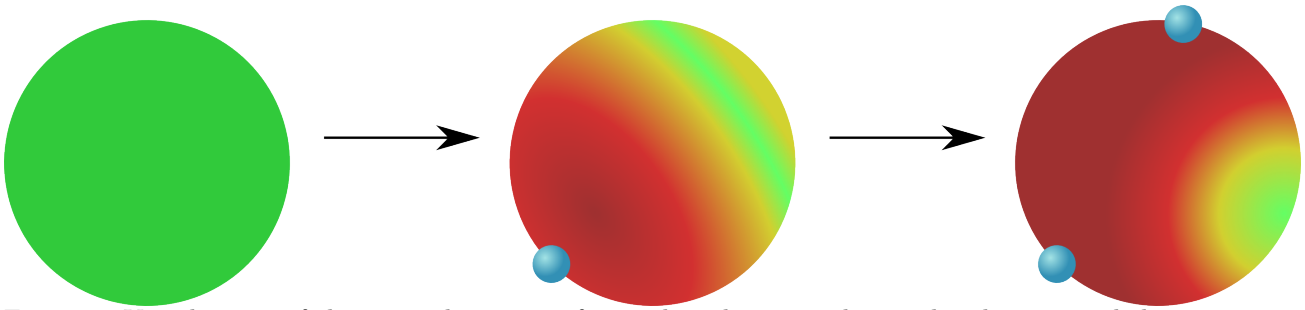


Figure 4: Visualization of the optimal positions for marker placement during the planning and the navigation process. The best positions for placing the next marker are shown in light green. The least effective positions are shown in dark red and the color for every other position is interpolated between light green and dark red. Shown in 2D for visualization purposes, actual rendering is in 3D.

The placement quality was verified by assessing the following metrics.

Accuracy of marker placement ΔS: By measuring the distance between markers and the surface of the planning sphere, the accuracy of the marker placement can be judged. The distance of the markers to the planning sphere was averaged for all 66 implanted markers. Since the planning sphere is not visible in the CT scan, the distance of the nearest point of the marker to the tumor was subtracted from the planned distance of 20 mm.

Quality of marker configuration ΔC_m: To assess the quality of marker placement, the distances between the center of mass of the markers and the center of mass of the tumor ΔC_m were calculated and averaged.

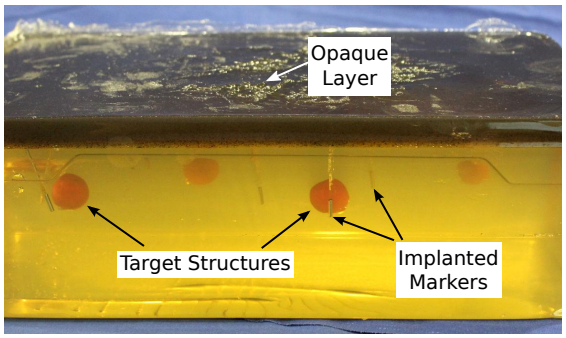
Distance between marker and tumor ΔT: After navigating to the planning sphere and implanting the marker, the resulting minimal distance between marker and tumor ΔT was measured.

These metrics were calculated three times: First by the system after the planning phase and then again at the end of the navigation after the markers were placed. Additionally, the duration of each intervention was measured. As a reference the metrics were assessed using CT scans of the phantoms after the intervention to compare the predictions of the systems to how the markers were placed in reality. Therefore, beacons and tumor were segmented as shown in Figure 6 and the segmentations were used to calculate the respective center of mass.

3. RESULTS

The results of the phantom study are shown in detail in Table 1. The CT control scans showed an average distance of the 66 implanted markers to the planning sphere of 2.1 ± 1.5 mm. The physician reached a slightly better distance value than the technician: 1.9 ± 2.4 mm vs. 2.4 ± 1.6 mm. The distance of the centers of mass of the target structures and the markers was 4.4 ± 2.0 mm (n = 22) on the CT scans. In 91% of the cases, the center of mass of the markers laid inside of the target. Here, the results of the technician were slightly better than the results of the physician: 3.5 ± 1.7 mm vs. 5.6 ± 2.0 mm. The average distance between marker and target was 18.9 ± 2.4 mm. The difference in measurement of the metric between the reference method (CT control scans) and the outputs of the system after planning and after implanting the markers was smaller than the standard deviation of the results. Hence there wasn't a pronounced difference measured between the predictions of the system and the calculations based on the CT control scans. The 22 interventions took 9 min 21 s ± 94 s on average. No pronounced differences between the durations of the interventions of the physician and the technician were measured.

(a) Custom-designed metal markers.



(b) Phantom of ballistic gelatin.

Figure 5: Metal markers with the size and the shape of *Beacons* of the *Calypso* system (a) were placed around target structures in gelatin phantoms (b) during the phantom study.

4. DISCUSSION

Inserting markers for motion compensation in radiation therapy is a difficult task that requires experienced personnel when performed conventionally. Performed percutaneously, it is complicated by long access trajectories and critical structures inhibiting access. Marker implantation during open liver surgery is easier, but rarely used due to separation of fields between surgery and interventional radiology. We propose a new concept for planning and visualizing the complex three dimensional arrangement between markers, tumors and critical structures, called *EchoTrack MarkerPlacement* that can address these issues.

A phantom study with two participants yielded encouraging results. None of the implanted markers came into contact with the tumor. The average distance of the marker positions to the planning sphere was 2.1 ± 1.5 mm and a distance of 4.4 ± 2.0 mm between centers of mass of the markers and the tumor was achieved on average. Thereby the markers were placed equally around the tumor as the center of mass of the markers was inside the

	Physician	**Technician**	**Total**
n_c/n_m	11/33	11/33	22/66
Planning			
ΔS	0.3 ± 0.1 mm	0.3 ± 0.1 mm	0.3 ± 0.1 mm
ΔC_m	6.6 ± 2.0 mm	2.6 ± 1.3 mm	4.6 ± 2.6 mm
ΔT	19.7 ± 0.1 mm	19.7 ± 0.1 mm	19.7 ± 0.1 mm
Navigation			
ΔS	1.4 ± 1.8 mm	0.7 ± 0.6 mm	1.0 ± 1.1 mm
ΔC_m	7.7 ± 3.3 mm	4.5 ± 1.5 mm	6.2 ± 3.0 mm
ΔT	20.9 ± 1.8 mm	20.4 ± 0.8 mm	20.6 ± 1.4 mm
Control Scans			
ΔS	1.9 ± 2.4 mm	2.4 ± 1.6 mm	2.1 ± 1.5 mm
ΔC_m	5.6 ± 2.0 mm	3.5 ± 1.7 mm	4.4 ± 2.0 mm
ΔT	19.6 ± 2.44 mm	18.2 ± 2.2 mm	18.9 ± 2.4 mm
Duration	9 min 16 s ± 106 s	9 min 25 ± 88 s	9 min 21 s ± 94 s

Table 1: Results of the marker implantations of physician and technician. Each participant implanted $n_c = 11$ marker configurations consisting of three markers each, resulting in $n_m = 33$ implanted markers per participant. Measured parameters were the divergence of the marker positions from the planning sphere of 20 mm ΔS, the distances between the centers of mass of targets and tumors ΔC_m, the average of the minimum distances between a marker and the tumor ΔT and the duration of the intervention. The distances of marker and tumor and the distances from the planning sphere were averaged over all 33 implanted markers of each test person. All three metrics were calculated twice by the system during the intervention (planning, navigation) and were measured on the CT control scans after the intervention. The duration was measured over the whole process of implanting the markers.

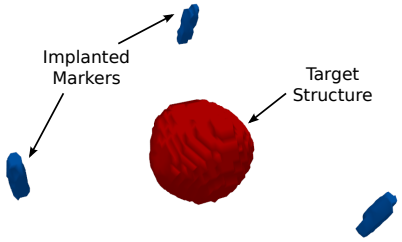


Figure 6: The markers and the targets were segmented on CT control scans after the implantation procedures to assess the accuracy of the marker positions.

tumor at 91% of the implantations. With markers placed in such configurations around the tumor, accurate tracking is possible in radiation therapy under most conceivable conditions. The procedure of planning and the insertion of three markers took approximately 9 minutes on average. After careful examination of the CT scans, a small but systematic deviation of marker placement in direction of the tumor was found. This can be attributed to the fact that the position of the needle was measured at the needle tip by the system, while the center of the markers got pushed out of the needle by approximately 1 mm during the insertion process. This does not directly translate into an equivalently large deviation from the planning sphere, as the marker orientation was not perpendicular to the sphere surface (see Figure 6). However, since the needle always points towards the surface to a degree, this could explain the systematic deviation.

Regarding the experimental conditions, the phantom study provided insight into the system behavior in a rigid body. However, this implies that tumor movement is not part of this evaluation. In order to negate deregistration trough tumor movement, we propose to attach a sensor to the liver surface to eliminate breathing motion for the open liver surgery case. Using a reference sensor in an open surgery setting is more difficult than for percutaneous interventions though it is feasible as shown by Oliveira-Santos et al.,[17] who used bio-compatible cyanoacrylate glue to attach optical markers to a liver surface and tested it with an ex-vivo liver. Due to the proximity of tumor and sensor, relative motion is mitigated. However, careful handling of the liver is necessary to avoid deregistration. Future work should include an analysis on the relative movement of tumor and sensor during the intervention. In case of the percutaneous intervention, a marker can be attached to the skin as proposed for the biopsy scenario in a previous study.[11] Another complicating factor are critical structures. In an open liver scenario, access to the liver is usually good, which reduces the need for critical structure tracking. This is different to the percutaneous case, where critical structures play a larger role. The software allows to mark and track critical structures. However, we decided against an evaluation of critical structure tracking in this study, as previous work has shown good results and focus was set on accurate marker positioning.[13]

We have already shown that the robustness of electromagnetic tracking using the mobile EMFG is high in both the liver surgery scenario and the percutaneous punction scenario.[13] Hence, future work encompasses further specialization of the software for open liver application. Using special linear arrays would allow to obtain high resolution US images of the tumor, which could allow real-time segmentation and tracking of the tumor using the US images. Real-time segmentation and tracking of the tumor using the US images would offer the advantage of no longer needing a reference sensor attached to the liver surface. Additionally, we plan to perform in-vivo studies to better assess applicability.

The achieved marker configurations can be regarded as good, which was confirmed by the radiology department of the DKFZ. The defined criteria have been fulfilled satisfactorily and the plans could be translated into practice reliably. In conclusion, we presented a novel system for navigated marker insertions that gives promising results in our initial study.

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REFERENCES

[1] Shirato, H., Shimizu, S., Kunieda, T., Kitamura, K., van Herk, M., Kagei, K., Nishioka, T., Hashimoto, S., Fujita, K., Aoyama, H., Tsuchiya, K., Kudo, K., and Miyasaka, K., "Physical aspects of a real-time tumor-tracking system for gated radiotherapy," *INT J RADIAT ONCOL* **48**(4), 1187 – 1195 (2000).

[2] Shirato, H., Shimizu, S., Kitamura, K., and Onimaru, R., "Organ motion in image-guided radiotherapy: lessons from real-time tumor-tracking radiotherapy," *INT J CLIN ONCOL* **12**(1), 8–16 (2007).

[3] Mate, T. P., Krag, D., Wright, J. N., and Dimmer, S., "A new system to perform continuous target tracking for radiation and surgery using non-ionizing alternating current electromagnetics," *INT CONGR SER - CARS 2004* **1268**, 425–430 (2004).

[4] Shirato, H., Shimizu, S., Kitamura, K., Nishioka, T., Kagei, K., Hashimoto, S., Aoyama, H., Kunieda, T., Shinohara, N., Dosaka-Akita, H., and Miyasaka, K., "Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor," *INT J RADIAT ONCOL* **48**(2), 435 – 442 (2000).

[5] Ellis, W. J., *Technique for Transrectal, Ultrasound-Guided Implantation of Beacon Transponders in the Prostatic Bed*. Calypso Medical Technologies (2009).

[6] Kothary, N., Heit, J. J., Louie, J. D., Kuo, W. T., Jr, B. W. L., Koong, A., Chang, D. T., Hovsepian, D., Sze, D. Y., and Hofmann, L. V., "Safety and Efficacy of Percutaneous Fiducial Marker Implantation for Image-guided Radiation Therapy," *J VASC INTERV RADIOL* **20**(2), 235239 (2009).

[7] Sindram, D., Swan, R. Z., Lau, K. N., McKillop, I. H., Iannitti, D. A., and Martinie, J. B., "Real-Time Three-Dimensional Guided Ultrasound Targeting System for Microwave Ablation of Liver Tumours: A Human Pilot Study," *HPB* **13**(3), 185191 (2011).

[8] Khati, N. J., Gorodenker, J., and Hill, M. C., "Ultrasound-guided biopsies of the abdomen," *ULTRASOUND Q* **27**, 255–268 (Dec. 2011).

[9] Maier-Hein, L., Tekbas, A., Seitel, A., Pianka, F., Müller, S. A., Satzl, S., Schawo, S., Radeleff, B., Tetzlaff, R., Franz, A. M., Müller-Stich, B. P., Wolf, I., Kauczor, H.-U., Schmied, B. M., and Meinzer, H.-P., "In vivo accuracy assessment of a needle-based navigation system for CT-guided radiofrequency ablation of the liver," *MED PHYS* **35**, 5385–5396 (Dec. 2008).

[10] Helbig, M., Krysztoforski, K., Kroll, T., Kucharski, J., Popek, M., Helbig, S., Gstoettner, W., May, A., and Kozak, J., "Navigation-supported and sonographically-controlled fine-needle puncture in soft tissues of the neck," *ULTRASOUND MED BIOL* **35**, 436–442 (Mar. 2009).

[11] März, K., Franz, A. M., Stieltjes, B., Iszatt, J., Seitel, A., Radeleff, B., Meinzer, H.-P., and Maier-Hein, L., "Mobile EM Field Generator for Ultrasound Guided Navigated Needle Insertions," in [*PROC IPCAI*], Barratt, D., Cotin, S., Fichtinger, G., Jannin, P., and Navab, N., eds., *LNCS* **7915**, 7180, Springer (2013).

[12] Franz, A. M., Haidegger, T., Birfellner, W., Cleary, K., Peters, T. M., and Maier-Hein, L., "Electromagnetic Tracking in Medicine A Review of Technology, Validation and Applications," *IEEE T MED IMAGING* **33**, 1702–1725 (Aug 2014).

[13] März, K., Franz, A. M., Seitel, A., Winterstein, A., Hafezi, M., Saffari, A., Bendl, R., Stieltjes, B., Meinzer, H.-P., Mehrabi, A., and Maier-Hein, L., "Interventional real-time ultrasound imaging with an integrated electromagnetic field generator," *INT J CARS* **9**, 759–768 (Mar. 2014).

[14] Nolden, M., Zelzer, S., Seitel, A., Wald, D., Müller, M., Franz, A. M., Maleike, D., Fangerau, M., Baumhauer, M., Maier-Hein, L., Maier-Hein, K. H., Meinzer, H.-P., and Wolf, I., "The Medical Imaging Interaction Toolkit: Challenges and Advances," *INT J CARS* **8**(4), 607620 (2013).

[15] Franz, A. M., Seitel, A., Servatius, M., Zöllner, C., Gergel, I., Wegner, I., Neuhaus, J., Zelzer, S., Nolden, M., Gaa, J., Mercea, P., Yung, K., Sommer, C. M., Radeleff, B. A., Schlemmer, H.-P., Kauczor, H.-U., Meinzer, H.-P., and Maier-Hein, L., "Simplified development of image-guided therapy software with MITK-IGT," *PROC SPIE* **8316**, 83162J83162J8 (2012).

[16] März, K., Franz, A. M., Seitel, A., Winterstein, A., Bendl, R., Zelzer, S., Nolden, M., Meinzer, H. P., and Maier-Hein, L., "MITK-US: real-time ultrasound support within MITK," *INT J CARS* **9**, 411–420 (May 2014).

[17] Oliveira-Santos, T., Peterhans, M., Hofmann, S., and Weber, S., "Passive Single Marker Tracking for Organ Motion and Deformation Detection in Open Liver Surgery," in [*PROC IPCAI*], Taylor, R. and Yang, G.-Z., eds., *LNCS* **6689**, 156167, Springer (2011).