Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2014)
13, 473–483
doi:10.1017/S1460396914000223

Literature Review

Calypso® 4D Localization System: a review

C. Silva[1,2], D. Mateus[2], M. Eiras[1], S. Vieira[2]

[1]*Escola Superior de Tecnologias da Saúde de Lisboa, Portugal,* [2]*Centro Clínico Fundação Champalimaud, Lisboa, Portugal*

(Received 18 February 2014; revised 9 May 2014; accepted 12 May 2014; first published online 5 August 2014)

Abstract

Purpose: Calypso® 4D Localization System is a system based on electromagnetic transponders detection enabling precise 3D localisation and continuous tracking of tumour target. This review intended to provide information in order to (1) show how Calypso® 4D Localization System works, (2) to present advantages and disadvantages of this system, (3) to gather information from several clinical studies and, finally, (4) to refer Calypso® System as a tool in dynamic multileaf collimator studies for target motion compensation.

Methods: A structured search was carried out on B-On platform. The key words used in this research were 'Calypso', 'Transponder', 'Electromagnetic Localization', 'Electromagnetic Tracking', 'Target Localization', 'Intrafraction Motion' and 'DMLC'.

Review: Treatment the implanted transponders are excited by an electromagnetic field and resonate back. These frequencies are detected and Calypso® software calculates the position of the transponders. If the movement detected is larger than the limits previously defined, irradiation can be stopped. The system has been proven to be submillimetre accurate.

Discussion: Calypso® System has been presented as an accurate tool in prostate radiotherapy treatments. The application of this system to other clinical sites is being developed.

Conclusion: The Calypso® System allows real-time localisation and monitoring of the target, without additional ionising radiation administration. It has been a very useful tool in prostate cancer treatment.

Keywords: Beacon® transponders; Calypso®; DMLC; lung; prostate

INTRODUCTION

The main goal in radiation therapy is to deliver a prescribed dose to a target volume while minimising toxicity to adjacent healthy tissues. One potential way to decrease radiation related toxicity would be to spare more normal tissues.[1–5] The latest equipment development now allows us to use more precise and conformal techniques when delivering radiation, such as intensity modulated radiotherapy (IMRT) and intensity modulated arc therapy techniques. The introduction of these techniques demands for precise target immobilisation and localisation so there is minimal movement during treatment.[6]

Correspondence to: Célia Silva, R. Outeiro Cacho, 6, Loureira, 2495-161 Sta Cat Serra, Portugal. Tel: 00351919628745. E-mail: celia.psilva@gmail.com

New imaging modalities have improved localisation and setup accuracy. The possibility to acquire a cone beam computed tomography (CBCT) before treatment allows professionals to make adjustments according to the target and surrounding organs position, instead of making adjustments according to boney position (MV planar images).[7–16] CBCT images can be acquired before and/or after treatment delivery or even between beams. Nevertheless, that does not account for movement that may occur during treatment and organ motion is a major obstacle to reducing margins without compromising dose to the target volume.[17] Camille Noel et al. studied this pre- and post-treatment CBCT acquisition as a way of predicting intrafraction movement in prostate patients. The conclusion of this study indicated that this imaging acquisition is not a good predictor of intrafraction prostate motion.[18]

In order to consider internal movement, various methods have been used for real-time tracking. Methods as fluoroscopy and megavoltage imaging (associated or not with gold fiducials) have the disadvantage of increasing the radiation delivered to the patient. On the other hand infrared tracking of external markers consider external movement as directly related to internal movement, but this correlation has been proven to be imperfect.[7–16,19–21]

The Calypso® 4D Localization System (Calypso® Medical, Seatle, WA, USA) is a wireless electromagnetic localisation system which aims to target tumours accurately before and during treatment delivery.[22]

This review provides information in order to (1) show how Calypso® 4D Localization System works, (2) to present advantages and disadvantages of this system, (3) to gather information from several clinical studies and, finally, (4) to refer Calypso® System as a tool in dynamic multileaf collimator (DMLC) studies for target motion compensation.

MATERIALS AND METHODS

The review was based on literature searched on B-On Platform. The key words used in this research were 'Calypso', 'Transponder', 'Electromagnetic Localization', 'Electromagnetic Tracking', 'Target Localization', 'Intrafraction Motion' and 'DMLC'. The search provided several articles since January 2005. After reading and analysing the B-On search, a selection of references mentioned in some of these articles was made and also analysed and included in this review.

THE CALYPSO® 4D LOCALIZATION SYSTEM

This system has five components: Beacon® transponders (specially created for Calypso® System), the console, the array, the optical localisation subsystem and the monitoring station.[23]

Each transponder consists of a sealed glass capsule containing a miniature electronic circuit. Transponders are 8·7 mm length and 1·85 mm in diameter and are biologically inert.[6,23,24] Typically, three Beacons are implanted in the patient. Only two transponders are necessary for the system to calculate translational movements. However, to have information about rotations a minimum of three transponders is needed.[23–25] The transponders resonate when excited with the electromagnetic field generated by the array. Each transponder has a unique frequency response. The transponders are also color coded with their intended position, which allows them to be distinguished individually. Sensors in the array measure the magnetic field strength from each transponder and the software can calculate the location of each transponder.[22,23,26,27]

The console is inside the treatment room. It is a movable unit that gathers a power supply, a computer with the software that calculates transponders location, cables and the array.[23]

The array contains source coils, sensors and infrared targets. The source coils generate the electromagnetic fields that excite the transponders. The sensors of the array receive the resonant signals of each transponder and the infrared targets are detected by infrared cameras.[22,23] The array is positioned above the patient, with minimum beam attenuation.[28]

Three infrared cameras are mounted in the treatment room so that the array position is continuously monitored. The array location yields the position of the centre of the target,

https://doi.org/10.1017/S1460396914000223 Published online by Cambridge University Press

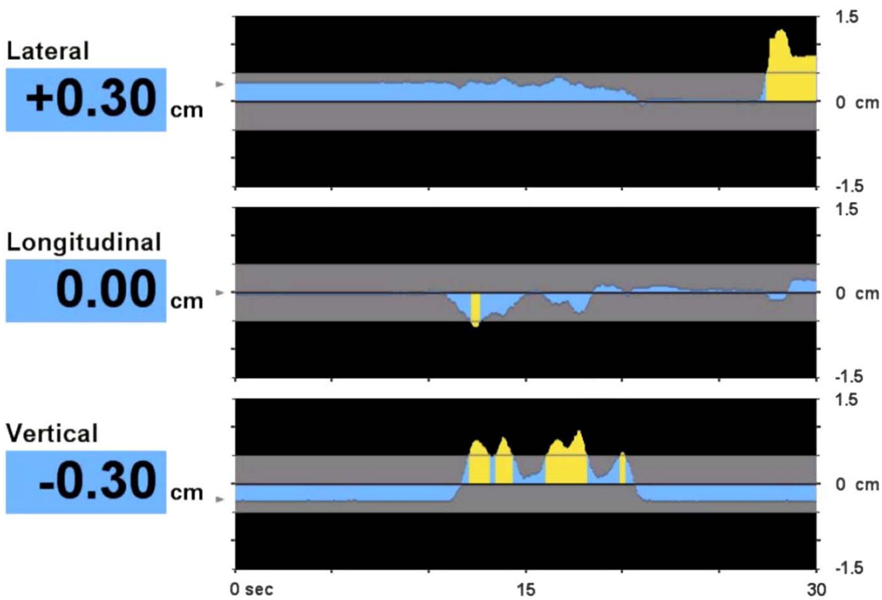

Figure 1. Tracking station display: in this example the patient is positioned in (0, 0, 0) Calypso® coordinates (black line) and during the monitoring period beacons' movements are within acceptable limits (grey zone) whenever the graph is blue, and outside acceptable limits (black zone) whenever the graph is yellow; the actual shift value for the three coordinates is on the screen left side (reproduced by kind permission of Calypso® from Calypso® System user's manual).

with respect to the machine isocenter. This means that the system calculates the table translation movements that are necessary to have the Beacons positioned at the treatment unit according to the planning computed tomography (CT) scan. The positional information is simultaneously displayed and updated in the console as it is in the control area[23,24,27,29] (Figure 1).

Radiation therapists are in the control area monitoring the movement of the target during the treatment delivery through the observation of the data that is being displayed on the monitoring station. Visual and audio alerts warn therapists that the target has exceeded the limits established.[23,30]

Advantages[22,31–35]

- No additional ionising radiation is delivered to the patient.
- The target is monitored continuously.
- Real-time information is provided so that action may be taken to limit the influence of intrafraction motion.[33]
- 3D target tracking.
- Not dependent on target size: the system relates to a virtual point about which the physician defined radiation volume is actually delivered.
- The transponders are implanted directly into the target volume.
- The implantation procedures are generally uneventful and well tolerated by the patients.[23]
- Compact.
- Biocompatible.
- Transponders are compatible with CT imaging and, in some cases, megavoltage imaging.
- Connection between Calypso® System and linear accelerator: the irradiation may stop automatically when the detected movement is superior to the threshold previously defined (available only for Varian Edge Platform).

Disadvantages[23,25,29,30,36,37]

- Extra imaging may be needed to assess fully the planning target volume (PTV) and the organs at risk (OARs) – for example the system may confirm that the prostate is in the right position, but no information is given regarding the size of the bladder, an image is required to evaluate that OAR.

- Need for implantation.
- Calypso® manual considers a localisation volume under the array of 14×14×27 cm^3 space in lateral, longitudinal and vertical directions[32] therefore the Beacons should be placed so that they are inside this volume during treatment.
- Implanted Beacons may result in a problem when magnetic resonance imaging follow-up exams are performed: the RF transmitters in the Beacons create huge image artefacts.[37]
- Patients with pacemakers should be handled with care.
- After implantation, Beacons stay inside the patient and cannot be re-used.
- Patients with certain prostheses may not be suitable candidates for this system.

Quality assurance

The accuracy of the system has been verified to submillimetre accuracy, in several laboratory and clinical studies.

Balter et al. report the results for several tests focused on the accuracy of transponder localisation relative to the array. First a single transponder was positioned at locations up to 8 cm in the X and Y planes from the center position, at Z distances of 8 and 27 cm from the array. A continuous readout of the transponder positions was recorded at these positions for periods up to 20 minutes. At 8 cm distance from the array the offset after 15 minutes the readouts were +0·03, +0·05 and −0·09 mm for the X, Y and Z directions, respectively. At 27 cm distance from the array after 15 minutes the readouts were +0·19, +0·22 and −0·2 mm for the same directions, respectively.[31]

The experiment was repeated with the beacon in 0·9% saline solution (concentration that simulates a conductivity environment compared to twice that of human tissue). At 27 cm distance from the array and 8 cm away from the centre the readouts after 20 seconds were +0·29, +0·43 and −0·33 mm for the same directions, respectively.[31]

After concluding that the system correctly detects one beacon, the experience was repeated at 8 and 27 cm offset from the array, this time with a set of three beacons: at Z distance of 8 cm the offset was +0·17, +0·03 and +0·05 mm and at Z distance of 27 cm the offset was +0·16, +0·18 and +0·12 mm for X, Y and Z, respectively, for both measurements.[31]

Ogunleye et al. compared Calypso® System with kV planar imaging for localisation of markers. In this case Beacons were the markers to be localised as they are detected by Calypso® System (magnetic resonance) and they are also detected in X-ray image (radio opaque).[38]

A stationary phantom was not aligned in the isocenter. The measured offset of the target isocenter from the correct position as indicated by the Calypso® System should be the exact opposite of the OBI shift required to move the target isocenter to the correct position. The values were compared for 30 different phantom positions. The difference between the two systems was 0·4 ($\delta = 0{\cdot}4$); 0·2 ($\delta = 0{\cdot}3$) and 0·4 ($\delta = 0{\cdot}3$) mm in the X, Y and Z directions, respectively.[38] The process was repeated with 259 prostate treatment fractions. The difference between the two systems was 0·7 ($\delta = 0{\cdot}5$); 1·1 ($\delta = 0{\cdot}9$) and 1·2 ($\delta = 0{\cdot}9$) mm in the X, Y and Z directions, respectively.[38]

Action protocol for treatment intervention

The above mentioned target positioning limits are inserted into the Calypso® software according to an Action Protocol for Treatment Intervention. Several protocols have been reported.

Shinohara et al. studied five locally advanced pancreatic cancer patients with a 3 mm-action protocol. The therapists were to interrupt radiation delivery every time intrafractional motion was >3 mm.[17] In a prostate study by Smith et al. the same action level was established.[39]

Also in a prostate study by Su et al. a 5 mm shift as threshold was used. A re-localisation was to be performed only if the Beacon centroid drifted more than 5 mm for 25 seconds continuously.[40]

One of the prone position studies was reported by Shah et al. In this study, therapists were

https://doi.org/10.1017/S1460396914000223 Published online by Cambridge University Press

instructed to observe the prostate gland position and intervene when the motion was larger than 3 mm. However, if the motion was transient as peristaltic movement, even if exceeding 3 mm, the therapists should not act. Also, intervention should be between beams.[38]

Clinical applications

The Calypso® 4D Localization System has been approved for marketing by FDA for target organ positioning and monitoring during delivery of radiation therapy in prostate cancer patients.[23] Most recently, CE Mark approved Calypso® Anchored Beacons to be used in lung treatments as well. Several studies considering future clinical applications have been performed.

Prostate

The implantation procedures are generally uneventful and well tolerated by patients. Quigley et al. refer that 52% of patients in their study (22/42) reported symptoms after the implantation procedure. Those symptoms were not revealed, but it was referred that those were usual symptoms after similar procedures as implantation of gold fiducials.[23,25,34,35]

It is to be mentioned that, after the implantation of fiducials, the prostate usually swells (inflammatory response). There may be a change in fiducials position when prostate swells and also when it returns back to its natural position. Litzenberg et al. reported that it is safe to acquire a planning CT scan 4 days after implantation, as any swelling appears to have resolved by then.[6]

Calypso® System has been a very important tool in the most recent studies of intrafraction prostate motion.[2,41–43] These movements are caused not only by repeating processes such as breathing, but also because of random processes like gradual rectal distention, peristaltic motion and bladder volume. This means prostate movement is random, sporadic and patient specific, which makes the prediction of the prostate motion difficult.

As above mentioned Calypso® manual considers a localisation volume under the array of $14 \times 14 \times 27\ \text{cm}^3$ which means that patients with protuberant abdomen may not be a suitable candidate for this system. When considering the localisation volume of the system, the recommendation is that the maximum distance between the array and the beacons should be <27 cm. On the other hand Bittner et al.[30] and Quigley et al.[23] assumed that this distance should not be more than 23 cm in their studies' patient selection. The latter led to several studies in order to present the prone position as an alternative position to treat these patients with Calypso® accurately.[36,38,44] Shah et al. refer that prostate displacements larger than 3 and 5 mm were higher in the prone position by a factor of three in comparison to the supine position. Displacements larger than 10 mm occurred as often in the prone as in the supine position.

Lung

Implantation of transponders in lung has some risks. The current design of the transponders was not the most appropriate for lung implantation: although they show good to moderate short-term fixation rates, long-term fixation rates are low.[45] Percutaneous implantation in the lung led to a significant rate of pneumothorax.[46] However, bronchoscopic implantation has been safer.[47,48]

In the meantime, Calypso® Medical has developed a new transponder design with a stabilisation feature: Calypso® Anchored Beacon. This improved Beacon is a regular Beacon with a five-legged nitinol stability feature. These five legs are to anchor the transponder in a small diameter airway (bronchoscopic implantation).[37] Mayse et al. refer that this lung transponder has 100% long-term fixation rates over 60-day period for 54 bronchoscopic implanted transponders in canine lungs.[49] In the European Union, the Beacons were approved to be used in lung treatments by CE Mark. The first application for lung tumour treatment was already conducted in August of this year in the Fundação Champalimaud in Lisbon, Portugal.

Pancreas

A study has been developed in The Vanderbilt Clinic, Nashville by University of Pennsylvania (2011), with five locally advanced pancreatic cancer patients (with no metastatic disease). Each patient underwent implantation of three regular Beacons. Transponder implantation was well tolerated in all patients, with minimal migration: a single transponder migrated in a patient who had intractable vomiting out of the 15 transponders implanted. To monitor the stability of the transponder placement, intertransponder distance was obtained before the start of each fraction using the Calypso® System.

Data from 164 treatments was analyzed. Mean intrafractional motion was superior 7·2 mm; inferior 11·9 mm; anterior 4·9 mm; posterior 2·9 mm; left 2·2 mm; and right 3·1 mm. All these values were smaller when applied breath holding while treating (157 treatments analysed): superior 4·3 mm; anterior 2·5 mm; posterior 1·7 mm; inferior 8·1 mm; left 1·0 mm; and right 2·1 mm.[17]

Electromagnetic Guided Real-Time Dynamic Multileaf Collimator Tracking System

In the past few years researchers have investigated DMLC tracking possibilities.[50–53] The goal of these investigations is to create a system able to find the target location and reposition the treatment beam to compensate for target motion. Considering this, Calypso® System can be the key tool on finding target location. To reposition the treatment beam a DMLC is used.[54–56]

There are some obstacles when integrating these systems. Once target movement is detected, the data stream is input to the DMLC tracking software, which generates the ideal beam aperture. Depending on the MLC, this ideal beam aperture may not be viable because of MLC physical limitations such as finite LMC leaf widths or the paired leaf structure. Another limitation is related to a finite time lag that is observed between motion detection and MLC response—system latency—which is spent in motion detection, the calculation of the new leaf positions and the time required by the MLC leaves to reach their new positions.[54–56]

To reduce the system latency, studies have been made on predictive algorithms to estimate future target positions.[56,57]

Wu et al. studied an algorithm capable of readjusting treatment beam for translational and also rotational intrafraction movements. They tested this integrated system with success. The system detected and adapted the treatment beam for translation and rotation movements.[54]

Sawant et al. refer to have built their system successfully. The system was tested on patient-derived 3D motion trajectories comprising two lung tumours and one prostate trace. Tracking accuracy was sub-2 mm for the respiratory motion and sub-1 mm for prostate motion.[55]

DISCUSSION

The Calypso® 4D Localization System is a technology based on electromagnetic transponders detection which enables precise 3D localisation and continuous tracking of tumour target. The main advantage of this system with respect to other systems continuous internal tracking with no extra ionising radiation delivered to the patient. Advantages and disadvantages should be considered when thinking of acquiring this system as well as costs and objectives on how to use the system in the clinic.

Quality assurance

Balter et al. tested the accuracy of Calypso® System when localising one and three transponders. The accuracy was higher for one transponder detection; still both tests resulted in submillimetre shift values. It was also performed a similar test in 0·9% saline solution—concentration that simulates a conductivity environment compared to twice that of human tissue. The accuracy of the system was lower, but the values were also below a millimetre, showing that transponder detection should be accurate in human body. For all these tests the accuracy decreased as the beacon(s) distance to the array increased, but the measured values kept being submillimetre.[31]

Ogunleye et al. evaluated the difference between Calypso® and kV planar image for 30 different phantom positions: values were submillimetre. When he repeated the process with 259 more fractions the difference between the two systems was higher than 1 mm (1·2 mm in the Z direction), so values are not that small. However, OBI system uncertainty should be taken in consideration in these tests, added to

Calypso® System inner uncertainty present in other studies.[38]

Action protocol for treatment intervention

Regarding action protocols on how to intervene when using Calypso® System to monitor a treatment several examples were presented.

The pancreatic study with the 3 mm action protocol was performed on patients treated with 3D conformal treatment using 4 fields and a 1–1·5 cm margin was added to the clinical target volume to construct a PTV_4500; there was no reference to the linac used to deliver the treatment.[17] The prostate study that used this same protocol referred that IMRT treatments were analysed on 44 prostate treatment fractions of 28 patients; there was mention neither to PTV margins nor to the linac used to deliver these treatments.[39]

Su et al. referred that each patient underwent 28 treatment sessions, each about 8 minutes long, but there was also no reference to the treatment plans (PTV margins, technique) or to the linac that delivered these treatments.[40]

Shah et al. treated their patients in 40 sessions. The PTV margins were 3 mm posterior and 5 mm in all other directions.[38]

There are no studies available on the validity of these protocols. It is however to note that the treatments administered in these studies were different from clinic to clinic so it is natural that the protocols were also different. More investigation should be performed regarding action protocols and the treatments they apply to. A recommendation for a future study on action protocols could include suggestions on how Calypso® margins should be defined according to PTV margins, time of irradiation (regular or FFF beams, 3D conventional or IMRT techniques), and target localisation (natural movement of target and surrounded OARs).

Clinical applications

Concerning prostate treatments, Calypso® System has been implemented and used in several clinics. It detects prostate movements due to breathing movements, peristaltic movements and other natural processes. However, depending on the protocol being used, it may be necessary to acquire images to assess OARs position related to the PTV (such as the rectum and the bladder).

Another obstacle for prostate treatment is the transponder implantation maximum depth in tissue. Prone position has been presented as an alternative.[36,38,44] It is to refer that previous literature presents studies on the stability of prone versus supine positions.

Several studies indicated that there is more interfraction movement when the patient is in prone position.[58,59] Considering that positioning the patient using Calypso® System already corrects interfraction motion, it makes sense to analyse intrafraction motion in prostate in both positions.

At Cancer Center of Irvine it was decided to treat prostate in supine position after a local study was performed in 15 patients by Wilder et al.[60] The study evaluated intrafraction movement in supine and prone position and position preference of the patients. The study was performed in patients with gold seeds implanted. Anteroposterior and lateral kV planar images were acquired to evaluate intrafraction movement. Mean values were 0·6 ($\delta = 0{\cdot}9$), 1·6 ($\delta = 1{\cdot}8$) and 1·7 ($\delta = 1{\cdot}4$) mm in the supine position and 1·0 ($\delta = 1{\cdot}2$), 2·2 ($\delta = 2{\cdot}0$) and 2·1 ($\delta = 1{\cdot}2$) in the prone position in the X, Y and Z directions, respectively. There was no significant difference in the intrafraction prostate motion of the two positions and 80% of the patients were more comfortable in the supine position.

Kitamura et al. analysed intrafraction motion using a real-time tumour-tracking system that uses two fluoroscopic images acquired 30 times per second and software that is able to detect gold markers position. Mean values for ten patients were 0·1 ($\delta = 0{\cdot}1$), 0·3 ($\delta = 0{\cdot}2$) and 0·3 ($\delta = 0{\cdot}4$) mm in the supine position and 0·5 ($\delta = 0{\cdot}4$), 1·4 ($\delta = 0{\cdot}5$) and 1·6 ($\delta = 0{\cdot}4$) in the prone position in the X, Y and Z directions, respectively. It was concluded that internal organ motion is less frequent in the supine position than in the pro position.[61]

https://doi.org/10.1017/S1460396914000223 Published online by Cambridge University Press

The decision on the patient position for prostate treatment lies in each radiotherapy department. On one hand supine position is more comfortable for the patient, and several studies indicate less inter- and intrafraction motion in this position; on the other hand a department that has Calypso® System available may consider that prone position is an appropriate alternative to treat large prostate patients so those movements can be detected and can be corrected by technicians.

It is of note that none of this studies compared supine and prone positions rotation shifts. More investigation should be performed in this area.

Clinical application of the Calypso® System in tumours other than prostate has not been approved in United States yet, and CE Mark approval for lung treatments with Anchored Beacons in EU is still very recent. Therefore, no published clinical results on this application are available yet, but it is understandable the advantage of the use of transponders in regions of significant target movement.

Electromagnetic Guided Real-Time Dynamic Multileaf Collimator Tracking System

In the near future, a few integrated systems have been created and tested in phantoms, with success for tracking target position. The integration of Calypso® 4D Localization System and DMLC is being developed in order to achieve an Electromagnetic Guided Real-Time Dynamic Multileaf Collimator Tracking System. Still, these algorithms have taken into account only the target position, OARs positions are not considered, yet.

CONCLUSION

The Calypso® 4D Localization System allows real-time localisation and monitoring of the target, with no ionising radiation additional administration. It is a very important tool in prostate cancer treatment. More studies are currently being developed.

Further research has to be performed: (1) prostate studies involving a larger cohort of patients, (2) clinical application in clinical sites other than the prostate and prostate bed, (3) the effect of the system on hypofractionated treatments, (4) studies involving rotational movement corrections besides translational movement corrections and (5) investigation and implementation of more advance prediction algorithms for DMLC systems.

Improvements and integrations are also expected in the future, such as (1) phantoms dedicated to Calypso® and/or DMLC tracking system studies, (2) integration of Calypso® System with linear accelerator, (3) integration of Calypso® System with robotic couch (6D) and (4) improvements in software design and speed of processing hardware allowing the clinical use of Calypso + DMLC integrated system into achieving adaptive radiotherapy.

Acknowledgements

The authors thank the staff of the Radiotherapy Department at Centro Clínico Champalimaud for their personal encouragement and Dr Andrew Macann for helping with English language revision.

Financial support

No monetary costs were involved in this review. Any cost related to publication is supported by the primary author herself.

Source of Support

This review was proposed in the master course Radiations applied to Health Technologies—Radiation Therapy, at Escola Superior de Tecnologias da Saúde de Lisboa. Revision of the review was kindly made by Sandra Vieira and Dalila Mateus, who have worked with Calypso, and also by Prof. Margarida Eiras.

Conflicts of Interest

None.

References

1. Kitamura K, Shirato H, Shimizu S et al. Registration accuracy and possible migration of internal fiducial gold marker implanted in prostate and liver treated with real-time tumor tracking radiation therapy (RTRT). Radiother Oncol 2002; 62: 275–281.

https://doi.org/10.1017/S1460396914000223 Published online by Cambridge University Press

2. Kitamura K, Shirato H, Seppenwoolde Y et al. Three-dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. Int J Radiat Oncol Biol Phys 2002; 53: 1117–1123.
3. Shirato H, Harada T, Harabayashi T et al. Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. Int J Radiat Oncol Biol Phys 2003; 56: 240–247.
4. Dawson L A, Brock K K, Kazanjian S et al. The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. Int J Radiat Oncol Biol Phys 2001; 51: 1410–1421.
5. Balter J M, Lam K L, Sandler H M et al. Automated localization of the prostate at the time of treatment using implanted radiopaque markers: technical feasibility. Int J Radiat Oncol Biol Phys 1995; 33: 1281–1286.
6. Litzenberg D W, Willoughby T R, Balter J M et al. Positional stability of electromagnetic transponders used for prostate localization and continuous, real-time tracking system and on-board kilovoltage imaging system. Int J Radiat Oncol Biol Phys 2007; 68 (4): 1199–1206.
7. Schweikard A, Shiomi H, Adler J. Respiration tracking in radiosurgery. Med Phys 2004; 31: 2738–2741.
8. Meeks S L, Bova F J, Wagner T H et al. Image localization for frameless stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 2000; 46: 1291–1299.
9. Bova F J, Meeks S L, Friedman W A et al. Optic-guided stereotactic radiotherapy. Med Dosim 1998; 23: 221–228.
10. Roberts D W, Strohbein J W, Hatch J F. A frameless stereotactic computerized tomographic imaging and the operating microscope. J Neurosurg 1986; 65: 545–549.
11. Watanabe E, Mayanagi Y, Kosugi Y et al. Open surgery assisted by the articulated, sensitive arm. Neurosurgery 1991; 28: 792–800.
12. Suess O, Suess S, Mularksi S et al. Study on the clinical application of pulsed DC magnetic technology for tracking of intraoperative head motion during frameless stereotaxy. Head Face Med 2006; 2: 10.
13. Keall P J, Todor A D, Vedam S S et al. On the use of EPID-based implanted marker tracking for 4D radiotherapy. Med Phys 2004; 31: 3492–3499.
14. Meeks S L, Buatti J M, Bouchet L G et al. Ultrasound-guided extracranial radiosurgery: technique and application. Int J Radiat Oncol Biol Phys 2003; 55: 1092–1101.
15. Tome W A, Meeks S L, Orton N P et al. Commissioning and quality assurance of an optically guided three-dimensional ultrasound target localization system for radiotherapy. Med Phys 2002; 29: 1781–1788.
16. Sharp G C, Jiang S B, Shimizu S et al. Tracking errors in a prototype real-time tumor tracking system. Phys Med Biol 2004; 49: 5347–5356.
17. Shinohara E T, Kassaee A, Mitra N et al. Feasibility of electromagnetic transponder use to monitor inter- and intrafractional motion in locally advanced pancreatic cancer patients. Int J Radiat Oncol Biol Phys 2012; 83 (2): 566–573.
18. Noel C, Parikh P J, Roy M et al. Prediction of intrafraction prostate motion: accuracy of pre- and post-treatment imaging and intermittent imaging. Int J Radiat Oncol Biol Phys 2009; 73 (3): 692–698.
19. Gierga D P, Brewer J, Sharp G C et al. The correlation between internal and external markers for abdominal tumors: implications for respiratory gating. Int J Radiat Oncol Biol Phys 2005; 61: 1551–1558.
20. Beddar A S, Kainz K, Briere T M et al. Correlation between internal fiducial tumor motion and external marker motion for liver tumors imaged with 4D-CT. Int J Radiat Oncol Biol Phys 2007; 67: 630–638.
21 Shirato H, Oita M, Fujita K et al. Feasibility of synchronization of realtime tumor-tracking radiotherapy and intensitymodulated radiotherapy from viewpoint of excessive dose from fluoroscopy. Int J Radiat Oncol Biol Phys 2004; 60: 334–341.
22. Murphy M J, Eidens R, Vertatschitsch E, Wright J N. The effect of transponder motion on the accuracy of the Calypso electromagnetic localization system. Int J Radiat Oncol Biol Phys 2008; 72 (1): 295–299.
23. Quigley M M, Mate T P, Sylvester J E. Prostate tumor alignment and continuous, real-time adaptive radiation therapy using electromagnetic fiducials: clinical and cost-utility analyses. Urol Oncol 2009; 27: 473–482.
24. Li H S, Chetty I J, Enke C H et al. Dosimetric consequences of intrafraction prostate motion. Int J Radiat Oncol Biol Phys 2008; 71 (3): 801–812.
25. Willoughby T R, Kupelian P A, Pouliot J et al. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2006; 65 (2): 528–534.
26. King B L, Butler W M, Merrick G S et al. Electromagnetic transponders indicate prostate size increase followed by decrease during the course of external beam radiation therapy. Int J Radiat Oncol Biol Phys 2011; 79 (5): 1350–1357.
27. Mate T P, Krag D, Wright J N, Dimmer S. A new system to perform continuous target tracking for radiation and surgery using non-ionizing alternating current electromagnetics. Int Cong Series 2004; 1268: 425–430.
28. Zou W, Betancourt R, Yin L et al. Effects on the photon beam from an electromagnetic array used for patient localization and tumor tracking. J Appl Clin Med Phys 2013; 14 (3): 72–80.
29. Rassian-Szegedi P, Wang B, Szegedi M et al. Individualized margins for prostate patients using a wireless localization and tracking system. J Appl Clin Med Phys 2011; 12 (3): 194–204.
30. Ogunleye T, Rossi P J, Jani A B, Fox T, Elder E. Performance evaluation of Calypso 4D localization and

kilovoltage image guidance systems for interfraction motion management of prostate patients. ScientificWorldJournal 2009; 9: 449–458.

31. Balter J M, Wright J N, Newell L J et al. Accuracy of a wireless localization system for radiotherapy. Int J Radiat Oncol Biol Phys 2005; 61 (3): 933–937.
32. Santanam L, Malinowski K, Hubenshmidt J et al. Fiducial-based translational localization accuracy of electromagnetic tracking system and on-board kilovoltage imaging system. Int J Radiat Oncol Biol Phys 2008; 70 (3): 892–899.
33. Litzenberg D W, Balter J M, Hadley S W et al. The influence of intra-fraction motion on margins for prostate radiotherapy. Int J Radiat Oncol Biol Phys 2006; 65: 548–553.
34. Berger A P, Gozzi C, Steiner H et al. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among three protocols with 6, 10, and 15 cores. J Urol 2004; 171: 1478–1480.
35. Henry A M, Wilkinson C, Wylie J P et al. Trans-perineal implantation of radio-opaque treatment verification markers into the prostate: an assessment of procedure related morbidity, patient acceptability, and accuracy. Radiother Oncol 2004; 73: 57–59.
36. Kimple R J, Wallen E M, Pruthi R, Marks L B. A simple algorithm to assess patient suitability for Calypso-seed implantation for four-dimensional prostate localization. J Appl Clin Med Phys 2010; 11 (1): 252–262.
37. Shah A P, Kupelian P A, Willoughby T R, Meeks S L. Expanding the use of real-time electromagnetic tracking in radiation oncology. J Appl Clin Med Phys 2011; 12 (4): 34–49.
38. Bittner N, Butler W M, Reed J L et al. Electromagnetic tracking of intrafraction prostate displacement among patients externally immobilized in the prone position. Int J Radiat Oncol Biol Phys 2009; 77: 490–495.
39. Smith R L, Sawant A, Santanam L et al. Integration of real-time internal electromagnetic position monitoring coupled with dynamic multileaf collimator tracking: an intensity-modulated radiation therapy feasibility study. Int J Radiat Oncol Biol Phys 2009; 74 (3): 868–875.
40. Su Z, Zhang L, Murphy M, Williamson J. Analysis of prostate patient setup and tracking data: potential intervention strategies. Int J Radiat Oncol Biol Phys 2011; 81 (3): 880–887.
41. Dawson L A, Litzenberg D W, Brock K K et al. A comparison of ventilatory prostate movement in four treatment positions. Int J Radiat Oncol Biol Phys 2000; 48: 319–323.
42. Langen K, Willoughby T, Meeks S et al. Observations on realtime prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys 2008; 71: 1084–1090.
43. Xie Y, Djajaputra D, King C R et al. Intrafractional motion of the prostate during hypofractionated radiotherapy. Int J Radiat Oncol Biol Phys 2008; 72: 236–246.
44. Bittner N, Butler W M, Reed J L et al. Electromagnetic tracking of intrafraction prostate displacement in patients externally immobilized in the prone position. Int J Radiat Oncol Biol Phys 2010; 77 (2): 490–495.
45. Mayse M L, Parikh P J, Lechleiter K M et al. Bronchoscopic implantation of a novel wireless electromagnetic transponder in the canine lung: a feasibility study. Int J Radiat Oncol Biol Phys 2008.
46. Whyte R I, Crownover R, Murphy M J et al. Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial. Ann Thorac Surg 2003; 75: 1097–1101.
47. Kupelian P A, Forbes A, Willoughby T R et al. Implantation and stability of metallic fiducials within pulmonary lesions. Int J Radiat Oncol Biol Phys 2007; 69: 777–785.
48. Imura M, Yamazaki K, Kubota K C et al. Histopathologic consideration of fiducial gold markers inserted for real-time tumortracking radiotherapy against lung cancer. Int J Radiat Oncol Biol Phys 2008; 70: 382–384.
49. Mayse M L, Smith R L, Park M et al. Development of a nonmigrating electromagnetic transponder system for lung tumor tracking. Int J Radiat Oncol Biol Phys 2008; 72: S430–S430.
50. Keall P J, Cattell H, Pokhrel D et al. Geometric accuracy of a realtime target tracking system with dynamic multileaf collimator tracking system. Int J Radiat Oncol Biol Phys 2006; 65: e1579–e1584.
51. Sawant A, Venkat R, Srivastava V et al. Management of three dimensional intrafraction motion through real-time DMLC tracking. Med Phys 2008; 35: e2050–e2061.
52. Poulsen P R, Cho B, Sawant A, Keall P. Implementation of a new method for dynamic multileaf collimator tracking of prostate motion in arc radiotherapy using a single kV imager. Int J Radiat Oncol Biol Phys 2010; 76: e914–e923.
53. Poulsen P R, Cho B, Ruan D et al. Dynamic multileaf collimator tracking of respiratory target motion based on a single kilovoltage imager during arc radiotherapy. Int J Radiat Oncol Biol Phys 2010; 77: e600–e607.
54 Wu J, Ruan D, Cho B et al. Electromagnetic detection and real-time DMLC adaptation to target rotation during radiotherapy. Int J Radiat Oncol Biol Phys 2012; 82 (3): 545–553.
55. Sawant A, Smith R L, Venkat R B et al. Toward submillimeter accuracy in the management of intrafraction motion: the integration of real-time internal position monitoring and multileaf collimator target tracking. Int J Radiat Oncol Biol Phys 2009; 74 (2): 575–582.
56. Krauss A, Nill S, Tacke M, Oelfke U. Electromagnetic real-time tumor position monitoring and dynamic multileaf collimator tracking using a Siemens 160 MLC: geometric and dosimetric accuracy of an integrated system. Int J Radiat Oncol Biol Phys 2011; 79 (2): 579–587.

57. Srivastava V, Keall P J, Sawant A et al. Accurate prediction of intra-fraction motion using a modified linear adaptive filter. Med Phys 2007; 34: 2546.

58. Bayley A, Catton C, Haycocks T et al. A randomized trial of supine vs. prone positioning in patients undergoing escalated dose conformal radiotherapy for prostate cancer. Radiother Oncol 2004; 70: 37–44.

59. Weber D, Nouet P, Rouzaud M, Miralbell R. Patient positioning in prostate radiotherapy: is prone better than supine? Int J Radiat Oncol Biol Phys 2000; 47 (2): 365–371.

60. Wilder R, Chittenden L, Mesa A et al. A randomized trial of supine vs. prone positioning in patients undergoing escalated dose conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010; 77 (1): 165–170.

61. Kitamura K, Shirato H, Seppenwoolde Y et al. Three dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. Int J Radiat Oncol Biol Phys 2002; 53 (5): 1117–1123.