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Abstract. Complete and homogeneous illumination of the target is necessary for the success of a photodynamic therapy (PDT) procedure. In most applications, light dosimetry is done using detectors placed at strategic locations of the target. In this study we propose a novel approach based on the combination of light distribution modeling with spatial localization of the light applicator for real time estimation and display of the applied dose on medical images. The feasibility approach is demonstrated for intrapleural PDT of malignant pleural mesothelioma.

Keywords: photodynamic therapy, intra-cavity application, light distribution modeling, dosimetry, real time tracking, imaging.

1- Introduction

Photodynamic therapy (PDT) is an emerging technic in oncology. Its mechanism of action is based on the interaction of a photosensitizer (PS) drug, a light source for the PS activation and oxygen in tissues. The combination of these three elements induces chemical reactions leading to the creation of reactive oxygen species (ROS) and tumor cell death.

The achievement of the desired therapeutic effect of a PDT procedure relies on the accurate PS concentration distribution and on the continuous and uniform light delivery to the tissues. This last issue is particularly critical due to the variability in target geometry: solid, hollow organs and cavities,…

For cavities, various types of light applicators were investigated as bare-fibers, having a directed radiation pattern and being applicable for small lesions, cylindrical diffusers [1] with scattering dome applicators which has a homogeneously distributed radiation pattern with various active lengths and lastly, flat or flexible 2D applicators as textile [2] or blanket [3] allowing obtaining planar illumination.

In addition to these applicators, sensors are used to monitor light application by the continuous measurement of the light fluence rate in different locations in the cavity. Most often, these sensors consist of isotropic probes collecting light from every direction [4]. This dosimetry method allows only obtaining punctual measurements of light distribution whereas continuous spatial feedback is required to estimate received dose at each target point.

This is particularly the case for Malignant Pleural Mesothelioma (MPM) treatment. Treating MPM remains a challenge with two main alternatives: palliative chemotherapy for inoperable patients, and multimodal treatment including surgery, combined with chemotherapy and radiotherapy for the others.

Surgery offers the best chance of survival for this still incurable disease, however after the most complete tumor resection, microscopic tumor cells persist and surgery should be associated with an adjuvant local treatment. PDT appeared as a potential option for an effective intra-operative complement to surgery. After extensive preclinical studies, first clinical results were reported by the University of Bern group [5]. Currently, the most complete studies, with a major impact on survival and minimum toxicity, are certainly those led by the Pennsylvania team [6-8]. The

photosensitizer (Porfimer sodium (Photofrin)) is administered to the patients 48 hours before a maximal surgical tumor resection. Then, a light applicator connected to a laser source (wavelength 635 nm) is moved inside the pleural cavity, to illuminate the cavity walls (the target), filled with dilute intra-lipid solution, until a fluence of 20 $J.cm^{-2}$ is obtained. The light delivery monitoring is achieved by 7 isotropic probes placed at strategic locations in the thorax and connected to a dosimetry system ([9], [4;10]).

However, this method does not provide information about the light delivered between these 7 locations. In this study, we describe a light applicator and introduce a new method for light dosimetry during PDT procedures of intra-cavities with complete and continuous feedback of the applied light dose. We present the feasibility of this approach on a phantom mimicking an intraoperative thorax cavity.

2- Materiel and Methods

The global approach proposed herein is based on three ideas. First, we present an unique action model that characterizes the light distribution around the applicator. The second idea is about using a spatial locator for real time tracking of the applicator movements inside the cavity in order to cumulate spatially and temporally the light dose applied to the target. The last idea requires the use of imaging to define the target and to be used as a spatial reference map for the real time display of the applied light dose.

2-1 Light applicator construction and setting

The proposed light applicator is an adaptation of the model used in the previous trials [11]. It consists of a cylindrical diffuser held in an endo-tracheal tube in which a carbon tube was inserted, to harden the tube and to correct its curvature. The cuff of the endo-tracheal tube is filled with intra-lipid solution at the concentration of 0.01% to act as a scattering agent.

For the real time localization of the applicator, an electromagnetic 3D tracking device is used to track the applicator movements. This tracking system (TrackStar, Ascension Technology Corporation, Burlington, VT, USA) is composed of a control unit with plugs to connect a transmitter and up to 4 six degrees-of-freedom sensors. One sensor (2 mm diameter at the distal end and 1.2 mm diameter for the cable) is fixed just above the cylindrical diffuser (Figure 1.a). It allows the localization of the sensor, and therefore the light wand, giving a 3D position and orientations regarding

to the reference defined by the transmitter with a precision of 0.5 mm. Figure 1.b represents the light wand assembled.

2-2 Characterization of a light distribution model

Light distribution around the diffusing tip of the applicator was characterized by direct measurements of the light fluence rate (irradiance ($W.cm^{-2}$)) using sensors completed with a digital photography to define fluence rate isosurfaces.

Measurements were done in a plastic tank of black color, limiting light reflection, filled with 0.01% dilute intralipid. The tip of the applicator was fixed horizontally in the tank through a cable gland and the optical fiber was connected to a medical diode laser 635 (Ceralas®, Biolitec)..

For the fluence rate measurements, an isotropic probe (Model IP 85, Medlight®S.A., Switzerland), collecting light in a large solid angle, was connected to an optical power meter (Model 841-PE,Newport® Corporation, Irvine, CA, USA). The isotropic probe was fixed vertically in a plastic tube and moved above the diffusing tip of the light wand, using a millimetric precision benchmark with vertical and horizontal freedom degrees.

A calibration factor was defined to convert the punctual power measurements (W) into fluence rate values ($W.cm^{-2}$). It was estimated by correlating pairwise power measures obtained by the isotropic probe and fluence measures obtained by a $1cm^2$ surface detector (Model PD300, OPHIR, Israel).

The previous method allowed only obtaining measurements for discrete positions on the light applicator. This dosimetry method with the powermeter only gave punctual measurements of the light distribution. In order to obtain a more complete and continuous light distribution characterization, a digital photography was taken above the tank. After spatial and chromatic calibrations of the picture, the measurements done previously and their respective positions were matched with the image to define iso-surfaces as represented in figure 2.

Complete description of the method is provided in Munck *et al.* [12].

2-3 Tridimensional Imaging

Radiation therapies (radiotherapy and brachytherapy) are always image-based techniques. Imaging allows to define the targets, to estimate their volumes and in

some cases, to define organs at risk to be spared. It is also used to optimize the ballistics and as a reference map for the dose display.

Regarding PDT, imaging is being increasingly used especially for interstitial applications as in prostate [13], Glioblastoma [14] and head and neck [15;16] diseases. As for radiotherapy, the goal is mainly to define the targets to treat.

For MPM management, 3D computed tomography (CT) imaging is the reference for pleural evaluation, fortumor staging and follow-up. We propose to use these images in the dosimetry process of the PDT procedure. First, these images are used to estimate volume and surface of the pleural cavity. Thereby, the total required fluence and light application duration can be estimated before the treatment.

Another benefit to CT scan images is to use them as a reference space for the real time light dose display during the treatment. However, as these images are acquired before the procedure, a spatial registration is required to compute the transformation between the pre-operative space and the per-operative space. Fiducial markers consisting of 5 mm diameter capsule filled with paraffin oil can be attached to the patient around the region to be imaged. These markers are multimodality imaging compatible and able to create clear patterns on the images.

2.4 Spatial mapping of light dose

In order to compute a 3D light dose (D), the action model established for the applicator is combined with the positions returned by the spatial locator. The dose is matched with the images space using the following transformation:

$$T_{Applicator}^{images} = T_{Transmitter}^{images} \circ T_{Applicator}^{Transmitter} \quad (1)$$

$T_{Applicator}^{Transmitter}$ is formed using the positions and the orientations given by the tracking device and continuously updated according to the tracking frequency rate, while $T_{Transmitter}^{images}$ is the registration transformation that locates the patient regarding to the localization system. It is computed by mapping the coordinates of the fiducial markers on the images and their coordinates in the tracking device space (transmitter space). These last coordinates are obtained using a second sensor that points them successively.

Once the 3D spatial mapping done, for each voxel point *p(x, y, z),* the cumulated

dose is estimated as:

$$D_{p(x,y,z)} = \int_{Treatment\ time} IrradianceModel(x,y,z).dt \quad (2)$$

Where *IrradianceModel* is the above defined unique action model that characterizes the light applicator.

3- Validation of the approach

3-1 Protocol

Experiments are done on an anatomically realistic phantom consisting of a human-sized hemithorax, made of plaster, and 3D printed into a right-side intra-operative and post tumor resection pleural cavity (Figure 3).

Four fiducial markers were attached to the phantom and CT images were acquired using standard protocol used for MPM exam (Figure 4).

A PDT procedure is simulated by moving the light applicator inside the cavity. The evaluation protocol consists in comparing the light dose measured by our proposed method and by the method of reference wi the 7 isotropic probes. First, the 3D positions of the probes are obtained using a spatial locator for each position; the model estimated fluence is extracted from the matrix D (equation 2). These values are referred as *Model_Measurements*. The values collected by the probes are referred as *Ref_Measurements.*

Six independent experiments (Exp1 to Exp6) were carried out by varying the light applicator movements (speed, trajectory,..) inside the cavity.

3-2 Results

Figure 5 shows the accumulated 3D light distribution (matrix D) combined with the CT images to locate the treated and untreated regions. A special color look up table (LUT) gives relative display regarding a reference dose value. Each color represents 10% of this dose.

Figures 6 depicts the temporal evolution of the cumulated fluence ($J.cm^{-2}$) measured by the two methods in one of the 7 intrathoracic locations (probes) respectively for (Exp1, Exp2, Exp5), and (Exp3, Exp4, Exp6). From this figure, it appears that the *Ref_Measurements* have a linear evolution. This result can be explained by the fact

that the probes were continuously collecting light through the intralipid liquid even when the applicator was far from their positions, while the *Model_Measurements* do not have this ability because the model has a limited volume as defined in section 2.2.

For the 7 probes, the mean error between the reference measurements and the estimated measurements was about 10% with under-estimation for the proposed method. Since this under-estimation was constant for the six experiments, a correction factor of 1.1 was established and a new experiment was carried out after correcting the *Model_Measurements* with this value. Figure 7 presents the temporal evolution of the mean light dose calculated in one position for all experiments after correction.

The difference between the two methods measurements decreased below 1%.

4- Discussion

The success of a PDT procedure depends on the optimal dosimetric configurations of the photosensitizer and the light. The first issue relies on the determination of the PS distribution to the target tissues, which remains particularly difficult to monitor in clinical conditions. In most applications, based on dose escalation trials, a defined concentration is considered as optimal with sufficient and homogeneous distribution in tissues, and limited toxicity. For Photofrin, used in PDT for MPM, a dose of 2mg/ Kg is commonly administered to the patient.

The second issue, light delivery, is to apply a sufficient light dose to each target point. The approach proposed herein constitutes a new trend in dosimetry for intrapleural PDT. Indeed, instead of the continuous measurement of the light delivered, using dedicated materiel (probes, spectrometer, power-meter,…), our dosimetry method relies on a unique action model that characterizes the light propagation from the light applicator. The model was established by defining the light distribution profile in the intra-lipid solution. It takes into account the absorption and the diffusion around the applicator but not the multiple scattering that occurs within the intralipid solution. This can explain the systematic under-estimation of the model.

Anyway, in this kind of treatment, the procedure is based on a continuous movement of the light source inside the cavity, which means that the time spent at a specific spatial position is short leading to a non significant impact of the light scattering.

The second originality of our dosimetry method resides in the real time tracking of light applicator's movements inside the cavity, using a spatial locator. Thus, by combining the model and the positions, a complete 3D light dose is estimated. Spatial locators were already used in laser applications to track the light applicator movements ([17], [18]) and were proved to be efficient tools to monitor light application, in addition to being safe and clinically suitable.

Actually, from a clinical point of view, the real time update and display of the applied light dose brings the physician three main benefits. The first is the continuous feedback about the light delivered to the treated area. It improves the homogenization of the light dose by adapting the light delivery to untreated or not completely treated regions. The second benefit comes from the fact that visual assessment of the dosimetry is more natural than the punctual evaluation of discrete measurements. Moreover, the use of a gradient dose display allows a quick appreciation of the dose being delivered. Ultimately, one can obtain images as those used in radiotherapy treatment planning (Figure 8).

The last benefit regards the procedure time. The proposed approach reduces the intervention time by avoiding the setting of the measurements probes inside the thorax which take about 15 minutes in te case of intrapleural PDT for MPM.

Conflict of interest
All the authors have no conflict of interest to declare.

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Figures captions

Figure 1: The light applicator. (a) The position of the 3D sensor according to the cylindrical diffuser. (b) Assembly of the applicator.

Figure 2:. Illumination profile of the applicator when connected to laser emitting 3 W.

Figure 3: (Left) Thoracic phantom with surgical opening and isotropic probes placement in the pleural wall. (Right) Photodynamic therapy procedure simulation.

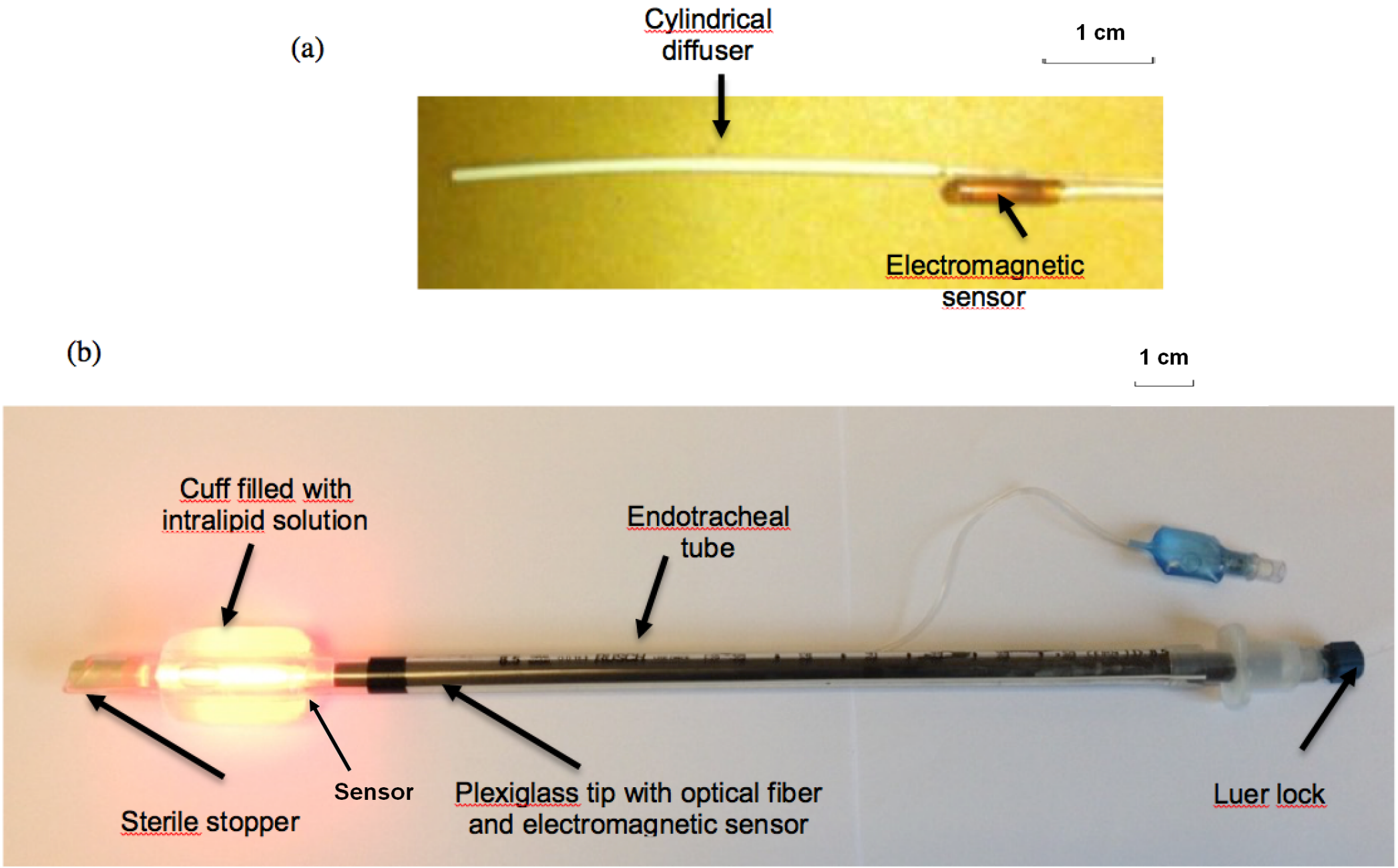
Figure 4: 3D Computerized Tomography of the thoracic phantom with patterns created by the fiducial markers. Images are displayed using three orientations: transversal, sagittal and coronal.

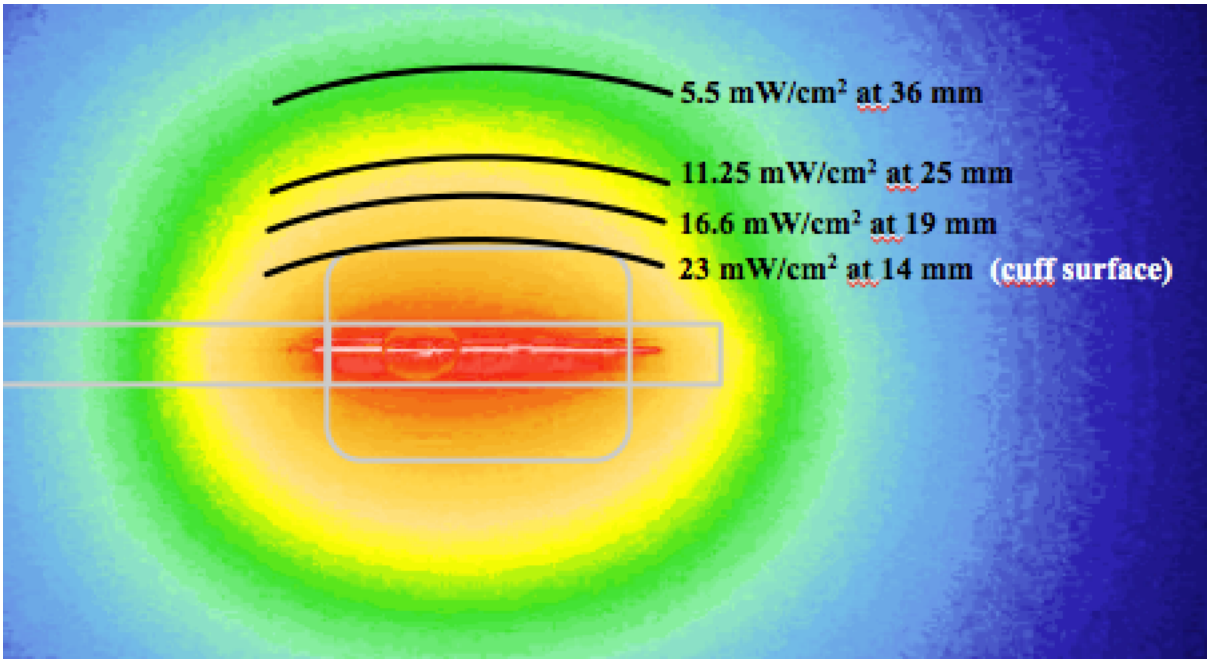
Figure 5: 3D light dose display combined with CT images of the thorax cavity phantom. Crossing lines (top left viewer (sagittal), top right viewer (coronal) and center right viewer (axial)) indicate the light applicator position inside the cavity.

Figure 6: Cumulated fluence measured in one unique position over time by the two methods: our proposed model based method (Model_Measurments) and the reference method based on a probe and a powermeter (Ref_Measurments). Six independent experiments were done. (a) Measurements: Exp 1, Exp 2 and Exp 5. (b) Measurements: Exp 4, Exp 3 and Exp 6.

Figure 7: Temporal evolution of the light dose (fluence $J.cm^{-2}$) measured in one position by the two methods: Reference method based on a dosimeter (power-meter) and Model method assuming a unique profile emission from the light applicator after correction.

Figure 8: Example of a treatment planning display for a lung radiotherapy showing the distribution of radiation doses delivered to the tumor. The prescription dose is 50 gray.


(a)
Cylindrical diffuser
1 cm
Electromagnetic sensor
(b)
1 cm
Cuff filled with intralipid solution
Endotracheal tube
Sterile stopper
Sensor
Plexiglass tip with optical fiber and electromagnetic sensor
Luer lock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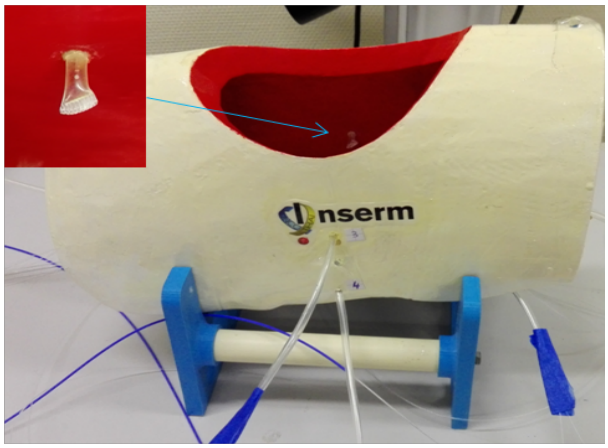
11.25 mW/cm² at 25 mm
16.6 mW/cm² at 19 mm
23 mW/cm² at 14 mm (cuff surface)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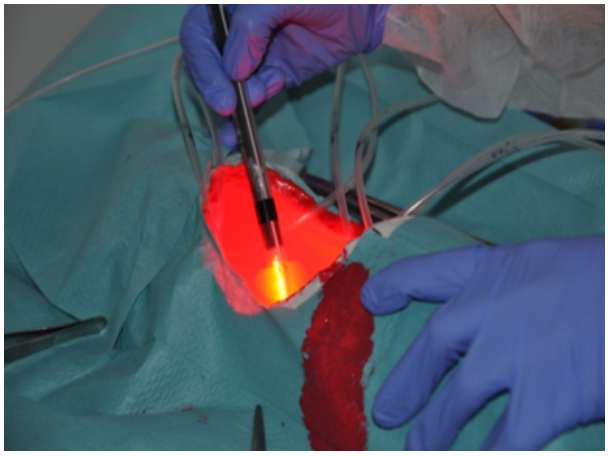

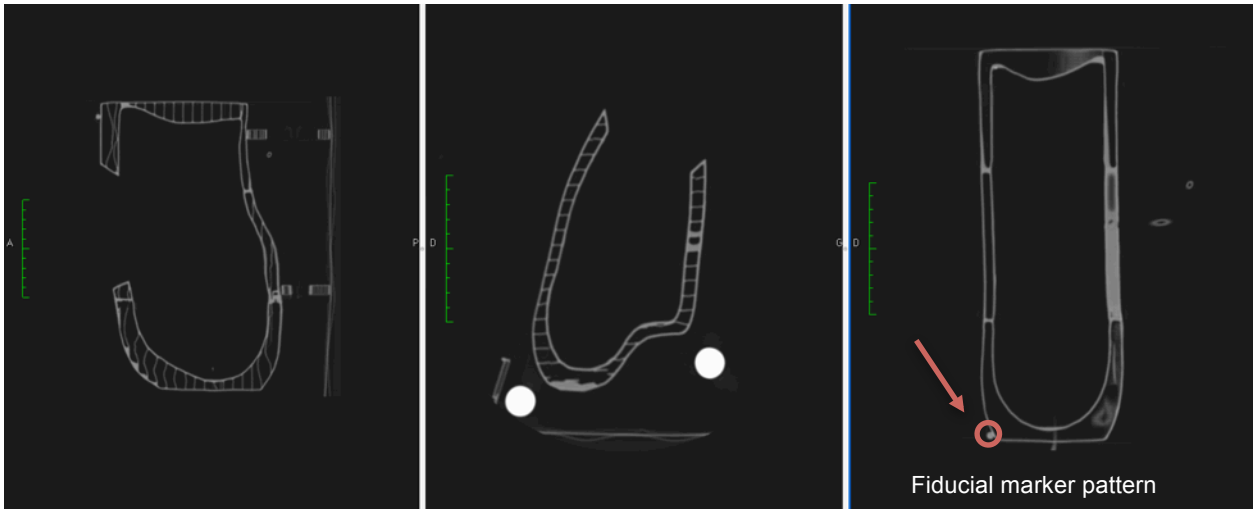
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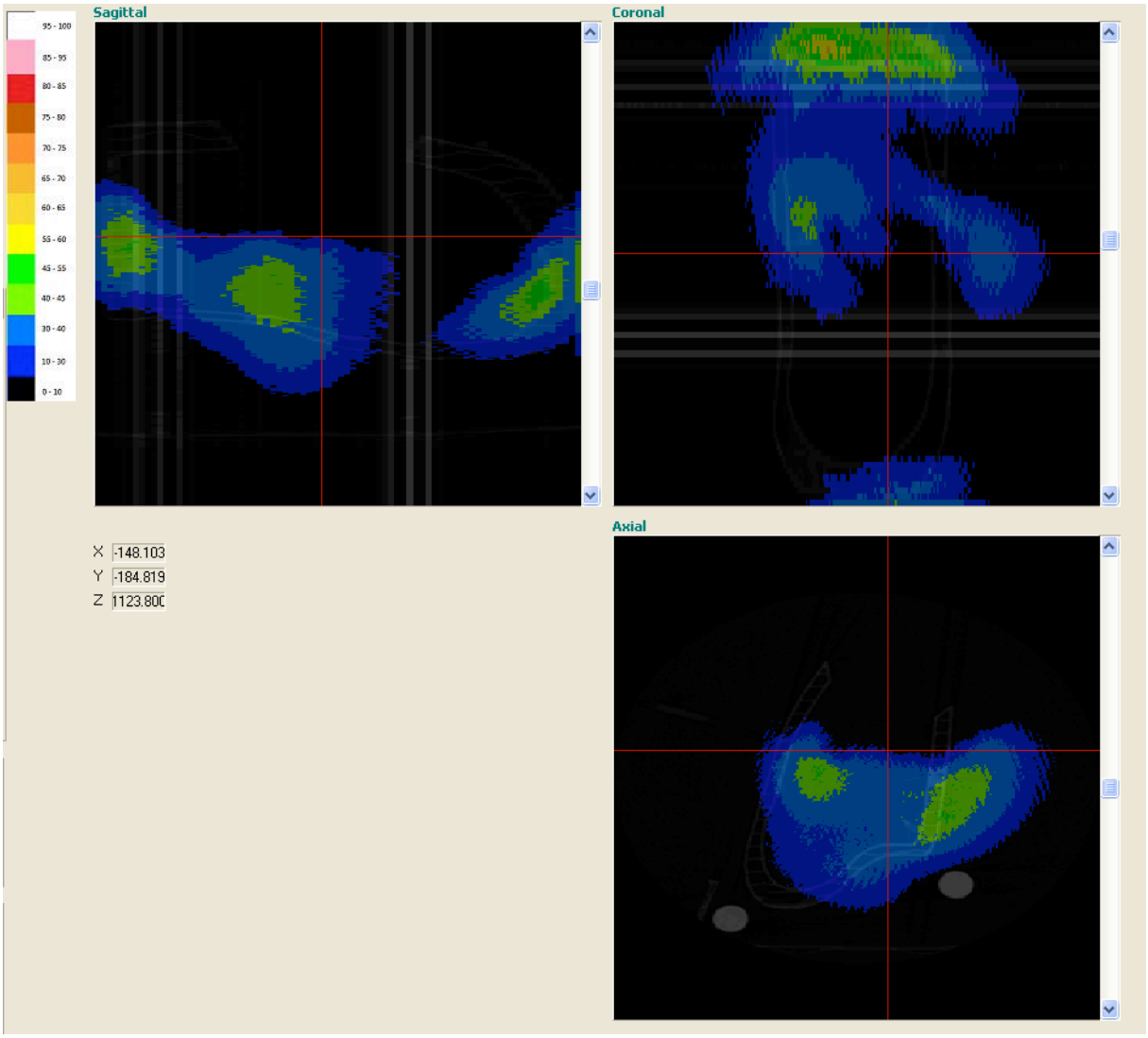
95 - 100
85 - 95
80 - 85
75 - 80
70 - 75
65 - 70
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45 - 55
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Sagittal
Coronal
Axial
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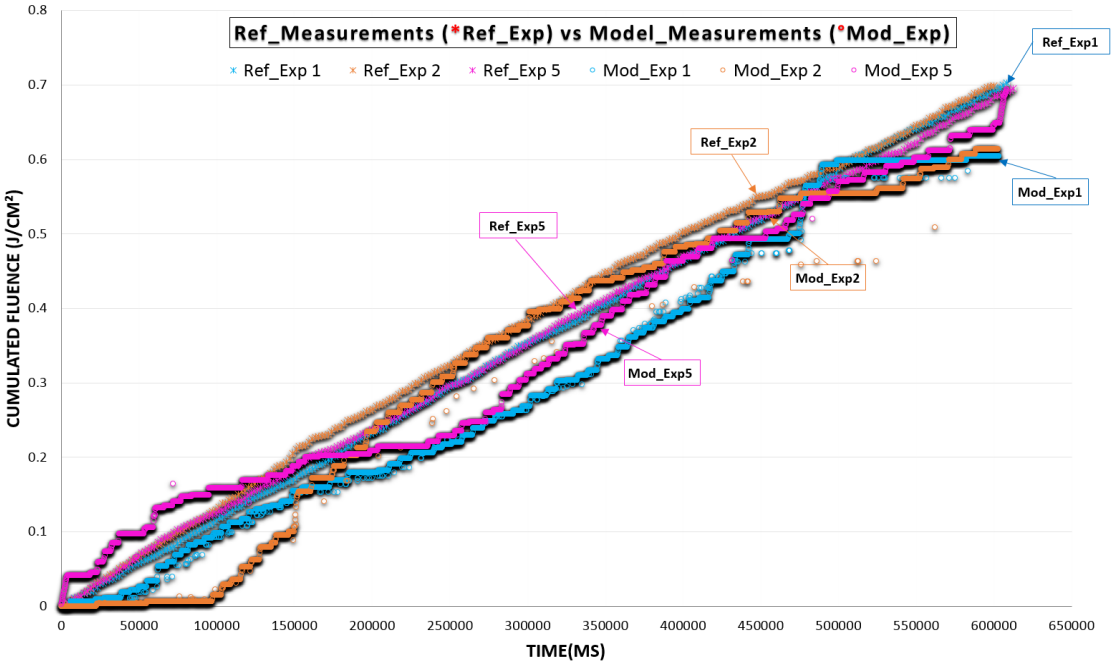
Y -184.819
Z 1123.80


Ref_Measurements (*Ref_Exp) vs Model_Measurements (°Mod_Exp)
Ref_Exp 1
Ref_Exp 2
Ref_Exp 5
Mod_Exp 1
Mod_Exp 2
Mod_Exp 5
Ref_Exp1
Ref_Exp2
Ref_Exp5
Mod_Exp1
Mod_Exp2
Mod_Exp5
CUMULATED FLUENCE (J/CM²)
TIME(MS)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
50000
100000
150000
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250000
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350000
400000
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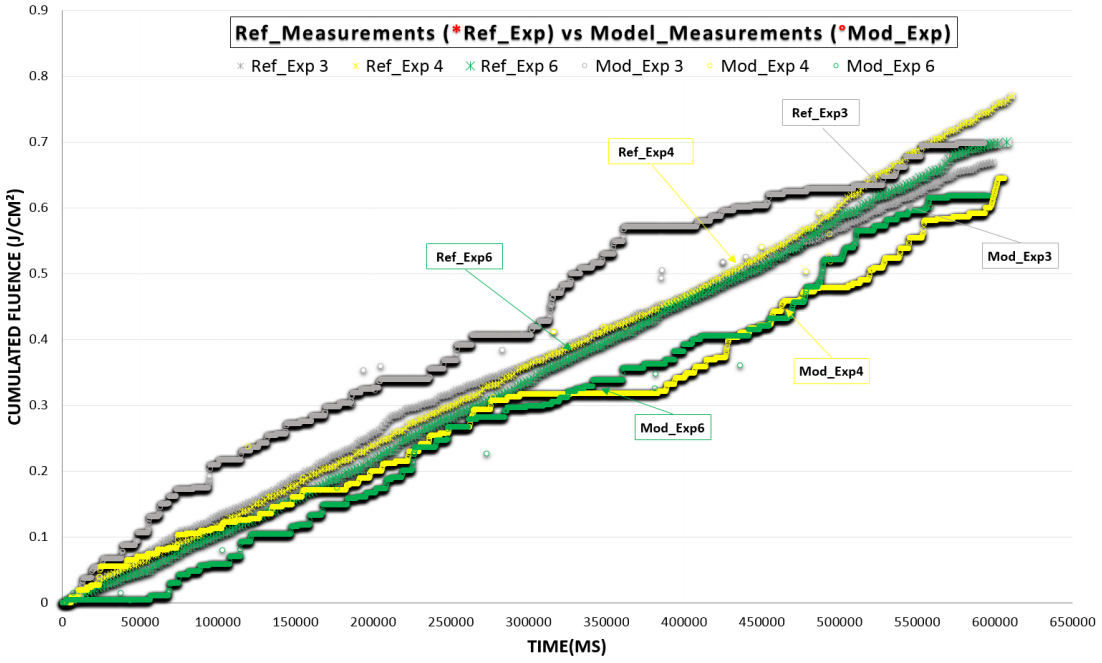
500000
550000
600000
650000

(a)


Ref_Measurements (*Ref_Exp) vs Model_Measurements (°Mod_Exp)
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Ref_Exp 4
Ref_Exp 6
Mod_Exp 3
Mod_Exp 4
Mod_Exp 6
Ref_Exp3
Ref_Exp4
Ref_Exp6
Mod_Exp3
Mod_Exp4
Mod_Exp6
CUMULATED FLUENCE (J/CM²)
TIME(MS)
0
0.1
0.2
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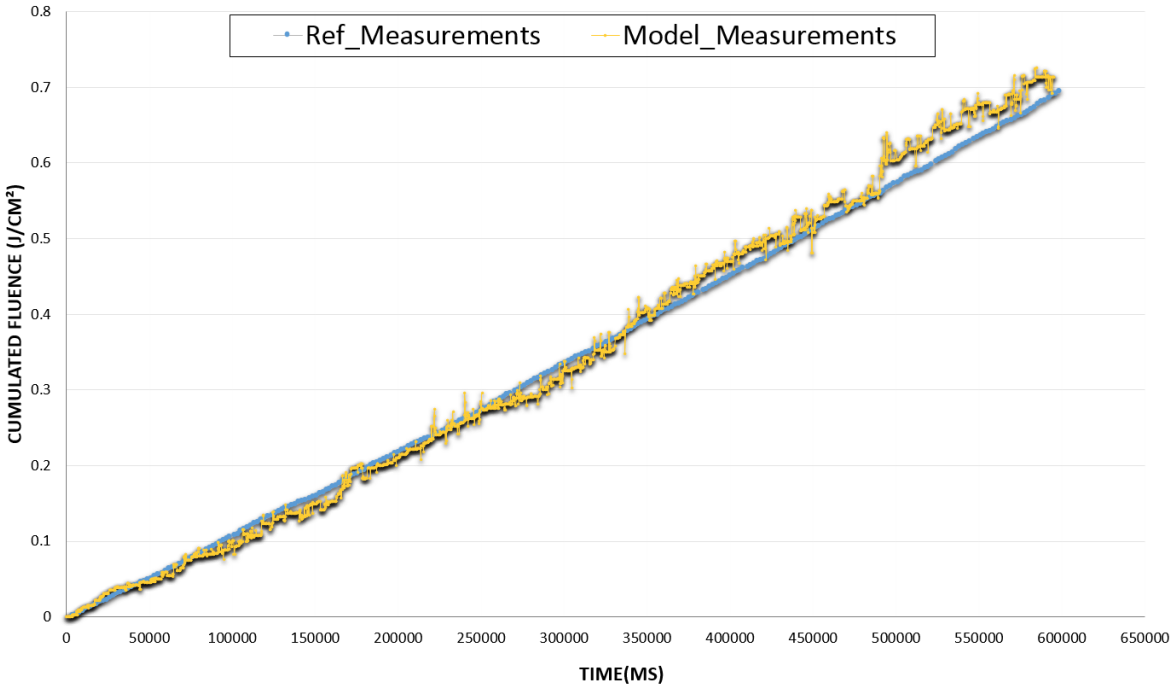
(b)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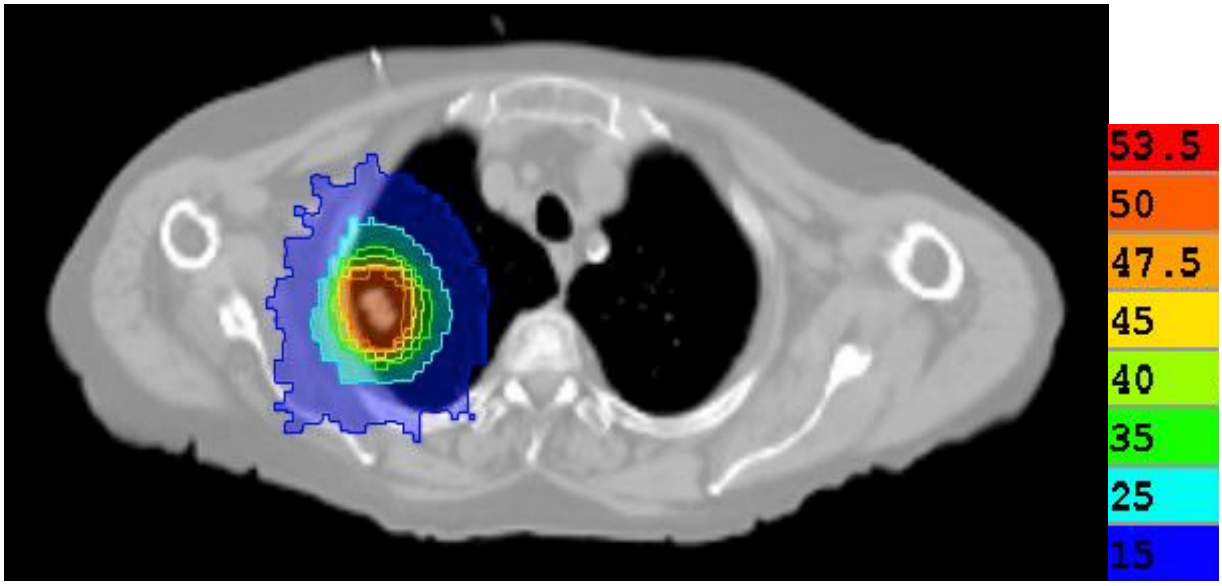
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