Physica Medica 59 (2019) 55–63

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

A platform for patient positioning and motion monitoring in ocular proton therapy with a non-dedicated beamline

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ABSTRACT

Purpose: At Centro Nazionale di Adroterapia Oncologica (CNAO, Pavia, Italy) ocular proton therapy (OPT) is delivered using a non-dedicated beamline. This paper describes the novel clinical workflow as well as technologies and methods adopted to achieve accurate target positioning and verification during ocular proton therapy at CNAO.

Method: The OPT clinical protocol at CNAO prescribes a treatment simulation and a delivery phase, performed in the CT and treatment rooms, respectively. The patient gaze direction is controlled and monitored during the entire workflow by means of an eye tracking system (ETS) featuring two optical cameras and an embedded fixation diode light. Thus, the accurate alignment of the fixation light provided to the patient to the prescribed gazed direction is required for an effective treatment. As such, a technological platform based on active robotic manipulators and IR optical tracking-based guidance was developed and tested. The effectiveness of patient positioning strategies was evaluated on a clinical dataset comprising twenty patients treated at CNAO.

Results: According to experimental testing, the developed technologies guarantee uncertainties lower than one degree in gaze direction definition by means of ETS-guided positioning. Patient positioning and monitoring strategies during treatment effectively mitigated set-up uncertainties and exhibited sub-millimetric accuracy in radiopaque markers alignment.

Conclusion: Ocular proton therapy is currently delivered at CNAO with a non-dedicated beamline. The technologies developed for patient positioning and motion monitoring have proven to be compliant with the high geometrical accuracy required for the treatment of intraocular tumors.

1. Introduction

Ocular proton therapy (OPT) is considered the elective treatment for different kinds of highly malignant intraocular tumor. Uveal, iris and conjunctival melanomas, ocular hemangioma and retinoblastomas are amongst the lesions typically treated with OPT, particularly if target thickness prevents the applicability of other treatment modalities such as brachytherapy [1–4]. A remarkable local control rate (well over 90%) was reported over the years by several institutions with over 28.000 patients treated worldwide [1,5,6], even though concomitant counter-effects, such as radiation induced damage to the lacrimal gland, glaucoma and iris rubeosis were described [7].

The OPT clinical protocol relies on a pre-treatment surgical procedure carried out to implant radiopaque tantalum clips on the eye globe surface in close proximity to the tumor site. Clips are then used as a geometrical reference to identify the target volume and to ensure, on a daily basis, a proper alignment of the eye and the tumor to the treatment beam. An OPT treatment plan consists of determining the optimal gaze direction (polar and azimuth angles) to minimize the dose to critical structures and achieve total coverage of the target by the prescribed dose. As a result, the patient actively participates in the treatment procedure by looking at a fixation light and reproducing the optimal planned gaze direction during set-up and irradiation. Patient position is verified and iteratively corrected using radiographic images of tantalum clips. In parallel, gaze reproducibility is qualitatively monitored by visual control of the stream of eye images acquired by a dedicated optical camera.

Most centers that currently offer OPT to patients use beamlines specifically dedicated to the treatment of ocular disease, based on passive scattering systems optimized to deliver small fields at shallow depth, with sharp dose gradients at the edge of the fields [8–11]. Also, treatment planning is typically performed using dedicated treatment planning systems (TPSs) such as OCTOPUS [12], EyePlan [13,14] and Eclipse Ocular Proton Planning (Eclipse Ocular Proton Planning, Varian

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https://doi.org/10.1016/j.ejmp.2019.02.020
Received 10 October 2018; Received in revised form 25 February 2019; Accepted 25 February 2019
Available online 02 March 2019

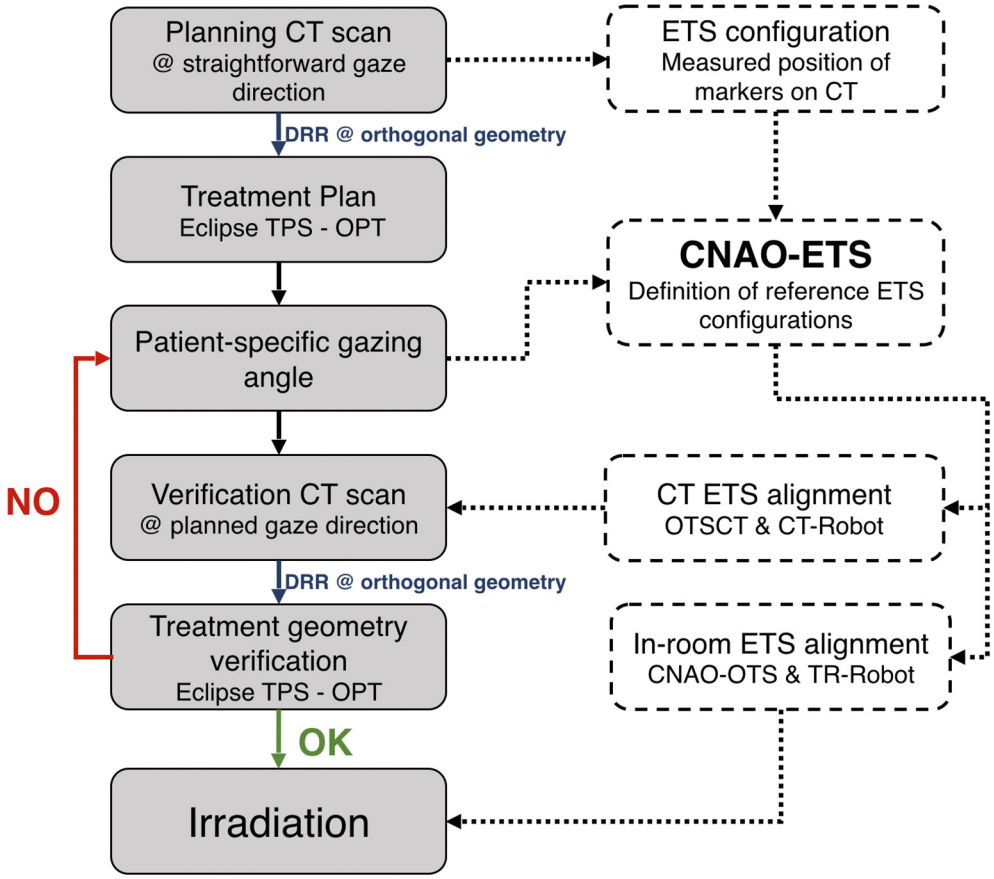

Fig. 1. Schematic representation of the OPT clinical workflow at CNAO including the ETS positioning procedures.

Medical Systems, Palo Alto, CA). As such, centers equipped with technologies specifically designed for OPT share similar clinical practice workflow of patient preparation, simulation, planning and treatment [9]. Treatment simulation consists of the acquisition of two orthogonal x-ray images while the patient is looking straight at a fixation light on the beam axis and is performed directly in the treatment room where the patient is seated on the treatment chair and immobilized with a thermoplastic mask. TPSs use a geometrical eye model adjusted to the patient-specific anatomy exploiting clips position as measured in the X-rays acquired during simulation. The lesion volume is defined within the eye model by integrating information on tumor base shape, fundus photograph and tumor thickness measured with ultrasound imaging. Ultimately, the TPS provides beam shaping parameters: range, modulation, collimator aperture and wedge size and position [15]. Also, virtual portal radiographies for the planned gaze direction are generated and used for patient position verification [16]. Positioning uncertainties in the sub-millimetric range are required in OPT considering the small volume of the lesion, the proximity to functional organs and the use of passive beam scattering techniques [17].

Despite dedicated technologies are still the most common choice for the treatment of intraocular tumors with protons, efforts towards the use of general-purpose beamlines for OPT have been recently proposed [18]. Hartsell et al. developed ad-hoc treatment planning procedures which do not rely on dedicated systems but are based on volumetric imaging (MRI scan with and without contrast, diffusion weighted imaging and CT) in combination with a three-dimensional geometrical eye model. Then, OPT is delivered using either fixed or inclined non-dedicated beamlines. However, MRI and CT imaging have shown limitation (gross volume underestimation, discrimination to retinal detachment) in the recognition of intraocular tumors [19]. Thus, the integration of other imaging modalities (fundus photography, ultrasound) should be considered [17].

At the Centro Nazionale di Adroterapia Oncologica (CNAO, Pavia, Italy) OPT treatment started in August 2016 using a dedicated treatment planning system but non-dedicated in-room technologies [20]. A general-purpose treatment room equipped with a fixed horizontal beamline, active scanning delivery system and a non-orthogonal X-ray imaging geometry are available for OPT [21,22]. The CNAO beamline commissioning for OPT is reported elsewhere [23]. Here, we focus on the technological and methodological solutions developed to achieve accurate patient positioning and monitoring in all steps of the clinical workflow. In particular, a technological platform based on active robotic manipulators and optical tracking systems was developed to properly integrate into the clinical workflow an eye tracking system (ETS) dedicated to provide a fixation light for patient gaze stabilization and to monitor eye motion using two optical cameras [24]. The effectiveness of these strategies was tested and subsequently evaluated on a clinical dataset of 20 patients treated at CNAO with OPT.

2. Materials and methods

2.1. Clinical workflow

In the following, we report the OPT clinical procedure applied at CNAO, in order to provide the context in which technologies related to patient positioning were developed. These will be thoroughly described in the following sections,

The combined use of a treatment planning system dedicated to OPT (Eclipse Ocular Proton Planning, Varian Medical System, Palo Alto, US) and non-orthogonal in-room X-ray imaging required the introduction of volumetric imaging for treatment planning and verification. As a result, the clinical protocol at CNAO can be divided into two phases: the

treatment simulation, which takes place in the computed tomography (CT) room with the patient in supine position and the treatment delivery where the patient is seated on the treatment chair. During both phases, the ETS is used to monitor qualitatively involuntary eye motion during imaging and irradiation and provide a fixation point to the patient. A schematic representation of the whole clinical workflow and procedures is depicted in Fig. 1.

2.1.1. Treatment simulation

The first part of the simulation phase involves the acquisition of a CT volume of the diseased eye, while the patient is looking in straightforward direction. This is performed after preparing the patient-specific head immobilization device, namely a patient-specific thermoplastic rigid mask. During this procedure, the patient diseased eye is carefully aligned to the CT gantry isocenter using the lasers as geometrical reference. Accordingly, the fixation light is adjusted to guarantee a straightforward gaze direction on a patient-specific basis (Fig. 3(c)). Before CT scan acquisition, the X-ray frontal scanogram is also used to double-check the alignment of the ocular globe to the isocenter in cranial-caudal direction (if needed, adjustment is done. A pair of orthogonal digitally reconstructed radiographies (DRRs) required by the Eclipse TPS generated by defining a virtual isocenter aligned to the fixation light in proximity to the eye center and fed to the TPS for treatment planning [13]. Finally, displacement of the isocenter against the ocular globe center is determined at the TPS during eye model creation and treatment simulation (3-D clip localization based on orthogonal DRRs). When deviations larger than 1.5 mm are found, a new corrected CT scan is acquired and used for reference simulation purpose.

Once the treatment plan is completed and approved by the clinical personnel, a new CT scan, during which the patient is looking in the planned gaze direction, is acquired to complete the simulation phase. The gaze direction assumed by the patient during this last CT scan is verified using the TPS and compared to the one defined during planning. In case the residual discrepancies are considered clinically acceptable on a geometrical (i.e. azimuthal and polar angle deviations within $\pm 1^{\circ}$) and dosimetric level, the marker configuration in the verification CT scan is adopted as the reference for irradiation. Otherwise, a new treatment plan, with a different gaze direction is created and verified with an additional CT scan. In case of severe visual impairment of the diseased eye, the healthy eye is used for fixation and the ETS is positioned accordingly. As a result, the ETS optical cameras monitor the healthy eye movement, while an additional camera, attached to a flexible arm, is pointed at the diseased eye ultimately achieving binocular motion monitoring (see Fig. 3(d)).

2.1.2. In-room technologies

As previously mentioned, a non-dedicated treatment room is used at CNAO for OPT treatments. The beamline design was modified specifically for OPT by the introduction of range shifters, enabling dose deposition at depths shallower than 3 cm, and a brass collimator with a patient-specific aperture (encompassing a 2.5 mm margin) to reduce the beam lateral penumbra. The treatment room is equipped with a pantographic robotic arm (CNAO-PPS moving at six degrees of freedom with geometrical accuracy below 0.3 mm and 0.3°) coupled with the patient treatment chair, an infrared optical tracking system (CNAO-OTS) and a stereoscopic X-ray imaging system (CNAO-PVS) [21,25]. CNAO-OTS verifies the treatment geometry by infrared 3D real-time tracking surface fiducials. CNAO-PVS features a non-orthogonal and tilted geometry for double and synchronous X-ray imaging and provides set-up correction possibilities through either 2D-3D image-based or point-based rigid registration, using the commercial software Verisuite PT (Medcom, Germany).

2.1.3. Treatment delivery

OPT treatment at CNAO is delivered in four subsequent daily fractions with the patient seated on the robotic treatment chair, wearing the thermoplastic mask and eyelid retractors. The patient is asked to fixate in the planned direction when radiographic images are acquired for treatment geometry verification. Set-up corrections are defined through point-based rigid registration and applied to the treatment chair for the alignment of the tantalum implanted markers identified on X-ray images to the reference configuration. This ultimately result in concurrent correction of the fixation light position, which is embedded in the eye tracking system and rigidly fixed to the treatment chair. These corrections are applied iteratively until clinically acceptable residual markers misalignments are obtained (i.e. maximum registration residuals inferior to 0.3 mm in the lateral, vertical and longitudinal directions). Due to three- dimensional scanning beam delivery at CNAO a relatively long beam time needed, typically around 3 min. Thus, the single fraction dose is divided into three identical fields that are delivered sequentially. Radiographic imaging is enabled also during irradiation for periodic verification: involuntary eye movements are continuously monitored by an operator visual control of the two eye images acquired by the ETS cameras or, in case of health eye fixation, through binocular eye monitoring using an additional camera (Fig. 3(d)). In case of beam interruptions, as well as during the irradiation itself, radiographic treatment geometry verification is available and patient position correction can be applied directly from the control room.

2.2. Eye tracking system

Two optical cameras are installed in the eye tracking system and an ad-hoc software application allows displaying real-time ocular images. The radiation oncologist draws outlines of convenient ocular features when the patient fixates steadily and then monitor involuntary movements by visual control guaranteeing gaze direction reproducibility.

In addition, the ETS embeds the patient fixation light. This consists in a red-light emitting diode, pre-positioned according to the optimal gaze direction, which the patient is asked to look at. This requires the accurate, reproducible and verifiable positioning of the fixation light during both first simulation and second verification CT scans, as well as at each irradiation fraction. As previously mentioned, the light target for patient gaze fixation is integrated in an eye tracking system, which features a mirror inclined 45° placed on its terminal part in a configuration inspired by the systems developed at the University of Wien [26,27]. The system was designed in order to couple the two fundamental functions of allowing eye position monitoring, by means of two optical cameras, and providing the patient with the fixation target, in the form of a red diode (see Fig. 2 (a)) [24]. However, as the red diode is embedded in the device and visible only to the patient through its reflection on the mirror, an indirect localization procedure, based on the reflection properties of a planar mirror, was required. Given the fixed geometry between the position and orientation of the mirror and the embedded red LED, one can safely assume that the LED reflection through the mirror, i.e. the fixation point provided to the patient, behaves as an element of the rigid device's body (Fig. 2(b)). Thus, by knowing the ETS pose in space, the position of the fixation point can be accurately estimated accordingly. For this reason, ETS is equipped with a configuration of external radiopaque infrared-reflective markers, whose geometry was calibrated with respect to the fixation point using a high-resolution CT scan (pixel spacing of $0.9 \times 0.9 \times 0.6$ mm). The result is that the direct monitoring of ETS fixation point is enabled both retrospectively on CT images, where radiopaque markers are clearly visible [28], and in real-time through IR optical tracking of the fiducials configuration.

2.3. ETS positioning platform

ETS positioning, aiming at aligning the embedded fixation light to the gaze direction prescribed by the treatment plan, is handled through

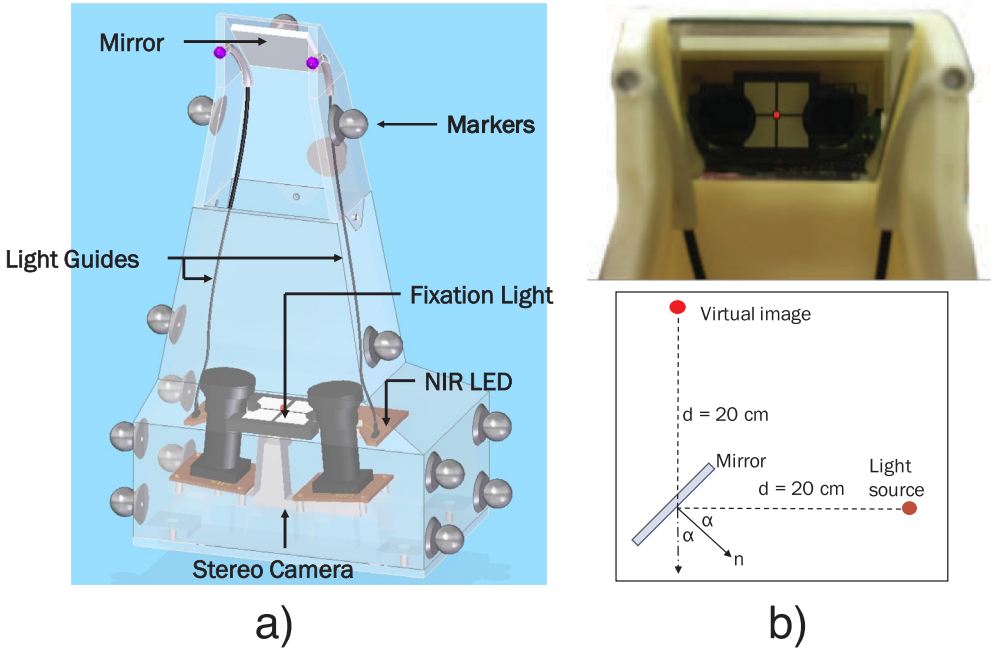

Fig. 2. On panel (a) a schematic representation of the ETS. Panel (b) depicts the fixation light, as seen by the patient, and a representation of the law of optics governing plane mirror reflections upon which the ETS geometrical calibration is based.

a technological platform based on robotics and optical tracking. Optical tracking is used to verify the device position and estimate misalignments, which are then mitigated by automatic robotic manipulator motion (see Fig. 4(a)).

Two different robotic manipulators were selected to implement the ETS alignment procedure in the CT and treatment rooms (CT-Robot, Computed Tomography Robot, TR-Robot, Treatment Robot). In the treatment room, an F-series RV-4FL-D (maximum reach: 515 mm, maximum load capacity: 4 kg) robot by Mitsubishi was mounted permanently on the treatment chair (Fig. 3(a)). Conversely, a custom-made mechanical coupling mechanism allowing temporary mounting was designed to set up a Mitsubishi F-series RV-2F-D (maximum reach: 504 mm, maximum load capacity: 2 kg) active manipulator to the CT couch (see Fig. 3(c-d)). Both robotic manipulators are equipped with a customized quick-release system designed to mount the ETS on the robot end effector.

ETS guidance to the desired position is controlled by two different infrared stereoscopic optical tracking systems: one (OTS-CT) specifically installed in the CT room and the other (CNAO-OTS) already available in the treatment room for patient position verification. The OTS-CT system features three calibrated optical cameras and provides the three dimensional position of surface fiducials in the visible spectrum and is exclusively used for ETS alignment [29,30] (Fig. 3(b)).

The procedure for ETS alignment in the CT and treatment rooms is performed as follows (see Fig. 4(a)):

i. A preliminary raw alignment is performed automatically by the robotic manipulators according to the prescribed patient gaze direction.
ii. The optical tracking system detects in real-time the position of the ETS fiducials and provides the motion correction parameters (6 degrees of freedom) for the accurate alignment of the fiducial configuration with respect to a predefined reference and indirectly of the fixation point.
iii. Corrections are recursively applied by acting on the robotic manipulator until sub-millimetric alignment residuals are obtained. The alignment process, including equipment installation, typically requires 15–20 min.

The geometrical consistency of this procedure is ensured by the fact that both the manipulators and optical tracking systems are geometrically calibrated with respect to the right-handed coordinate systems of the treatment and CT rooms (RCS – Room Coordinate System and CTCS – Computed Tomography Coordinate System). As a result, the corrections estimated through optical tracking are executed by the robotic systems in a geometrically consistent way. Corrections of the ETS position are estimated from a point-based rigid registration between the current ETS fiducials configuration measured in real-time by optical tracking system and a pre-defined geometrical reference. The definition of this reference is a crucial step of the whole workflow and represents that particular device configuration described by specific 3D positions of the ETS fiducials, that grants that the gaze fixation point embedded in the device is aligned along the prescribed gaze direction with respect to RCS and CTCS.

This reference configuration is generated by a custom-made Matlab® (The Mathworks, Inc, Natick, US) application (CNAO-ETS) specifically developed to provide the 3D positions of the ETS fiducials given the prescribed gaze direction. This is achieved by a sequence of geometrical transformations of the ETS starting from its position measured during planning CT scan [28].

- At first, the ETS configuration measured during the planning CT is mapped in the treatment room geometry.
- Then, two rotations are applied to adjust the fixation light according to treatment planning gaze direction prescriptions. As shown in Fig. 4(b) the first transformation is applied to divert the gaze from the straightforward direction according to the planned polar angle, while the second allows adjusting to the azimuthal gaze direction.
- Once the fixation light, is aligned to the prescribed gaze direction, the device pose can be furtherly optimized. The ETS can be rotated around or translated along the axis defined by the patient gaze direction without compromising treatment geometry and, therefore, the in-room set-up can be optimized.
- Finally, the position of the ETS during verification CT is established by transformation of the ETS/eye relative geometry from the treatment room (RCS) to the CT (CTCS) room geometry.

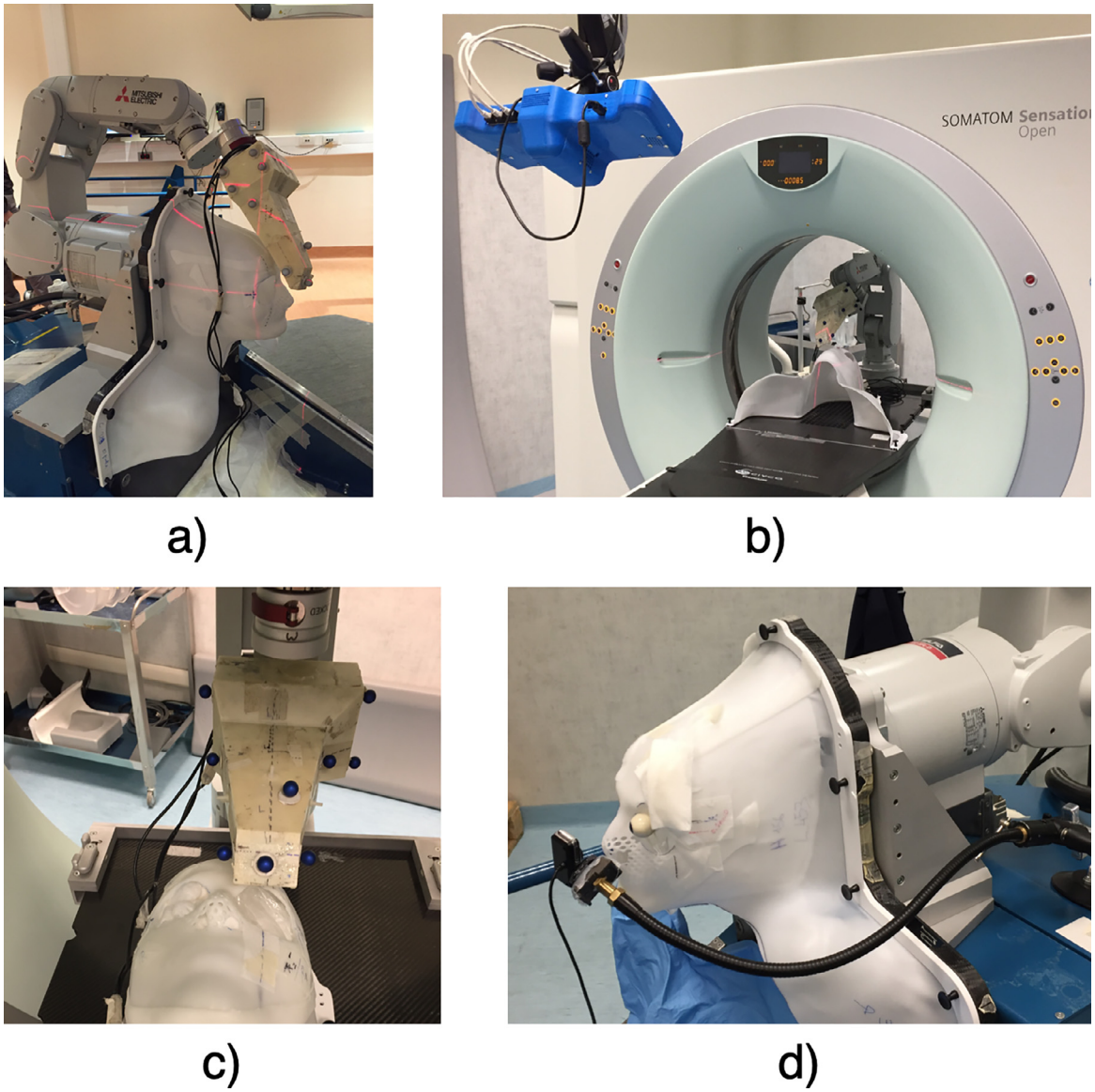

Fig. 3. On panel (a) the treatment room set-up for OPT is depicted. The Mitsubishi RV-4FL-D active manipulator installation is shown. Panel (b) depict the elements for ETS alignment in the CT room: the OTS-CT, in blue, and the Mitsubishi RV-2F-D robot for ETS guidance and mobility are shown. On panel (c) the ETS position used for Ct planning image acquisition is shown. The fixation point is projected along the patient straight-forward gaze direction. On panel (d) the set-up of the additional camera used in case of healthy eye fixation is depicted. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3.1. *Experimental testing*

The accuracy of the ETS alignment procedure was investigated in both set-ups by retrospectively measuring the ETS orientation on CT scans acquired after its alignment and direct measurement with CNAO-OTS in the treatment room. Ten ETS configurations with polar angles and azimuthal angles ranging between 33–40° and 0–180° respectively were tested in the CT room. In the treatment room, the analysis focused on the reproducibility of ETS positioning against manipulator movements and treatment chair docking/undocking.

In addition, the uncertainties associated with the clips-based registration process at the Verisuite PVS workstation were evaluated by simulating the clinical workflow on a custom phantom. The phantom consisted in a rubber sphere simulating the ocular globe fixed to a thermoplastic mask and fitted with four tantalum clips on its posterior surface. The phantom was first CT scanned and a plan was calculated and sent to Verisuite. Finally x-ray verification images were acquired and registered against DRRs. Point-based registration was independently performed by three well-trained radiotherapy technologists and repeated five times for each operator (for a total of 15 registrations). The standard deviation of correction vectors estimated by the Verisuite software was considered as a figure of merit of the workflow robustness.

2.4. *Evaluation on clinical data*

Achieving an accurate alignment of the fixation target to the planned direction is not sufficient to guarantee precise patient positioning which depends on the patient ability to steadily fixate the fixation target. Thus, quantitative ocular geometry referencing is required and performed through radiographic imaging of the implanted radiopaque markers. To evaluate the effectiveness of the developed strategies, the accuracy of patient positioning during treatment was evaluated on 20 choroidal melanomas patients, who received OPT at CNAO.

During the verification CT scan, the patient gaze direction is inferred with the TPS using the measured radiopaque implanted clips

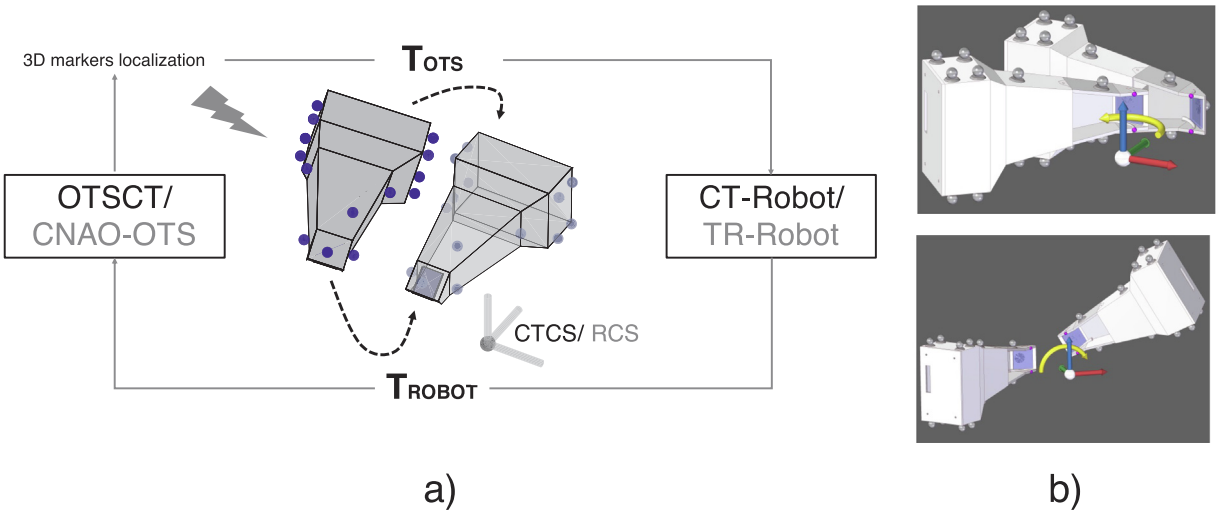

Fig. 4. On panel (a) a schematic representation of the ETS alignment procedure is shown. Panel (b) represents the geometrical transformations applied to the ETS configuration to achieve the alignment of the fixation light to the planned gaze direction.

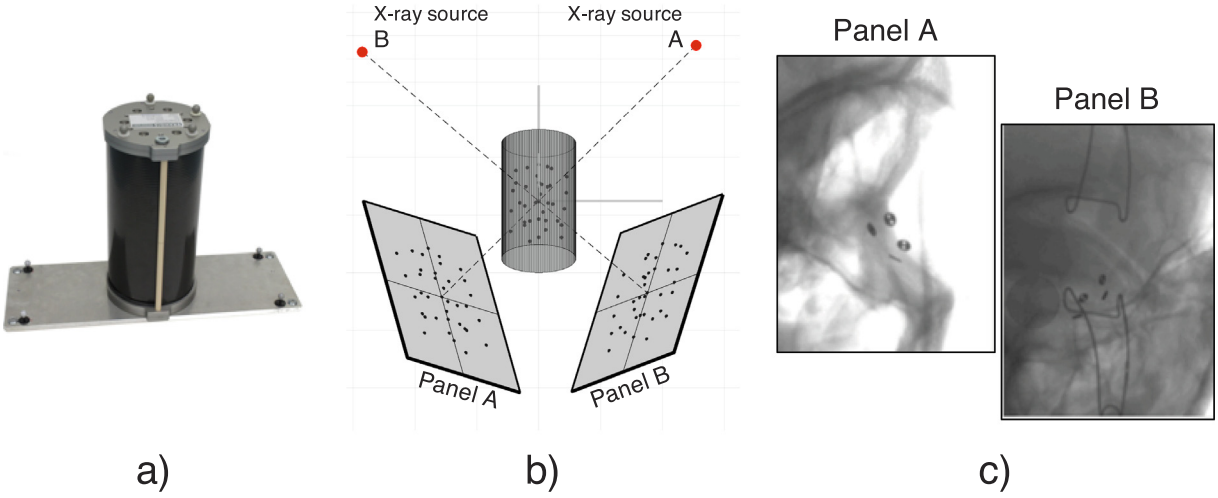

Fig. 5. Panel (a) depicts the phantom dedicated for QA of CNAO patient positioning systems. On panel (b) a schematic representation of the X-ray system geometry along with the phantom radiopaque beads and their projection on panels is shown. Also, radiographic images acquired on one patient are presented (panel c).

configuration. Conversely, prior and during treatment, the patient position is verified by direct measurement of the radiopaque clips position in the RCS through CNAO-PVS. However, the commercial Verisuite software gives as output exclusively treatment chair corrections resulting from 3D referencing of clips position. Therefore, to directly evaluate the effectiveness of patient positioning strategies through the 3D localization of radiopaque clips, the CNAO-PVS imaging system was calibrated with an independent procedure based on an initial description of the imaging system geometry, i.e. panels' position and orientation and relative position of the sources (see Fig. 5(b)). This was corrected based on optimized minimization of back-projection errors of a set of ball bearings within a dedicated phantom, routinely used at CNAO for daily quality assurance (QA) of CNAO-PVS, CNAO-PPS and CNAO-OTS (Fig. 5(a)). The resulting dataset for X-ray calibration consists of 13 couples of images of the phantom, one for geometry definition and twelve for validation, collected during QA performed at the specific CNAO-PVS set-up used during OPT treatments.

This calibration allowed to directly estimate the 3D positions on markers in the RCS identified on stereoscopic radiographic images (Fig. 5(c)). By comparison with the planned position defined in the simulation phase, set-up error and intrafraction motion of 20 patients (80 treatment fractions) under OPT treatment at CNAO were quantified.

Eleven patients (55%) presented the lesion in the left eye. The average volume of the lesion was 671.9 mm^3 ranging from 92.3 to 1964 mm^3. In ten cases (50%) the location was posteriorly located whereas for two patients (10%) the tumor was limited to the equatorial region. The remaining eight patients (60%) presented tumor in the eye anterior segment, with involvement of the ciliary body in just one instance (5%). All patients included in the study exhibited sufficient visual acuity in the diseased eye and, therefore, healthy eye fixation was not necessary.

Point-based rigid registration, limited to translations, and three-dimensional marker-to-marker distances were adopted as figure of merit of patient positioning accuracy. In addition, the entrance surface air kerma (EMAK) during stereoscopic radiographic imaging was measured

with a calibrated solid-state detector (Barracuda X-ray multi-purpose detector MPD, RTI Electronics AB, Mölndal, Sweden) to quantify the imaging dose delivered to the patient.

3. Results

3.1. Experimental testing

As far as the ETS alignment in the CT room is concerned, median errors of 0.9° (Inter-quartile range (IQR): 0.7°) and 0.6° (IQR: 1.7°) of polar and azimuthal gazing angles respectively were found. Tests in the treatment room highlighted the ability of the robot and treatment chair to reposition the ETS with errors in the polar and azimuthal angles lower than 0.2°.

The standard-deviation of the correction vector calculated by Verisuite after clips-based registration was 0.02, 0.03 and 0.04 mm, in the X, Y and Z direction respectively.

3.2. Patient positioning verification

The accuracy of the X-ray imaging system calibration was tested on 12 pairs of radiographic images of the QA phantom. A median 3D reconstruction error of 0.41 mm (IQR: 0.24 mm) was measured.

Planned polar angles of fixation ranged from 25 to 40° while azimuthal angles ranged between 90 to 330° and 80 to 180 for lesions located in the left and right eye respectively. On average (± standard deviation) 15.4 ± 3.9 X-ray images were acquired per fraction and 2.1 ± 1.1 patient position corrections were required to achieve a clinically acceptable alignment of the implanted clips. An ESAK of 0.76 mGy (variability inferior to 1%) was measured for one single radiography acquisition. This results in an average imaging dose delivered to the patient of 22.8 mGy per fraction. A median 3D clip misalignment of 1.49 mm (IQR:2.28 mm) and 0.58 mm (IQR: 0.48 mm) was measured prior and after patient position correction, respectively. Clips median misalignment increased by 15% (0.09 mm) during irradiation as a result of involuntary eye movements. Results are summarized in Table 1.

Fig. 6 shows 3D marker-to-marker misalignments for every imaging acquisition during four fractions of one patient.

4. Discussion

In this study, the technologies and methods adopted at CNAO to activate ocular proton therapy with a non-dedicated beamline were reported. Given the remarkable clinical success of conventional OPT reported over the last three decades, the efforts were focused toward the adaptation of the technologies available at CNAO to the dedicated treatment planning and dose delivery procedures. An OPT-dedicated TPS was used and, as an orthogonal portal X-ray system is not available in CNAO rooms, a treatment simulation phase carried out using volumetric radiographic imaging was introduced in the frame of a novel clinical workflow. CT images were used to generate DRRs in a geometry compatible with the TPS for planning and treatment geometry verification purposes. The treatment delivery was designed to incorporate a set of radiographic imaging of the implanted radiopaque clips and automatic alignment to the reference clips configuration defined and verified in the simulation phase. Point-based registration is used to calculate set-up corrections and the uncertainties related to the resolution of flat panel detector and TV monitor, registration algorithm and inter-observer variability in the localization of clip centers were quantified. Results, well below 0.1 mm, confirmed the robustness and suitability of the proposed procedure. The patient gaze direction is controlled and monitored using an eye tracking system specifically developed for clinical use at CNAO, equipped with a pair of optical cameras and carrying the patient' fixation light target.

This approach differs greatly with respect to the methodologies reported by Hartsell [18], another example of ocular proton therapy delivered with a non-dedicated beamline. In that study, the treatment planning was not performed with a dedicated TPS for OPT based on orthogonal X-ray imaging, but it was based on a general-purpose treatment planning system and volumetric imaging. Furthermore, unlike the reported CNAO case, eye motion monitoring was achieved using an optical camera detached from the fixation light. Similar handling of set-up corrections estimations was administered through point-based registration of clips position using the same commercial software applied at CNAO.

We calibrated the eye tracking system in order to achieve direct control of the embedded fixation light position through three-dimensional referencing of a configuration of fiducial markers attached to its outer surface. For this purpose, a specific procedure to define and achieve a desired ETS configuration aligning the fixation light to the prescribed gaze direction through optical tracking guidance and coordinated robotic movements was implemented and tested.

The experimental activities demonstrated the platform effectiveness in positioning the ETS with errors lower to one degree for the patient's gaze direction. The procedure was replicated in both scenarios included in the clinical workflow (CT and treatment room) proving sufficiently accurate control over the patient gaze direction. However, within the context of OPT at CNAO, the ETS capabilities in the automatic detection of eye position and orientation, presented in previous publication [24,31], have not yet been investigated. Quantitative optical-based ocular referencing should significantly improve the workflow efficiency by sparing the patient of non-treating dose and will be the subject of future research efforts.

An analysis on 20 patients treated at CNAO was performed to evaluate the efficacy of the developed technologies in a clinical scenario and quantify set-up errors and eye motion during dose delivery. Treatment geometry verification and involuntary eye motion monitoring were achieved using the ETS in combination with in-room X-ray imaging. On one hand, the ETS provides visual feedback on eye movements while quantitative measurement of the treatment geometry is carried out by acquiring X-ray images of the eye-implanted surgical markers. During irradiation, radiographic imaging is also performed for qualitative evaluation of eye steadiness. To enable 3D reconstruction of clips position expressed with respect to the RCS, a geometrical calibration of the in-room X-ray imaging system was required. A median accuracy of 0.41 mm was found on a dedicated phantom. Set-up errors were evaluated considering radiographies acquired before irradiation and comparing clips three-dimensional position with the corresponding nominal configuration. A median marker-to-marker misalignment of −0.17 mm, 0.03 mm and −0.11 mm was found in the lateral longitudinal and vertical direction respectively. This result is similar to those reported in literature for OPT delivered with passive scattering techniques and comply with the strict requirement of OPT [16,32]. The

Table 1
Set-up errors and intrafraction motion during OPT at CNAO. Markers 3D misalignment and residuals of three degrees of freedom (DOF) point-based registration is reported. Lateral, longitudinal and vertical refer to the axis of the room coordinate system (RCS).

	3D [mm]	Residuals of 3 DOF registration [mm]		
		Lateral	Longitudinal	Vertical
	Before Set-up Corrections			
Median	1.49	−0.42	0.29	−0.39
IQR	2.28	1.06	1.30	1.55
	After Set-up Corrections			
Median	0.58	−0.17	0.03	−0.11
IQR	0.48	0.30	0.19	0.42
	Dose delivery			
Median	0.67	−0.20	0.06	−0.01
IQR	0.48	0.39	0.31	0.62

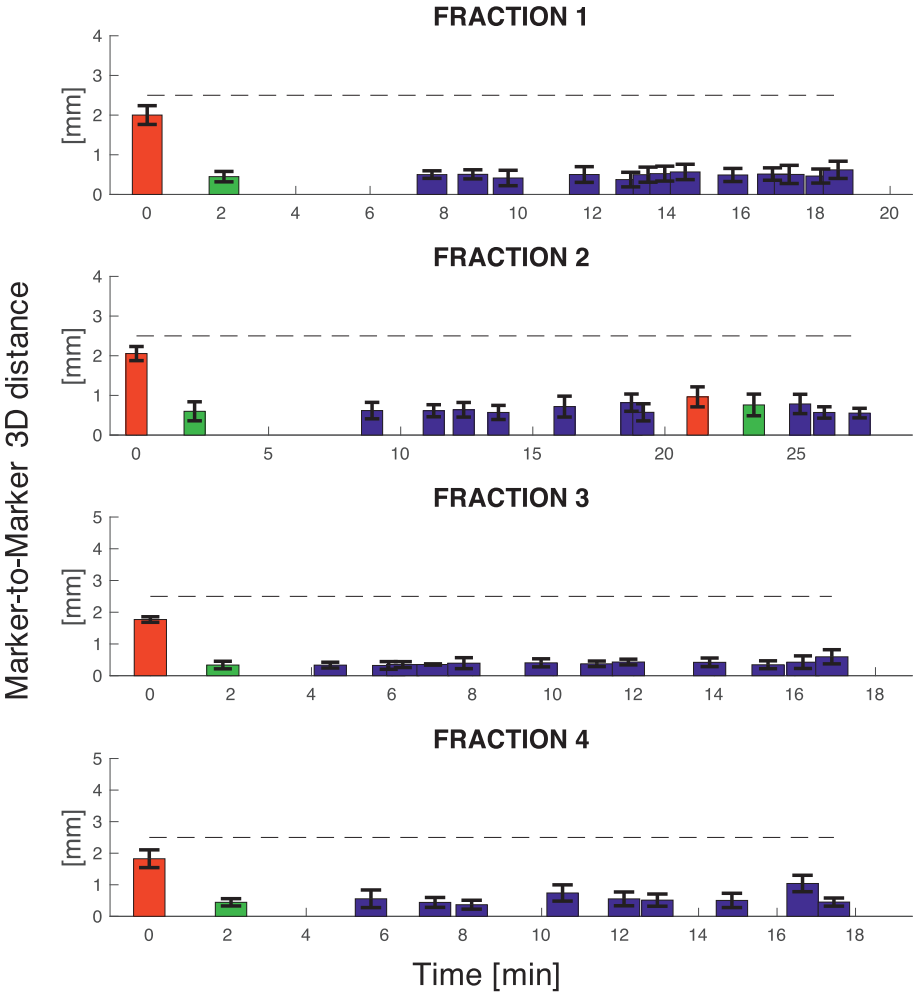

Fig. 6. Markers discrepancies to the planned position during four fractions of one patient. Misalignments are presented as error bars corresponding to marker-to-marker 3D distances for a single X-ray acquisition. Red bars correspond to X-ray acquisition after which a patient position correction was applied. Green bar represents set-up acceptance and verification radiographies. Blue correspond to X-rays performed during irradiation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

same approach was adopted to evaluate involuntary eye motion, but only radiographic images acquired during dose delivery were analyzed. The median discrepancy increased by 0.1 mm during dose delivery. This result attests the quality of the motion monitoring technologies during treatment when involuntary eye movements may occur. Even though the quantitative analysis suggests that the applied enlargement of the collimator aperture and distal and proximal safety margins of 2.5 mm should be sufficient to mitigate the effect of intra-fraction eye motion, automatic and quantitative eye localization is expected to further improve geometrical accuracy of the treatment procedure. Further development will focus on the implementation of gaze-driven automatic beam gating technologies in the framework of ocular proton therapy at CNAO.

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