CATANA PROTONTHERAPY FACILITY: THE STATE OF ART OF CLINICAL AND DOSIMETRIC EXPERIENCE

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Abstract

After 10 years of activity, about 300 patients have been treated at the CATANA Eye Protontherapy facility. A 62 MeV proton beam produced by a Superconducting Cyclotron is dedicated to radiotherapy of eye lesions, as uveal melanomas.
Research and development work has been done to test different dosimetry devices to be used for reference and relative dosimetry, in order to achieve dose delivering accuracy.
The follow-up results on 220 demonstrated the efficacy of proton beams and encouraged us in our activity in the fight against cancer.

1 INTRODUCTION

Since 2002 ocular tumors are treated with 62 MeV proton beams at LNS-INFN in cooperation with Azienda Policlinico-Vittorio Emanuele of Catania; the goal of the Proton Beam Radiation Therapy (PBRT) is to achieve local tumour control and retention of organ and vision; uveal melanoma is the most frequent treated neoplasia, but other less frequent eye diseases have been treated by means of protontherapy, like choroidal metastases, conjunctival and eyelid tumors [1, 2].

The project started in 1998 in collaboration with Physics and Astronomy Dept of Catania University and Centro Siciliano di Fisica Nucleare e Struttura della Materia, and was funded with the 488/92 funds.

Physical properties make protons suited for the irradiation of eye tumours; proton therapy permits to use a single port to irradiate a defined eye target volume whilst sparing critical structures in its vicinity, as optic disk, macula, lens and anterior segment.

The 62 MeV proton beam, produced by a superconducting cyclotron, is passively prepared for conformal irradiation of the eye tumour.

The energy of 62 MeV confines maximal range of proton beam to about 30 mm, sufficient for the irradiation of intraocular tumours. The required maximum range for a specific treatment is set by a simple Perspex absorber, variable in thickness in steps of 0.2 mm. The sharp distal (< 1 mm) and lateral (< 1.5 mm) fall-offs of the SOBP improves sparing of the healthy eye tissue , demonstrating high dose conformality of eye proton therapy.

2 THE PROTON BEAM LINE

The CATANA passive proton beam line has been entirely built at INFN-LNS of Catania (Figure 1). The proton beam exits in air through 50 μm kapton window placed at about 3 meters from isocenter. Just before the exit window the first scattering foil made of 15 μm tantalum is placed in vacuum. The first element of the beam in air is a second tantalum foil 25 microns thick provided with a central brass stopper of 4 mm in diameter. The double foils scattering system is optimised to obtain a good homogeneity in terms of lateral off-axis dose distribution, minimizing the energy loss. Figure 2 shows the experimental transversal dose distribution for the 62 MeV proton beam measured with a final 25 mm diameter circular brass collimator (reference collimator). Beam data are acquired in a water phantom with a Hi-*p*Si diode (0.6 mm detector diameter) at a depth of 12 mm, corresponding to the middle of a Spread Out Bragg Peak (SOBP).

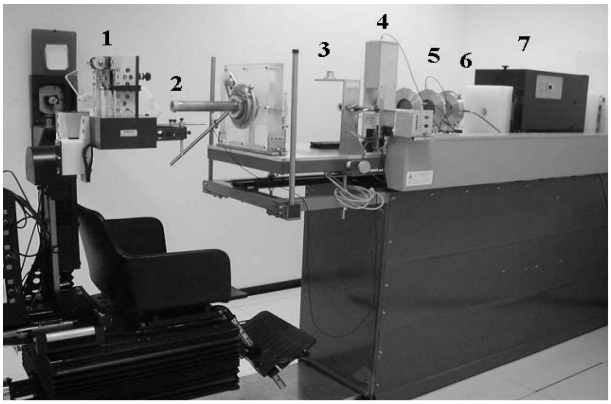

Figure 1: View of the CATANA beam line: 1. Treatment chair for patient immobilization; 2. Final collimator; 3. Positioning laser; 4. Light field simulator; 5. Monitor chambers; 6. Intermediate collimator; 7. Box for the location of modulator wheel and range shifter.

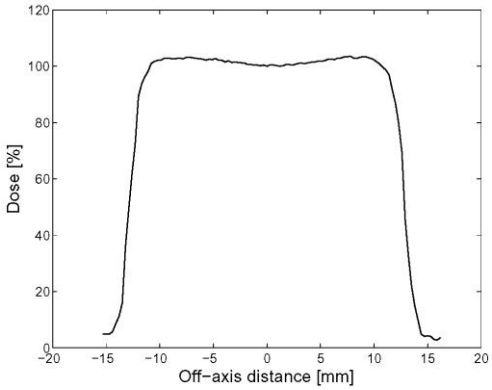

Figure 2: Experimental lateral dose distribution acquired with a silicon diode

Range shifter and range modulator are placed inside a box, downstream of the scattering system. Two diode lasers, located orthogonally and coaxially to beam line, provide a system for the isocenter identification and for patient centering. The radiation field is simulated by a light field with cross-air indicating the principal axis. A key element of the treatment line is represented by two transmission monitor ionization chambers, which provide on-line control of the dose delivered to the patient. The last element before isocenter is the brass shaped patient collimator located 83 mm upstream of the isocenter [3, 4].

3 PROTON DOSIMETRY AT CATANA FACILITY

As in conventional radiotherapy, clinical proton dosimetry includes reference dosimetry, consisting in determination of the absorbed dose at a reference point in the user's beam, and relative dosimetry, i.e. determination of dose distribution in a water phantom (x,y,z). The first is essential for monitor unit calculations and to verify the prescription of the protocol, the second for planning and quality assurance purpose.

For reference dosimetry an Advanced Markus plane-parallel PTW Ion Chamber has been adopted, with an electrode spacing of 1 mm and a collection volume of 0.02 cm^3. According to IAEA TRS 398 protocol [5], proton beam calibration is performed in a water phantom.

The absorbed dose to water per monitor unit (cGy/M.U.) is measured at the isocenter, for each combination of modulator and range shifter used in the clinical practice. Measurements are carried out at the depth of the middle of the SOBP, using the reference 25 mm diameter circular collimator [5]. The clinical proton beam calibration is performed just before each treatment fraction; the variation of beam calibration on the four consecutive days of treatment resulted to be within ±5%.

As for all passive proton therapy facilities, the proton beam calibration resulted to be strongly dependent on the modulator and the range shifter adopted in the clinical practice; for the same modulator, the dose/(monitor unit) decreases of about 35% if the thickness of the range shifter increase from 6 to 12 mm.

To investigate whether narrow irregular fields used in clinical practice will affect the radiation output, *output factors* are experimentally determined, by using small-size detectors, as Scanditronix Hi-p Si stereotactic diode detector (0.6 mm detector diameter) and TN-502RDM micromosfet detector (1×1 mm^2 sensitive area) [6].

The *Output factor* is determined [5] as the ratio of small-size detector signals for the patient and reference collimators for the the same M.U. setting.

Based on experimental results on several collimators, we can state that the dose delivered per monitor unit decreases by less than 3% for collimator areas in the range of 490 mm^2 (reference collimator) to 100 mm^2, the latter representing the lowest limit of collimator areas associated to the clinical practice.

For mono-energetic and modulated proton beams, depth-dose distributions are measured in a home made motorized computer-controlled water phantom with a scanning resolution less than 0.1 mm in the Bragg peak region. Also in this case, an Advanced Markus chamber is used due to small electrode spacing and high electrical field (4000 Vcm^{-1}), the latter providing a collection efficiency close to 1 up to 100 Gy/min in the cyclotron continuous beam.

For the modulated clinical proton beams a set of physical beam parameters are measured, according to the ICRU Report No 78, related to the clinical requirements (fig.3):

1) Beam range (depth of penetration) is measured by the depth of 90% distal point.

2) Width of the SOBP is defined as the distance of 90% dose points, proximal and distal.

3) Distal fall-off (DDF) amounts to the distance of 80% and 20% distal points.

4) Target (or treatment) length is defined as the distance between two DDF lengths (2·DDF) proximal to the distal 50% dose level of the SOBP, and one DDF length (1×DDF) distal to the proximal 90 percent doses level of the SOBP.

4) Reference depth (z_{ref}) is defined at the middle of the SOBP and corresponds to the dose prescription point (ICRU point).

5) Beam quality (Q) is measured by the value of the residual range, defined as $R_{res}= R_p-z_{ref}$, where R_p is the depth at which the absorbed dose beyond the SOBP falls to 10%.

6) Longitudinal Homogeneity, defined as $[(D_{max} / D_{min}) \times 100]$ % within the SOBP.

A software, entirely developed at INFN-LNS, controls the data acquisition and provides data analysis.

Experimental depth dose profiles have been compared with a Monte Carlo simulation application, developed by us using the Geant4 toolkit [7]. The application reproduces in details all the elements of the CATANA proton beam line as well as the detectors used for dosimetric measurements, accurately simulating the tracking and physical interactions of protons with the traversed materials. Results of these comparisons are extensively reported in some publications [8]

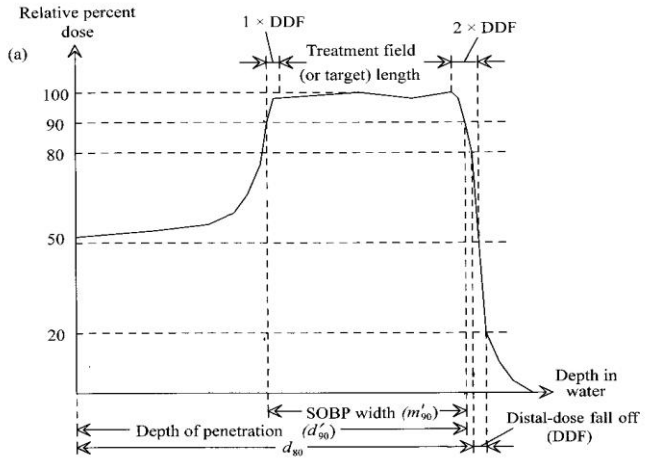

Figure 3: Physical beam parameters related to tha clinical requirements for the modulated proton beam.

Lateral beam profiles are characterized in terms of *field size* ($W_{50\%}$), *lateral penumbra* (LP, $d_{80\text{-}20\%}$), *target* (or *treatment*) *width*, defined as the distance between two LP widths (2·LP) from the 50 percent dose level of the lateral profile, *flatness* and *symmetry* defined as in conventional radiotherapy and evaluated in the target width.

New EBT radiochromic films [9] have been chosen as reference detector for the measurement of lateral profiles; EBT film is nearly tissue equivalent [(Zeff/A)=6.98], with a sensitive range between 0.1Gy and 8 Gy, providing high spatial resolution up to 100 μm.

Epson Expression 10000XL flatbed colour scanner is used to analyze EBT irradiated films; they are scanned in transmission mode in the 48 bit RGB mode (16 bit per colour) and data saved as TIFF files. The maximum of the absorption spectra for this type of film is about 636 nm and, therefore, the red component of the image is extracted to maximize the response.

EBT calibration is carried out with 62 MeV mono-energetic proton beams, using the reference 25 mm diameter circular collimator. Several strips 3×3 cm^2 are irradiated in a solid water phantom at 1 mm depth in the entrance plateau of the Bragg curve. Films are irradiated at a dose rate of 15 Gy/min, corresponding to the clinical dose rate.

Calibration curve (fig.4) is well in agreement with the corresponding curve for 6 MV photons, demonstrating the water equivalence of EBT film.

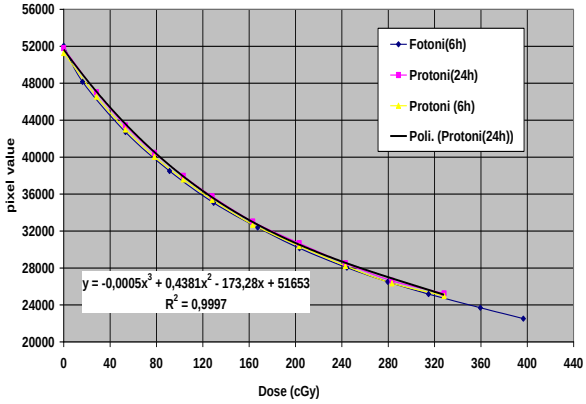

Figure 4: Calibration curve for EBT film.

The response of the EBT films at the middle of the SOBPs associated to ocular proton therapy resulted to be energy-independent within the experimental uncertainty (± 3%), in clinical modulated beams; as a consequence, only one calibration file is needed to evaluate films exposed at different depths.

In ocular proton therapy, EBT films are used for dosimetry verification of standard circular collimators and of irregularly shaped patient collimators with very small lateral extension, down to 8 mm diameter.

Fig.5 shows the lateral profile along the central axis of the 62 MeV proton beam for the reference circular collimator of the eye proton therapy.

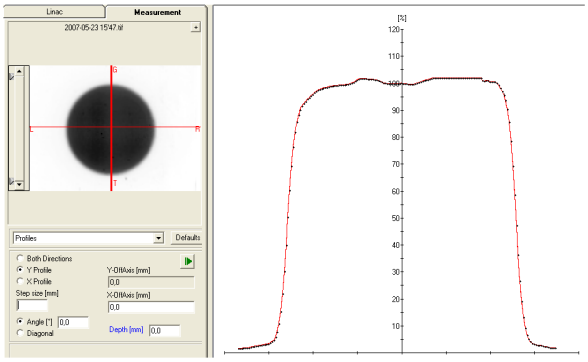

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Figure 5: Lateral profile along the central axis performed with EBT film.

Preliminary in vivo dosimetry has been carried out on Catana patients, by using micro-mosfets; detectors are placed on the patient eyelid immediately before the treatments.

Micro-mosfet calibration is performed individually for each patient, by placing the detector on a SW phantom surface; a calibration factor is determined relating the measured entrance (surface) dose to the dose at the clinical point of interest, i.e. the middle of SOBP.

First in vivo results are promising, with a maximum difference between expected and measured doses smaller than 10%; a lot of correction factors are to be determined in order to obtain an agreement within ±5%

4 TREATMENT PROCEDURES

As explained before, protons allow a high dose deposition in a small deep-seated space, with precise irradiation of the target.

Treatment procedures have been modelled on the specific characteristics of the most frequent tumor of the ocular region, that is uveal melanoma: it is located most frequently in the posterior part of the eye, so it requires a surgical application of 4 tantalum clips around its base on the outer sclera to determine the tumor localisation. The other orbital tumors treated are clinically evident, so a prior surgical phase is not required.

During the ophthalmological work-up, the ophthalmologist defines the tumor position and dimensions, like transverse and longitudinal base diameters, elevation or height, distance to the optic disk, to the macula, to the limbus. Eye anatomical parameters (axial length, transverse diameter, thickness of the coats, distance between anterior cornea and posterior lens, limbus diameter) and clips measurements (distance between clips to limbus, clips to clips and clips to tumor) are also provided to the radiation oncologist. The final result is the draw of a precise fundus view model with tumor and clips locations. The ophthalmologist makes use of A-mode and B-mode ultrasound scan, retinal

fluorangiography, wide-angle fundus photographs and, especially, surgical measurements to define all those parameters. Other relevant information are provided concerning the visual acuity of the affected as well as of the fellow eye, the presence of exudative retinal detachment, ocular pressure and all other information considered to be significant. After the surgical phase, the simulation procedure starts inside the treatment room. Here the patient is immobilized on a motorized computer controlled treatment chair by means of a customized thermoplastic mask and a bite block (Figure 6).

Two orthogonal X-ray pictures (axial and lateral) are taken with the Digital Acquisition System (DAS), consisting of two orthogonal X-ray tubes Philips Practix 33, two flat panels HAMAMATSU mod. C7921 CA02 and a PC Workstation connected to the treatment chair. A homemade software provides X-rays image acquisition and treatment chair movement.

In order to optimize the geometrical reconstruction of the eye and the tumor, 5 pairs of X-ray images for five different fixation angles of the eye are acquired. A measurement of the eyelid thickness and slope is also needed for the planning procedures. All the information are then elaborated by means of the 3-D treatment planning system EYEPLAN [10]. The software provides the treatment position of the clips, isodose curves, dose-volume histograms, the clinical beam range, the required modulation and the shape of the patient collimator. The DAS software matches the clip position provided by Eyeplan with the X-Ray images and sends the required movements (D_x, D_y, D_z) to the chair control program for the treatment position of the patient.

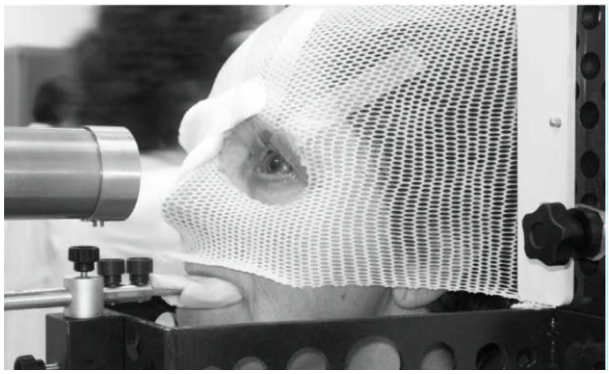

Figure 6: Thermoplastic mask and bite block.

For eye proton therapy 60 Gy (RBE) are delivered to uveal melanoma in 4 fractions on 4 consecutive days; a constant RBE of 1.1 is applied over the SOBP.

Before each treatment fraction the eye position is verified and compared to the planned position. A video camera is directed to the eye to verify its position outside the treatment room during the irradiation. The treatment time ranges are between 15 and 60 sec.

5 CLINICAL ACTIVITY AND RESULTS

Patients were affected by the following neoplastic diseases: uveal melanoma 192 patients, conjunctival melanoma 7 patients, conjunctival rhabdomyosarcoma 1 patients, conjunctival lymphoma 3 patients, conjunctival papilloma 1 patient, eyelid carcinoma 10 patients, lachrymal gland carcinoma 1 patient, choroideal metastases 3 patients. The majority of them came from the south of Italy, but at least one third came from north Italy, four patients came from outside Italy.

For many years the treatment of uveal melanoma has been the eye enucleation, but several studies have demonstrated no advantage of such an approach regarding tumor control and metastatic spread compared to eye-sparing treatments, like PBRT. Proton beam radiation therapy (PBRT) has been applied for the treatment of uveal melanoma since the last 70s, and now is considered by most the treatment of choice for the high degree of tumor control and organ preservation obtained and the acceptable rates of side effects [11-14].

The follow-up ranges from 6 months to 9 years for all patients with uveal melanoma treated (192 patients). According to the international classification of malignant tumors TNM (tumor, node, metastases), the TNM staging of the patients at the recruitment was as follow: T1 for 11 patients, T2 for 58 patients, T3 for 123 patients. About 70 % of the lesions were posteriorly located, in close vicinity to the optic disc or to the macula.

The tumor thickness is reduced in 73% of patients, while 21% have a stable tumor elevation with increased reflectivity. Eigth patients were early enucleated for radiation-induced toxicity, but only for four of them a tumor regrowth was detected. A local tumor control was obtained in 95% of patients treated.

A secondary end point of ocular tumor protontherapy is the maintenance of the eye, while the surgical alternative is, in most cases, the eye enucleation [12]. In our series, almost 90 % of patients have retained their eye. The remain patients

have been enucleated at various follow-up time, the majority of them for radiation-induced toxicity, mainly neovascular glaucoma, due to the big tumor volume and the consequent large retinal surface irradiated.

The visual function was evaluated by the referring ophthalmologist during the follow-up; at the recruitment, only 65% of patients had an acceptable visual acuity, but, after treatment the percentage falls to 43 %, due to the location of the tumor, which in most cases was close to the optic disc or to the macula. For that reason, the treatment isodose must include those structures, causing the loss of the visual acuity [15, 16].

The development of radiation-induced damages is well known in ocular protontherapy. In our experience, an exudative retinal detachment of various degree has been detected in 35 % of patients, radiation retinopathy of various degree was seen in 22% of patients. A radiation-induced cataract or an increasing of a pre-existing cataract was detected in 35% of patients, most of whom underwent surgery. A neovascular glaucoma developed in 15 patients and 8 of them were enucleated for that reason.

During the follow-up a metastatic disease was recognised in 35 patients after a median time of 23 months; almost all patient have been treated with chemotherapy with a median survival of 18 months. The cause-specific survival for uveal melanoma patients is 92 %, since 165/192 patients are still alive, taking in account that seven patients died from intercurrent disease. The other ocular tumors treated with PBRT are all alive and under local control, with the exception of squamous cell papilloma that relapse several times after 12 months and enucleation was required [17].

6 RECENT DEVELOPMENTS AND FUTURE PERSPECTIVES

Physicists, medical physicists and medical doctors are continuing the improvement of the quality of the proton treatments at INFN-LNS either from a dosimetric point of view as well as regarding the optimization of the transport beam line control. Regarding the latter the new MOPI [18] microstrip detectors has been installed as device for the control of the beam symmetry during the patient treatment.

Characterization of the CVD diamond detectors is also in progress, in order to improve the dosimetric procedures, especially for small field proton dosimetry.

For the next year, the CATANA facility will continue its activity and 4/5 treatment sessions are programmed.

7 CONCLUSIONS

Clinical results show an high percentage of local tumor control with a limited acute and subacute toxicity and visual outcome according to the previsions. The results are in agreement with those reported in the literature, regarding the treatment of uveal melanoma by means of hadrons.

Even if CATANA should not be the clinical answer for all the Italian patients affected by this kind of disease, it represents the first successfully Italian example of the collaboration between Nuclear and Medical Physicists together with Medical Doctors in fighting tumors with hadrons. CATANA is the first milestone in Italy through the extensive use of hadrontherapy in cancer treatment.

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