A 62-MeV Proton Beam for the Treatment of Ocular Melanoma at Laboratori Nazionali del Sud-INFN

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Abstract—At the Istituto Nazionale di Fisica Nucleare-Laboratori Nazionali del Sud (INFN-LNS) in Catania, Italy, the first Italian protontherapy facility, named Centro di AdroTerapia e Applicazioni Nucleari Avanzate (CATANA) has been built in collaboration with the University of Catania. It is based on the use of the 62–MeV proton beam delivered by the $K = 800$ Superconducting Cyclotron installed and working at INFN-LNS since 1995. The facility is mainly devoted to the treatment of ocular diseases like uveal melanoma. A beam treatment line in air has been assembled together with a dedicated positioning patient system. The facility has been in operation since the beginning of 2002 and 66 patients have been successfully treated up to now. The main features of CATANA together with the clinical and dosimetric features will be extensively described; particularly, the proton beam line, that has been entirely built at LNS, with all its elements, the experimental transversal and depth dose distributions of the 62-MeV proton beam obtained for a final collimator of 25-mm diameter and the experimental depth dose distributions of a modulated proton beam obtained for the same final collimator. Finally, the clinical results over 1 yr of treatments, describing the features of the treated diseases will be reported.

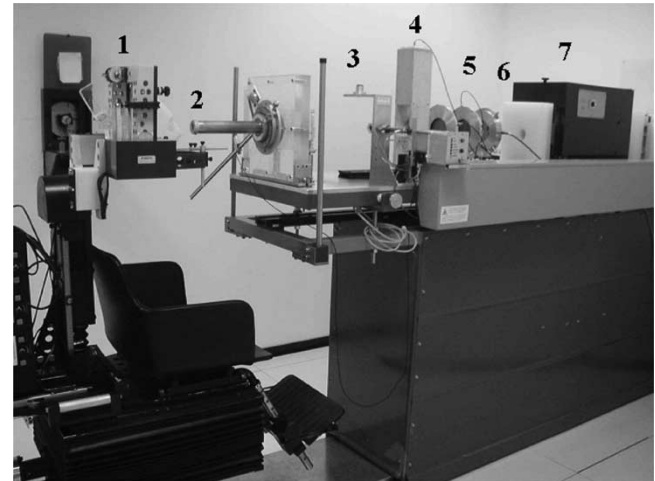*Index Terms*—Ocular melanoma, proton beam, protontherapy.

Fig. 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.

I. INTRODUCTION

THE use of proton beams offers the advantage to improve tumor control, especially for the treatment of small tumors, where it is necessary to obtain a localized dose distribution while sparing the surrounding normal tissues [1]–[3]. The hadrons allow conformation of the dose distribution better than photons or electrons, so the use of these charged particles has developed rapidly in recent years. There are nearly 20 hadrontherapy facilities worldwide, among them about 10 in Europe. In Italy, the first and actually unique protontherapy facility, the Centro di AdroTerapia e Applicazioni Nucleari Avanzate (CATANA) was built in Catania, at the Istituto Nazionale di Fisica Nucleare-Laboratori Nazionali del Sud (INFN-LNS). Here a 62-MeV proton beam, produced by a Superconducting Cyclotron (SC), is used for the treatment of shallow tumors like those of the ocular region. The CATANA project was developed to treat ocular pathologies like uveal melanoma, which is the most frequent eye tumor in adults. Moreover, we treat other
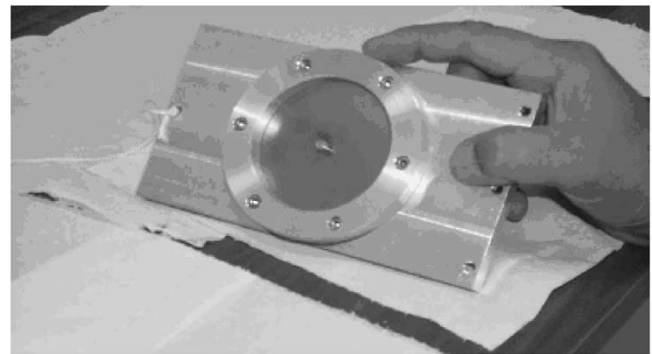
Fig. 2. The second tantalum scattering foil with the central brass stopper.

less frequent lesions like choroidal hemangioma, conjunctiva melanoma, eyelid tumors, and embryonal sarcoma.

II. THE PROTON BEAM LINE

The CATANA proton beam line has been entirely built at INFN-LNS and its global view is shown in Fig. 1. The proton beam exits in air through a 50-μm Kapton window placed at about 3 m from isocenter. Just before the exit window, under vacuum, is placed the first scattering foil made from 15-μm tantalum. The first element of the beam in air is a second tantalum foil 25-μm thick provided with a central brass stopper of 4 mm in diameter (Fig. 2). The double foils scattering system is optimized to obtain a good homogeneity in terms of lateral off-axis
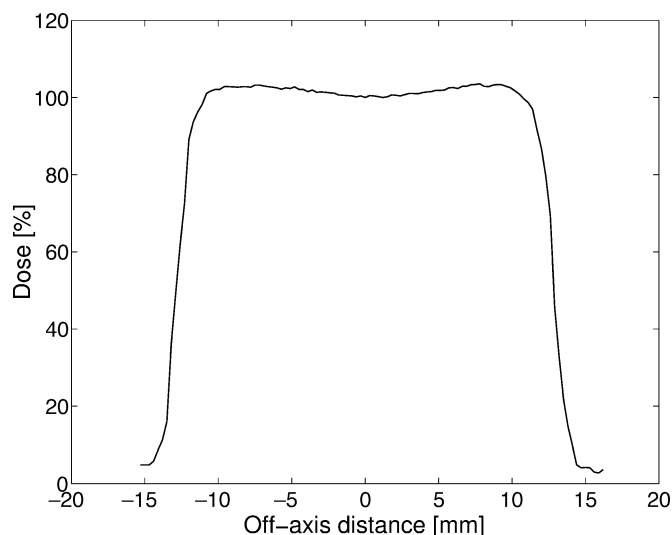
Fig. 3. Lateral dose distribution for a 62-MeV proton beam.

TABLE I
CLINICAL PERFORMANCE SPECIFICATIONS OF THE THERAPEUTIC PROTON
BEAM AT CATANA FACILITY

Field Ratio $H = \frac{Width_{90\%}}{Width_{50\%}}$	Penumbra $P_{80\% \div 20\%}$ (mm)	Symmetry (%)	Homogeneity $Width_{95\%}$ (mm)
0.92	0.85	2.40	22
H>0.90	P<1.5 mm	S<3%	$Width_{95\%}$>20 mm

dose distribution, minimizing the energy loss. Fig. 3 shows the experimental lateral dose distribution for the 62-MeV proton beam measured with a final 25-mm diameter circular brass collimator (reference collimator). Beam data are acquired with a silicon diode in a water phantom, at the treatment depth of 12 mm, corresponding to the middle of the Spread Out Bragg Peak (SOBP). In Table I, the main characteristics of the lateral distribution, together with the clinical tolerances adopted in our facility, are reported.

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 emission light of a third laser is spread out to obtain the simulation field. A key element of the treatment line is represented by two transmission monitor ionization chambers (Fig. 4) and a four-sector ionization chamber. The aim of the chambers is, respectively, to provide the on-line control of the dose delivered to the patient and of the beam symmetry. The last element before isocenter is the patient collimator located at 8.3 cm upstream of the isocenter. Finally, two Philips X-ray tubes, with axes defined by crosshairs, are placed perpendicular and coaxial to beam line, to provide lateral and axial view of the tumor, during simulation of treatment [4], [5].

III. DOSIMETRIC CHARACTERIZATION OF THE PROTON BEAM

The CATANA collaboration is planning to devote particular care to the development of dosimetric techniques and two-dimensional (2-D) and 3-D dose distribution reconstruction.
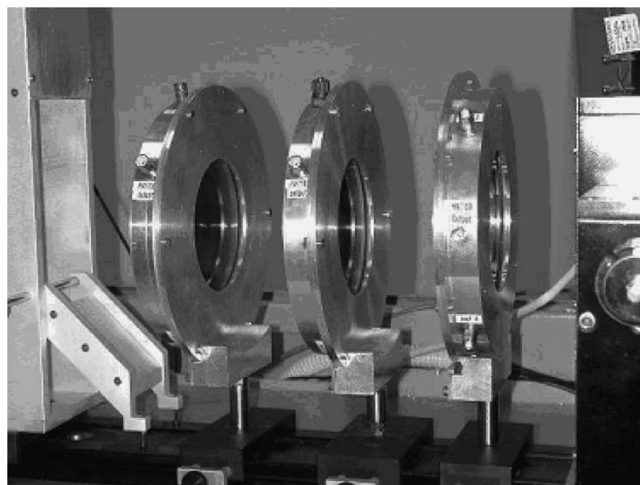

Fig. 4. A view of the two monitor chambers and the four sectors chamber.

A plane-parallel *advanced PTW 34045 Markus Ionization Chamber* has been adopted for reference dosimetry (beam calibration). The Markus chamber has an electrode spacing of 1 mm, a sensitive air-volume of 0.02 cm^3, and a collector electrode diameter of 5.4 mm. The dose measurements are performed in a water phantom, according to International Atomic Energy Agency Technical Report Series (IAEA TRS) 398 Code of practice [6]. The absorbed dose to water per monitor unit (cGy/M.U.) is measured at isocenter, for each combination of modulator and range shifter used for treatment; the measurement is carried out at the depth corresponding to the middle of SOBP, for the reference collimator [6]. The clinical proton beam calibration is performed just before each treatment fraction; the variation of dose/(monitor unit) on the four consecutive days of treatment results within $\pm 3\%$. The proton beam calibration is strongly dependent on modulator and range shifter adopted in the clinical practice; for the same modulator, the decrease in dose/(monitor unit), when the range shifter thickness increases from 6 to 12 mm, is about 35%. To investigate whether small irregular fields used in the clinical practice will affect the radiation output, an *output factor* is determined, by using the Scanditronix Hi-p Si diode detector [7]. This diode has a 0.6 mm detector diameter and is designed for field measurements in small proton beams in water. The value of the *output factor* is determined [6] as the ratio of diode signals for the patient and reference collimators with the same M.U. setting. Considering the experience so far gained, the dose/(monitor unit) decreases by less than 3% for areas between 490 mm^2 (reference collimator) and 100 mm^2. The latter represents the lower limit of collimator areas associated to the clinical practice. For relative dosimetry we use radiochromic films, radiographic films [Kodak X Verification (XV) and Kodak Extended Dose Range2 (EDR2)], ThermoLuminescent Detectors (TLD), natural and Chemical Vapor Deposition (CVD) diamond and silicon detectors [8], [9]. Depth dose curves and transverse dose distributions, either for the full energy or the modulated proton beams, are acquired with a water-tank system provided with three fully computer-controlled stepping motors. A software, entirely developed at INFN-LNS, controls this system and provides the
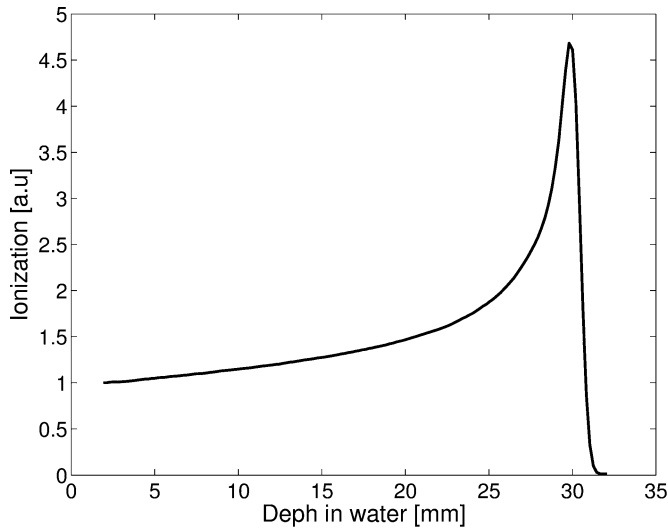
Fig. 5.   Bragg peak of 62-MeV proton beam acquired in a water-tank with the Markus ionization chamber at CATANA facility.

Fig. 7.   Dose-response curves [Net Optical Density (N.O.D.) versus Dose versus R_{res}] of EDR2 film.

A. Use of Kodak EDR2 Films in CATANA Relative Dosimetry

The advantages of radiographic films to determine relative dose distributions include a higher spatial resolution, a short beam-time, and the ability to provide dose distributions in a single exposure. A new type of radiographic film, Kodak Readypack EDR2 film [12], has been tested for measurements of lateral beam profiles at the horizontal eye beam line of the CATANA protontherapy facility. Film calibrations were carried out with the reference collimator; the films were placed in a solid water phantom perpendicular to the proton beam axis and irradiated to a dose up to 12 Gy. For the full energy proton beam, the calibration curve was measured at 1 mm depth on the entrance plateau of the Bragg peak, corresponding to a 30-mm *Residual Range* (R_{RES}) [6]. In addition, two calibrations were carried out in modulated clinical proton beams, at the depth of the middle of the SOBP, for $R_{\mathrm{RES}} = 7.2$ mm $(E_{\mathrm{p,eff}} \approx 24$ MeV, superficial iris lesion) and $R_{\mathrm{RES}} = 15$ mm $(E_{\mathrm{p,eff}} \approx 40$ MeV, extended lesion) [13]. Despite a significant decrease of film sensitivity with decreasing the R_{RES} from 30 up to 7 mm, the linear region of the calibration curves covers the same dose range $(0.5 \div 5 Gy)$ for the three tested energies (Fig. 7). This energy dependence may be related to different spatial energy distribution pattern. As shown in Fig. 7, at a constant depth the ratio of doses is the same as the ratio of optical densities within the linearity range; therefore, EDR2 films can be safely and conveniently used to measure the distributions perpendicular to proton beam direction [14].

The linearity range is much higher than in typically used radiotherapy Kodak XV films, so this represents a useful tool for dose profile measurements. Lateral off-axis profiles were obtained at 1 mm depth in the unmodulated beam for the reference collimator; moreover, transverse distributions were measured in modulated beams at different depths, corresponding to the middle of 8, 17, 25 mm SOBPs for the shaped patients collimators; all the films were irradiated to a proton dose of 5 Gy. Lateral profiles measured with EDR2 films are well consistent with the corresponding obtained with High Sensitivity (HS) [16] radiochromic films (Fig. 8), considered at the moment the
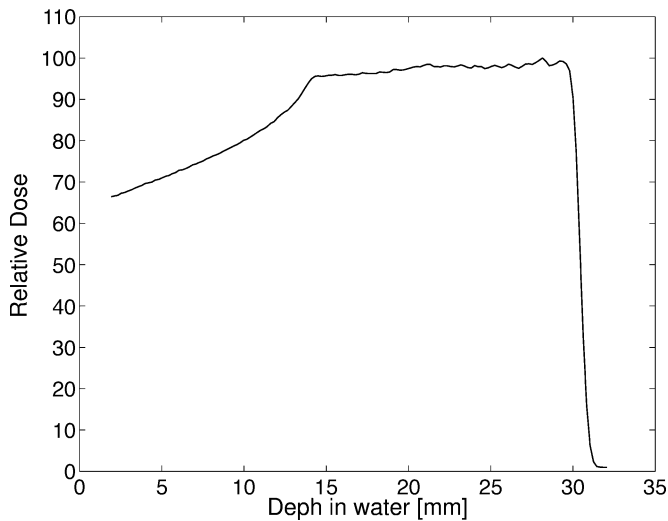

Fig. 6.   SOBP obtained with a modulator wheel.

acquisition and dosimetric analysis data. Fig. 5 shows the depth dose distribution obtained with the Markus chamber for the unmodulated full energy (62–MeV) beam. The maximum error on the relative dose is $\pm 0.5\%$. The Full Width at Half Maximum of the Bragg Peak is 2.76 mm. The 90%-10% and 80%-20% distal fall-offs are 0.8 and 0.6 mm, respectively, and the peak to entrance ratio is 4.72. We have developed, in collaboration with the Clatterbridge Center for Oncology (UK), wheel modulators to obtain therapeutic SOBPs. Proton beam energies lower than 62 MeV are obtained inserting PolyMethylMethAcrylate (PMMA) range shifters of different thickness along the beam path. Finally, Fig. 6 shows the SOBP obtained with the first prototype of the modulator wheel. Actually a set of modulator wheels (10, 12, 15, 20, 25 mm SOBP) has been tested and currently used in clinical practice. Experimental depth dose profiles reported in Figs. 5 and 6, have been compared with a Monte Carlo simulation application, using the Geant4 toolkit, developed by us. Results of this comparison are extensively reported in [10] and [11].
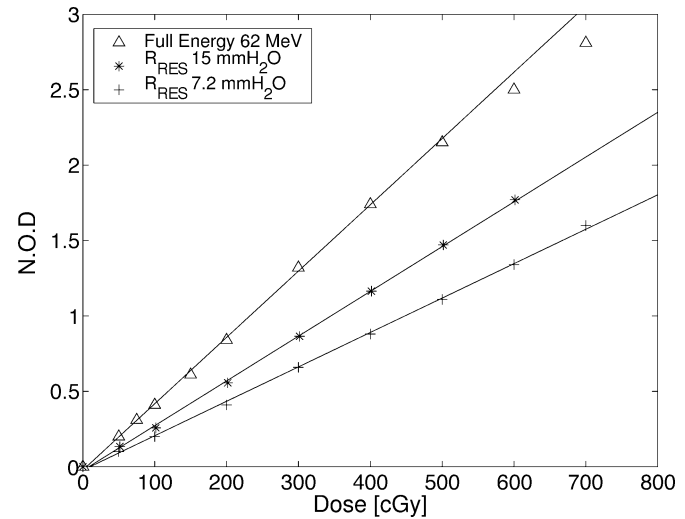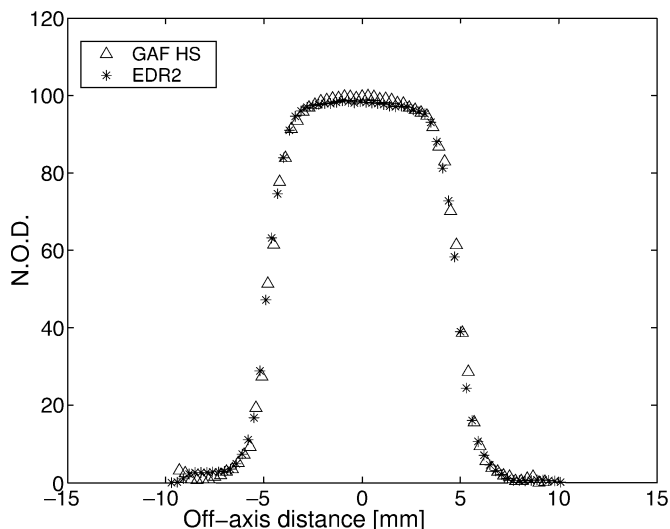
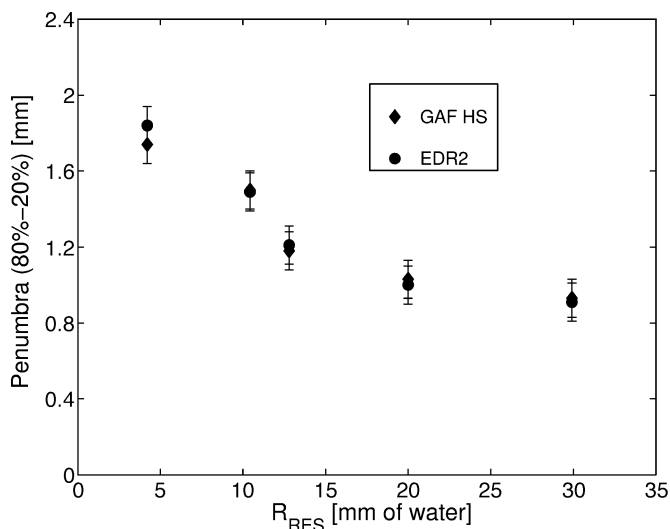Fig. 8. Lateral X profile (EDR2 versus HS GAF) film.

Fig. 9. Lateral penumbra versus $R_{\rm res}$.

detector of choice for measurement of lateral distributions, in proton beams [15].

Beam profiles from both films are in agreement in the dosimetric characterization of the proton beams, in terms of lateral penumbra, $\text{width}_{95\%}$, $\text{width}_{50\%}$, and symmetry. As results, we could use both radiochromic and radiographic films to check the proton beam; in practice, however, we prefer to use a EDR2 film thanks to its less cost. So, before each treatment period, we use a EDR2 film for a quick check of the lateral profiles of the full energy beam for the reference collimator. EDR2 films are also used to test every clinical setup, especially to measure lateral penumbra, depending on modulator and range shifter adopted (Fig. 9), $\text{width}_{95\%}$, $\text{width}_{50\%}$, and symmetry on principal and diagonal axes. In this way, we may get a permanent hardcopy of the clinical shaped proton beam. Work is in progress to verify the reliability of the 2-D dose distribution provided by EDR2 film.
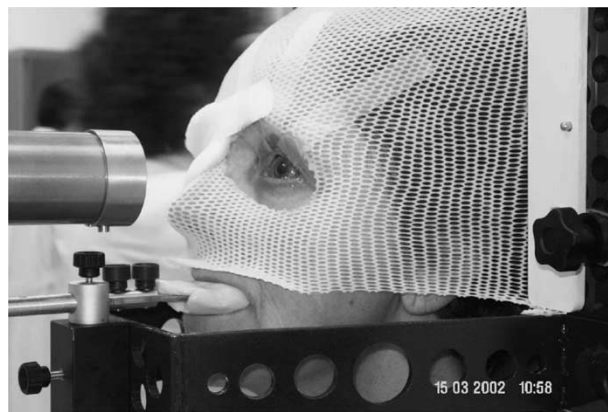

Fig. 10. Thermoplastic mask and bite block.

IV. TREATMENT PROCEDURES

As explained before, protons allow a high dose deposition in a small deep-seated space, with precise irradiation of the target. The radiotherapist therefore needs to know the exact position of the tumor. To do that, tantalum clips are placed around the lesion on the outer sclera by the opthalmologist, generally very close to the tumor. The surgeon also defines the tumor position and measurements, as transverse and longitudinal base diameters, elevation or height, distance to the optic disk, to the macula, to the limbus. He also makes the radiotherapist know about the eye measurements (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). The final result is the drawing 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. He also informs the radiotherapist about the visual acuity of the effected as well as the fellow eye, the presence of exudative retinal detachment, ocular pressure and all other information he considers to be significant. A total retinal detachment or the presence of a glaucoma are contraindications to a conservative approach. Together with the diagnosis, for all patients a systemic staging is provided through a total body spiral Computed Tomography (CT) scan to exclude metastatic disease, which is, obviously, another contraindication. After this first phase, the patient arrives at the INFN-LNS, where the workup by the physicist and radiotherapist begins. First of all, a fixation device is made by means of a customized thermoplastic mask and bite block, with the patient in a seated position (Fig. 10).

The patient is invited to gaze at a light point and two orthogonal X-ray pictures (axial and lateral) are taken. This step is repeated 3–6 times with the patient gazing at different points, depending on the tumor position in order to make the physician sure about the position of the clips. A measurement of the eyelid thickness and slope is also needed for the planning procedures. All the informations are then elaborated by means of 3-D therapy planning program EYEPLAN, developed at the Massachusetts General Hospital for eye tumor therapy using proton beams [17]. Actually, the improved version of EYEPLAN, by
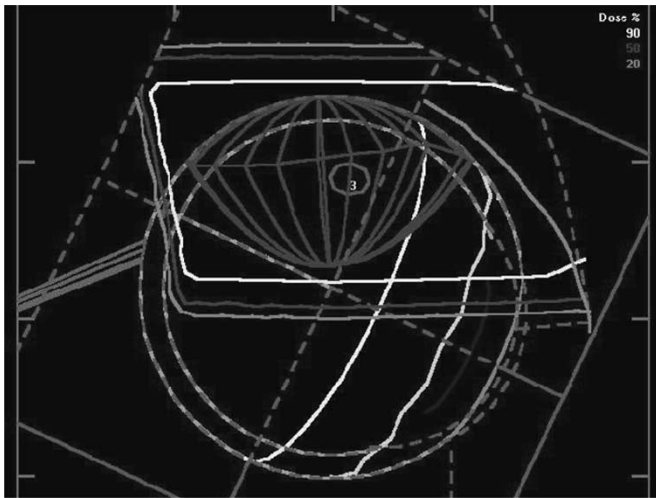
Fig. 11. Typical output from EYEPLAN.

Fig. 12. Patient's place of origin.

Sheen [18], is used in our facility. This software schematically displays a model of the patient's eye, including the lens, optic nerve, and fovea, where the tumor is finally drawn by means of the specified measurements and position reference. In Fig. 11 is shown a typical output from EYEPLAN.

Isodose levels for 90%, 50%, and 20% of the prescribed dose are reported. Proton beam irradiates eye tumor, completely sparing optic nerve and optic disc. A second simulation is performed on the first day of the treatment week, with the eye in the final position to verify and to accept the treatment. If the eyelids cannot be retracted completely outside of the irradiation field, they have to be calculated in the treatment plan. For uveal melanoma a total dose of 60 Gray Equivalent (GyE) is delivered in four fractions on four consecutive days, using a constant Relative Biological Effectiveness (RBE) of 1.1 over the modulated Bragg peak. 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 is between $30 \div 60$ s.

V. CLINICAL RESULTS

A. Patient Data

Since March 2002, 66 patients with different ocular tumors have been treated at the CATANA facility. All patients had localized disease, with no systemic metastasis, and had specific indications for a conservative approach by means of proton beams, depending on their tumor size or location [19]. Most which of them suffered from uveal melanoma (61 pts, 92%), is the most common tumor of the ocular region in the adult. We have also treated other pathologies with proton beams, like conjunctival melanoma (2 patients), conjunctival rhabdomyosarcoma (1), eyelid carcinoma (1), and conjuntival Mucosa-Associated Lymphoid Tissue-Non Hodgkin Lymphoma (MALT-NHL) (1). Twenty-six patients came from Sicily, 40 from the other Italian regions (Fig. 12).

Among the 66 patients, 34 were women (51%) and 32 men (49%). Patient age ranged from 14–81 yr (mean 55.6). As show in Table II, among the uveal melanomas, 46 patients were stage
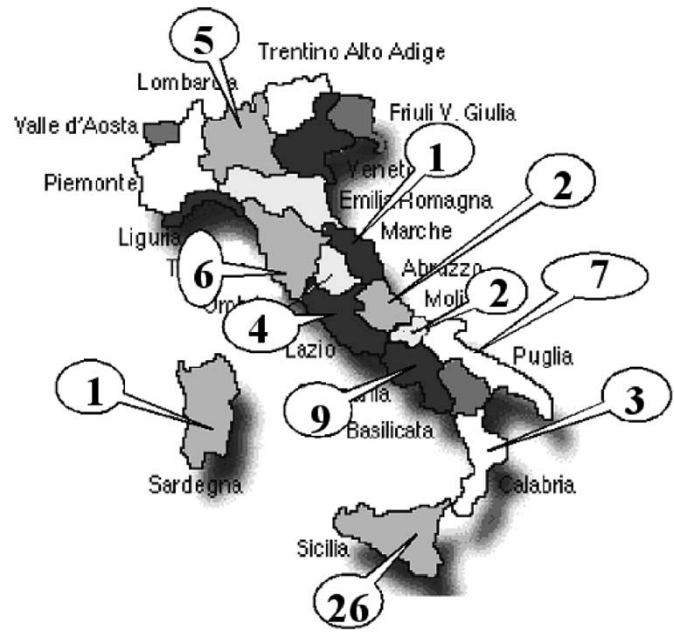
TABLE II
TUMOR CLASSIFICATION FOR UVEAL MELANOMA

Diameter <10 mm and/or thickness ≤ (3 mm)	Small lesions (S) or T_1 (TNM)	2 patients (4%)
Diameter 10–15 mm and/or thickness 4–5 mm	Medium-size lesions (M) or T_2	13 patients (21%)
Diameter 16–20 mm and/or thickness 6–10 mm	Large lesions (L) or T_3	46 patients (75%)

T3 (75%), 13 stage T2 (21%), and 2 stage T1 (4%), according to the new Tumor Node Metastasis (TNM) classification 2002 (VI edition) [20]. The tumor infiltrated the choroid only in 35 patients (57%), choroid plus ciliar body in 23 patients (38%), all uveal parts in 2 cases (3%), and iris only in 1 case.

B. Results

During the follow-up, the first data regarding local tumor control are available only after 6–8 mo from the end of the treatment. Actually, we have the preliminary results of the follow-up for 52 patients at 6–8 mo, and for 32 patients at 1 yr. The local control is defined as a tumor shrinkage or cessation of growth at B-Mode ultrasonography, or as an increase of ultrasound reflectivity at A-Mode ultrasonography (a surrogate for tumor control). A size reduction, especially regarding the thickness of the tumor, was seen in 39 patients (75%), while 13 patients maintain a stable dimensional lesion (25%). An increased A-Mode ultrasound reflectivity was detected in almost all patients. These data clearly show a tumor control, particularly for those patients with 1 yr follow-up. No major side effects requiring eye enucleation have been detected: an exsudative retinal detachment at the time of the diagnosis was seen in 40% of the patients and it remains stable in about half of them. In 25 patients, a new cataract formation related to the treatment, generally at the periphery of the lens, was diagnosed. About 40% of the patients still maintain a

useful visual acuity. This is obviously not always possible, especially when the tumor infiltrated directly or is located close to the optic disc or the macula.

VI. CONCLUSION

The preliminary results show an high percentage of local tumor control, despite the limited follow-up period (1 yr for 32 patients, 6–8 mo for 52 patients), 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 [21], [22]. 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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