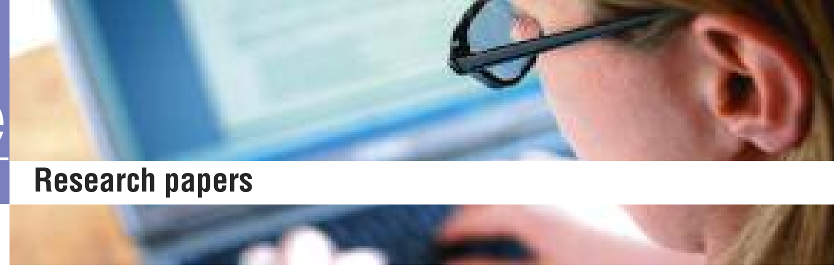

Perspectives of the use of a compact linear accelerator for protontherapy

The use of hadrons in oncological radiotherapy is due to the excellent ballistic properties of the heavy particles that loose their energy at the end of the path in tissue ("Bragg peak") with a modest lateral diffusion, preserving the surrounding healthy organs during tumor irradiation. At present, all the hadrontherapy centers in operation or under construction are based on circular accelerators: cyclotrons and synchrotrons. However, due to the increase of precision of X-rays radiotherapy and to the high costs of the HRT (Hadron Radio Therapy) facilities, the HRT community well recognizes that hadron sources need further development. On the basis of its expertise in design and realization of linear particle (electron/protons) accelerators, ENEA has studied an alternative scheme based on a compact high frequency full-linear proton accelerator that is expected to offer an optimal solution to the present challenge of protontherapy. The paper describes two applications of this concept: a multi-room protontherapy center to be sited in Rome as provided for by the ENEA TOP-IMPLART Project – launched in collaboration with the Italian National Institute of Health (ISS) and Regina Elena National Cancer Institute-IFO-Rome – and a cheaper single-room facility based on a compact self-shielded accelerator. The proton beam will also be used for radiobiology experiments devoted to the developments of "in vivo" and "in vitro" models for studying the cellular mechanisms involved in the carcinogenesis process and characterizing the beam in terms of the Relative Biological Effectiveness (RBE), cell survival, time to repair, cell proliferative activity and bone resorption after treatment. The first assembly and tests of the accelerator will be done at the Research Center in ENEA-Frascati, in a specific area dedicated to the accelerator's development

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Prospettive dell'uso di un acceleratore lineare compatto per protonterapia

L'uso di adroni in terapia oncologica è dovuto alle eccellenti proprietà balistiche delle particelle pesanti che perdono la loro energia al termine del percorso nel tessuto ("picco di Bragg") con una modesta diffusione laterale consentendo di irradiare il tumore preservando gli organi sani circostanti. Attualmente tutti i centri in operazione o in costruzione sono basati su acceleratori circolari: ciclotroni e sincrotroni. Tuttavia, il continuo miglioramento di precisione della radioterapia convenzionale e i costi elevati degli impianti di adroterapia tendono a ridurre considerevolmente i vantaggi di quest'ultima a meno di ulteriori sviluppi delle sorgenti di adroni. Sulla base della esperienza nella progettazione e realizzazione di acceleratori lineari di particelle (elettroni/protoni) l'ENEA ha studiato uno schema alternativo basato su un acceleratore di protoni compatto ad alta frequenza completamente lineare, che ci si attende offra una soluzione ottimale alle presenti sfide nel campo della protonterapia. L'articolo ne descrive due applicazioni: un centro di protonterapia con più sale di trattamento da installarsi a Roma come previsto dal Progetto TOP-IMPLART lanciato da ENEA in collaborazione con l'Istituto superiore di Sanità (ISS) e l'Istituto Regina Elena-IFO e una "facility" più economica a singola sala di trattamento basata su un acceleratore compatto "auto-schermato". Il fascio di protoni sarà anche utilizzato per esperimenti di radiobiologia dedicati allo sviluppo di modelli "in vivo" e "in vitro" per lo studio dei meccanismi cellulari coinvolti nel processo di carcinogenesi e la caratterizzazione del fascio in termini di efficacia radiobiologica. Il primo assemblaggio e i test preliminari dell'acceleratore verranno effettuati presso il centro ENEA di Frascati in un'area specifica dedicata

The number of hadron cancer therapy facilities is continuously growing all around the world due to many advantages with respect to the already existing X-ray treatments (using electron accelerators) [1]. The advantages are in much more localized effects with much smaller influence on surrounding healthy cells. Nevertheless, due to the increase in precision of X-rays RT, and to the high costs of HRT (Hadron Radio Therapy) facilities, the HRT community well recognizes that hadron sources need further development to better match their use in clinical environments. It is agreed that progress in HRT must pursue the following developments: 1) adaptive cancer therapy, 2) treatment with higher dose localization, 3) more compact and/or advanced machines.

On the basis of the expertise in design and realization of linear particle (electron/protons) accelerators, and a long lasting cooperation on radiotherapy established with the Italian National Institute of Health (ISS) and Regina Elena National Cancer Institute-IFO-Rome, ENEA has proposed the development and realization of a compact, modular, cost-effective, proton therapy system, built around a specifically designed innovative linear proton accelerator. The main peculiarities of a linear accelerator with respect to the conventional protontherapy (PT) machines, usually based on circular accelerators, are modularity, the use of a technology similar to the conventional radiotherapy electron machines, a very low emittance beam, the possibility to perform active, fast energy variation and pulse-to-pulse current modulation. This novel approach has lead to the design of a "full-linear" accelerator for a protontherapy facility to be realized at IFO in Rome in the framework of the TOP-IMPLART Project [2], jointly conducted by the three institutes, and to the concept of a low-cost single treatment room facility.

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Protontherapy by means of particle accelerators

Background of clinical applications

Radiation therapy (RT) is a therapeutic strategy that consists in dispensing precise doses (released energy per mass unit) of radiation for the treatment of tumors. The majority of modern RT equipments is based on the use of accelerated particles, electrons for X-rays or electron therapy and protons or light ions (carbon or helium) for HRT. PT (that is HRT with protons) is used since several years in most industrialized countries for some diseases, such as uveal melanoma, and tumors of the skull base and spine (chordoma, sarcomas and meningiomas), but has acknowledged benefits in many other cases, such as the treatment of prostate, lung, liver, esophagus and head and neck-cephalic, or in all cases where the disease is well located and adjacent to critical normal organs (i.e., radiosensitive) to be saved and in pediatric treatment. The rationale of the use of hadron beams [3] lies in the ballistic properties

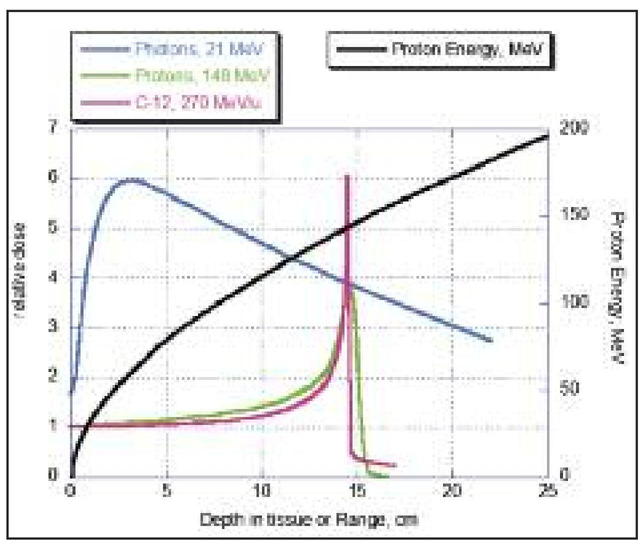

FIGURE 1 (Left) Dose distribution vs depth in tissue for different types of ionizing radiation, (Right) Proton Energy vs proton Range for proton in tissue

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and in the spatial selectivity of these particles, due to the presence of the Bragg peak (the area where the dose delivered assumes the maximum value) (Figure 1 left) at the end of the path of the particles, and also to their low lateral diffusion. These characteristics allow a highly conformed dose distribution to target volumes, that is a lower dose both to healthy tissue surrounding the target and to non-target tissues in general, reducing long-term induced late effects and the probability of radiation-induced secondary tumors. Hadrons have therefore attracted interest for cancer treatment since the half of last century, but their use was very limited because of the higher energy required to reach the desired depths in tissue (max 230 MeV for protons (Figure 1 right), 400 MeV/u for carbon ions), with respect to X-rays or electrons (max 25 MeV).

Conventional X-rays RT is rather widespread. Nonetheless, HRT proves superior in many cases, so a big effort has been dedicated to realize HRT facilities, despite their higher costs and larger dimensions with respect to electron based machines.

Most modern RT treatments are based on hypo-fractionated and dose escalation protocols. In fact, the current radiation techniques with photons are reaching out more to the conformation of the dose using the technique of intensity modulated radio therapy (IMRT), which can be obtained with much simpler techniques using protons. Indeed, Intensity Modulation Proton Therapy (IMPT) has been introduced, in which the intensity and energy of each proton beam are varied on a spot-by-spot basis and beams from many multiple directions are able to deliver an arbitrarily complex 3D dose distribution. The optimization of beam intensity is driven by a specific software (treatment planning systems i.e., TPS), which is machine and modulation delivery dependent, generating the optimal fluence to be delivered and checked by using on-line monitoring systems. Similarly to conventional RT, most PT facilities require the beam to be directed from several different directions onto the patient. A large mechanical structure called gantry rotates 360° around the patient bed axis, and it is screened to his view. Upon it, a huge magnetic transport line directs the beam according to the treatment plan. Usually this device, carrying several tons of magnets, is 10m in diameter for protons and 15m - 20m for ions. The system needs to be integrated with a dedicated couch, patient immobilization devices and a positioning verification system, including a respiratory gating system to correctly manage organs and target motions [4]. Finally, a bunker is required to fulfill the radioprotection requirements, together with air conditioning and security systems.

Hadron sources for hadrontherapy

Thanks to its proven effectiveness, PT is worldwide utilized in clinical practice and on more than 75,000 patients. Albeit initially in the form of beams from large accelerators developed for nuclear physics experiments, PT has been used with dedicated facilities for 15 years. Ion (carbon) therapy is by far less diffused and still considered a research therapy, but successfully tested on more than 7,000 patients. Up to 2010, there were 30 operating PT facilities, while carbon-ion RT was provided at 5 facilities. In the USA many PT centers are operative, while no ion therapy facility is running or considered to be used for the very next years. Worldwide, more than 20 hospital-based facilities are under construction or planned within the next 10 years.

The HRT facilities in service in the world are based on circular accelerators (synchrotrons and cyclotrons). Generally cyclotrons are preferred for protons, while synchrotrons for combined ion/proton facilities. In Europe, besides nine operating PT centers that mainly use cyclotrons (with normal or superconducting technology), some large proton/ion therapy centers are being built. The GSI (Gesellschaft für Schwerionenforschung) study was used for the construction at Heidelberg (Germany) of the HIT facility, based on a synchrotron provided with two horizontal fixed ports and one rotating gantry for both proton and carbon-ion RT. In Italy, a first experimental proton therapeutic beam of 60 MeV has been realized at the INFN South Laboratory in Catania (CATANIA facility), while a clinical proton/carbon-ion RT facility has been constructed by CNAO in Pavia and first proton treatments have been started in 2011. Other European projects are on-going in Austria (Med-Austron) and France (ETOILE).

HTR facilities are large and expensive, and mainly ion therapy centers. The building typically covers about 3000 m^2. Even with multi-room approach (3–5 treatment rooms), a PT (cheaper than ion therapy) is today about 2.5 times more expensive than the best X-ray IMRT [5]. The overall cost of a therapy centre including the proton accelerator and one or more gantries can be as high as 100-180 M€, depending on the equipments. The very high investment costs required by HRT facilities can hardly survive only on the treatment income and for this reason several hospitals cannot even consider the possibility of installing PT, although equipped with a very advanced RT service. The HRT community often stresses in thematic workshops and conferences that, in absence of serious development, the cost of an ion therapy, but also PT costs will soon become a too serious concern, and these treatments, despite the demonstrated advantages, will have to be seriously reconsidered. Therefore some accelerator companies or research laboratories are pushed to design novel machines, miniaturized and less expensive but, at the same, time with outstanding performances.

The ENEA proposal: a "full linac" approach

Application of the Proton Linear Accelerator (PLA) technology in PT

Linear accelerators' development started since the end of the 2nd world war and followed two different roads: electron accelerating radiofrequency structures were developed in S-band or above (3-11 GHz, transverse dimensions 10-2 cm, high accelerating gradients) for high energy (multi GeV) physics, while proton accelerating radiofrequency structures in UHF or L-band (200-800 MHz) for nuclear physics and high-current beams. Conventional RT uses electron linacs either to directly deliver electron beams for surface treatment, or to hit a target generating X-Ray emission as secondary process. The accelerator structure is composed of an electron gun and a linear sequence of radiofrequency (RF) cavities operating in S-band (3 GHz) using a klystron as RF source. The structure is very compact (transverse dimension about 10 cm and overall length about 1 m) and the construction technology is very robust and substantially cheap. In the clinical X-rays machines the structure is mounted horizontally on an isocentric gantry, and the beam is magnetically bent onto the X-rays target for RT or directly onto the patient for electron therapy.

As to proton linear accelerators, their development has been addressed to high-power beam applications like, nowadays, spallation neutron sources, where even small (10^{-9}) particle losses can give problems to accelerating structures themselves and generate radiation leaks in radioprotection system. Hence, in order to maximize beam transmission, large bore holes in the cavities are used and the structures are, therefore, built at low RF frequency: this implies larger transverse dimensions (typically 40–100 cm), and lower specific accelerating gradients than the electron linacs. Thus the large size has not allowed linear accelerators to be proposed as proton sources for clinical applications. Nevertheless all the linac technology is based on the same principles, and is by far mature for the development of compact proton linacs operating in S-band. In fact since PT is a middle energy, very low current (hundreds of MeV, few nA average) application for PLAs, the bore hole for the beam transmission can be reasonably small (a few mm). So in principle no major technical difficulty should be foreseen in the design and realization of a proton high frequency (namely S-band) RF linear accelerator dedicated to PT. The S-band choice allows several important improvements with respect to standard proton linacs: a dramatic reduction of dimensions, an increase of the accelerating gradient and therefore a reduction of costs. Moreover, the use of the S-band technology, so well known both in the RT technical area of hospitals and in the conventional RT supplier companies, further reduces realization and maintenance costs and eventually guarantees a wider distribution of the equipment.

On the basis of these considerations, ENEA designed a *protontherapy linac* specifically composed of a low frequency (UHF band, 428 MHz) injector followed by a sequence of *high frequency* (S-band, 2.998 GHz) accelerating modules. The injector is chosen to be a 7 MeV linear pre-accelerator, consisting of a low energy proton source plus a combination of two smaller linacs, an RFQ and a DTL. An injection energy lower than 5 MeV was discarded in previous studies because of the need of overcoming parametric resonances that can give an unsustainable emittance growth [6]. The operating frequency should be a sub-harmonic of 2.9979 GHz. The higher sub-harmonic frequency is used (7th at 428.27 MHz, 6th at 0.4997, 5th at 0.5996, 4th at 0.7495 GHz) the larger advantages in particle transmission are obtained, but this RF increase has a major impact on realization and costs of the system. The machine is pulse-operated and is able to deliver a beam current with 100% variation on a pulse-to-pulse basis by controlling the source current and using a special pulsing einzel lens power supply. After the injector, a short LEBT (Low Energy Beam Transport) with quadrupoles will match transverse emittance and Twiss parameters at the output of the 428.27 MHz injector to the following linear accelerating structure. The intermediate energy linac, from 7 MeV to around 35 MeV, is a 2.998 GHz linac booster based on the *SCDTL* (Side Coupled Drift Tube Linac) structure, a novel type accelerating structure invented [7] to satisfy the requirement to get a high shunt impedance (i.e., a high efficiency) in the low-velocity part of the linac. It consists of short DTL tanks (each having 4 to 6 cells of $\beta\lambda$ length, with β=relativistic factor between 0.12 and 0.266 and λ=10 cm), coupled together by side cavities extending in a space left free on the axis for the accommodation of a very short (3 cm long, 2 cm o.d., 6 mm i.d.) demountable PMQ (Permanent Magnet Quadrupole) for transverse focusing (Figure 2).

The high-energy section up to 200-230 MeV will consists of a sequence of modular units, based on accelerating *CCL* (Coupled Cavity Linac) more conventional structures using the 3 GHz technology as SCDTL. The RF power distribution system will be based on commercial standard 10 MW klystrons powered by a high peak power commercial modulator, a system widely used in conventional RT units. Beam energy is changed indeed switching off the last modules and carefully varying the drive power between 0% and 100% in the last active accelerating structure, at constant phase and frequency. From beam dynamic calculations, a final beam transmission around 30% of the injector output is

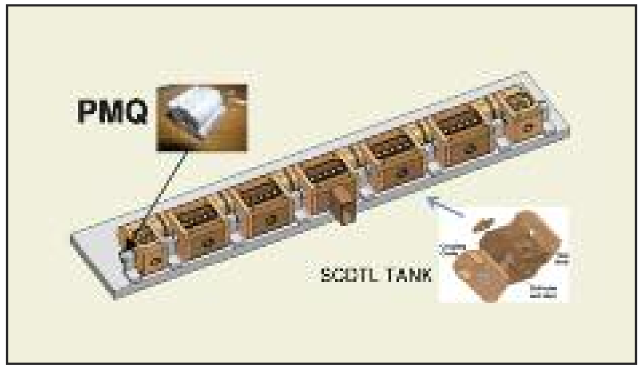


FIGURE 2 SCDTL structure schematic

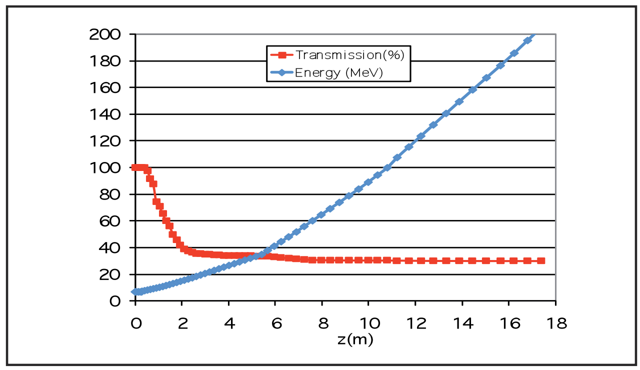


FIGURE 3 Computed beam energy and transmission

expected (Figure 3). The average energy of the lost particles does not exceed 15 MeV, that supports an easy design of an adequate local shielding system. The expected quality of the final beam is pretty good, corresponding to a small normalized emittance of 0.2 p mm-mrad, one order of magnitude lower with respect to the beams produced by circular machines, which entails smaller apertures of elements in the beam delivery lines.

Beam delivery and diagnostics

A 4D scanning scheme will be adopted, by performing the beam scan in the two transversal directions through the use of two fast laminated iron magnets, placed in a delivery line at the exit of the accelerator, and covering the depth dimension by moving the energy as described before and changing the intensity pulse by pulse. The absence of passive absorbers is advantageous in terms of reliability, maintenance and radiation protection. The possibility to vary the intensity on a pulse-to-pulse basis combined with an electronic feedback system allows to get the required dose uniformity (±2.5%) reducing the number of re-paintings. The beam delivery system does not provide for a rotating gantry, but the use of two fixed beams one horizontal and the other coming downward from an oblique direction, while the patient is placed on an innovative treatment chair/bed with six degrees of freedom. This combination gives the system the same functionalities of an expensive gantry, replacing its movement by flexible patient alignment to the beam. A dedicated mobile CT scanner will take images of the patient in the treatment position.

The beam monitoring will be based on recent Micro Pattern Gaseous Detector technology operating in ionization regime providing, for each pulse, direct measurement of beam intensity profile, centroid position and direction, in order to ensure that the prescribed dose is correctly delivered. A wide dynamic range will be achieved by novel readout electronics, based on auto-ranging sample and hold. The monitor will use data from the TPS to provide the proper feedback to the beam control system, which will adjust the therapeutic plan in real-time or shut down the beam delivery.

Innovative aspects

The application of the linac technology to PT was considered also in other proposals [8], but unlike the scheme described above, linear accelerators are combined with invasive injectors (up to 30-70 MeV, long UHF linacs or cyclotrons), adding serious complications to the accelerating system. The present design, entirely based on a sequence of linear modules, is a completely new idea introducing technology innovations on the proton source:

- full linac acceleration scheme based on high-frequency technology,
- improved beam quality performances (focusing capabilities),
- reduced beam losses so minimizing the needs for radiation shielding during the acceleration,
- minimized final device cost (both in terms of components, maintenance and operation).

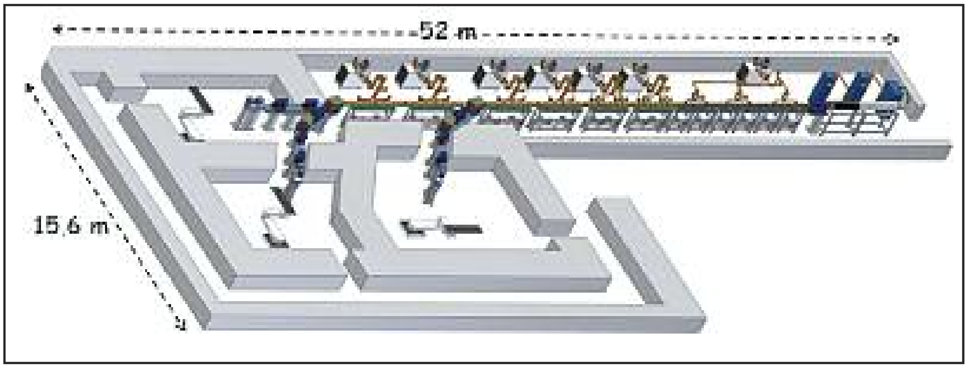
Specific improvements towards an easy use of PT are also expected thanks to the possibility of changing the pulse energy and intensity on a pulse-to-pulse basis. The speed in changing the parameters (10 ms) is much faster than synchrotrons, that work on a 100 ms scale and cyclotrons, that are even slower. This fast control opens to new, more effective techniques like IMPT, with multi-painting for a better dose match to the treatment plan and, mainly, image guided RT, in which the beam delivery is connected to an online imaging system, driving a fast respiratory gating of the irradiation.

Full-linac based protontherapy plants

The TOP-IMPLART Project

The TOP-IMPLART project [2], launched by ENEA, ISS and IFO is devoted to the realization of a proton therapy centre to be sited at IFO. The centre is based on a sequence of linear accelerators according with the scheme described above and de-

FIGURE 4 TOP-IMPLART layout



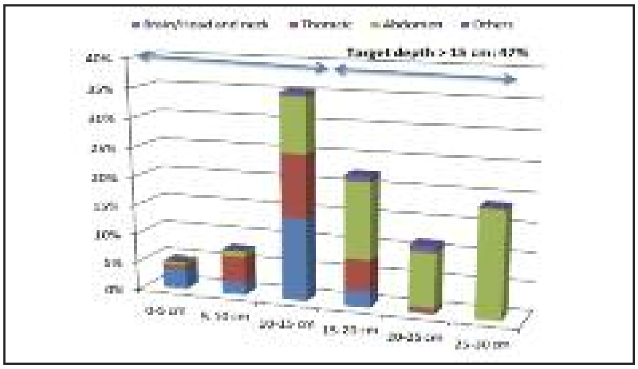


FIGURE 5 Number of patients versus target depth expected to be treated in the IMPLART proton-therapy centre

Parameter	Value
Beam energy phase 1	69-85/150 MeV
Beam energy phase 2	69-85/230 MeV
Pulse duration	1-3.5 µsec
Repetition frequency	10-100 Hz
Average beam current	2nA
Peak beam current	7µA
Dose	1-10 Gy/min
Typical beam spot	7Hx7V mm
Normalized emittance	0.2 π mm-mrad

TABLE 1 TOP-IMPLART main parameters

signed with three treatment rooms (Figure 4): one with a 150 MeV beam for shallow tumors and two with a 230 MeV beam for deep tumors.

The first part of the acronym remarks the heritage from the TOP (Oncological Therapy with Protons) Project [6] developed in 1998-2005 by ISS and ENEA, whilst the second part ("Intensity Modulated Proton Linear Accelerator for RadioTherapy") points out the possibility to perform a highly conformational therapy based on spatial and intensity modulation of the beam.

The Project, recently approved by Latium Region, provides for two phases of construction: in the first phase the maximum energy will be 150 MeV corresponding to a penetration depth in tissue of about 15 cm, allowing to treat about half of the lesions eligible for protontherapy (Figure 5); in the second phase the system will be extended to get up to 230 MeV beam energy. The main parameters of the accelerator are reported in Table 1.

Figure 6 left shows how a continuous energy variation in a range between 85 and 150 MeV can be obtained by changing the power of the klystrons supplying the last four modules operating in the phase-1 (named CCL3A, CCL3B, CCL4A, CCL4B), by switching off the last modules and varying the electric field amplitude in the last active module from 0 to 100%. Above 85 MeV each module provides an energy gain of 15-16 MeV; by extensive calculations, this has proven to be an upper limit that permits beam transmission when the last module is powered at low fields levels. In the right plot in Figure 6 the computed Root Mean Squared (RMS) energy spread versus the average output energy is shown at different energies. The solid curve represents the tolerated RMS energy spread corresponding to a distal fall-off of 2 mm.

Radiobiology experiments will also be done aimed

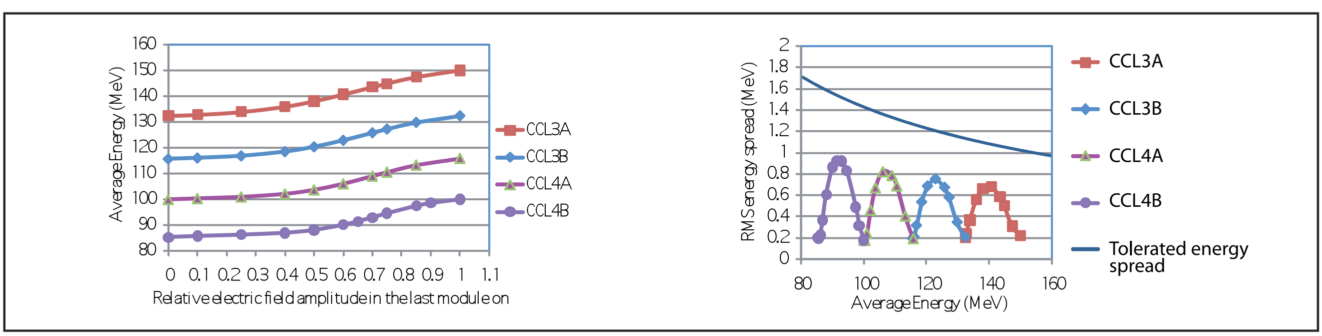


FIGURE 6 (Left) Average energy versus the electric field amplitude in the last switched-on module, (Right) RMS energy spread compared with the limiting curve

to the biological characterization of the beams in terms of Relative Biological Effectiveness (RBE), cell survival, time to repair.
The project will be carried on by ENEA in cooperation with ISS and IFO, according to the respective expertise: ENEA takes care of accelerator design and realization, and of radiobiology; ISS takes care of dosimetry, monitoring and radioprotection and participates to radiobiology; IFO takes care of preclinical studies, irradiation protocol and accessories for the final facility.

COMPLIANT, a low-cost single-room facility

The acronym COMPLIANT stands for "COMPact LInear Accelerator for ProtoN Therapy" and indicates a full-linac single-room PT system (Figure 7), based on a 200 MeV proton linear accelerator. It is equipped with a local shielding structure (only for the accelerator), with two fixed (not rotating) beams, with pure digital 3D scanning and is capable of intensity modulated therapy (IMPT) and respiratory gating. The entire facility, that should cost around 25 M€ all included, is intended to comply with a high-quality RT department in medium-size specialized hospitals. The low investment cost, along with the low installation impact on the hospital site, also changes the perspective of the use of the therapy with protons in the general framework of an RT: the combined use of X-rays and protons would allow a better treatment quality and increase the use of hypo-fractioned treatments for all tumor types, reducing the treatment times.

Description of the test facility at ENEA-Frascati

The innovative capabilities of the proposed scheme require a phase of testing and validation before its application to a clinical environment. A first part of the machine is assembled and tested, reaching the energy of 85 MeV at the ENEA Research Centre in Frascati in a specific area equipped with a 30m long and 3m wide bunker (Figure 8), where a 425 MHz-7 MeV ACCSYS PL7 injector is running for radiobiology experiments in the framework of the ISPAN (Proton experimental irradiation facility for cell and animal models) Project[2]. Since the frequency of 2.998 GHz is not properly sub-harmonic, a reduction in particle transmission (from 30% to 10%) will occur; this is, however, easily compensated due to the really low current requirements of the application. All SCDTL modules will be realized according to the main design followed by only 2 CCL units. Two klystron units will be required to drive the modules. Radiobiology and preclinical experiments, conducted on cells (V79), laboratory animals (mice) and human phantoms will permit to optimize both machine performances in terms of beam quality and operational schemes. Parallel dosimetric studies will allow to validate the reduced shielding requirements in treatment rooms. Based on the results obtained from the prototype,

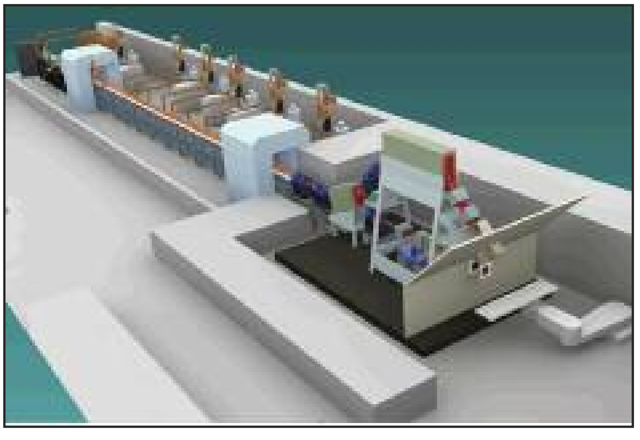


FIGURE 7 The COMPLIANT scheme

FIGURE 8 The existing 7 MeV ISS proton injector at ENEA-Frascati

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an upgraded machine will be designed, as a second step, to reach the energy required for deep tumors treatment.

Conclusions

On the basis of a long-time cooperation ENEA, ISS and IFO-IRE have proposed the development and realization of innovative PT systems based on a sequence of linear accelerators. The use of a linear machine, instead of a circular accelerator, allows to proceed by steps in the construction, measurement, testing/verification and certification of each added module of the accelerator. The modular construction may also help to match a partial financial support available during the realization. In addition, the low intrinsic beam losses of the linac reduce the size of protection barriers, positively affecting the general plant costs. The proton beam will be fast actively modulated in energy, intensity and transverse direction at the same time, thus offering the maximum flexibility for RT. The realization of a smaller scale prototype in an equipped experimental area at ENEA-Frascati will allow to perform tests and validation of all the most innovative treatments on phantoms, living cells and small animals. The results will lead to the development of protocols and software to thoroughly operate the machine in a clinical environment once it will be built.

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