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The issue of radioprotection in a proton therapy facility: a critical analysis

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S278156

A Flora Valerio,

il cui ricordo non potrà mai spegnersi.

❤

To Flora Valerio,

whose memory will never die out.

Declaration of originality

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Edoardo Gili

Turin, 20 February 2022

[1] NormATTIVA: Presidenza del Consiglio dei Ministri, Legge 19 Aprile 1975, n°475: "*Repressione della falsa attribuzione di lavori altrui da parte di aspiranti al conferimento di lauree, diplomi, uffici, titoli e dignità pubbliche*". Entry into force: 14 May 1925; last update of the Act: 31 December 1999.
[2] Master's Degree in *Energy and Nuclear Engineering*: Guida Dello Studente 2021-2022 – "*Linee Guida Esami Finali di Laurea e Laurea Magistrale*".

Index

Abstract

The hadron therapy technique might be the new horizon of cancer treatment. Although its underlying principles have been well-known for half a century, the employment of heavy ions in radiotherapy (conjointly with the contemporary technological progress) has seen a worldwide boost only over the past two decades. Several Authors emphasized how the hadron therapy technology might supersede, in the near future, some of the existing treatments to cure many forms of neoplasia.

Notwithstanding, there is still an overarching dubiety on hadron therapy – firstly its outrageous cost – along with a paucity of data concerning the long-term effects of the massive usage of heavy ions onto the human tissues. Many questions remain pending, and some clinical outcomes are quite moot and debatable.

The purport of this monograph is to investigate, to elaborate and critically discussing the major radiological hazards inside a hadron therapy facility utilizing protons, with particular regard to the effects of ionizing radiation onto the human body. Hence, this dissertation might be considered – without any pretence of exhaustiveness – as a sort of *vademecum* of the so-called "best practises" in the superintendence of any centre using particle accelerators, in strict connection with the most recent discoveries.

During the development of this work, a huge amount of scientific literature has been perused and compared, with the purpose of finding potential discrepancies – which have actually surfaced – amidst the different papers and publications on this theme, as well as pinpointing further potential risks that were not mentioned therein. Additionally, the very rich bibliography of this monograph shall not be intended as a mere substantiation of the contents reported, but as a mean which gives the reader the opportunity to deepen many of the principal subjects, along with the secondary ones that have not been completely broached.

Abstract

La terapia adronica potrebbe essere la nuova frontiera per la cura del cancro. Quantunque i suoi meccanismi nucleari di base siano noti dalla seconda metà del Novecento, nell'ultimo ventennio si è assistito – in concomitanza con il progresso tecnologico contemporaneo – ad un notevole incremento nell'uso di ioni pesanti a fini radioterapeutici. Invero, diversi Autori ritengono che la terapia adronica potrebbe rimpiazzare, negli anni a venire, molti dei restanti trattamenti per la cura delle principali forme tumorali.

Ciononostante vi è ancora un certo scetticismo nella piena accettazione della terapia adronica, ascrivibile perlopiù ai suoi costi esosi e ad un'insufficienza di conclamate evidenze circa l'uso reiterato di ioni pesanti su determinati organi. Gli effetti a lungo termine del trattamento necessitano ulteriori approfondimenti, e talune conclusioni riportate in letteratura medica sono ritenute controverse e opinabili.

La presente monografia mira all'individuazione e all'analisi critica dei principali rischi radiologici in un centro di terapia adronica, con particolare rifermento agli effetti (sia intenzionali che non) delle radiazioni ionizzanti sul corpo umano. Questa dissertazione può essere pertanto considerata – senza alcuna pretesa di esaustività – come un *vademecum* delle pratiche più idonee nella sovrintendenza di una qualsiasi struttura dotata di acceleratori di particelle, in correlazione con gli sviluppi tecnologici di questi ultimi due decennî.

La stesura del presente elaborato ha richiesto la consultazione e la collazione di un gran numero di testi, articoli e pubblicazioni medico-scientifiche, onde individuare potenziali discrepanze – che sono in effetti emerse – nelle opinioni e nei risultati ottenuti dai varî Autori. Pertanto, la ricca bibliografia di questa tesi (oltre a validare ogni asserzione ivi riportata) offre al lettore ulteriori fonti e collegamenti per approfondire le principali tematiche trattate, nonché gli aspetti più secondari affrontati superficialmente.

Structure of the work

This document is equipped with hypertext links to all the sources and external information it refers to. Hence, it suffices to click on the URLs highlighted in underlined blue in order to be redirected to the website of interest.

Each link of the bibliography – which is, for a prompt consultation, in the footer of every page – has been consulted and checked at 20 February 2022, and it was allegedly accessible in such date: the author of this work therewith declines any responsibility related to the persistence of the URLs from such date onwards. Likewise, it is not possible to guarantee that the contents of such websites will remain accurate and up-to-date into the near future (however, owing to the high reliability of the selected sources, this circumstance is unlikely to occur).

The bibliography of the figures and charts is reported at the end of the document.

The footnotes also report the definitions of many characteristic terms of the nuclear discipline (*e.g.* cross section, specific activity, decay constant, *et cetera*), which will not be always taken for granted.

Introduction to the chapters:

The dissertation consists of four macro-sections, each one of equal importance.

A brief compendium of each chapter's content is herein reported.

1) *Proton therapy:*

This chapter aims at expounding the salient points of the medical treatment underlying the dissertation, which is a subset of the hadron therapy technique. Before introducing the proton therapy, a few quick recalls about the radiotherapy in general are presented. Thereafter, the layout of an existing facility for hadron therapy – the *Heidelberger Ionenstrahl-Therapiezentrum* (HIT) in Germany – is briefly enucleated, with particular reference to the typologies of particle accelerators presently employed all over the world. Ultimately, the chapter elucidates the main advantages of proton therapy over the traditional treatments for the cure of tumours.

2) *Radiation Protection:*

This second section delineates the key points of the discipline of *radioprotection*, as well as its overarching bonds with this work. After a critical analysis of the Three Principles of Radioprotection (and a few "sociological" considerations thereof), the chapter expounds the ways in which the ionizing radiation can be expressed in the SI. Thence, a thoroughgoing discussion about the biological effects of ionizing radiation in the framework of proton therapy is presented, with mention of a few irresolute queries in scientifical literature. Eventually, a general overview of the Italian Legislation on radioprotection is reported, with particular emphasis to the dose limits prescribed for the workers, the general public and the patients.

3) Radiological hazard in a proton therapy facility:

After having quoted some prominent documentation in the field of hadron therapy safety, the chapter commences with an outline of the proton-matter interaction mechanisms. Thence the issue of secondary neutron radiation is addressed, with reference to the shielding difficulties and the complications it can entail (like the massive neutron production within the degrader bunker). In connection therewith, a critical scrutiny of the most employed materials for the degrader is carried out, by underlining their advantages and their drawbacks. Afterwards, the chapter explicates the major risks during a proton therapy treatment, such as beam losses, skyshine and groundshine effect, activation of air and materials, with particular emphasis to the hazardousness of the principal radionuclides therein produced.

4) Mitigation of risk:

The last section explicates the ongoing techniques to dampen the risks of ionizing radiation, prefaced by a few considerations on the Safety and Risk Analysis discipline. After a preamble about the "time-distance-shielding" tenet, all the focus is shifted towards the shielding design within a proton therapy facility, and the way it shall be properly fulfilled: the right choice of the materials, the selection of the best shielding layout (*e.g.* mazes), the existing design methodologies (*i.e.* Monte Carlo simulations *versus* analytical approach), and all the crucial factors influencing the design (*e.g.* type of accelerators, workload, intensity of the beam, *et cetera*). Thereafter, the neutron shielding principles are thoroughly discussed, with proper comparisons amidst the different shielding materials, their combinations and their limitations. In the end, a semi-empirical formula for a first assessment of the equivalent dose (the Moyer's correlation) is presented.

Proton therapy

The radiotherapy – general overview:

In general, the radiotherapy is a medical treatment for the healing of several forms of *neoplasia* – *i.e.* the uncontrolled proliferation of malignant cells into the healthy tissues, habitually denoted as "cancer" – by means of the employment of ionizing radiation onto the affected area. It is one of the most widespread techniques to treat cancer: as of 2010, nearly 50% of the cancer sufferers underwent a radiotherapy treatment at least once in their life [3], and this percentage is expected to drastically increase into the near future [4].

The chief reason which renders the radiotherapy possible is the higher responsiveness of tumoral cells, with respect to normal ones, to the detriment caused by ionizing radiation [5]: indeed, the tumoral cells have a poor capability to auto-repair the damage, which will thereby experience a cellular death for apoptosis or necrosis [6]. Notwithstanding, the tumoral mass is always surrounded by a large number of healthy cells, which will unavoidably receive a certain amount of ionizing radiation: even though the normal cells have better restoring capacities, there is a threshold above which these mechanisms become ineffective. It can be therefore stated that one of the biggest challenges in radiotherapy is the ability of eradicating the tumoral cells (or reducing the metastasis thereof) whilst sparing the healthy ones – which is, as it will be discussed, the very hallmark of proton therapy.

The proton therapy – general overview:

The proton therapy technique can be intended as a branch of *hadron therapy*: this last one designates all the types of radio-therapeutical approaches utilizing heavy particles (such as protons, neutrons, carbon ions and others) in place of the more conventional ones (such as photons or electrons) [7]; as the name suggests, the proton therapy utilizes only protons. Although the therapeutical employment of these particles was first

[3] R. Baskar, K. A. Lee, R. Yeo, K. Yeoh; "*Cancer and radiation therapy: current advances and future directions*" – International Journal of Medical Sciences; published 27 February 2017.
[4] J. M. Borras, Y. Lievens, M. Barton *et al.*; "*How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis*" – Radiotherapy and Oncology; published 24 February 2016.
[5] R. Baskar, J. Dai *et al.*; "*Biological response of cancer cells to radiation treatment*" – Frontiers in Molecular Bioscience; published 17 November 2014.
[6] G. Rainaldi, A. Ferrante *et al.*; "*Induction of apoptosis or necrosis by ionizing radiation is dose-dependent in MG-63 osteosarcoma multicellular spheroids*" – Anticancer Research; published in May-June 2003.
[7] A. Degiovanni, U. Amaldi; "*History of hadron therapy accelerators*" – European Journal of Medical Physics; published 05 March 2015.

propounded in 1946 by the physicist Robert. R. Wilson [8], this up-and-coming technique became widespread only a few decades later: as of August 2018, there are approximatively 70 proton therapy centres fully operating all over the world, and at least 45 are under construction [9], [10]. Heretofore, only three facilities in Italy can provide a fully hadron therapy treatment: the Proton Therapy Centre of Trento, the INFN of Catania and the National Oncologic Hadron Therapy Centre (CNAO) of Pavia.

The foremost strong points of proton therapy are:

- Precision: it is possible to impart a very high dose in a very restricted region, by leaving unscathed the healthy tissues [11]. This peculiarity is very suited whenever a tumour is located in a critical region of the body (such as hearth, bone marrow or specific areas of the brain [12]), whereby the detriment of the surrounding tissues shall be contained as much as possible.
- Paediatric scope: since the sparing of healthy tissues drastically subsides the likelihood of developing a second radiation-induced cancer, the proton therapy is eligible for children and infants [13]. Indeed, the youngsters' body is very sensitive to X-rays, thereby being more prone to the typical side-effects that a traditional radiotherapy might cause; some Authors demonstrated how the employment of protons in place of X-rays can significatively curb the onset of problems during the growth, as well as the eventuality of secondary tumour insurgence [14]. This last circumstance, in fact, becomes crucial whenever the patient life expectancy is very high (since the development of a tumour can require several years) and it less worrisome in the middle-aged or elderly patients. Contrarily, other studies emphasized that, as far as the current knowledge is concerned, there is not enough evidence to assert the total paediatric suitability of proton (and hadron) therapy treatments over the other ones [15].

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[8] R. R. Wilson; "*Radiological use of fast protons*" – Radiology, Volume 47, No. 5, Pag. 487; published 01 November 1946.
[9] M. Hu, L. Jiang, X. Cui *et al.*; "*Proton beam therapy for cancer in the era of precision medicine*" – Journal of Hematology & Oncology; published 12 December 2018.
[10] S. Byeong Lee; "*Proton therapy review: proton therapy from a Medical*" – Progress in Medical Physics; published in September 2020.
[11] E. J. Moding, M. B. Kastan, D. G. Kirsch; "*Strategies for optimizing the response of cancer and normal tissues to radiation*" – Nature Reviews Drug Discovery; published in July 2013.
[12] S. E. Combs, N. Lapierre, M. Brada; "*Clinical controversies: proton radiation therapy for brain and skull base tumors*" – Seminars in Radiation Oncology; published in April 2013.
[13] R. Leroy, N. Benahmed *et al.*; "*Proton therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers*" – International Journal of Radiation Oncology; published 01 May 2016.
[14] M. Mizumoto, H. Fuji, M. Miyachi *et al.*; "*Proton beam therapy for children and adolescents and young adults (AYAs): JASTRO and JSPHO Guidelines*" – Cancer Treatment Reviews, Volume 98; published in July 2021.
[15] D. R. Olsen, O. S. Bruland *et al.*; "*Proton therapy: a systematic review of clinical effectiveness*" – Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology; published in May 2007.

Besides the unquestionable advantages of proton therapy, it ought to be remarked its excessive outlay with respect to the other therapies. According to a publication by the Oncology Nurse Advisor [16], the construction and the commissioning of an ordinary proton therapy facility may cost (in the United States) more than $225 million – which drastically exceeds the expense of a classical X-ray generator. The outlay of a full healing session cycle is dependent upon the severity and the typology of tumour, but it is generally costly as well (averagely 2,4 times higher than a traditional photon therapy treatment [17]). This is one of the reasons which hinders the proton therapy from wholly replacing the traditional oncological treatments – conjointly with its only applicability in a few specific typologies of tumours [18].

Actually, several Authors [19] started questioning the real cost-effectiveness of hadron therapy treatments over the traditional ones, in the attempt to comprehend if the elevated outlay could entail significant long-term benefits. But the answer to this query necessitates an observational horizon of several years, since the cancer metastasis may arise even after decades; the available data are quite scant, and more clinical surveys are necessary [20]. Notwithstanding, even when the economical facet is not a concern, the oncologists are not supposed to always recommend a proton therapy treatment in place of other therapies (wherein the same benefit might be achieved with a lesser cost), because of the current paucity of evidence [21].

Furthermore, it ought to be noticed how this matter is also dependent upon the governmental refunding situation: if a proton therapy treatment is fostered and reimbursed by the National Health System, a higher number of specialists will advise the treatment, and more clinical data on its effectiveness will be accessible for the next generations. This would engender a virtuous circle: the proof of its (expected) efficaciousness will entail more research in this field, conjointly with a higher therapy reimbursement from the government – therewith allowing the proton therapy cost to diminish. Conversely, a rampant scepticism about ion therapy gives the opposite

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[16] B. Furlow; "*Cost vs Benefits: The Controversy Over proton Beam Radiotherapy*" – Oncology Nurse Advisor; published in February 2018.
[17] M. Pijls-Johannesma, J. Grutters; "*Cost, effectiveness and cost-effectiveness of hadron therapy*" – 2nd Workshop on Hadron Beam Therapy, Erice (Italy); published in 2011.
[18] A. A. Almahwasi; "*Does Hadron therapy Offer Enough Effectiveness in Treating Cancer to be Worth the Cost?*" – Master of Science from University of Survey, UK; supervised by Prof. Patrick Regan; published in September 2011.
[19] M. Lodge, M. Pijls-Johannesma *et al.*; "*A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer*" – Radiotherapy and Oncology, Volume 83, Issue 2, Pages 110-122; published in May 2007.
[20] A. M. Allen, T. Pawlicki *et al.*; "*An evidence-based review of proton beam therapy: The report of ASTRO's emerging technology committee*" – Radiotherapy and Oncology, Volume 103, Issue 1, Pag. 8-11; published in April 2012.
[21] M. Brada, M. Pijls-Johannesma, D. De Ruysscher; "*Proton therapy in clinical practice: current clinical evidence*" – Journal of Clinical Oncology; published 10 March 2007.

outcome, by not permitting to draw a significant statistic on its advantageousness (which necessitates a larger sample of observations).

Layout of a hadron therapy facility:

Aside from possible differences in the arrangement and types of devices, every hadron therapy facility (utilizing either protons or other heavy ions) is characterized by a set of common elements: an ion source, one or more particle accelerators, a transportation line for the beam, the delivering nozzles, one or more treatment rooms, and the premises for the personnel and other attendees.

By way of example, the layout of the German *Heidelberger Ionenstrahl-Therapiezentrum* (*Heidelberg Ion-Beam Therapy Centre* in English language) is briefly enucleated [22].

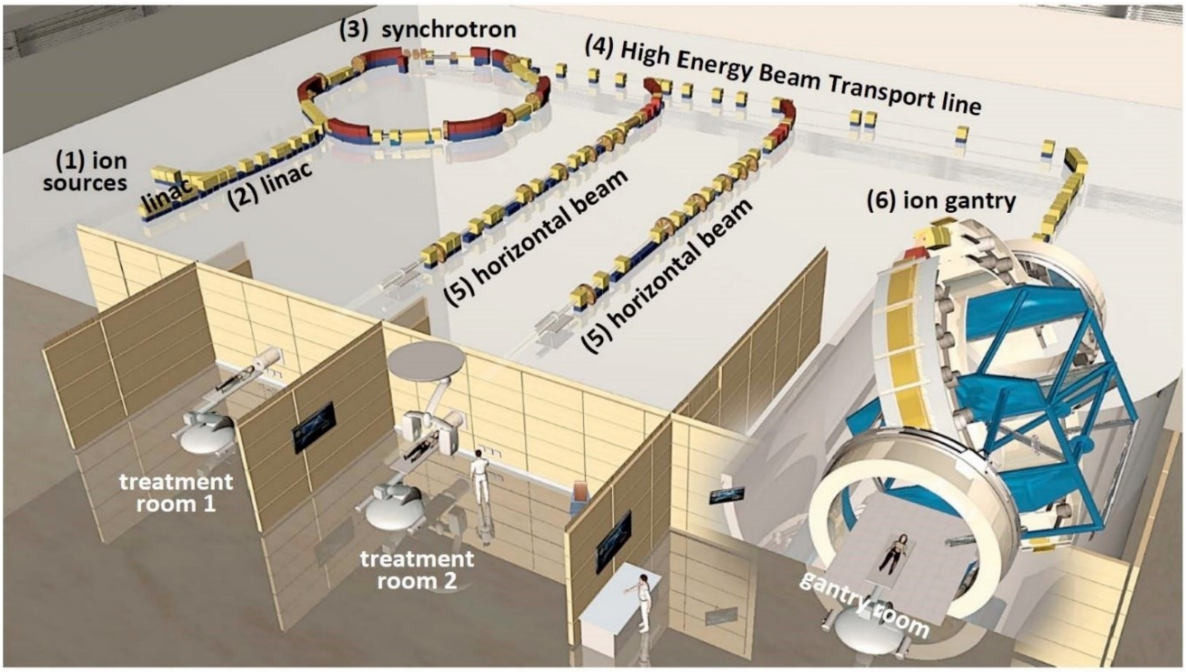

***Figure 1**: layout of Heidelberg Ion-Beam therapy Centre (HIT) in Germany.*

With reference to the nomenclature of **Figure 1**, the originating heavy ions are produced by an *Ion Source (1)*: it may consist of a gaseous volume of hydrogen, wherein some strong electrical discharges are generated [23]. Such electrical fields are able to turn the hydrogen into plasma, by causing the separation of atoms in their elementary particles, *i.e.* electrons and protons [24]. Thence, the ions are injected into a series of *Particle*

[22] Official website of the Heidelberg Ion-Beam therapy Centre (HIT) facility; Heidelberg University Hospital – Layout of the facility illustrated by Professor Dr. Jürgen Debus; last update in June 2021.
[23] R. Scrivens; "*Proton and Ion Sources for High Intensity Accelerators*" – 9th European Particle Accelerator Conference, Lucerne, Switzerland. Report number: CERN-AB-2004-075. Published 17 August 2004.
[24] M. Muramatsub, A. Kitagawa; "*A review of ion sources for medical accelerators*" – Review of Scientific Instruments, Vol 83, No. 2; published 12 September 2011.

Accelerators, namely a *LINAC (2)* and a *Synchrotron (3)*, wherein – as it will be discussed afterwards – they can reach a speed around 60% the speed of light, as well as energies of approximatively 250 MeV [25], [26]. Thereafter, the protons are sent towards the *High Energy Beam Transport Line (4)*, which is the stage with the purpose of leading the ion beam into the treatment rooms, as well as tuning their energy.

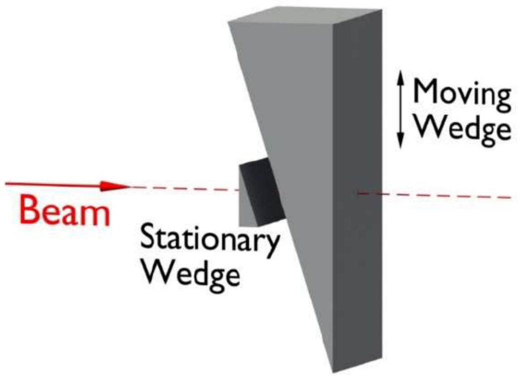

Figure 2*: schematic representation of a degrader, which aims at adjusting the ion beam energy.*

In fact, the ion beam energies exiting the accelerators do not always fit with the ones requested for the treatment, which can span in the range 70-230 MeV averagely [27]: in such occurrence the energy adjustment is performed by means of the *energy selection system*, which comprises a *degrader* and a *momentum analyser* [28]. In its more simplistic description (**Figure 2**), a degrader is constituted by a stationary wedge and a moving wedge, both of them made up of an absorbing material: by translating the moving wedge upwards or downwards, it is respectively possible to diminish or to augment the ion energies. Thereafter, the ions exiting the degrader pass through the momentum analyser, which has the purpose of filtering out the particles with an energy not in the requested range; indeed, for a faultless spatial irradiation of the tumoral region, the proton beam shall be monoenergetic.

The particles are thence conducted, with the desired energy and trajectory, toward *Treatment Room (1)*, *Treatment Room (2)* and the *Gantry Room*. The variations in the beam trajectory are imposed by using a set of magnets, which deflect the beam by exploiting the ion electrical positivity (such as protons). For the treatments necessitating a fixed and static beam position, *Treatment Room (1)* and *Treatment Room (2)* are employed. Instead, when the irradiation is needed in a wide range of directions, the patient is placed within the *Ion Gantry (6)*: this big donut-shaped device is able to rotate

[25] B.J. Holzer; "*Introduction to particle accelerators and their limitations*" – Published in November 2014 by CERN (Switzerland), in the Proceedings of the CAST-CERN Accelerator School.
[26] M. Vretenar (edit by W. Herr); "*Linear accelerator*" – Published in August 2013 by CERN (Switzerland), in the Proceedings of the CAST-CERN Accelerator School.
[27] Z. Liang, K. Liu, B. Qin, W. Chen; "*Design and optimization of an energy degrader with a multi-wedge scheme based on Geant4*" – Nuclear Instruments and Methods in Physics Research, Section A; published 05 November 2018.
[28] Z. Liang, W. Chen, B. Qin; "*Design of the Energy Selection System for proton therapy Based on GEANT4*" – Huazhong University of Science and Technology, Wuhan, China; published in 2017.

the ion beam of 360 degrees around the patient's body, by allowing the tumour irradiation in any possible angle [29].

By way of example, the gantry treatment room ProteusONE© commercialized by IBA [30] (i.e. *Ion Beam Applications*, a Belgian medical technology company in the field of proton therapy) is shown in **Figure 3**.

Figure 3*: Gantry Treatment Room of IBA™ Proteus proton therapy system.*

The accelerator nozzle, indicated with ①, is the rotating part which delivers the beam. The typology of gantry shown in **Figure 3** is called *isocentric*: such gantry rotates around only one axis, and all the beam directions, for all the different angles of nozzle ①, pass through the same focal point (named *isocentre*). This peculiarity permits a reduced number of adjustments during patient repositioning (lying on the support denoted with ②, which can translate and rotate too), as well as a higher precision in the delivery of

[29] L. Bottura, E. Felcini *et al.*; "GaToroid: A novel toroidal gantry for hadron therapy" – Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; Volume 983; published 11 December 2020.
[30] Official website of Ion Beam Application (IBA) company; Proteus®ONE - IBA proton therapy technology – last updated: August 2021.

the beam [31]; in fact, in order for the treatment to be effective, a high degree of accuracy is required, which shall be in the range of the millimetre [32].

Depending upon the manufacturers, a gantry has a diameter of averagely 10 meters (like the one of German HIT Centre [33]), and an overall weight of around 100 tons [34].

Indeed, with respect to an ordinary X-rays radiotherapy, the proton therapy necessitates a particle accelerator, which can be a very bulky device. Owing to the largess of all the remaining equipment, a room devoted to proton therapy cannot be a simple ward of a generic hospital: there is the need of an entire building specifically built at that purpose [35].

Particle accelerators:

A particle accelerator is a device conferring a very high velocity to many charged particles, by means of an adequate disposition of electrodes and the employment of high electric voltages. The original particles to be accelerated are usually produced by *thermionic emission* [36], which is a physical phenomenon whereby electrons and ions are emitted from a metal (usually a filament) when it is heated up to very high temperatures. In order to attain such temperatures, the filament is subjected to a strong electric current, which incrementally heats it up owing to the *Joule Effect*. Furthermore, in order not to perturb the travelling particle trajectories, the region in which the acceleration takes place is ordinarily put under vacuum, as to circumvent the collision with other air molecules [37].

Hereafter, the three main typologies of particle accelerators are briefly delineated.

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[31] P. Mayles, A. Nahum, J. C. Rosenwald; "*Handbook of radiotherapy physics*" – Boca Raton: Taylor & Francis, published in 2007; ISBN 97-8-14200-120-26.
[32] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility"* – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[33] *ibidem.*
[34] U. Weinrich; "*Gantry Design for proton and Carbon Hadrontherapy Facilities*" – Published by CERN (Switzerland), in the Proceedings of the CAST-CERN Accelerator School.
[35] S. Devicienti, L. Strigari *et al.*; "*Patient positioning in the proton radiotherapy era*" – Journal of Experimental & Clinical Cancer Research; published 13 May 2010.
[36] B. Whelan, S. Gierman, L. Holloway *et al.*; "*A novel electron accelerator for MRI-Linac radiotherapy*" – Medical Physics; published in March 2016.
[37] Oleg B. Malyshev; "*Vacuum in Particle Accelerators: Modelling, Design and Operation of Beam Vacuum Systems*" – Wiley-Vch; ISBN 978-3-527-80914-1; published in October 2019.

Linear accelerator:

The first model of particle accelerator was the *Linear Particle Accelerator* (LINAC): it is constituted by a set of electrodes, amidst which a difference of potential is imposed (**Figure 4**).

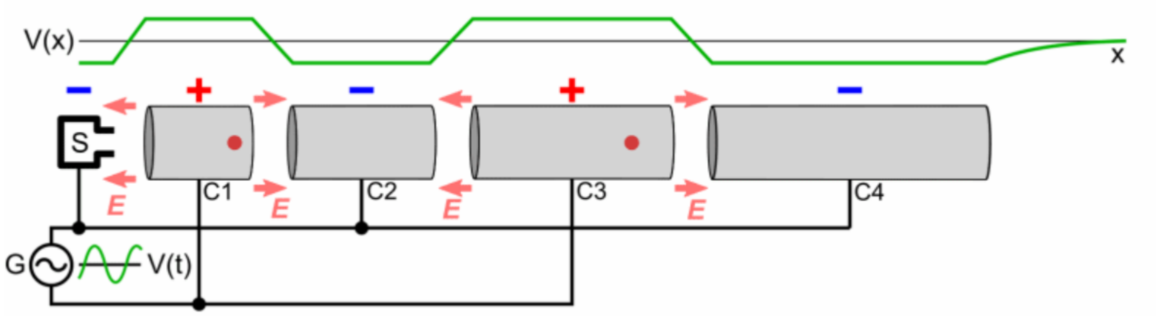

***Figure 4**: schematic representation of a Linear Particle Accelerator.*

Each pair of electrodes, which together constitutes a *stage*, is alternatively connected to the positive pole and negative pole of a sinusoidal voltage generator. The acceleration of the particles eventuates in the only spaces between one electrode and the other, whilst the electric field inside the electrodes themselves is almost null [38]. In order for the linear accelerator to work, the transit time of each particle within a single electrode shall be equal to one-half of the sinusoidal voltage wave period: by denoting with t_{trans} such transit time and with T the wave period, the following relation shall be always verified:

$$t_{trans} = \frac{T}{2}$$

By expressing the time t_{trans} as a function of the velocity of the particle v_p and of the length L_{el} of the electrode, it also stands that:

$$t_{trans} = \frac{L_{el}}{v_p} = \frac{T}{2}$$

Now, the issue is that the transit time t_{trans} progressively diminishes, owing to the augmentation of the velocity v_p (which is due to the stepwise acceleration conferred to the particle). Since it is mandatory to keep the transit time equal to $T/2$, the solution is to increasingly augment the electrode lengths (*i.e.* the numerator of the fraction), in order to offset the increase of velocity (*i.e.* the denominator of the fraction) [39]; this peculiarity can be appreciated in **Figure 4** as well.

[38] C. R. Vane, S. Datz; "*Methods in Experimental Physics*" – Academic Press, Volume 29, Part A, Pag. 1-463; ISSN 0076-695X; published in 1995.
[39] Lecture notes of the master's degree course "*Biomedical and industrial applications of radiation*" of Politecnico di Torino, held by Prof. Gianni Coppa – academic year 2020/2021.

It ought to be noticed how the length of the electrodes cannot tend to infinity: the maximum length is reached when the velocity v_p becomes equal to the speed of light $v_p = c$, namely:

$$L_{el} = c \cdot \frac{T}{2}$$

Even though such system is perfectly feasible, the excessive length of the total set of electrodes makes the installation of a linear accelerator technically burdensome within a medical facility. In order to overcome this issue, a few more compact accelerators have been devised: the *cyclotron* and the *synchrotron*.

Cyclotron:

The first model of cyclotron was devised by Robert R. Wilson in 1946, during his professional career at Harvard University [40]. In its more simplistic description (**Figure 5**), a cyclotron is composed by two low-height semicylinders (called *dees*), amidst which a voltage is imposed. The overarching difference of cyclotron with respect to LINAC is the imposition of a not-straight trajectory to the particle, by means of the employment of some magnetic fields: two magnets are thereby located over and beneath the dees, whose magnetic fields – according to the Lorentz's Force – are able to curve the trajectory of the charged particle into some semi-circular paths [41]. The radii of such paths diminish from one dee to the other, by making the trajectory appear like a sort of spiral.

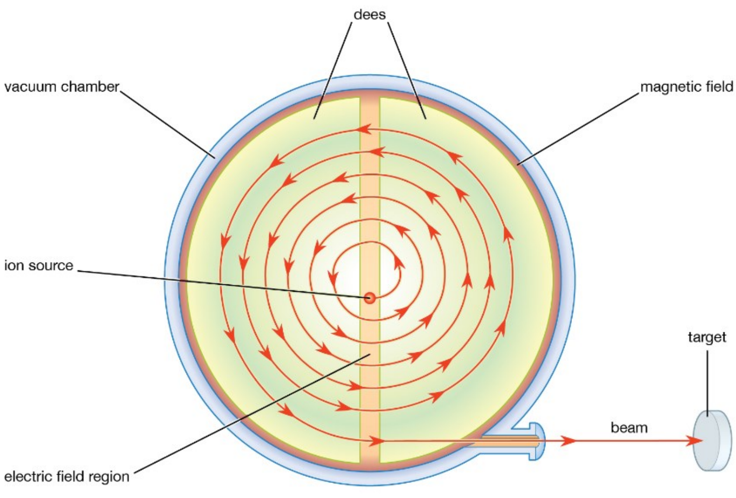

***Figure 5**: schematic representation of a Cyclotron Accelerator.*

[40] E. Mashairo; "*Robert R. Wilson (1914–2000): the first scientist to propose particle therapy – use of particle beam for cancer treatment*" – Radiological Physics and Technology; published 20 October 2017
[41] G. B. Coutrakon; "*Accelerators for Heavy-charged-particle Radiation therapy*" – Technology in Cancer Research and Treatment, Volume 6, Supplement Number 4; ISSN 1533-0346; published in August 2007.

Between the two dees there is a gap (highlighted in dark orange in **Figure 5**): this is the only region wherein the acceleration occurs on account of the voltage, since the electric field into the two dees is almost null [42].

Eventually, the protons exiting the accelerator are sent to a certain number of deflection units (not represented in the Figure), in which they are forced to follow a precise trajectory by means of other magnetic fields, so as to be precisely addressed to the patient's body.

The cyclotron is the typology of accelerator presently employed in the INFN Centre of Catania (one of the most sophisticated centres in Italy for the ocular cancer treatment) [43]. Nonetheless, one of the issues related to cyclotron is the exigency of putting under vacuum a very big volume, which can be an operation both onerous and expensive; in order to overcome this problem, a variant of this device has been devised: the *synchrotron*.

Synchrotron:

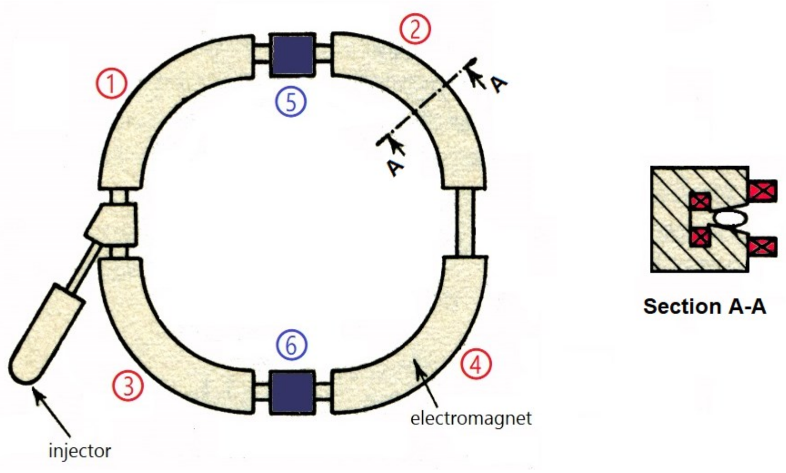

***Figure 6**: schematic representation of a Synchrotron.*

The synchrotron can be intended as a series of both cyclotron units and linear accelerator units: in the former ones (*i.e.* elements ①, ②, ③, ④ of **Figure 6**), the conversion of a rectilinear trajectory into a circular one occurs; in the latter ones (*i.e.* elements ⑤ and ⑥ of **Figure 6**) the actual acceleration takes place. Unlike the cyclotron, the particle trajectory within the synchrotron is approximatively circular: on account of this, there is the necessity of a smaller volume to put under vacuum [44], [45].

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[42] W. M. Saslow; "*Electricity, Magnetism, and Light*" – Academic Press; ISBN 978-0-12-619455-5; published in 2002.
[43] Istituto Nazionale di Fisica Nucleare (whose website is endorsed by Ministero dell'Istruzione, dell'Università e della Ricerca); CATANA: Centro di AdroTerapia ed Applicazioni Nucleari Avanzate.
[44] G. B. Coutrakon; "*Accelerators for Heavy-charged-particle Radiation therapy*" – Technology in Cancer Research and Treatment, Volume 6, Supplement Number 4; ISSN 1533-0346; published in August 2007.
[45] Lecture notes of the master's degree course "*Biomedical and industrial applications of radiation*" of Politecnico di Torino, held by Prof. Gianni Coppa – academic year 2020/2021.

Currently the CNAO of Pavia utilizes a synchrotron, which is able to confer an energy to the heavy ions and to the protons of, respectively, 400 MeV and 250 MeV [46]. The diameter of the synchrotron is averagely 25 meters [47].

Advantages of proton therapy:

Hereafter, the explication of the proton therapy advantages will pass through two important concepts, which are related to the interaction of particles with matter: the *penetration depth* and the *stopping power*.

Penetration depth:

The penetration depth can be defined as the spatial coordinate wherein the kinetic energy of a travelling particle becomes null [48].

Figure 7: *trajectory of four 22 MeV α-particles in photographic emulsion.*

Unlike photons, the penetration depth of heavy ions is well-defined, and it has a low degree of uncertainty [49]: this means that, with a proper placement of the accelerator nozzle, it is possible to precisely send the particles in a clear-cut region of the patient's body (as well as avoiding the detriment of the healthy tissues located after the tumoral region). This peculiarity is illustrated in **Figure 7**, which represents the trajectories of four different α-particles (having an energy of 22 MeV each) travelling into a medium: every particle enters the body at the level of the horizontal blue line, and it stops where the trajectory lines end, namely in the nearby of the horizontal red line.

[46] A. Porta, S. Agosteo, F. Campi; "*Monte Carlo simulations for the design of the treatment rooms and synchrotron access mazes in the CNAO Hadrontherapy facility*" – Radiation Protection Dosimetry, Volume 113, Issue 3; published 15 February 2005.
[47] Official website of *Centro Nazionale di Adroterapia Oncologica* (CNAO) of Pavia: Il sincrotrone di CNAO – last update in February 2020.
[48] Lecture notes of the master's degree course "*Biomedical and industrial applications of radiation*" of Politecnico di Torino, held by Prof. Gianni Coppa – academic year 2020/2021.
[49] R. Mohan, D. Grosshans; "*Proton therapy: present and future*" – National Centre of Biotechnology Information, Advanced Drug Delivery Review; published in January 2015.

It can be observed how the four α-particles stop approximatively at the same depth (represented by the distance between the blue line and the red line). The picture also shows that, due to the limited lateral scattering of heavy ions, the trajectory of an α-particle is quite akin to a straight line [50]: this further peculiarity limits the detriment within the surrounding tissues as well. All these last considerations stand for the protons too, whose trajectory and motional behaviour within the human tissues is extremely similar to the ones of α-particles [51].

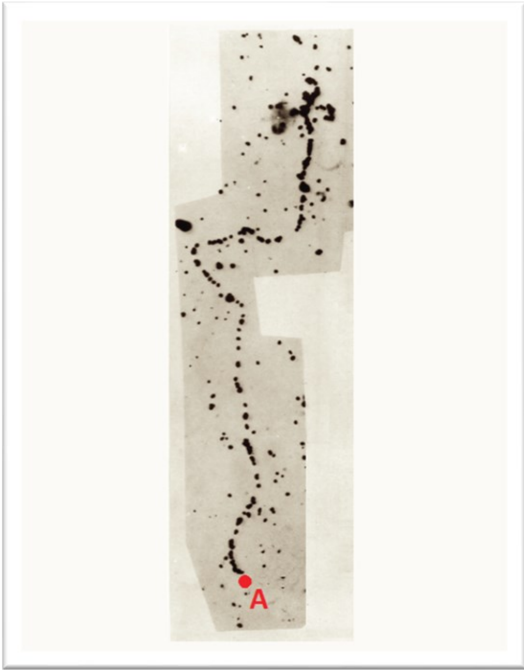

Figure 8*: trajectory of an electron into a medium (with energy of 250 keV).*

As a comparison, in **Figure 8** it is represented the trajectory of an electron inside a medium, which starts its path in Point A. Unlike the behaviour of the heavy particles (**Figure 7**), the electron trajectory looks erratic and quite unpredictable: this is a consequence of the high number of scattering events with the other electrons in the medium, which bring about recurrent direction changements. In view of this, the electron cannot be considered a precise "bullet" for radiotherapy – even though they are currently utilized to treat some form of skin cancers [52].

Stopping power:

The stopping power $\mathcal{S}$ can be defined as the energy released per unit of length by a particle beam travelling within a medium [53]. Into a monodirectional reference system, it boils down to the first derivative of the function $\mathcal{E}(x)$, namely:

$$\mathcal{S} = \mathcal{S}(\mathcal{E}_0, x) = -\frac{d\mathcal{E}}{dx}$$

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[50] W. D. Newhauser, R. Zhang; "*The physics of proton therapy*" – Physics in Medicine and Biology; published 21 April 2016.
[51] Oral source by Prof. Gianni Coppa (August 2021), Member of Collegio di Ingegneria Energetica and Collegio di Ingegneria Biomedica of Politecnico di Torino.
[52] A. I. Zablow, T. R. Eanelli, L. J. Sanfilippo; "*Electron beam therapy for skin cancer of the head and neck*" – Head & Neck Cancer Research Journals; published in May-June 1992.
[53] Michael F. L'Annunziata; "*Handbook of Radioactivity Analysis (Second Edition)*" – Academic Press, ISBN 978-0-12-436603-9; published in 2004.

The stopping power is therefore a function of the initial energy $\mathcal{E}_0$, and it generally has not a constant value over length. During the planning of a proton therapy treatment, the capability to predict the stopping power trend is of paramount importance; indeed, by the integration of the stopping power over space, it is possible to know the punctual dose deposition $\mathcal{E}$ throughout the entire trajectory of the beam:

$$\mathcal{S}(\mathcal{E}_0, x) = -\frac{d\mathcal{E}}{dx} \qquad \Longrightarrow \qquad \mathcal{E}(x) = \int_0^x \mathcal{S}(\mathcal{E}_0, x)\, dx$$

The staggering advantage of a proton therapy treatment over the traditional ones can be comprehended by looking at **Figure 9**, which juxtaposes the trends of the absorbed relative dose for several types of particles as a function of their penetration.

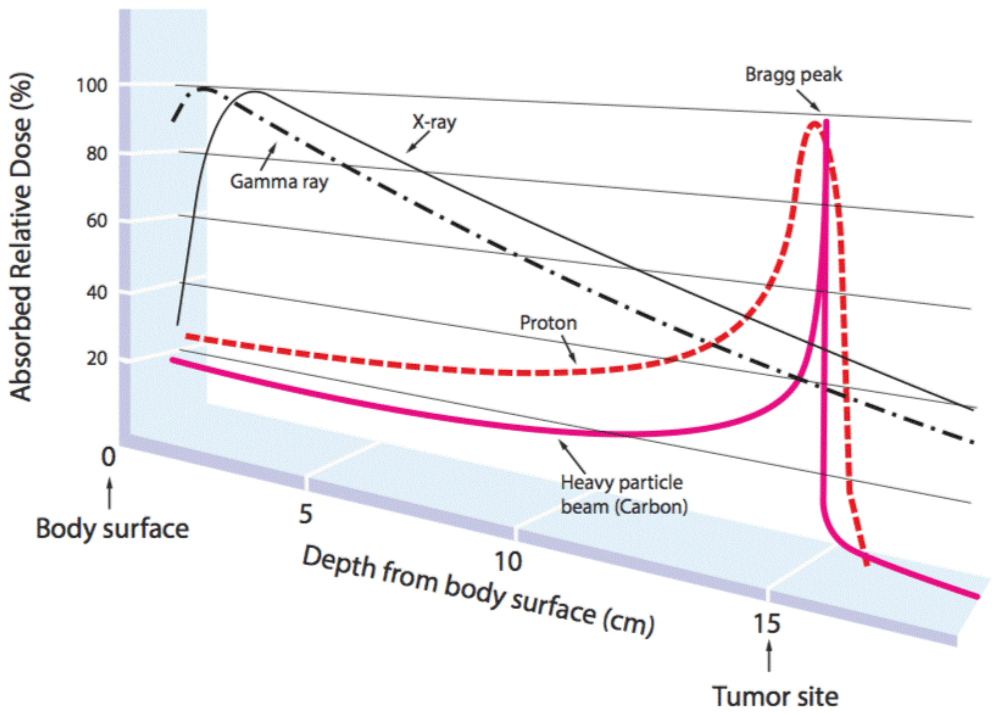

***Figure 9**: trend of the absorbed relative dose for the main typologies of particles as a function of their penetration into the human tissues.*

As shown, the relative dose deposition of a heavy particle (fuchsia and dashed red lines) presents a considerable value in close proximity of the target, whereas it is relatively low in the region which precedes [54]. This means that there is a high energy deposition in the tumoral region (which is the coveted effect) and a modest dose release in the healthy tissues situated between the source and the tumour itself (which is, again, another desired condition). Such prerogative of the heavy particles has been actually known for a century, and it was scientifically demonstrated as early as 1903 by William

[54] W. D. Newhauser, R. Zhang; "*The physics of proton therapy*" – Physics in Medicine and Biology; published 21 April 2016.

H. Bragg [55]; notwithstanding, several years had to go by before seeing this propriety massively applied in the nuclear medicine field.

The conjunction of these two peculiarities (*i.e.* stopping power trend and precise penetration depth) renders the hadron therapy very preferable to the employment of X-rays and gamma rays: in fact, their great downside is the high energy deposition in the first layers of non-cancerous tissues, followed by a little dose release in the region of interest [56]. Such characteristic can be appreciated in **Figure 9** too (solid black line and dash-dot black line): it is possible to observe how the highest release eventuates at the very entrance of the body surface, and the peak takes place at approximatively 2/3 cm depth. Instead, with the employment of hadron beams (either protons or carbon ions) the maximal dose deposition occurs in the tumour site – located, in this example, at around 15 cm depth. Indeed, some studies substantiated how the employment of protons in place of photons can reduce the imparted dose to the healthy tissues up to 50% [57]. The phenomenon regarding the strong local augmentation of dose due to the utilization of hadrons is (eponymously) called *Bragg's Peak*.

Of course, the localization of the tumour does not always coincide with the Bragg's Peak position in the energy-penetration chart: in this circumstance, the peak displacement toward the region of interest is performed by means of the degrader (as described in the chapter "*Layout of a hadron therapy facility*"). This kind of adjustment is also adopted whenever the tumoral mass is widespread, and there is the necessity to irradiate a larger region.

[55] A. Brown, H Suit; "*The centenary of the discovery of the Bragg peak*" – Radiotherapy and Oncology 73; published 01 December 2004.
[56] X. Tian, K. Liu, Y. Hou, J. Cheng, J. Zhang; "*The evolution of proton beam therapy: Current and future status*" – Molecular and Clinic Oncology; published in January 2018.
[57] T. F. Delaney, H.M Kooy; "*Proton and charged particle radiotherapy*" – Philadelphia: Lippincott Williams and Wilkins; published in 2008 (partially available on Google Books at this link).

Radiation Protection

First overview:

The interaction of ionizing radiation with the human body can cause a multifariousness of effects, which can even culminate with the death of the person: this is why the radioprotection of patients and personnel is one of the fundamental facets during all the treatments involving ionizing radiation (both for therapeutic and diagnostical purposes). The detriment can be manifold, and it is dependent upon a variety of factors: the amount of energy released, the exposure time to radiation, the sensitivity of the affected organ, the distance between body and source, the nature of the radiation itself [58].

The discipline of *radiation protection* (or *radioprotection*) can be – unofficially – defined as the ensemble of procedures, protocols and protective devices which aim at eliminating, or lessening as much as possible, the effects of ionizing radiation towards the single person and the entire community. According to the definition of International Atomic Energy Agency (IAEA) [59], the radiation protection is – officially – defined as «*the protection of people from harmful effects of exposure to ionizing radiation, and the means for achieving this*».

Organizations and bodies in the field of Radiation Protection:

The laws and prescriptions to be referred to in the framework of a proton therapy facility are, of course, the ones dictated by the Legislation of the country thereof. However, there are some institutions and internationally recognized bodies which can advance recommendations and general standards in the field of radiation protection, which are subsequently utilized as a guidepost during the law implementation process of each single country.

One of the chief organizations is the International Commission on Radiological Protection (ICRP), which is an international body aiming at guaranteeing the protection of people and the environment from the potential detriment caused by ionizing radiation. Although the ICRP is a non-governmental organization, nearly all the international regulations concerning radioprotection rely upon the guidelines that it periodically puts forward [60].

[58] Lecture notes of the bachelor's degree course "*Fondamenti di ingegneria nucleare*" of Politecnico di Torino, held by Prof. Piero Ravetto – academic year 2017/2018.
[59] A Publication by International Atomic Energy Agency (IAEA); "*The IAEA Safety Glossary: Terminology Used in Nuclear Safety and Radiation Protection*" – 2018 Edition. ISBN: 978-92-0-104718-2
[60] A. Wambersie; "*The role of the ICRU in quality assurance in radiation therapy*" – National Library of Medicine; published in 1984.

Another leading institution concerning radioprotection (but not only) is the International Atomic Energy Agency (IAEA), which is a worldwide organization aiming at fostering the peaceful use of nuclear energy, as well as averting its employment for military purposes [61]. Came into force in 1957 [62], it thenceforth commenced to issue guidelines and recommendations regarding radioprotection too; one of its most renowned publications is the *International Basic Safety Standards on Radiation Protection and Safety of Radiation Sources* [63], which reports all the requisites and directives for protecting the people and the environment from ionizing radiation. In order to keep pace with the new advances and findings in the discipline, such publication is periodically updated.

Principles of Radiation Protection:

The ICRP proposed the Three Principles underlying the discipline of radioprotection [64], verbatim:

1. Principle of justification:
   «Any decision that alters the radiation exposure situation should do more good than harm».
2. Principle of optimization:
   «The likelihood of incurring exposures, the number of people exposed, and the magnitude of their individual doses should be kept as low as reasonably achievable, taking into account economic and societal factors».
3. Principle of application of dose limits:
   «The total dose to any individual from regulated sources in planned exposure situations other than medical exposure of patients should not exceed the appropriate limits recommended by the Commission».

From a critical reading of the above, a few perplexities might arise.

It should be noticed how the Three Principles present a considerable degree of subjectivity, as well as serious difficulties of applicability [65]. In the Principle of Justification, the ICRP does not specify what exactly means “*more good than harm*”, since it is not reported how to gauge the “goodness” of an intentional radiation exposure with respect to the expected benefits. Likewise, the pace “*as low as*

[61] Official website of International Atomic Energy Agency; “*IAEA: History*”.
[62] Official website of International Atomic Energy Agency; “*IAEA: Statute*”.
[63] IAEA; “*Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards*” – IAEA Safety Standards Series No. GSR Part 3, ISBN 978-92-0-135310-8; published in 2014.
[64] ICRP Publication n° 103; “*Recommendations of the International Commission on Radiological Protection (Users Edition)*” – Ann. ICRP 37; published in March 2007.
[65] Lecture notes of the master’s degree course “*Radiation Protection and Safety of Nuclear Plants*” of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.

reasonably achievable" – oftentimes referred to as *ALARA Principle* in nuclear medicine [66], and thoroughly discussed in other ICRP Publications [67], [68] – presents a vague and indefinite purport, therewith left to the medical practitioner's free interpretation (who shall be able to commensurate the risks and the benefits during each radio-therapeutical exposure) [69], [70].

Furthermore, as reported in some medical literature too [71], there ought to be a sort of "Forth Principle" (which might be denoted as "*Principle of the valid alternative*" [72]), namely: if there is a viable alternative to the therapeutical exposure to ionizing radiation, which might bring about the same benefits to the patient, then a radiotherapy treatment should be avoided (and such alternative shall be adopted). Hence, an oncologist ought to opt for a proton therapy treatment only when other approaches for the cure of cancer – surgery, chemotherapy, hormonal therapy or immunotherapy – are expected to be less effective.

Some further considerations can be made on the pace "*…taking into account economic and societal factors*" in the Principle of Optimization, which may sound as a sort of "exception" to the compliance with the ALARA principle. This suggests a link with the branch of biomedical research involving ionizing radiation, wherein the main radioprotectional tenets are seemingly violated [73]. Indeed, in such framework the exposure of the single individual may not be kept *as low as reasonably achievable* whatsoever, but it can be purposely augmented: but the higher detriment towards the single person goes on behalf of the entire community's benefit, which will take advantage from an unnecessary exposure in order to improve their knowledge in the biomedical field – that is to say, in the hope of receiving lower doses in the future by virtue of the acquired experience. Other ethical considerations in this regard can be found in ICRP Publication n°63 "*Radiological Protection in Biomedical Research*" [74]. Moreover, in order to choose the right balance between the individual detriment and the social benefit, it is firstly necessary to understand what "community" means (the

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[66] M. Gholami, V. Karami; "*Addressing as Low as Reasonably Achievable (ALARA) in Pediatric Computed Tomography (CT) Procedures*" – Journal of Research in Medical and Dental Science; published in October 2018.
[67] ICRP Publication n°22; "*Implications of Commission Recommendations that Doses be Kept as Low as Readily Achievable*" – Pergamon Press, Oxford; published in 1973.
[68] ICRP Publication n°26; "*Recommendations of the ICRP*" – Ann. ICRP 1; published in 1977.
[69] M. D. Cohen; "*CT radiation dose reduction: Can we do harm by doing good?*" – Pediatric Radiology; published in February 2012.
[70] D. L. Miller, D. Schauer; "*The ALARA principle in medical imaging*" – Advanced FTIR Spectroscopy, ThermoFisher Scientific; published in January 2015.
[71] M. Gholami, V. Karami; "*Addressing as Low as Reasonably Achievable (ALARA) in Pediatric Computed Tomography (CT) Procedures*" – Journal of Research in Medical and Dental Science; published in October 2018.
[72] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[73] K. Do; "*General Principles of Radiation Protection in Fields of Diagnostic Medical Exposure*" – Journal of Korean Medical Science; published 29 January 2016.
[74] ICR Publication n°63; "*Radiological Protection in Biomedical Research*" – Ann. ICRP 22; published in 1992.

entire world or a single region?), whose definition is not reported in any of the Three Principles.

One may furtherly wonder: it is morally good to partially sacrifice the health of a single individual on behalf of the benefit (along with the medical progress) of the entire community? Even better: how significant such benefit should be, in order to justify an unneeded exposure? Although the IAEA imposes some restrictions on the biomedical research involving ionizing radiation [75], these sociological queries have not been wholly answered yet.

It can be thereby stated that the Three Principles of Radioprotection may serve as guidance during the law-making procedure in the field of radioprotection – as it is occurred in the case of the Italian Legislation [76] – but they utterly lack specificity in quite many facets.

How to measure the ionizing radiation – the concept of dose:

In order to comprehend the prosecution of this work, it is useful to recall the ways in which the energy imparted by radiation can be expressed. The ensuing three definitions of dose can be found in D.Lgs 101/2020, Titolo II "*Definizioni*", Art. 7 [77].

Absorbed dose:

The ionizing radiation is a form of energy: it can be therefore measured for what it is, namely in *joule* [J]. In the usual applications it is convenient to decouple the energy from the mass: it has been thereby introduced the *gray* [Gy], which is the ratio between the imparted energy $\mathcal{E}$ and the receiving mass m. This unit of measurement is called *absorbed dose*, oftentimes denoted with D.

$$D\ [Gy] = \frac{\mathcal{E}}{m}; \qquad\qquad 1\ [Gy] = 1\left[\frac{J}{kg}\right]$$

Just to get a sense of its magnitude: the detriment suffered by the human body after a 1 Gy exposure is quite modest (although not negligible); it can entail a slight decrease in the blood cell count, but the survival of the person is almost certain – even without any medical care. In contrast, an exposure greater than 10 Gy is extremely likely to cause death – even with immediate medical care [78].

[75] IAEA; "Radioactivity in biomedical research" – Official Website of IAEA; last updated in June 2020.
[76] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo I, Art. 1*"; as reported in Titolo 1, Art. 1 (in Italian language): «*Il presente decreto stabilisce […] che il sistema di radioprotezione si basa sui principi di giustificazione, ottimizzazione e limitazione delle dosi.*»
[77] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo II, Art. 7*".
[78] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.

Equivalent dose:

The only knowledge of the absorbed dose cannot be used for an utter quantification of the biological damage: this is because, at equal absorbed dose, different types of particles can cause very different consequences. It has been thereby introduced the concept of *equivalent dose* [79], habitually denoted with H, whose unit of measurement is *sievert* [Sv].

The equivalent dose is defined as the product between the absorbed dose D and a dimensionless quantity QF, named *quality factor*:

$$H\ [Sv] = QF \cdot \frac{\mathcal{E}}{m} = QF \cdot D$$

The quality factor is related to the nature of radiation, to its energy and to its biological effects on the human body. For instance, the quality factor is unitary for photons, whereas it takes the highest value in the case of heavy ions (such as α-particles and fission fragments) [80].

Effective dose:

On account of the different sensitivity of each organ to ionizing radiation, it is necessary a further unit at this purpose: it has been thereby introduced the concept of *effective dose* (habitually denoted with E), which is defined as a weighted average between the equivalent dose H and a dimensionless factor w, named *tissue weighting factor*.

$$E\ [Sv] = \sum_i w_i \cdot H_i$$

As a general rule, the most sensitive cells are the ones with an elevated mitotic index: this is the reason why the tissue weighting factor of the bone marrow is very high (because of the presence of white blood cells, which are ceaselessly regenerating) whilst it is very low for the muscle cells (owing to their slower reproduction rate) [81], [82]. This facet can be summarized in the *Law of Bergonié and Tribondeau*, which claims that

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[79] ICRP publication n° 92; "*Relative Biological Effectiveness, Quality Factor and Radiation Weighting Factor*" – ICRP, 2003. Ann. ICRP 33.

[80] Task Group on Radiation Quality Effects in Radiological Protection, Committee 1 on Radiation Effects, International Commission on Radiological Protection; "*Relative biological effectiveness (RBE), quality factor (Q), and radiation weighting factor (w). A report of the ICRP*" – Annals of the ICRP; published in 2003.

[81] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.

[82] N. Connor; "*What is Direct Effect and Indirect Effect of Radiation*" – Radiation Dosimetry; published 14 December 2019.

the radiation sensitivity of a tissue is directly proportional to the cellular reproductive activity, and it is inversely proportional to the degree of differentiation thereof [83].

Effect of ionizing radiation on human body:

The detriment due to radiation exposure can eventuate by means of two different mechanisms, in accordance with the nature of the elements undergoing ionization: a direct damage in the cellular structure is habitually referred to as *direct effect*, whereas the ionization of living matter by means of other ions (usually water) is denoted as *indirect effect* [84].

Direct effects:

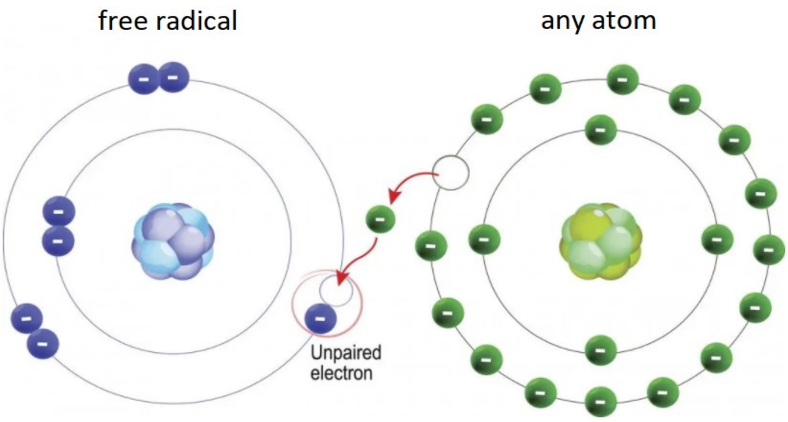

***Figure 10**: chemical reaction between a free radical and a generic atom of living matter.*

The *direct effects* are caused by ionization of the living matter (principally DNA, proteins and lipids [85]) which causes the creation of *free radicals* [86] – *i.e.* biological species lacking one electron in an atomic orbital, typically the outermost one [87]. Owing to their instability, the free radicals are very reactive with the surrounding molecules, by causing a high number of possible diseases and premature signs of aging [88]. **Figure 10** illustrates a free-radical induced chemical reaction into a generic atom of the living matter, which loses an electron.

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[83] J. Bergonie, L. Tribondeau; "*Interpretation de quelques resultats de la radiotherapie et essai de fixation d'une technique rationnelle*" (in French language) – Comptes Rendu de l'Académie des Sciences; published in 1906.
[84] W. M. Dale; "*Direct and indirect effects of ionizing radiations*" – Encyclopaedia of Medical Radiology; ISBN: 978-3-642-99899-7; published in 1966.
[85] I. S. Young, J. V. Woodside; "*Antioxidants in health and disease*" – Journal of Clinical Pathology; published in March 2001.
[86] K. Bagchi, S. Puri; "*Free radicals and antioxidants in health and disease: a review*" – Eastern Mediterranean Health Journal, ISSN 1020-3397; published in 1998.
[87] V. Lobo, A. Patil, A. Phatak, N. Chandra; "*Free radicals, antioxidants and functional foods: impact on human health*" – Pharmacognosy Review; published in December 2010.
[88] D. Harman; "*Aging: a theory based on free radical and radiation chemistry*" – Donner Laboratory of Biophysics and Medical Physics, University of California; published in 1956.

Indirect effects:

The *indirect effects* are more complex, since they are dependent upon the chemistry of the body and many energy loss mechanisms (*e.g.* Compton Scattering and photoexcitation); they are also less immediate than the direct effects. In addition to the prompt damage of DNA molecules, the ionizing radiation can cause the radiolysis of water, by splitting the H_2O molecule in a hydroxyl OH^- and hydron H^+ [89]: these ions thence attack the surrounding living matter, by breaking-up or altering many cellular structures. Owing to their high reactivity, the hydroxyl ions are more prone to attack DNA molecules, by resulting in apoptosis or some genetic mutations [90]. Furthermore, the high percentage of water in the human body (around 50-65% [91]) make the indirect effects possible to a very great extent [92].

■

In accordance with the delay of occurrence and the dose level threshold, the effects of ionizing radiation on the human body can be furtherly categorized in two big classes: the *deterministic effects* and the *stochastic effects*.

Deterministic effects:

The *non-stochastic effects* – term suggested in the ICRP Publication n°26 [93], but nowadays known as *deterministic effects* [94] – can be observed only when the exposure overtakes a certain dose threshold, which is orders of magnitude higher than the dose limits prescribed by law within a proton therapy facility [95]. This is the reason why the deterministic effects can be only observed as a consequence of nuclear accidents or severe inadvertent exposures.

The first evidence of radiation exposure manifests on skin, through a wide spectrum of appearances: the early effects include erythema, inflammation or dry desquamation, whilst the later ones can be ulceration or necrosis [96]. In general the effects on skin

[89] N. Connor; "*What is Direct Effect and Indirect Effect of Radiation*" – Radiation Dosimetry; published 14 December 2019.
[90] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[91] A. M. Helmenstine; "*How Much of Your Body Is Water? What Percentage?*" – ThoughtCo; published 07 September 2021.
[92] J. Ravanat, T. Douky; "*UV and ionizing radiations induced DNA damage, differences and similarities*" – Radiation Physics and Chemistry, Volume 128; published in November 2016.
[93] ICRP; "*Recommendations of the ICRP*" – Publication 26, Ann. ICRP 1; published in 1977.
[94] N. Hamada, Y. Fujimichi; "*Classification of radiation effects for dose limitation purposes: history, current situation and future prospects*" – Journal of Radiation Research; published in July 2014.
[95] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[96] *ibidem*.

become visible for exposure levels greater than 1 Gy, and their severity can be used as a yardstick to perform a first estimation of the received dose.

If the dose level is higher than 1 Gy, the exposure eventuates in a short elapse of time and a large surface of the body is concerned, the deterministic effects may escalate into the *Acute Radiation Syndrome* (ARS) [97]. The prodromal symptoms of the disease include vomiting, nausea, headache and diarrhoea, and their delay of appearance (averagely a few hours after exposure [98]) is an indication of the illness acuteness: the earlier they manifest, the higher the imparted dose has been – and the rarer are the possibilities of patient's full recovery [99].

Stochastic effects:

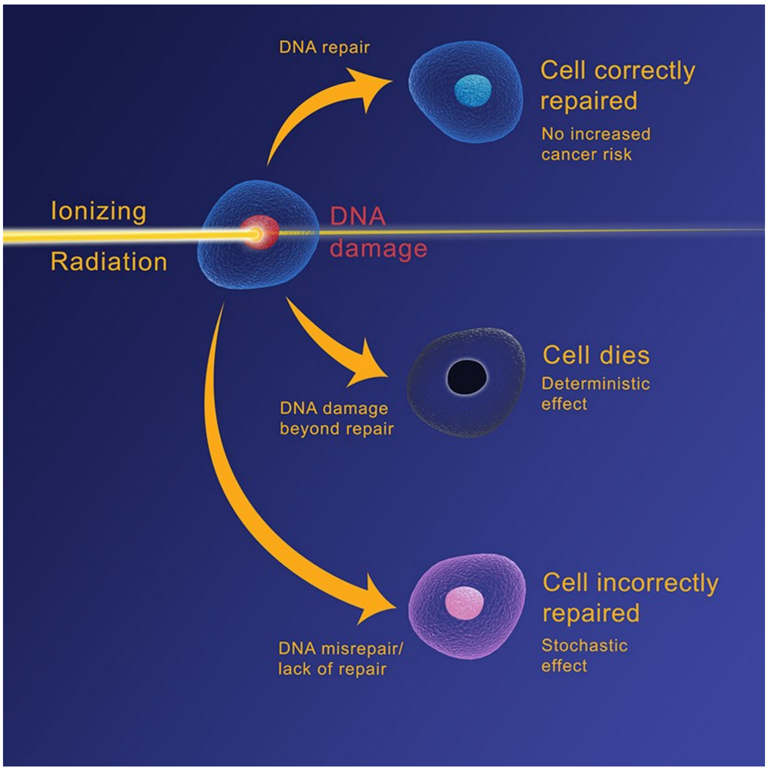

***Figure 11**: all the possible events occurring whenever a radiation beam hits a cell. If the dose is moderate, the cell is successfully repaired. If the dose is very high, the cell dies. In all the intermediate circumstances, the repair occurs only partially, and some genetic mutations may eventuate (which can entail the birth of a neoplastic colony).*

Whenever a radiation beam hits a cell, a certain detriment eventuates. In accordance with the energy of radiation and the cell responsiveness, the detriment can be either repaired or not: in the latter case, the cell simply dies (and this falls in the deterministic effect category). Instead, in the former eventuality, the cellular recovery process can be accomplished either totally or partially. If the dose level was below a certain threshold, the repair concludes successfully, and the cell does not mutate. If the repair is only partial, the cell will survive, but it will keep on functioning in an improper way; the defects will be transmitted to the cell's descendants during reproduction, by giving rise to

[97] B. I. Gerashchenko, V. G. Nikolaev; "*Tackling the acute radiation syndrome: Hemoperfusion with activated carbon revisited*" – Medical Hypotheses, Volume 146; published in January 2021.
[98] *ibidem*.
[99] V. K. Singh, T. M. Seed; "*Entolimod as a radiation countermeasure for acute radiation syndrome*" – Drug Discovery Today, Volume 26, Issue 2; published in January 2021.

genetic mutations of the cell's progeny [100]. The aforesaid cause-and-effect sequence is depicted in **Figure 11**.

Contrary to the deterministic ones, the peculiarity of stochastic effects – as remarked in ICRP Publication n°41 [101] – is the non-existence of a certain dose threshold for their emergence. The ionizing radiation can jeopardize the proper functioning of DNA and the cellular chromosomes, by entailing an alteration of some instructions concerning their reproduction rate, which is governed by the mitotic index [102], [103]. An augmentation of the mitotic index in a bunch of cells implies, as a consequence, a reproduction rate which is higher than ordinary, by leading to the formation of a neoplastic colony. If the number of mutating cells is contained, the human body can succeed in pinpointing and eradicating them: this occurs for low values of the imparted dose, or whenever it is delivered over a long elapse of time (thus giving the organism enough time to repair the detriment, like it is ordinarily scheduled in any proton therapy cycle) [104]. Occasionally, not all the cells are spotted: this is the reason why the stochastic effects can emerge even years or decades after radiation exposure.

■

It shall be remembered that the current knowledge concerning the effects of ionizing radiation on human beings has been built upon the consequences of unintended exposures and nuclear accidents occurred in the past, which (thankfully) have not been so many [105]. This paucity of data, along with their potential inaccuracy – the dose received by a person during an accident is actually an estimation – leaves room to many further questions. For instance, a few studies conjectured the existence of a threshold dose for a few stochastic effects too, like in the case of skin cancer [106]: if there were such threshold, a deterministic-threshold model applied on a stochastic-based phenomenon would overrate the hazard of developing a cancer for exposure levels

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[100] Official Website of Canadian Nuclear Safety Commission: Radiation Health Effects – Government of Canada; published 12 September 2019.
[101] ICRP; "*Nonstochastic Effects of Ionizing Radiation*" – ICRP Publication No. 41, Ann. ICRP 14; published in 1984.
[102] The mitotic index can be defined as the ratio of the number of cells experiencing mitosis to the overall number of cells. In other words, it is the piece of genetical information dictating the reproduction rate of a cell for gemmation (*i.e.* the partition of a cell in other two cells).
[103] W. E. Gerner, R. E. Meyn, R. M. Humphrey; "*The Effects of Ionizing Radiation on the Kinetics of DNA Replication in Synchronized Chinese Hamster Ovary Cells*" – Radiation Research Society, Vol. 60, No. 1, Pag. 62-74; published in October 1974.
[104] A. Mehdipourab, A. Yousefi-Ahmadipour; "*Ionizing radiation and toll like receptors: A systematic review article*" – Human Immunology, Volume 82, Issue 6; published in June 2021.
[105] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[106] R. J. M. Fry; "*The Question of Thresholds for Carcinogenesis*" – Cancer Investigation, Volume 7, Issue 3; published in 1989.

under the said threshold. The content of these studies, albeit reliable, has not been fully substantiated yet.

As a matter of fact, a great deal of the debate rests upon the significance ascribed to the concept of "threshold"; in accordance with ICRP Publication n°103 [107], the threshold is defined as the dose value upon which a detectable effect can be found in at least 1% of the exposed persons. If such definition were to change, it could be claimed that a threshold might not exist for the deterministic effects too. In support of this, several surveys conducted on the bomb survivors of Hiroshima and Nagasaki [108], [109] advanced the hypothesis of an absence of threshold between the incidence of posterior lenticular opacities (*i.e.* cataract) and the neutron and gamma radiation exposure. But, as already mentioned, the samples are usually scant and statistically insignificant.

As far as the latest knowledge is concerned, these are the most accredited trends reporting the incidence of effects as a function of dose, also referred to as *dose-response curves* (**Figure 12**).

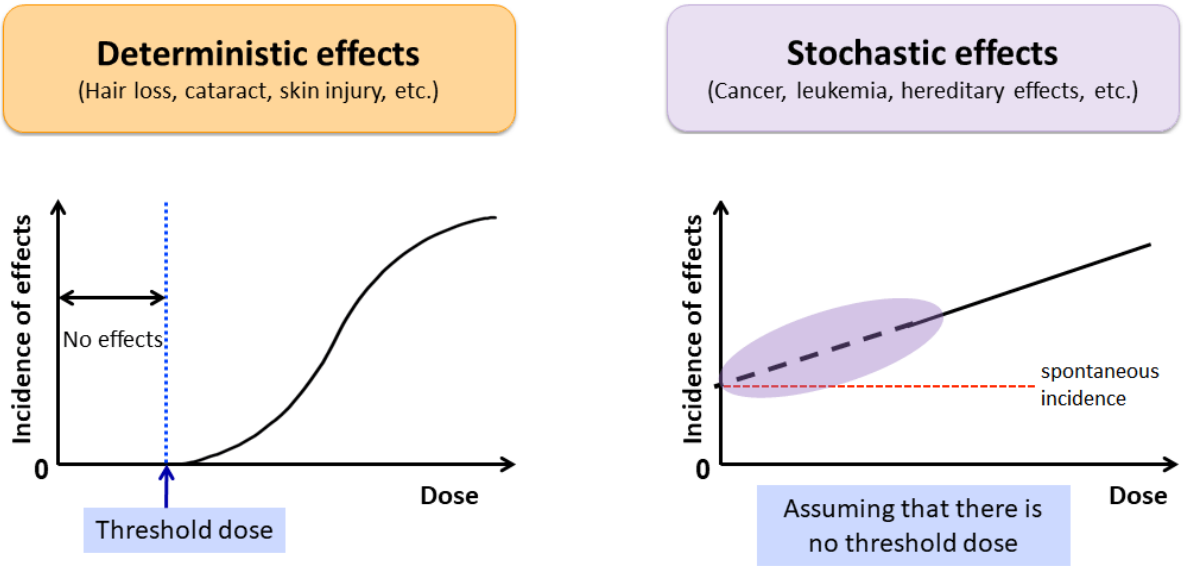

Figure 12*: percentage incidence of effects as a function of imparted dose, on a given sample of exposed persons. On the right: stochastic effects. On the left: deterministic effects. The two upper blocks report a few possible effects of the related category.*

The dashed line in the oval purplish region (chart on the right), wherein the uncertainties are high and few data are available, assumes that the effects of radiation would emerge in linear dependence with the dose levels. The dashed-horizontal red line in the

[107] ICRP Publication n° 103; "*Recommendations of the International Commission on Radiological Protection (Users Edition)*" – Ann. ICRP 37; published in March 2007.
[108] M. Otake, W. J. Skull; "*The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki*" – Radiation Research; published in December 1982.
[109] M. Otake, W. J. Skull; "*Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system*" – Radiation Research; published in January 1990.

stochastic effect chart represents the normal incidence: this is because cancer is a disease occurring also spontaneously [110].

Exposure modes:

Though the little thickness, the skin may offer a valuable protection towards many types of impinging particles, such as α-particles and β-particles. Contrarily, the lack of a protective tissue in the interior of some organs (such as lungs and bronchi) allows a higher detriment to eventuate, by rendering very treacherous the abovementioned particles too [111], [112]. In this respect, the exposure modes have been classified into *external exposures* and *internal exposures*.

An external exposure eventuates every time that the hadron radiation pathway does not concerns internal cavities, and it is directed onto the external skin (or the hair) [113]. This is the exposure mode occurring whenever the accelerator nozzle is oriented toward the tumour, or when the secondary neutron beam inadvertently impinges onto other regions of the body.

As regards the internal exposure, every person during a proton therapy treatment will receive a certain dose internally, since the atmosphere within the facility – as it will be discussed afterwards – is always partially radioactive [114]. A radionuclide may enter the body through several pathways, primarily via the respiratory tract; once inside, it can chemically react with many molecules along its course, by remaining fixed in a few specific organs. The affected organ, and the permanence period therein, is dependent upon the chemical relationship of the radionuclide with the living cells, which also dictates the spontaneous removal velocity (*e.g.* via excreta or exhalation) [115].

A further source of internal dose in a proton therapy facility is represented by dust or aerosol activation [116]. These radioactive contaminants, which can hover in the air for quite a long time, can easily settle on the people's skin and hands, thereby being inhaled or ingested; they may also enter the bloodstream in the eventuality of exposed wounds

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[110] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, M. J. Thun; "Cancer statistics, 2007" – A Cancer Journal for Clinicians; published in January-February 2007.
[111] M. F. L'Annunziata; "Radioactivity: Introduction and history": *Alpha particles* – Elsevier Science B.V, Pag. 71-84; ISBN 9780444527158; published in 2007.
[112] M. F. L'Annunziata; "Radioctivity: introduction and history": *Beta radiation* – Elsevier Science B.V, Pag. 119-140; ISBN 9780444527158; published in 2007.
[113] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[114] B. Mukherjee, R. Hentschel, X. Ding; "Estimation of the air activation in the treatment rooms of proton therapy cyclotrons" – 52nd Annual Conference of the Particle therapy Co-Operative Group-PTCOG 52; Essen (Germany); published in June 2013.
[115] M. G. Stablin; "Radiation protection and dosimetry" – Springer Science & Business Media; ISBN 978-144-1-923912; published 29 October 2010.
[116] IAEA; "Radiological Safety Aspects of the Operation of Proton Accelerators" – Technical Reports Series No. 283; published in 1988.

[117]. If they deposit on people's cloths, the radioactive dust can be brought outside the facility too. In the areas with high secondary neutron radiation (such as the degrader bunker [118]) the dust concentration shall be ceaselessly monitored, since it can be moved by the ventilation system towards non-supervised areas (such as the Gantry Room) [119]. In accordance with some measurements conducted in the CERN Proton Synchrotron, the principal radionuclides detected in a sample of activated dust are ^{7}Be, ^{54}Mn, ^{51}Cr, ^{48}V and ^{59}Fe; the most abundant one is ^{54}Mn (averagely half of the total concentration) [120], [121]. Notwithstanding, with a proper system of ventilation and filtration, and under ordinary conditions of the accelerator, the dust activation (much lower than air activation [122]) is not one of the major concerns [123].

Italian legislation on Radiation Protection:

As remarked by IAEA [124], the dose limit values prescribed by the current Legislation are the cardinal parameters which shall lead the entire shielding design of a proton therapy facility. The Legislation on radioprotection can significatively differ from country to country, along with the dose limits thereof: this monograph will make reference to the Italian regulation up to February 2021.

The Italian Legislation on radioprotection currently in force is the Legislative Decree 31 July 2020 n°101 [125], which conglobates (and reorders) in a unique Text a large number of foregoing Decrees the previous Legislation (such as D.Lgs. 230/1995, D.Lgs. 241/2000 and others) – which was often jumbled and contradictory.

Hereafter, a brief summarization of the current dose limits is reported.

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[117] Official Website of World Health Organization; "*Ionizing radiation, health effects and protective measures*" – published 29 April 2016.
[118] V. Anferov; "*Energy degrader optimization for medical beam line*" – Indiana University Cyclotron Facility, Bloomington, Nuclear Instruments and Methods in Physics Research; published in 2003.
[119] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, No. 1891.
[120] S. T. Charalambus, A. Rindi; "*Aerosol and dust radioactivity in the halls of high-energy accelerators*" – Nuclear Instruments and Methods, Volume 56, Issue 1, Pag. 125-135; published in 1967.
[121] S. T. Charalambus, A. Rindi; "*Airborne radioactivity produced at high-energy accelerators*" – Nuclear Instruments and Methods, Volume 47, Issue 2, Pag. 227-232; published 01 February 1967.
[122] G. R. Stevenson; "*Induced Activity in Accelerator Structures, Air and Water*" – Radiation Protection Dosimetry; published in February 2001.
[123] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, No. 1891.
[124] *ibidem.*
[125] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: attuazione della Direttiva 2013/59 EURATOM*".

Protection of medical personnel:

The medical personnel – defined in the aforesaid Legislation as "*lavoratori esposti"*, Art. 7, Titolo II "*Definizioni*" [126] – are the workers who are susceptible to receive a higher dose on account of the kind of profession they are practising, as specified in Art. 133 of Titolo XI [127].

Indeed, the category of persons who shall be protected the most are the medical personnel: if a patient (together with his/her attendees) may receive a certain amount of secondary radiation in a limited number of occasions during his/her life, a medical practitioner can be exposed to radiation each single day, for many years of one's own working life.

As reported in Art. 146 "*Limiti di dose*" of Titolo XI "*Esposizione dei lavoratori*" [128], an exposed worker shall not receive an effective dose which exceeds:

a) 20 mSv per calendar year;

and, notwithstanding the above-stated limit a), he/she shall not receive an effective dose to specific regions of the body which exceeds:

b) 20 mSv onto the eye lens, per calendar year;
c) 500 mSv onto the skin, per calendar year;
d) 500 mSv onto the extremities (*i.e.* hands and feet), per calendar year.

Protection of general public:

The protection of general public – defined as "*individui della popolazione*" in Art. 7, Titolo II "*Definizioni*" [129] – is normed within Titolo XII "*Esposizione della Popolazione*" [130], which treats and regulates all the general measures as to avoid the population exposure to ionizing radiation.

The dose limit values for the general public are listed in Art. 146 "*Limiti di dose*" of Titolo XI "*Esposizione dei lavoratori*" [131] – even though the section title wherein such limits are reported, namely "*Exposure of the workers*", looks quite improper.

The dose received by a member of the general public shall not overtake:

a) 1 mSv per calendar year;

[126] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo II, Art. 7*".
[127] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo XI, Art. 133*".
[128] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo XI, Art. 146*".
[129] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo II, Art. 7*".
[130] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo XII*".
[131] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101: Titolo XI, Art. 146*".

and, notwithstanding the above-stated limit a), he/she shall not receive an effective dose to specific regions of the body which exceeds:

b) 15 mSv onto the eye lens, per calendar year;
c) 50 mSv onto the skin, per calendar year.

■

It should be noticed that the dose limit values are not the same for all the people: the persons working in the nuclear medicine field (such as oncologists and physicians) are permitted to receive higher annual doses, whilst the limits for the rest of the people are far lower.

Protection of patient:

Although an ordinary patient is meant to be part of the "general public", the situation is different when he/she has to undergo a medical radiotherapy treatment. The protection of people from ionizing radiation in the field of medical applications is treated into Titolo XII "*Esposizioni Mediche*" of D.Lgs. 101/2020 [132]; the ultimate result is that the Italian Legislation, wilfully, does not fix any constraint to the intentional exposure for medical purposes: neither for the dose, nor for the exposure time.

Indeed, this part of the Legislation refers back to the foregoing Principles of Radioprotection: that is to say, the dose to be imparted is a strict responsibility of the oncologist and the other specialists, who shall be able to expertly evaluate the specific situation of each patient and understanding – in conjunction with the Principle of Justification – when the radiation exposure can actually do "*more good than harm*". This particular facet has been emphasized in ICRP Publication n°105 as well [133]. Actually, a dose limit imposed on the individual patient might (paradoxically) bring more detriment than benefit, since a little dose may not be high enough as to eradicate the tumour, but sufficiently elevated as to cause unneeded damage [134].

Furthermore – as highlighted in ICRP Publication n° 103 [135] – a few members of the general public may fall into the medical exposure category too: this is the case of people assisting the patient during or after the treatment (usually his/her relatives, close friends or other caregivers), which might receive a dose due to patient's tissue activation that is higher than the natural background radiation (which is approximatively 6,2 mSv

[132] Gazzetta Ufficiale della Repubblica Italiana; "*D.Lgs 31 luglio 2020, n°101; Titolo XII*".
[133] ICRP Publication n° 105; "*Radiological Protection in Medicine*" – Ann. ICRP, 2007.
[134] ICRP Publication n° 103; "*Recommendations of the International Commission on Radiological Protection (Users Edition)*" – Ann. ICRP 37, published in March 2007.
[135] ICRP Publication n° 103; "*Recommendations of the International Commission on Radiological Protection (Users Edition)*" – Ann. ICRP 37, published in March 2007.

per year [136]). Another issue can be the unintended exposure or embryos/foeti of pregnant women undergoing a radiotherapy treatment, which fall again into the medical exposure category.

[136] Official Website of United States Environmental Protection Agency (EPA); "Radiation Sources and Doses"; updated 09 April 2021.

Radiological hazards in a proton therapy facility

First overview:

Because of ionizing radiation, the only physical presence in a proton therapy facility always exposes people to a certain extent of risk.

As discussed earlier, in reliance on Article III of its Statute [137], the IAEA has the authorization to propose safety standards in the field of radioprotection. In view of that, in 2019 the IAEA issued the publication "*Regulatory control of the safety of ion radiotherapy facility*" [138], which aims at expounding the current best-practises of radioprotection (both technical and behavioural) to be adopted in the management of an ion therapy facility, under a wide range of possible scenarios. Owing to the authoritativeness of the body emanating such document (as well as the document itself), the abovementioned publication will be used as one of the prime references in the development of this chapter.

Another chief publication, designated as a benchmark by IAEA too, is the "*International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Source*", issued and revised by a considerable number of organizations (see the footnote [139]). However, it should be noticed how the technology in nuclear medicine field has profoundly evolved over the past two decades, particularly in the ion therapy sector: new healing strategies entailing higher dose values are emerging (such as *FLASH proton therapy* [140]), the machinery design has mutated, and the footprint of the new accelerators is nowadays more and more compact [141]. These and other technological advancements might question the contents of this last publication, which is quite old (*i.e.* 21 March 1996); notwithstanding, the basic principles of radio-therapeutical safety thereof are still valid.

The foremost hazards within a proton therapy facility are listed hereafter, many of which are dependent and interrelated each other.

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[137] IAEA; "*The Statute of the IAEA: Functions of IAEA*" – approved 23 October 1956, and came into force on 29 July 1957; currently in force (with further amendments).
[138] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[139] IAEA, Food and Agriculture Organization of the United Nations, International Labour Organization, World Health Organization, Nuclear Energy Agency of the Organization for Economic Co-operation and Development *et al.*; "*International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources*", IAEA Safety Series No. 115 – published 21 March 1996; ISBN: 92-0-104295-7.
[140] J. R. Hughes, J. L. Parson; "*FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy*" – International Journal of Molecular Science; published 5 September 2020.
[141] H.X.Q. Norman *et al.*; "*Review of Technologies for Ion Therapy Accelerators*" – ResearchGate; published in May 2021 (University of Manchester, UK).

- neutron radiation production;
- beam losses;
- skyshine and groundshine effect;
- activation of air;
- activation of matter;

Proton-matter interaction mechanism:

Before delving into the perils correlated to the medical employment of heavy ions, it is opportune to recall the possible ways by which a high-energy proton can interact with the surrounding matter. Whenever a proton encounters a nucleus along its path, it can occur:

1. a proton-electron Coulombic interaction;
2. a proton-nucleus Coulombic interaction;
3. a nuclear reaction.

For the sake of completeness, it ought to be mentioned the possible occurrence of Bremsstrahlung Effect – *i.e.* the emission of electromagnetic radiation whenever a charged particle decelerates. Although Bremsstrahlung is theoretically possible, in the therapeutical proton energy range this phenomenon is quite negligible [142], [143].

Proton-electron Coulombic interaction:

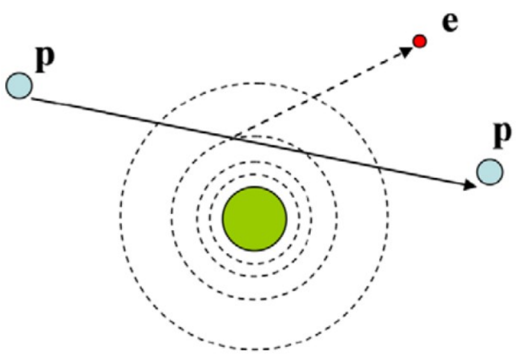

Figure 13*: Coulombic interaction between a proton (in light blue) and an electron (in red).*

As represented in **Figure 13**, the interaction between a proton and an electron does not entail significant changes in the beam direction: this is due to the very little mass of the electron with respect to the one of proton (which is approximatively 2000 times bigger [144], [145]); hence, a limited exchange of momentum takes place. Furthermore, the proton-produced recoil electron (the red particle in **Figure 13**) does not travel much into

[142] W. D. Newhauser, R. Zhang; "The physics of proton therapy" – Physics in Medicine and Biology; published 21 April 2016.
[143] Oral source by Prof. Massimo Zucchetti, Member of Collegio di Ingegneria Energetica of Politecnico di Torino (at 2021).
[144] IUPAC; "Compendium of Chemical Terminology, 2nd ed. (the Gold Book): mass of the proton" – Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997); ISBN 0-9678550-9-8.
[145] IUPAC; "Compendium of Chemical Terminology, 2nd ed. (the Gold Book): mass of the electron" – Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997); ISBN 0-9678550-9-8.

the matter, even for considerable energies of the colliding protons: by way of example, the maximum transferable energy by a 200 MeV proton towards an electron at rest is only 150 keV [146], which corresponds to a displacement of approximatively 2 mm into water (*i.e.*, into the most akin medium to human tissues [147]). Accordingly, it is reasonable to assert that the proton-generated recoil electrons do not constitute any significant radiological hazard.

Proton-nucleus Coulombic interaction:

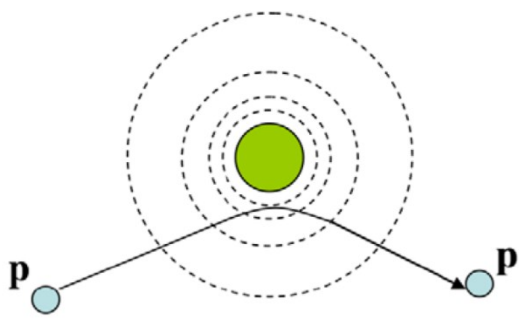

Figure 14*: Coulombic interaction, and subsequent deflection, of a proton (in light blue) with the nucleus of an atom (in green).*

On account of the Coulombic interaction, a proton approaching a nucleus of another atom undergoes a deflection (**Figure 14**). Although the proton does not lose much energy during the single interaction, it can be scattered of a few degrees: it is thereby necessary to pay a great attention to this phenomenon during the design phase, since the multiple scatterings can imply strong deviations of the beam from the targeted region [148].

Nuclear reaction:

From the radioprotectional standpoint this is undoubtedly the most crucial interaction, since it brings about the emission of other particles (**Figure 15**). If the proton energy does not overtake 100 keV, the electrostatic repulsion is likely to impede the proton from approaching the nucleus, and the particle is simply deflected [149]. Instead, if the Coulombic barrier is overpowered, the particle enters the nucleus (which is irreversibly transformed), and it may not be any longer in a stable configuration. In order to attain stability, the emission of one or more particles is required. Within the therapeutical proton energy range, the emitted particles can be another proton, a neutron, ^{2}H, ^{3}H or other heavy ions (such as ^{3}He or ^{4}He) [150].

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[146] W. D. Newhauser, R. Zhang; "The physics of proton therapy" – Physics in Medicine and Biology; published 21 April 2016.
[147] *ibidem*.
[148] H. Paganetti; "Proton Therapy Physics (Second Edition)" – CRC Press ; ISBN 978-036-757078-1; published 30 June 2020.
[149] S. Tavernier; "Interactions of Particles in Matter" – Experimental Techniques in Nuclear and Particle Physics, Pag. 23-53; published 14 September 2019.
[150] D. S. Smith, J. R. Kramer; "Multi-site proton interactions with natural organic matter" – Environment International, Volume 25, Issue 2-3; published in February-April 1999.

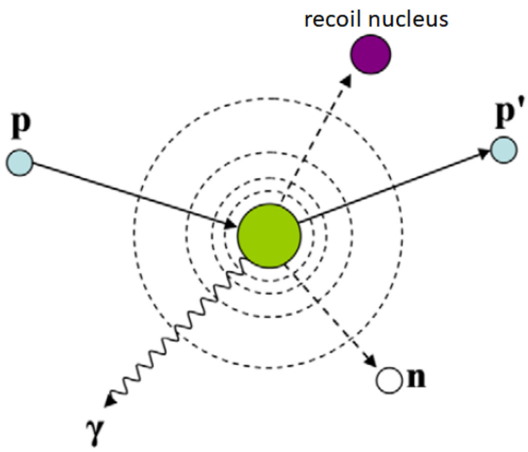

Figure 15*: nuclear reaction between a proton (in light blue) and a nucleus (in green), with subsequent emission of a few typical particles.*

It ought to be noticed how the proton capture implies the removal of such particle from the beam, which causes a decrement in the number of available "projectiles" for the therapy. Notwithstanding, this circumstance is largely compensated by the emission of secondary protons as a consequence of the captures themselves – which can contribute, in an ordinary proton therapy treatment, up to 10% of the total absorbed dose [151].

Neutron radiation production:

One of the foremost concerns in a proton therapy facility is the production of secondary neutron radiation. Because of the considerable energy of primary protons, the secondary neutron beam is highly energetic as well: since the attenuation is inversely proportional to the velocity of the impinging particles, elevated thicknesses of the facility walls are required. As remarked by several Authors [152], the production of neutrons in a proton therapy treatment, with respect to a traditional photon therapy, is a lot higher. The energy of such neutrons is higher as well – in a conventional radiotherapy it can only span from 1 to 10 MeV averagely [153], *i.e.* some tens of times lower with respect to proton therapy. The neutron beam can be very perilous for the patient, since it can augment the likelihood to develop a second radiation-induced cancer.

Another facet which makes the neutron shielding more burdensome is related to their electrical neutrality. Whilst protons, electrons and other charged particles significatively interact during the passage through matter because of Coulombic forces, so it does not occur in the case of neutrons, which can travel longer distances without being perturbed. Actually, the only perturbances are related to the physical collisions with other particles. **Figure 16** illustrates a juxtaposition between the fluence trend related to a 200 MeV proton beam and to a 200 MeV neutron beam in water, achieved by means

[151] W. D. Newhauser, R. Zhang; "*The physics of proton therapy*" – Physics in Medicine and Biology; published 21 April 2016.
[152] M. De Saint-Hubert, C. S. Vargas, O. V. Hoey, W. Schoonjans, V. De Smet, G. Mathot *et al*.; "*Secondary neutron doses in a proton therapy centre*" – Radiatiaton Protection Dosimetry; published in 2015.
[153] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, No. 1891.

of a Monte Carlo simulation [154], [155] (the Monte Carlo Methods will be addressed afterwards).

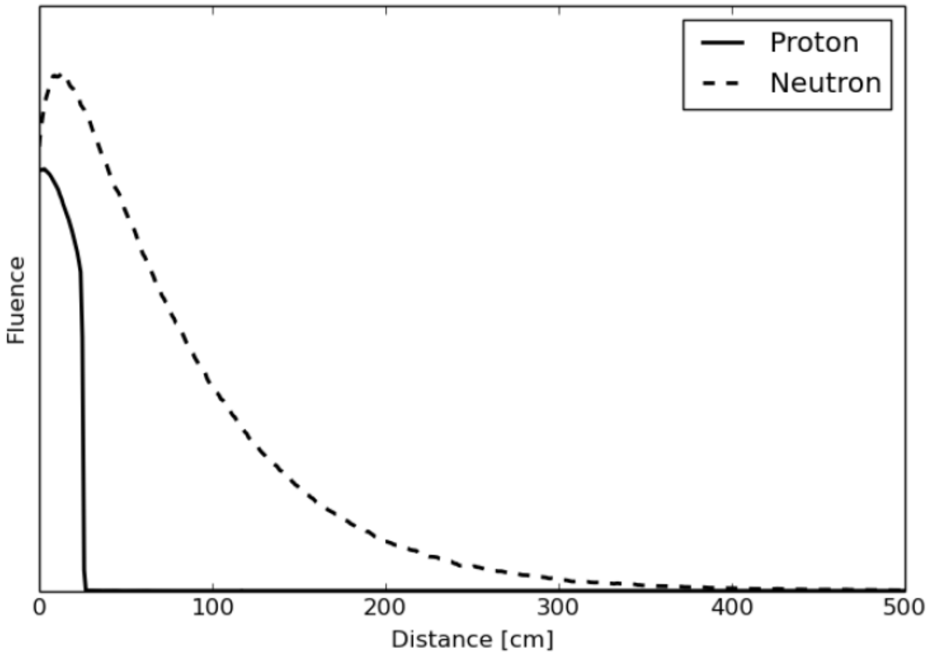

***Figure 16**: Monte Carlo simulation of fluence in water for a 220 MeV proton beam and for a 220 MeV neutron beam.*

In this simulation no proton can overtake the distance of 26 cm, whereas some neutrons may still be travelling after 300 cm. Owing to the near equality of mass in the two particles ($1{,}672 \cdot 10^{-27}$ kg for the proton [156] and $1{,}675 \cdot 10^{-27}$ kg for the neutron [157]), the primary cause rendering the two fluences different can be ascribed to the absence of electrical charge in neutrons.

Into the degrader:

In every proton therapy facility the highest amount of neutron radiation comes from the degrader [158]. Indeed, an undesired effect therein occurring is beam scattering: at equal thicknesses, which entail equal energy degradations, the amount of scattered radiation depends upon the constituting material of the degrader. According to the

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[154] J. A. Brennsæter; "*The Influence of the Energy Degrader Material for a Therapeutical proton Beam*" – Norwegian University of Science and Technology, Department of Physics; published in June 2015.
[155] The *fluence*, oftentimes denoted with Ψ, is defined as the number of particles colliding on a surface; its unit of measurement is usually [cm^{-2}].
[156] IUPAC; "*Compendium of Chemical Terminology, 2nd ed. (the Gold Book): mass of the proton*" – Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997).
[157] IUPAC; "*Compendium of Chemical Terminology, 2nd ed. (the Gold Book): mass of the neutron*" – Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997).
[158] V. Anferov; "*Energy degrader optimization for medical beam line*" – Indiana University Cyclotron Facility, Bloomington, Nuclear Instruments and Methods in Physics Research; published in 2003.

research "*Energy degrader optimization for medical beam line*" performed on the Indiana University Cyclotron [159] (hereinafter referred as "Publ. A"), an estimation of the scattered radiation for a range of different materials can be achieved by means of classical analytical relations, such as the Bethe-Block formula. As a result, the entity of the neutron beam (produced by a 250 MeV proton beam) turns to be directly proportional to the atomic number of the material, which is very low for the light ones: from the radioprotection standpoint, the best solid slowing material is thereby the lithium. However, the very low melting temperature (around 180 °C [160]) makes lithium unsuitable for a degrader. By looking at the periodic table, the second-best candidate is thus beryllium, with a melting temperature of around 1287 °C [161].

It is worth mentioning how the results of Publ. A, achieved through a merely analytical approach, have been drastically refuted by a more recent publication from Norwegian University of Science and Technology [162] (hereinafter referred as "Publ. B"), which has been investigating the influence of the degrader material by means of FLUKA™ approach (*i.e.* a Monte Carlo simulation package for the particle-matter interactions). Such simulation has been conducted for a 250 MeV proton beam as well. Although both Publ. A and Publ. B agree on the dependence of scattered radiation upon the angular spread, the simulation of Publ. B (which has been conducted with an experimental approach) demonstrated how the degrader made up of beryllium generates the highest amount of neutrons – completely at odds with the result of Publ. A.

Be that as it may, the beryllium is a degrader material presently employed in many facilities all over the world, like in the Midwest Proton Radiation Institute in the United States [163]. Notwithstanding, it should be mentioned the extreme perniciousness of beryllium, defined as one of the most noxious elements in all the periodic table [164]; because of mechanical frictions and recurrent thermal stresses (these last ones very common in a degrader), this metal may detach from the degrader surface in the form of dust, thence being inhaled or ingest. A reiterated exposure to beryllium, either during

[159] V. Anferov; "*Energy degrader optimization for medical beam line*" – Indiana University Cyclotron Facility, Bloomington, Nuclear Instruments and Methods in Physics Research; published in 2003.
[160] PubChem; "*National Library of Medicine: Lithium*", PubChem Element Summary for Atomic Number 3, Lithium. Updated 2 October 2021.
[161] PubChem; "*National Library of Medicine: Beryllium*", PubChem Element Summary for Atomic Number 4, Beryllium. Updated 2 October 2021.
[162] J. A. Brennsæter; "*The Influence of the Energy Degrader Material for a Therapeutical proton Beam*" – Norwegian University of Science and Technology, Department of Physics; published in June 2015.
[163] V. Anferov, M. Ball, G.P. Berg *et al.*; "*The Indiana University Midwest proton Radiation Institute*" – IUCF, Bloomington, IN 47408, USA (validated by CERN).
[164] T. P. Taylor, M. Ding, D. S. Ehler *et al.*; "*Beryllium in the environment: a review*" – Journal of Environmental Science and Health, Part A: Toxic/Hazardous Substances and Environmental Engineering; published in February 2003.

maintenance or in the disposal phase, may give rise to many occupational lung diseases (such as Berylliosis) [165].

The employment of plastic materials for the degrader, like the polycarbonate lexan [166], presents a far lower degree of jeopardy, which also offer several advantages in the proton slowdown.

Another common degrader material is carbon, in the form of graphite [167]. Even though graphite is allegedly non-toxic [168], there is the downside of ^{11}C production. This unstable isotope, with a half-life of only 20 minutes [169], can decay either for electronic capture or for positron emission as follows:

$$^{11}C \longrightarrow {}^{11}Be + e^{+} + \nu_e + 0{,}96\,MeV$$

$$^{11}C + e^{+} \longrightarrow {}^{11}Be + \nu_e + 1{,}98\,MeV$$

The relatively short half-life of ^{11}C poses a great radiological concern, with dose rates in the order of [Sv/h] in the proximity of the degrader during beam operations [170]. This is the reason why the thickest walls in a proton therapy facility are the ones of the energy selection system bunker.

Other unstable nuclides produced into a graphite degrader are ^{7}Be and ^{3}H [171], with half-lives of, respectively, 53 days [172] and 12,3 years [173]. The relatively long half-life of ^{3}H (*tritium*) implies a moderate activity rate, which does not constitute an immediate hazard for the personnel. The real concern rises up during the facility decommissioning, or whenever parts of the degrader must be replaced or dismissed: because of their long-time radioactive emission, a safe storage for the activated component and all the related monitoring procedures shall be set up.

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[165] P. Harber, S. Bansal, J. Balmes; "*Progression from beryllium exposure to Chronic Ceryllium Disease: an analytic model*" – Environmental Health Perspectives; published in June 2009.
[166] V. Anferov, "*Energy degrader optimization for medical beam lines*" – Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, vol. 496, no. 1, Pag. 222–227; published in 2003.
[167] J. A. Brennsæter; "*The Influence of the Energy Degrader Material for a Therapeutical proton Beam*" – Norwegian University of Science and Technology, Department of Physics; published in June 2015.
[168] J. K. Kim, J. H. Shin *et al.*; "*28-Day inhalation toxicity of graphene nanoplatelets in Sprague-Dawley rats*" – Nanotoxicology; published in September 2016.
[169] Z. Tu, R. H. Mach; "*C-11 radiochemistry in cancer imaging applications*" – Current Topics in Medical Chemistry; published in 2010.
[170] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[171] *ibidem.*
[172] PubChem; "*National Library of Medicine: Beryllium*", PubChem Element Summary for Atomic Number 4, Beryllium. Updated 2 October 2021.
[173] PubChem; "*National Library of Medicine: Hydrogen*", PubChem Element Summary for Atomic Number 1, Hydrogen. Updated 2 October 2021.

Beam losses:

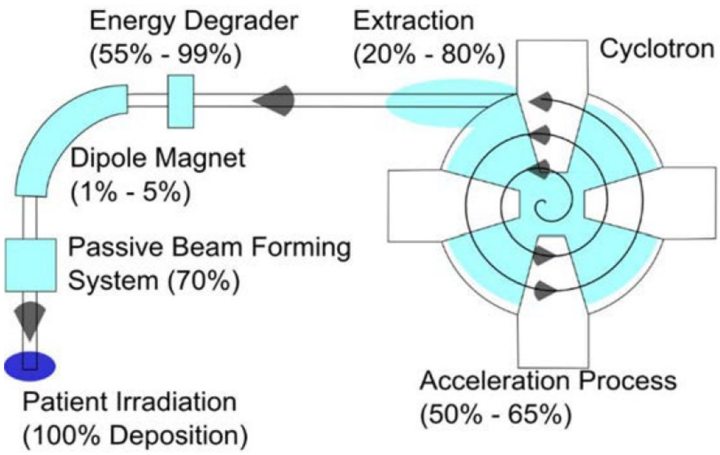

***Figure 17**: indicative beam loss repartition in a proton therapy facility utilizing a cyclotron.*

In a usual ion therapy facility, less than 1% of the generated beam is actually utilized for the treatment [174]: the remnant 99% of ions undergoes several losses throughout the different parts of the equipment, whose localization determines the facility shielding design.

Figure 17 shows a rough repartition of the loss percentages in the components of a facility utilizing a cyclotron.

In the case of a synchrotron, owing to the lack of energy selection system and beam transportation line, the losses are usually more limited [175]. In accordance with the aforesaid publication from IAEA [176], the majority of losses takes place in the region between the exit of LINAC (which pre-accelerates the ions) and the entrance of synchrotron (which brings the ions to the energy level requested for the treatment). The average loss percentages are reported in **Figure 18**.

The evaluation of loss localizations within a synchrotron accelerator can be carried out in several manners. In reliance on some research conducted within an Australian synchrotron in 2018 [177], it has been possible to pinpoint the beam losses on the basis of the Cherenkov Radiation phenomenon [178]: on account of this effect, the original

[174] G. B. Coutrakon; "*Accelerators for Heavy-charged-particle Radiation therapy*" – Technology in Cancer Research and Treatment, Volume 6, Supplement Number 4; ISSN 1533-0346; published in August 2007.
[175] *ibidem.*
[176] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility"* – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[177] P. J. Giansiracusa, M. J. Boland, E. B. Holzer *et al.*; "*A distributed beam loss monitor for the Australian Synchrotron*", Department of Physics and Engineering Physics, University of Saskatchewan (Canada); published 16 December 2018.
[178] The *Cherenkov radiation* is a phenomenon occurring in a material whose molecules get polarized by a travelling charged particle (under certain constraints on the velocity); the result is the emission of electromagnetic radiation, which can be seen with the naked eye too. This is the phenomenon causing the emission of the characteristic blue light inside a nuclear reactor.
About this subject: ⇨ A. P. Kobzev; "*The mechanism of Vavilov-Cherenkov radiation*" – Physics of Particles and Nuclei, published in May 2010.

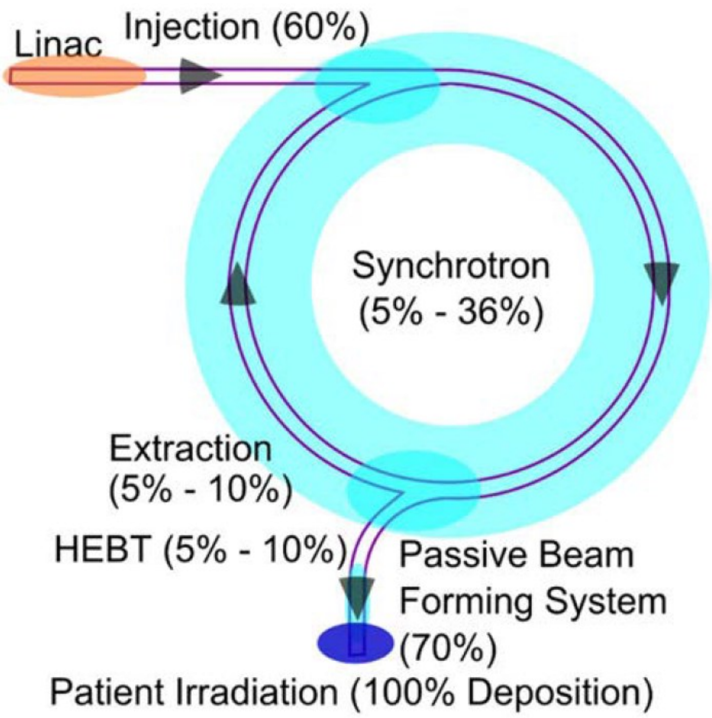

Figure 18*: indicative beam losses in a proton therapy facility utilizing a synchrotron.*

heavy-ion beam produces a photon beam within an array of optical fibre tubes (the so-called *Beam Loss Monitoring System*), which is displaced along the overall length of the synchrotron. At the outset, this tube system was conceived as an only mean to protect the accelerator from perilous beam losses; however, by knowing the precise localization of the emitted photons and the flight time measurement thereof, it is possible to draw information about the placements of such losses. In general, this study confirmed the loss percentage values reported in the IAEA publication [179].

Skyshine effect and groundshine effect:

Whenever a radiation beam is produced within a gaseous mass, like the internal atmosphere of a proton therapy facility, the particles can interact with the air molecules along their path. The multiple collisions cause recurrent shifts in the direction of the radiation beam (along with a progressive decrement of their energy): this phenomenon is called *skyshine effect*. An official definition of skyshine effect can be found in the IAEA Safety Glossary [180].

The chief consequence of the skyshine effect is the exposure to radiation of a certain body, like a person, despite the interposition of a shield along the airline crossing the source and the said body. This specific aspect is depicted in **Figure 19**.

[179] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[180] IAEA; "*IAEA Safety Glossary: 2018 Edition*" – Non-serial publication; ISBN: 978-92-0-104718-2; published in 2018.

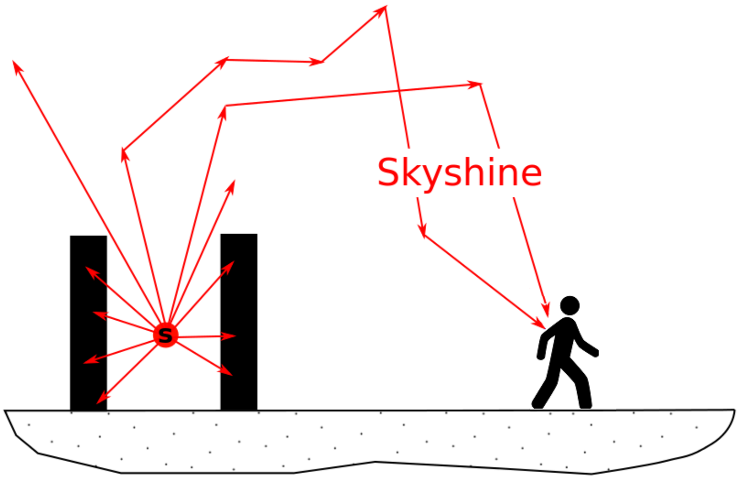

Figure 19*: graphical depiction of the skyshine effect onto a person situated at the exterior of the shielded area.*

Of course, there is no facility which is opened at the top (although the situation was different in the late 1950s, when the skyshine effect was still unknown and the particle accelerators were equipped with little or no roof [181]). Notwithstanding, a certain fraction of radiation beam is always capable of traversing the shielded roof, by posing a hazard for the people and the external environment. The countermeasures to be undertaken against this effect are also dependent upon the typology of surrounding area. As discussed in the paragraph "*Italian Legislation on Radiation Protection*", the dose limits vary in accordance with the category of exposed persons; since such limits are more stringent within the areas meant for the general public, if the surrounding site is not a *controlled area* or a *supervised area* – as defined in the General Safety Guide No. GSG-7 of IAEA [182] – the roof and the shielding walls are supposed to be thicker.

It is very hard to prefigure beforehand the skyshine radiation spatial field, along with the beam arrival point. Apart from the internal layout, it can be also dependent upon weather conditions, since a mutation of the air density may entail different scattering phenomena: this is why this kind of evaluations always rely upon Monte Carlo Methods. One of the most up-and-coming simulation packages purposely developed for the skyshine effect analysis is SHINE-III [183], which permits to carry out dose calculations for neutron beams with an energy up to 3 GeV, with a maximal distance from the source of 2 km.

However, a few empirical correlations for the skyshine effect have been developed too. A very acknowledged formula is the one of G. R. Stevenson and R. H. Thomas [184],

[181] A. Rindi, R. H. Thomas; "*Skyshine: a paper tiger?*" – Health Physics Department, Lawrence Berkeley Laboratory, University of California (USA). Revised by CERN; published 27 May 1975.
[182] IAEA; "*Occupational Radiation Protection, General Safety Guide No. GSG-7*" – IAEA Safety Standards, ISBN 978–92–0–102917–1, ISSN 1020–525X; published in 2018 (Vienna).
[183] T. Tsukiyama, R. Tayama, H. Handa, K. Hayashi, K. Yamada *et al.*; "*SHINE-III : Simple Code for Skyshine Dose Calculation up to 3GeV Neutrons*" – Journal of Nuclear Science and Technology, ISSN 0022-313; published 27 August 2014.
[184] G. R Stevenson, R. H. Thomas; "*A simple procedure for the estimation of neutron skyshine from proton accelerators*" – Health Physics; published in January 1984.

which provides a good estimation of the neutron equivalent dose H in a point located at a distance ℓ from the source:

$$H\ [\mu Sv] = 2{,}8 \cdot \frac{Q}{4}\pi\ \ell^2\ e^{-\frac{\ell}{\lambda}} \cdot \left(1 - e^{-\frac{\ell}{56\ [m]}}\right)$$

wherein Q is the neutron source intensity expressed in $[\mu Sv]$, and the distance ℓ is in $[m]$; λ is the neutron dose attenuation length within the air, which is an energy-dependent parameter: for neutron energies lower than 5 MeV, λ is around 270 m [185]. In order for the correlation to provide reliable outcomes, the distance ℓ must be higher than 50 m [186].

The kind of radiation posing the foremost concerns in the skyshine effect is indeed the neutron radiation. Although the secondary radiation consists of both neutrons and photons, the neutrons are the ones scattering the most with air molecules, as well as giving the highest contribution to the total off-site dose: this facet has been also brought out in a study conducted in the American SLAC National Accelerator Laboratory (which aimed at evaluating the different radiative components of the skyshine effect through the FLUKA™ package) [187].

Additionally, the skyshine effect may be also generated by primary radiation, because of proton beam losses along the beam transportation line or in the adjacent bunkers [188]. The only other plausible scenario wherein the primary radiation can escape the facility may eventuate in the Gantry Room, if the gantry rotational angle implies a direction of the nozzle which is partially upwards. Even though this circumstance is rather uncommon, the primary proton beam certainly causes the so-called *groundshine effect*, namely the external attainment of radiation because of scattering through the ground.

The compresence of the two effects in an ordinary facility is depicted in **Figure 20**.

[185] B. Mukherjee; "*Radiation safety issues relevant to proton therapy and radioisotope production medical cyclotrons*" – Radiation Protection and Environment; published in June 2012.
[186] *ibidem.*
[187] T. T. Liang, C. J. Liu, H. S. Rokni; "*Evaluation of Skyshine from an Accelerator Facility: Dependence on Distance and Angle*" – Health Physics Society; published on 13 December 2019.
[188] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

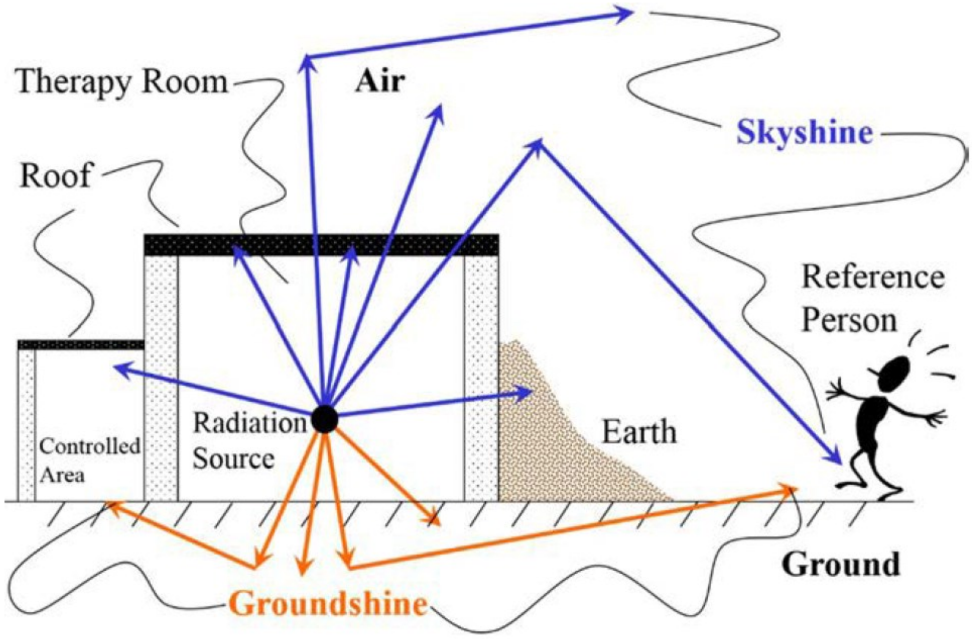

***Figure 20**: graphical depiction of the skyshine effect and the groundshine effect in a bunker of a proton therapy facility.*

Activation of air:

In addition to the scattering phenomenon, the stray radiation is capable of activating the air molecules it interacts with, by producing a variety of radioactive nuclides. The most plentiful ones are ^{11}C and ^{41}Ar, along with lower quantities of ^{13}N, ^{18}F, ^{15}O, ^{7}Be, ^{37}Ar and ^{14}O [189], [190]. These radionuclides are primarily generated by the secondary neutron beam within the accelerator bunker, by means of nuclear and spallation reactions.

The nuclide ^{41}Ar is produced whenever a thermal neutron interacts with ^{40}Ar (*i.e.* the most stable isotope of argon in the air [191]) via the $^{40}Ar(n,\gamma)^{41}Ar$ reaction [192]. Amidst the aforesaid most abundant nuclides, ^{41}Ar has the longest half-life (around 110 minutes [193]): depending upon wind velocity and psychrometric air condition, it has therefore the time to migrate way far from its point of production, by hovering into the atmosphere for a relatively long time. Additionally, the neutron cross-section for the

[189] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[190] W. Roser, B. Amrein, O. Morath; "*Reduction of radioactive waste production of a proton therapy facility*" – Paul Scherrer Institute for Natural and Engineering Sciences (Switzerland); published 08 June 2019.
[191] J. K. Bohlke; "*Variation in the terrestrial isotopic composition and atomic weight of argon (IUPAC Technical Report)*" – Pure and Applied Chemistry; published in January 2014.
[192] B. Mukherjee, R. Hentschel, X. Ding; "*Estimation of the air activation in the treatment rooms of proton therapy cyclotrons*" – 52nd Annual Conference of the Particle therapy Co-Operative Group-PTCOG 52; Essen, (Germany); published in June 2013.
[193] PubChem; "*National Library of Medicine: Argon*", PubChem Element Summary for Atomic Number 18, Argon. Updated 2 October 2021.

reaction $^{40}Ar(n,\gamma)^{41}Ar$ (in the therapeutical secondary neutron energy range) is considerably higher than the others [194]: as discussed later on, ^{41}Ar is an aeriform posing possible issues.

The air activation eventuates on a large scale along the tunnel of the beam transportation line, or wherever the beam losses are higher. In order to hamper the radioactive air leakage from the inside out, a negative pressure gradient within the accelerator bunkers shall be always maintained, conjointly with a moderate ventilation rate [195]: ordinary air exchange values are 0,20 m^3/s [196]; once the accelerator has been shut off, the ventilation rate is forthwith augmented up to 5 m^3/s for a rapid air exchange [197]. The remnant radioactive air is channelled through an ejection network, whereby the internal atmosphere is driven towards a high-efficiency particulate filtering system. This stage aims at lowering the residual radionuclide concentration to the authorized safety levels, which are measured by means of a monitoring system. Ultimately, the radionuclides are dispersed into the environment through a very high chimney on the top of the facility [198]. A further issue of ^{41}Ar is related to the filtering potential: since argon is a noble gas, the scrubbing procedure may be little effective, and the exploitation of chemical reactions for its capture can result unfeasible [199]. Notwithstanding, this turns to be an advantage as regards the internal dose exposure: since argon hardly takes part in chemical processes, it cannot fix within our body during breathing; it can therefore stay in our lungs for the only time intercurrent between an inhalation and an exhalation span.

In any case, the argon constitutes a nearly negligible percentage of the terrestrial atmosphere (approximatively 0,95% [200]), and so it is for the activated argon: on a global scale, its release is not thus so worrisome.

The real concern is the air activation inside the Gantry Room, wherein the presence of the medical practitioners and the patients cannot be avoided. The attendees recurrently breathe the radioactive air, therewith receiving a certain internal dose; the persons are

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[194] C. W. Lee, Y. O. Lee, Y. S. Cho; "*Evaluation of the residual radiation field in the proton accelerator facility of the proton Engineering Frontier Project (PEFP) in Korea*" – Nuclear Instrument and Methods in Physics Research, Section A: Volume 580, Issue 1, Pag. 656-659; published 21 September 2007.
[195] R. J. Sheu, S. H. Jiang; "*Predicting induced radioactivity for the accelerator operations at the Taiwan Photon Source*" – Health Physics; published in December 2010.
[196] Y. Min, C. W. Lee *et al.*; "*Off-gas Ventilation System Design for the Shielding Structure of the 100MeV proton Accelerator of PEFP*" – Journal of Nuclear Science and Technology; published in August 2014.
[197] S. Zhuangab, Q. Wuab, Y. Wang *et al.*; "*Online monitoring of air activation at the China spallation neutron source*" – Journal of Environmental Radioactivity, Volume 234; published in August 2021.
[198] Q. Wu, Q. Wang, J. Wu, Z. Ma; "*Study on induced radioactivity of China Spallation Neutron Source*" – Chinese Physics C, Volume 35, Issue 6, Pag. 596-602; published in June 2011.
[199] R. A. Meck; "*Argon-41 Production by the OSU TRIGA III Reactor*" – General Science and Radiological Physics; published 29 August 1967.
[200] B. G. Fritz; T. R. Alexander *et al.*; "*Comparison of near-background concentrations of Argon-37 and Xenon-133 in the atmosphere*" – Journal of Environmental Radioactivity, Volume 233; ISSN 0265-931X; published in July 2021.

also immersed within a radioactive gaseous mass, which causes an external exposure too. In pursuance of the maximum allowable dose limits, a ceaseless air monitoring in a proton therapy facility – as emphasized by IAEA [201] – is always mandatory. The monitoring process can be accomplished by means of *gamma spectroscopy*, namely the measurement of gamma-ray energies in order to typify the radionuclides [202]: for instance, ^{41}Ar decays in ^{41}K by emitting photons, with an energy of approximatively 1,294 MeV each [203]. The majority of other radionuclides (namely ^{11}C, ^{13}N and ^{15}O) are β^+ emitters: the annihilation of the positron with another electron gives rise to the emission of two photons, each one with an energy of around 0,51 MeV [204]. **Table 1** lists the decay modes and the half-lives of the main air activation products.

Just to get an idea about the activity value magnitudes, the fourth column of **Table 1** reports the results of a Monte Carlo simulation conducted in the tunnel of China Spallation Neutron Source LINAC Accelerator (CSNS) [205], referred to a beam loss value of 1 W/m and to an ordinary air composition [206].

[201] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[202] M. S. Badawiab, A. A. Thabetc; "*Calibration of cylindrical NaI(Tl) gamma-ray detector intended for truncated conical radioactive source*" – Nuclear Engineering and Technology; published 14 October 2021.
[203] PubChem; "*National Library of Medicine: Argon*", PubChem Element Summary for Atomic Number 18, Argon. Updated 2 October 2021.
[204] Y. Gu, W. Lin, L. Ge; "*Electron-positron annihilation ray deduction for airborne gamma-ray spectrometry*" – Radiation Physics and Chemistry, Volume 173; published in August 2020.
[205] J. Wei, H. Chen, Y. Chen *et al.*; "*China Spallation Neutron Source: Design, R&D, and outlook*" – Nuclear Instrument and Methods in Physics Research, Section A: Volume 600, Issue 1, Pag. 10-13; published 21 February 2009.
[206] S. Zhuangab, Q. Wuab, Y. Wang *et al.*; "*Online monitoring of air activation at the China spallation neutron source*" – Journal of Environmental Radioactivity, Volume 234; published in August 2021.

Radionuclide	Half-life	Decay mode	Activity [Bq/m³]	Source for half-life values and decay modes
C-11	20 min	β^+ decay	884	[207]
Ar-41	109 min	β^+ decay and γ decay	8920	[208]
N-13	10 min	β^+ decay	5540	[209]
O-15	2 min	β^+ decay	2040	[210]
Be-7	53 days	ε decay	2,9	[211]
Ar-37	35 days	ε decay	2,3	[212]

***Table 1**: Half-lives and decay modes of the principal air activation products within a proton therapy facility. The activity values come from a Monte Carlo simulation carried out in the tunnel of China Spallation Neutron Source LINAC Accelerator (CSNS), with a beam loss value of 1 W/m and the ensuing mass percentage air composition: nitrogen 75,56%; oxygen 23,16%; argon 1,28%. The simulated air density was 0,001225 g/m³.*

As reported, ^{41}Ar has the highest activity value, as well as a relatively long half-life: this is why ^{41}Ar should be constantly monitored [213]. Conversely, ^{37}Ar and ^{7}Be have even longer half-lives, but their limited activity values make these nuclides not so worrisome.

Activation of materials:

Once a material has been activated, the mass number usually changes. A variation in the atomic number implies the transmutation into another chemical element, which can have nuclear, mechanical, thermal, electric or shielding proprieties totally different. Instead, if the atomic number does not vary, the chemical behaviour remains unaltered, but so it is not from the nuclear viewpoint.

Activation of shielding:

In order to ensure that the activation does not undermine the shielding material functionalities, periodic inspections and material testing throughout the lifespan of the

[207] PubChem; "*National Library of Medicine: Carbon*", PubChem Element Summary for Atomic Number 6, Carbon. Updated 2 October 2021.
[208] PubChem; "*National Library of Medicine: Argon*", PubChem Element Summary for Atomic Number 18, Argon. Updated 2 October 2021.
[209] PubChem; "*National Library of Medicine: Nitrogen*", PubChem Element Summary for Atomic Number 7, Nitrogen. Updated 2 October 2021.
[210] PubChem; "*National Library of Medicine: Oxygen*", PubChem Element Summary for Atomic Number 8, Oxygen. Updated 2 October 2021.
[211] PubChem; "*National Library of Medicine: Beryllium*", PubChem Element Summary for Atomic Number 4, Beryllium. Updated 2 October 2021.
[212] PubChem; "*National Library of Medicine: Argon*", PubChem Element Summary for Atomic Number 18, Argon. Updated 2 October 2021.
[213] IAEA; "*Radiological Safety Aspects of the Operation of Proton Accelerators*" – Technical Reports Series No. 283; published in 1988.

facility shall be scheduled and carried out [214]; indeed, values of the neutron beam fluence in concrete – a common shielding material addressed later on – which are greater than 10^{19} neutrons/cm^2 may have deleterious consequences on many mechanical proprieties thereof, such as the modulus of elasticity [215]. However, as remarked in the previously mentioned IAEA publication [216], the ordinary fluence values within a proton (and hadron) therapy facility do not pose a great concern for the structural integrity of the majority of shielding barriers. Nonetheless, they can be sufficiently high as to trigger off mechanical strains in some apparatuses, such as the delivering nozzle and a few parts of the accelerator. In general, the facility area wherein the shields suffer the highest detriment is the degrader bunker, because of the considerable values of particle fluence therein occurring [217]. Such particles, which are primarily neutrons [218], are able to activate the concrete through several types of nuclear reactions, with the ensuing production of unstable isotopes. According to a study carried out on the Cyclotron and Radioisotope Centre of the Japan Tohoku University [219], the main isotopes produced by a fast or moderated neutron beam impinging onto a concrete shield are ^{22}Na, ^{24}Na, ^{52}Mn, ^{54}Mn, ^{56}Co, ^{60}Co, ^{134}Cs and ^{152}Eu. Their radiological jeopardy depends upon their half-lives and decay modes. A short half-life $t_{1/2}$ poses a hazard in the short-term period, since it entails a large activity value forthwith after the isotope production: this is for instance the case of ^{52}Mn ($t_{1/2}$ = 5,59 days [220]) and ^{56}Co ($t_{1/2}$ = 77,23 days [221]); another hazardous activation product in concrete can be ^{24}Na, with a half-life of only 14,96 hours [222].

The origination of short-lived isotopes within the shielding materials entails the access denial of the affected area for a certain lapse of time. This may be an issue from the productivity standpoint: if a failure eventuates in such areas, the radioactivity levels

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[214] IAEA, Food and Agriculture Organization of the United Nations, International Labour Organization, World Health Organization, Nuclear Energy Agency of the Organization for Economic Co-operation and Development *et al.*; "*International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources*" – IAEA Safety Series No. 115; ISBN: 92-0-104295-7; published 21 March 1996.
[215] H. K. Hilsdorf, J. Kropp, H. J. Koch; "*The Effects of Nuclear Radiation on the Mechanical Proprieties of Concrete*" – Symposium Paper, Volume 55, Pag. 223-254; published 01 August 1978.
[216] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[217] S. Boogert, L. Nevay, W. Shields; "*Simulations of the Activation of a proton therapy Facility Using a Complete Beamline Model With BDSIM*" – Proceedings, 10th International Particle Accelerator Conference (IPAC2019) : Melbourne, Australia; ISBN 978-3-95450-208-0; published 24 June 2019.
[218] J. A. Brennsæter; "*The Influence of the Energy Degrader Material for a Therapeutical Proton Beam*" – Norwegian University of Science and Technology, Department of Physics; published in June 2015.
[219] M. S. Uddin, S. Kamada, M. Hagiwara, T. Itoga, M. Baba; "*Measurements of neutron induced activation of concrete at 64,5 MeV*" – Annals of Nuclear Energy, Volume 36, Issue 8, Pag. 1133-1137; ISSN 0306-4549; published in 2009.
[220] PubChem; "*National Library of Medicine: Manganese*", PubChem Element Summary for Atomic Number 25, Manganese. Updated 2 October 2021.
[221] PubChem; "*National Library of Medicine: Cobalt*", PubChem Element Summary for Atomic Number 27, Cobalt. Updated 2 October 2021.
[222] PubChem; "*National Library of Medicine: Sodium*", PubChem Element Summary for Atomic Number 11, Sodium. Updated 2 October 2021.

might be too high as to permit a prompt maintenance (which shall be deferred). On the other hand, the nuclides with very long half-lives (such as ^{60}Co and ^{152}Eu, $t_{1/2}$ = 5,27 years [223] and $t_{1/2}$ = 13,52 years [224] respectively) are characterized by very low activity values: this can be advantageous as regards the maintenance, since it is possible to approach the shielding materials forthwith after irradiation and without any risk. Notwithstanding, the long-lived activated materials pose significant problems in terms of decommissioning, since their residual radioactivity can drop below the safety levels even after decades. A thorough disquisition concerning the best-practises in the radioactive waste management within a medical facility can be found in the IAEA Safety Standard No. SSG-49, "*Decommissioning of Medical, Industrial and Research Facilities*" [225].

Another facet to be broached regards the heat generated by neutron and photon radiation onto the shielding material. In the case of concrete, the overtemperature might cause the migration and/or evaporation of the water therein contained: the ensuing hydrogen deficiency worsens the neutron moderation potential (and the neutron absorption accordingly), by jeopardizing its shielding capability [226]. The heat can also provoke other sort of detriment, such as cracking and fissuring. In relation to the maximum temperatures attainable on the shielding walls, this issue can be easily overcome during the design phase with a proper distancing from the radiation sources [227].

Activation in electronic components:

Another class of materials very susceptible to the radiation detriment are the electronic components of the monitoring equipment. The radiation can provoke a multifariousness of effects, *e.g.* impairment of memory bits, software glitches, power consumption augmentation, reduction in speed performances, component lifetime reduction, up to the outright unserviceability of the device [228]. The typology of affected components is also dependent upon the energy of the secondary neutron beam: the thermal neutrons can cause detriment in the integrated circuits containing ^{10}B as a dopant [229]

[223] PubChem; "*National Library of Medicine: Cobalt*", PubChem Element Summary for Atomic Number 27, Cobalt. Updated 2 October 2021.
[224] PubChem; "*National Library of Medicine: Europium*", PubChem Element Summary for Atomic Number 63, Europium. Updated 2 October 2021.
[225] IAEA; "*Decommissioning of Medical, Industrial and Research Facilities*" – IAEA Safety Standards Series No. SSG-49, ISBN 978-92-0-110118-1; published in 2019.
[226] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[227] *ibidem.*
[228] M. Bagatin, S. Gerardin; "*Ionizing Radiation Effects in Electronics: From Memories to Imagers*" – CRC Press; ISBN 978-149-8-722636; published 03 September 2018.
[229] G. Yang, K. Wu *et al.*; "*Enhanced Low-Neutron-Flux Sensitivity Effect in Boron-Doped Silicon*" – Experimental and Numerical Modelling of Nanostructures Processing, Structure and Properties; published 05 May 2020.

(owing to the high neutron capture cross section thereof [230]), whilst the fast neutrons may seriously damage the microchip material, by reason of the presence of silicon and oxygen therein [231], [232]. These problematics can be overcome with an adequate choice of the electronic components, which must be purposefully designed to operate within a highly energetic radiation field. Other protection measures comprise circuit redundancy (*i.e.* more than one circuit engaged in the same task) and device shielding [233], [234]; notwithstanding, this last countermeasure may result poorly effective against the secondary photon beam, which is much penetrating. Moreover, the shielding barriers cannot exceed a certain thickness, since the personnel must be able to easily handle the electronic device, like using dials and knobs. Actually there is not much to be done for a complete gamma ray shielding in the electronic components; the only valuable countermeasure is limiting the electronic equipment to the very minimum necessary [235] – as well as relying upon the great deal of experience acquired in the field of nuclear power plants.

Activation in the collimator:

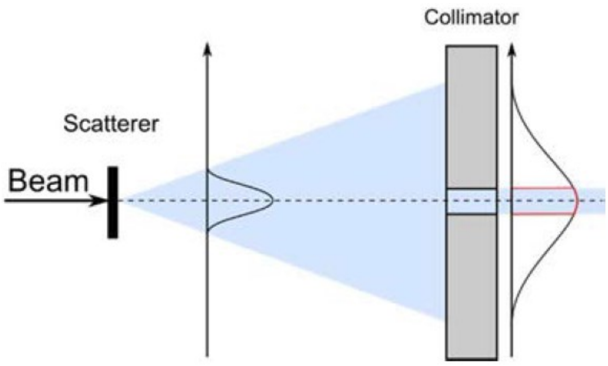

***Figure 21**: passive scattering technique for the beam size magnification during a proton therapy treatment.*

Some piece of equipment which can become a secondary neutron radiation source are the *collimators* (or *apertures*), *i.e.* the parts of the accelerator with the purpose of magnifying the beam size for a whole tumour irradiation. The magnification takes place because of radiation scattering within the collimator itself, usually made up of brass [236]. **Figure 21** shows a graphical sketch of the

[230] S. A. Wynchank, A. E. Cox, C. H. Collie; "*The thermal neutron capture cross section of a natural boron*" – Nuclear Physics, Volume 62, Issue 3, Pag. 491-496; published in February 1965.
[231] A. Volborth; "*Fast-Neutron Activation Analysis for Oxygen, Nitrogen, and Silicon in Coal, Coal Ash, and Related Products*" – Analytical Methods for Coal and Coal Products, Academic Press, 1979, Pag. 303-336, ISBN 978-012-3-999030; published in 1979.
[232] J. Herrington, C. Ferreira, Y. Chen, S. Ahmad; "*Neutron radiation effects on microcomputers in radiation therapy environments*" – Journal of Radiotherapy in Practice; published 08 September 2020.
[233] W. D. Newhauser, R. Zhang; "*The physics of proton therapy*" – Physics in Medicine and Biology; published 21 April 2016.
[234] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[235] H. Spieler; "*Introduction to Radiation-Resistant Semiconductor*" – Ernest Orlando Lawrence Berkeley National Laboratory, Physics Division; published in 2018.
[236] H. Chen, W. Matysiak *et al.*; "*Dosimetric evaluation of hybrid brass/stainless-steel apertures for proton therapy*" – Physics in Medicine & Biology; ISSN 1361-6560; published in 2014.

working principle of such technique (also known as *passive scattering*) [237].

The collimator represents one of the utmost neutron radiation sources in an ion therapy facility [238], and it can notably augment the likelihood of secondary cancer insurgence within the patient's body. In accordance with some experiments conducted in the Massachusetts General Hospital, the neutron dose levels generated by brass aperture activation at the isocentre of the gantry are in the range 0,03-0,13 mSv [239].

In recent times, a few Monte Carlo simulations have been carried out on a bunch of brass apertures in the West Germany Proton Therapy Centre [240], in view of determining the activation products generated within the material. The brass samples have been irradiated with two fixed energy values, namely 100 MeV (the lowest accelerator energy) and 226,7 MeV (the uttermost accelerator energy). At the 226,7 MeV energy level, the activation products with the higher specific activities [241] (*i.e.* one order of magnitude greater than the others) were found to be ^{63}Zn, ^{60}Cu, ^{61}Cu; likewise, for the 226,7 MeV energy level, the ones with the higher specific activity were ^{62}Cu, ^{63}Cu and ^{60}Cu. It is worth mentioning that the outcomes of the abovementioned study show an excellent match with some former investigations conducted by other Authors (M. Baldytchev *et al.* [242]).

The presence of these radionuclides is very hazardous for the personnel: during the superintendence of a treatment, the medical practitioners may touch the brass apertures after irradiation, by receiving a certain amount of dose. As emphasized by IAEA [243], the Legislations shall make compulsory the employment of personal dosimeters for the personnel handling the collimators, or otherwise placed in their close proximity. At the end of the treatment, the collimators are displaced towards an *interim* storage; the storing period therein shall be sufficiently long for the radioactivity to safely

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[237] J. A. Bradley, M. W. Ho, Z. Li *et al.*; "*A Technical Guide for Passive Scattering Proton Radiation Therapy for Breast Cancer*" – International Journal of Particle Therapy, Volume 3, Issue 4; published 11 July 2017.
[238] A. Pérez-Andújar, W. D. Newhauser, P. M. DeLuca; "*Neutron production from beam-modifying devices in a modern double scattering proton therapy beam delivery system*" – Physics in Medicine & Biology, Volume 54, Number 4; published 16 January 2009.
[239] J. Dartz, M. Bangert *et al.*; "*Characterization of a mini-multileaf collimator in a proton beamline*" – Medical Physics; published in May 2009.
[240] C. M. Bäcker, C. Bäumer, M. Gerhardt *et al.*; "*Evaluation of the activation of brass apertures in proton therapy using gamma-ray spectrometry and Monte Carlo simulations*" – Journal of Radiological Protection, Volume 40, Number 3; published 24 July 2020.
[241] The *specific activity* is the number of disintegrations per unit of time and per unit of mass of a given unstable nuclide. It is usually measured in [Bq/kg] (namely [kg^{-1} s^{-1}] in SI units).
[242] M. Baldytchev, P. Bloch, R. Maughan, J. McDonough; "*Activation Induced by proton Interactions in a Multileaf Collimator in proton therapy*" – The International Journal of Medics Physics Research and Practice; published 26 May 2005.
[243] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

decrease, which usually occurs after four or five months [244]. Thereupon, the activated material is moved out of the facility for final disposal or reutilization.

[244] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

Mitigation of risk

First overview:

For an utter comprehension of what follows, one should firstly understand the purport of "to mitigate the risk".

Before all else, what is *risk*?

In accordance with many Authors [245] – even though there is not an agreed definition of this concept [246] – the risk can be deemed as a technical "measure" assessing how far a certain scenario is from *safety*.

But what does *safety* mean?

According to the IAEA Safety Glossary [247] and other Authors [248], [249], the *safety* can be defined as "a condition of total protectiveness", *i.e.* the situation wherein a person is wholly protected from harm, hazard and any undesirable outcome (in this framework represented by the unintended exposure to ionizing radiation). Of course, the concept of "safety" sounds quite utopian, since it is impossible to attain a scenario whereby a person is fully safe: the risk can be subsided (or, how they say, *mitigated*) with the adoption of proper safety countermeasures, but it can never be totally suppressed – this is why the term *acceptable risk* is oftentimes employed [250]. A graphical illustration of the concept of safety, in its notional purport, is given by what in scientific literature is defined as "Parmesan Cheese Model" [251], [252] (**Figure 22**): a person situated on the other side of the parmesan slice finds oneself in a condition of *full safety*. It should be noticed how, in this model, a single barrier is sufficient to reach the purpose, and the failure of the barrier is not contemplated.

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[245] N. Möller; "*Handbook of risk theory*", *The Concepts of Risk and Safety*, Pag. 55-85 – Springer, Dordrecht; ISBN 978-94-007-1432-8; published in 2012.
[246] T. Aven; "*The risk concept: historical and recent development trends*" – Reliability Engineering & System Safety; Volume 99, Pag. 33-44; published in March 2012.
[247] IAEA; "*IAEA Safety Glossary: 2018 Edition*" – Non-serial publication; ISBN: 978-92-0-104718-2; published in 2018.
[248] Y. P. Elagin; "*The concept of safety*" – Atomic Energy, Volume 80; published in June 1996.
[249] M. Boholm, N. Möller, S. O. Hansson; "*The Concepts of Risk, Safety, and Security: Applications in Everyday Language*" – Risk Analysis: an Official Publication of the Society for Risk Analysis, Volume 36, Issue 2, Pag. 320-388; published 18 August 2015.
[250] B. Fischhoff, S. Lichtenstein *et al.*; "*Approaches to acceptable risk: a critical guide*" – Decision Research, Eugene, OR (USA); published 01 December 1980.
[251] Lecture notes of the master's degree course "*Monte Carlo methods, safety and risk analysis*" of Politecnico di Torino, held by Prof. Nicola Pedroni and Prof.ssa Sandra Dulla – academic year 2020/2021.
[252] J. Moloney; "*Error modelling in anaesthesia: slices of Swiss cheese or shavings of Parmesan*" – British Journal of Anaesthesia, Volume 113, Issue 6, Pag. 905-906; published 10 July 2014.

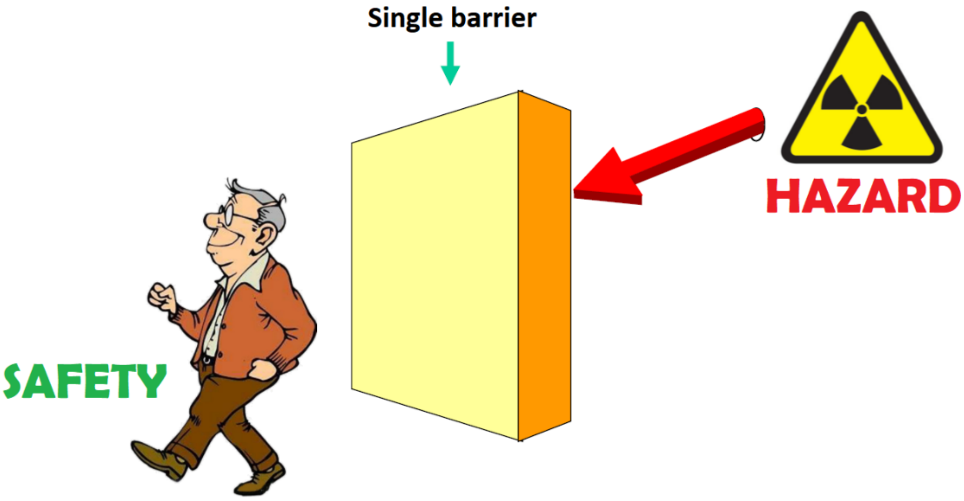

Figure 22: *Graphical representation of the Parmesan Cheese Model principle: the condition of full safety is attained by means of a single barrier. In this model, no failure of the barrier is expected.*

However, the safety of people shall not rely upon a single object. In a proton therapy facility the mitigation process must be accomplished through the employment of multiple barriers (oftentimes referred to as *redundancy* [253]): these can be both physical barriers (*e.g.* radiation shields or hazmat suits) and conceptual barriers (*e.g.* training of the personnel, monitoring devices or evacuation procedures). Though the barrier multiplicity, there is always a certain failure probability in such defences, which implies a nonzero risk: in Safety and Risk Analysis this conception is represented by the "Swiss Cheese Model" [254], [255] (**Figure 23**). The cheese slices represent the multiple barriers, and the holes symbolize potential failures in such barriers (like a damaged neutron shield): if the alignment of all the holes fortuitously eventuates (*i.e.* the contemporary failure of several safety systems), the person is not safe any longer.

[253] Online lessons of Prof. R. Supple; "*Redundancy Systems for Safety Professionals: Definition & Elements*" – *www.study.com*; published 04 April 2020.
[254] T. V. Perneger; "*The Swiss cheese model of safety incidents: are there holes in the metaphor?*" – BMC Health Services Research; published 09 November 2005.
[255] J. Reason; "*Understanding adverse events: human factor*" – Quality in Health Care, Pag. 80-89; published in 1995.

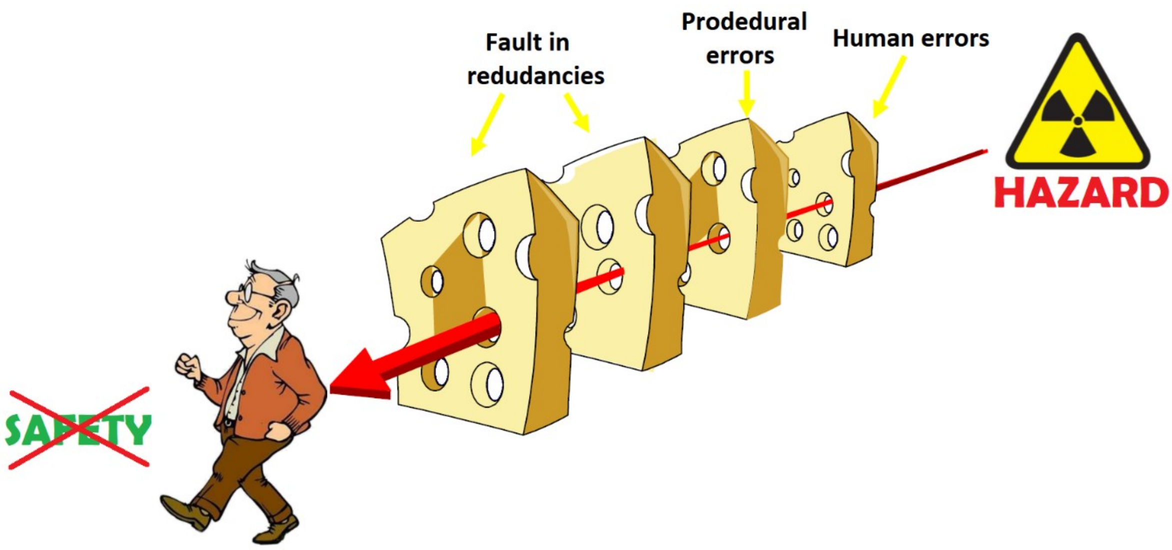

Figure 23*: graphical representation of the Swiss Cheese Model principle. Even though there are multiple barriers, one or more failures in each one may occur; if all the holes are aligned, the person is not safe any longer.*

Safety and Risk Analysis:

The discipline of Safety and Risk Analysis deals with all the aforesaid concepts, by aiming at pinpointing the optimal setup of all the safety systems – in terms of layout, redundancy, failure probabilities, *et cetera* – which exposes the people to the lowest extent of risk [256]. A study of risk analysis is propaedeutic to the commissioning of each facility utilizing hazardous materials or ionizing radiation, and so it is for a proton therapy facility. This analysis shall be performed through a determined step-by-step procedure, which commences with the system boundaries definition and the identification of all the possible risks: this stage can be carried out by means of several methodologies, such as HAZOP [257], HAZID [258], FMECA [259] or historical data perusing (*e.g.* data log of past accidents or scientifical literature).

As mentioned by IAEA [260], the FMECA method (acronym of *Failure Modes, Effects and Criticality Analysis*) is the most suitable one for the risk analysis in a proton therapy facility (regardless the typology of plant, FMECA is actually the most widespread risk

[256] Lecture notes of the master's degree course "*Monte Carlo methods, safety and risk analysis*" of Politecnico di Torino, held by Prof. Nicola Pedroni and Prof.ssa Sandra Dulla – academic year 2020/2021.
[257] F. Crawley, B. Tyler; "*HAZOP: Guide to Best Practice*" – Elsevier; ISBN 978-0-323-39460-4; published in 2015.
[258] F. Crawley; "*A Guide to Hazard Identification Methods (Second Edition)*", Chapter 5: HAZID – Elsevier; ISBN 978-0-128-19543-7; published in 2020.
[259] F. Crawley; "*A Guide to Hazard Identification Methods (Second Edition)*", Chapter 12: Failure modes and effects analysis (FMEA) and failure modes, effects and criticality analysis (FMECA) – Elsevier; ISBN 978-0-128-19543-7; published in 2020.
[260] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

analysis technique [261]). In a nutshell, the FMECA approach aims at identifying all the component failure modes which can, in turn, fail the entire system [262]. Here an example: if a proton therapy facility is devoid of auxiliary power generators, and the electrical-fed air radioactivity control system is thereby relying upon a single power-unit, a failure of such power-unit will fail the entire safety system (*i.e.* the radioactivity levels are not any longer under control, and the people find themselves in a hazardous situation). In this example, in order to augment the reliability of the radioactivity control system, an ancillary power-unit shall be installed accordingly.

Briefly, the FMECA procedure is articulated in three different steps [263]:

1) Splitting up the system in functionally independent subsystems: these can be, for instance, the accelerator nozzle, the degrader, the beam transportation line, the ventilation unit, and so forth.
2) Defining the mission phases of each subsystem (and the expected duration thereof): for example, in the case of the ventilation unit, the mission phases can be the start-up phase, the shut-down phase, the running phase and the maintenance period.
3) Filling out a FMECA table for each subsystem, and for every mission phase thereof: this is the most critical step, since it entails a thorough scrutiny of all the possible failure modes and failure causes of every component in each subsystem; this stage is performed by virtue of the designer's expertise, who shall ascertain not to miss a single failure mode (otherwise the overall system may fail).

By way of example, a portion of a possible FMECA table for the ventilation system of the degrader bunker is herein reported, referred to the "start-up" operational phase (**Table 2**).

[261] Lecture notes of the master's degree course "*Monte Carlo methods, safety and risk analysis*" of Politecnico di Torino, held by Prof. Nicola Pedroni and Prof.ssa Sandra Dulla – academic year 2020/2021.
[262] *ibidem.*
[263] *ibidem.*

SUBSYSTEM: *VENTILATION UNIT OF THE DEGRADER BUNKER*							
OPERATIONAL PHASE: *Start-up*							
COMPONENT	FAILURE MODE	FAILURE CAUSE	CONSEQUENCE			SAFEGUARD	RECOMM.
			LOCAL EFFECT	SYSTEM EFFECT	FACILITY EFFECT		
Pump	Impeller does not start	Electricity blackout	No airflow in the pipe	No airflow in the system	Impossibility of radionuclide removal	Emergency auxiliary power generator	Choose a reliable energy supplier
Suction vent	Fail to open	Vent blocked	No airflow in the pipe	No airflow in the system	Impossibility of radionuclide removal	Redundancy (*i.e.* two suction vents)	Scheduled inspections
Electric power-unit	Wrong electronic signal	Software glitch	Improper start-up	Improper functioning of the ventilation system	Partial or no radionuclide removal	Redundancy (*i.e.* two independent software units)	Periodic software debugging
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

***Table 2**: part of a FMECA table of the ventilation system of the degrader bunker in a proton therapy facility, for the "start-up" operational phase. For the sake of simplicity, the table lacks the "Risk Index" column.*

The "Component" column lists a few possible constituents of the ventilation system, whilst the "Failure Mode" and "Failure Cause" columns are related, respectively, to the reason impeding each component from starting and the associated preventing cause. Thence, the "Consequence" column reports the effects of failure at three different spatial levels. The "Safeguard" indications are linked to the possible preventive or mitigative actions to guarantee the system functionality even when the failure occurs, whereas the "Recommendation" column lists a few pieces of advice to avert such failure.

In each FMECA table there is also the "Risk index" column (not reported in **Table 2**), which assigns a frequency index and a damage index to each failure mode as a function of their criticality: the product between these two indices gives the risk index, which is thence utilized to rank the jeopardy of each failure mode [264].

[264] Lecture notes of the master's degree course "*Monte Carlo methods, safety and risk analysis*" of Politecnico di Torino, held by Prof. Nicola Pedroni and Prof.ssa Sandra Dulla – academic year 2020/2021.

How to mitigate the radiation hazard:

In any scenario involving the exposure to ionizing radiations towards a human being, not only in the nuclear medicine field, there are essentially three countermeasures to undertake for risk mitigation (**Figure 24**):

1) diminishing the time spent by the person in proximity of the radiation source;
2) augmenting the distance between the radiation source and the person;
3) interposing a shield between the radiation source and the person.

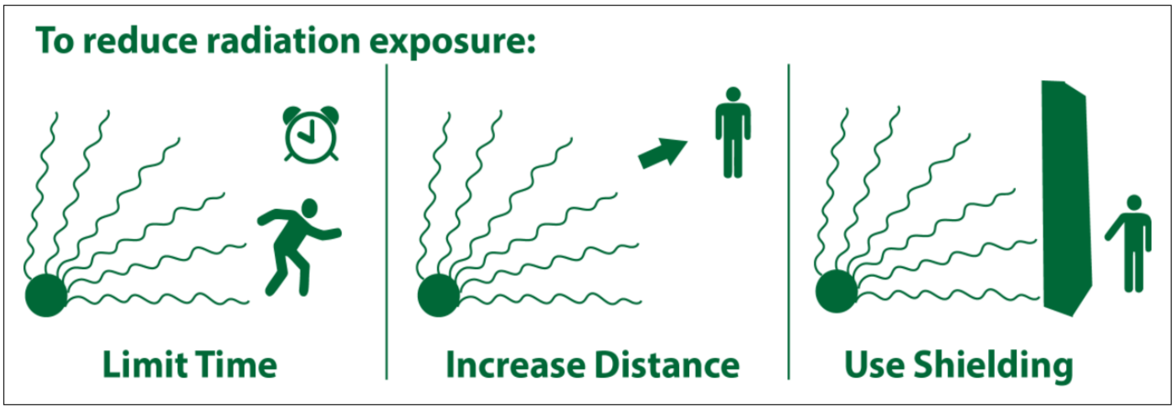

***Figure 24**: Graphical illustration of the "time-distance-shield" principle.*

The "time-distance-shielding" trilogy in the field of radiation safety is one of the chief tenets put forward by several organizations: it is formally discussed in the Specific Safety Guide N° SSG-46 of IAEA Safety Standards [265], adopted as general recommendation by the United States Nuclear Regulatory Commission (USNRC) [266] and the US Environmental Protection Agency (EPA) [267], as well as widely scrutinized by many other Authors [268].

An outline of the principle applicability is expounded hereafter.

Reducing the time:

The reduction of radiation exposure time for the personnel can be lessened with adequate safety measures, although it cannot be totally suppressed: in the course of a proton therapy treatment, the medical practitioners need to execute specific operations in close proximity to the patient, such as device manoeuvring or patient's body

[265] IAEA; "*Radiation Protection and Safety in Medical Uses of Ionizing Radiation*", IAEA Safety Standards for protecting people and the environment, *Specific Safety Guide No. SSG-46*; Vienna, 2018.
[266] USNRC; Minimize Your Exposure – Official website of the United States Nuclear Regulatory Commission; last review in March 2020.
[267] EPA; Protecting Yourself from Radiation – Official website of the US Environmental Protection Agency; last review 21 May 2021.
[268] J. H. Kim; "*Three principles for radiation safety: time, distance, and shielding*" – The Korean Journal of Pain; published in July 2018.

repositioning. These operations can be partially assisted by robotic equipment or other machine-driven systems, like the mechanical arms performing the roto-translation of the patient's bed [269]. However, this kind of automation can be realized till a certain extent, since specific stages of the patient repositioning phase require a manual intervention of the operator; in these circumstances, a certain degree of risk cannot be avoided [270]. As a general rule – as remarked by IAEA and ICRP [271], [272] – the stationing time in proximity of radiation sources in a hadron therapy facility shall be always as little as possible: this is of paramount importance during maintenance within areas with high activity levels, wherein many regulations prescribe a maximum working time for the single operator (or compulsory remote maintenance) [273].

Another successful strategy for the exposure time reduction is the alternation of the personnel during maintenance [274]. If the replacement of a mechanical component in the nearby of a radioactive source requires a certain time (for instance, an hour), the work might be executed by four operators instead of one: this would entail a much lower dose to the single individual, due to its shorter stationing time (in this example only fifteen minutes, thus a four-time smaller dose).

Increasing the distance:

A proper distancing from any radioactive source, such as the accelerator nozzle during beam operation or the activated materials during maintenance, shall be actuated whenever possible [275]. Indeed, this countermeasure provides excellent results for very large distances, since the amount of imparted dose per unit of body area (in the case of a point-like source) is dependent upon the inverse square of the distance. In plain words: whenever a person, for instance, doubles the distance between him/her and the source, the danger diminishes of a factor four (instead of two) [276]. Notwithstanding, this principle cannot be exploited to eschew the jeopardy caused by

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[269] L. Bottura, E. Felcini *et al.*; "*GaToroid: A novel toroidal gantry for hadron therapy*" – Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; Volume 983; published 11 December 2020.

[270] S. Devicienti, L. Strigari *et al.*; "*Patient positioning in the proton radiotherapy era*" – Journal of Experimental & Clinical Cancer Research; published 13 May 2010.

[271] ICRP Publication n°105; "*Radiological Protection in Medicine*" – Ann. ICRP, 2007.

[272] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

[273] IAEA; "*Occupational Radiation Protection, General Safety Guide No. GSG-7*" – IAEA Safety Standards, ISBN 978–92–0–102917–1, ISSN 1020–525X (Vienna); published in 2018.

[274] Lecture notes of the bachelor's degree course "*Fondamenti di ingegneria nucleare*" of Politecnico di Torino, held by Prof. Piero Ravetto – academic year 2017/2018.

[275] IAEA, Food and Agriculture Organization of the United Nations, International Labour Organization, World Health Organization, Nuclear Energy Agency of the Organization for Economic Co-operation and Development *et al.*; "*International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources*", IAEA Safety Series No. 115 – ISBN: 92-0-104295-7; published 21 March 1996.

[276] J. H. Kim; "*Three principles for radiation safety: Time, distance, and shielding*" – The Korean Journal of Pain; published in July 2018.

radioactive air, dust and other aerosols within the internal atmosphere, wherefrom a person cannot easily move away. Additionally, it shall be remembered the skyshine effect and the radiation scattering in general, which can bring the radiation very far from its generation point [277].

Interposing a shield:

This is the most employed countermeasure for the protection of personnel, population and environment outside the facility.

The general shielding design blueprint is carried out with reference to a multifariousness of aspects, such as:

- typology of accelerator;
- intensity of the beam;
- workload;
- maximum energy of the beam;
- arrangement of the shielding;

and many others.

Hereafter, the above-stated constraints are thoroughly investigated.

Typology of accelerator:

The typology of particle accelerator can markedly influence the safety design of the facility, in terms of both shielding layout and shielding thickness.

As formerly discussed, the degrader is one of the biggest sources of secondary radiation. Since a cyclotron accelerator is not capable of modulating the exiting extraction energy, the presence of the degrader is always required. Conversely, a synchrotron accelerator is able to produce protons with variable energies by the only modulation of magnetic and electrical field [278]: the degrader is not a part of the equipment. One might thence assert that the shielding of a facility utilizing a cyclotron ought to entail a greater effort, since a higher secondary neutron beam is generated; notwithstanding, the synchrotrons have usually a bigger footprint, thereby necessitating more walls and more shields in the overall facility [279].

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[277] A. Rindi, R. H. Thomas; "*Skyshine: a paper tiger?*" – Health Physics Department, Lawrence Berkeley Laboratory, University of California (USA); revised by CERN; published 27 May 1975.
[278] J. M. Slater, J.O. Archambeau *et al.*; "*The proton treatment center at Loma Linda University Medical Center: rationale for and description of its development*" – International Journal of Radiation Oncology; published in 2010.
[279] S. Fujumoto; "*Cyclotron versus Synchrotron for Proton Beam Therapy*" – KEK National Laboratory for High Energy Physics 1-1 OHO; published in 2001.

Hence, from the radioprotection standpoint, it is not immediate to establish which kind of particle accelerator needs the lowest precautions.

Intensity of the beam:

This facet is correlated to many different factors, such as the delivered dose in each treatment session. In a single therapy sitting, the imparted dose habitually varies between 5 and 15 Gy [280] – albeit it may attain higher values for tumours in peculiar zones. In reliance on a publication from the British Journal of Radiology [281] (which aimed at assessing the timings and the delays of nozzle operation during a proton therapy treatment), if the logistic times devoted to machinery setting-up and patient preparation are ruled out, the actual period wherein the nozzle releases the proton beam is averagely 2 minutes [282] (but it can be also much higher [283]). This entails an average dose rate in the Gantry Room comprised between 2,5 Gy/min and 7,5 Gy/min, which will be one of the data utilized to dimension the shielding thicknesses.

Nonetheless, as far as the dose level is concerned, a variant of the ordinary proton therapy treatment commenced to take hold lately, called *hypo-fractionating* [284]: this alternative implies a lower number of proton beam sessions for the patient, with a higher delivered dose in each single shot (even though the total delivered dose throughout the entire treatment remains the same). Indeed, the prime cause which have always curbed a higher dose delivery in each session, which ought to speed up the eradication of tumour, is related to the undesired detriment of the healthy cells, and to the body's incapacity to repair the damage in such a short time. Because of the increasing precision of delivering nozzles, accompanied by the technological enhancement of the overall equipment, it is nowadays possible to impart higher doses by leaving nearly unscathed the other tissues [285]. Owing to the higher energy deposition, a proton therapy facility practising the hypo-fractionating delivering technique necessitates shielding surfaces that are thicker and more performing.

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[280] H. Liu, J. Y. Chang; "*Proton therapy in clinical practice*" – Chinese Journal of Cancer; published in May 2011.

[281] A. H. Aitkenhead, D. Bugg *et al.*; "*Modelling the throughput capacity of a single-accelerator multitreatment room proton therapy centre*" – British Journal of Radiology; published in December 2015.

[282] A. Cesana, E. Mauro, M. Silari; "*Induced radioactivity in a patient-specific collimator used in proton therapy*" – Physics Research, Section B: Beam Interactions with Materials and Atoms, Volume 268, Issue 13, Pag. 2272-2280; published 01 July 2010.

[283] IAEA publication; J. Gueulette, A. Wambersie *et al.*; "*Dose reporting in Ion Beam Therapy*" – IAEA-TECDOC-1560; ISBN 978–92–0–105807–2, Vienna; published in 2007.

[284] A. M. Laine, A. Pompos, R. Timmerman *et al.*; "*The Role of Hypofractionated Radiation therapy with Photons, Protons, and Heavy Ions for Treating Extracranial Lesions*" – Frontiers in Oncology; published 11 January 2016.

[285] *ibidem.*

Workload:

In reliance on the aforesaid IAEA publication [286], the workload is one of the leading parameters in the shielding dimensioning of a facility. The actual workload depends upon the number of treatment rooms, the dose imparted in each session and the number of patients to be treated in a certain time. By the knowledge of the workload, it is possible to achieve a rough estimation of the delivered particles in a given operational period (like a workweek).

Let us take a numerical example.

In 2011, a researcher team of the University of Texas carried out a study within the MD Anderson Cancer Centre (Houston, US) [287]. By perusing all the data-logs of the facility in the period 2007-2010, it has been possible to draw up a statistical report on the maximum daily treatment capacity of the hospital; according to their historical archives, such facility is able to treat 133 ± 35 patients per day.

As it stands for any engineering computation, the dimensioning shall be carried out in the most critical conditions. Hence, if the estimation is performed with the maximum capacity and with the highest deliverable dose rate per session (*i.e.* 15 Gy), and by supposing a workweek of 5 days, it turns out a workweek dose $\mathcal{D}$ equal to:

$$\mathcal{D} = 15 \left[\frac{Gy}{patient}\right] \cdot 135 \left[\frac{patient}{day}\right] \cdot 5 \left[\frac{day}{workweek}\right] = 10125 \left[\frac{Gy}{workweek}\right]$$

Maximum energy of the beam:

The energy of the beam is dependent upon the depth and the tumour extension. In the ordinary proton therapy treatments, a maximum depth in the tissues of around 30 cm is required [288]: this entails a kinetics energy of approximatively 220 MeV [289] – although a maximum value of 250 MeV is ordinarily adopted during the

[286] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[287] K. Suzuki, M. T. Gillin *et al.*; "*Quantitative analysis of beam delivery parameters and treatment process time for proton beam therapy*" – The International Journal of Medical Physics Research and Practice; published 30 June 2011.
[288] G. B. Coutrakon; "*Accelerators for Heavy-charged-particle Radiation Therapy*" – Technology in Cancer Research and Treatment, Volume 6, Supplement Number 4; ISSN 1533-0346; published in August 2007.
[289] E. Sengbusch, A. Pérez-Andújar *et al.*; "*Maximum proton kinetic energy and patient-generated neutron fluence considerations in proton beam arc delivery radiation therapy*" – Medical Physics; published in February 2009.

design phase [290]. This is one of the prime parameters determining the shielding thicknesses of the particle accelerator bunker and the energy selection system.

Arrangement of the shielding – Monte Carlo Methods:

Hereafter, a brief outline on the Monte Carlo Methods is presented.

Usually the shielding design of an entire facility presents a very high degree of intricacy. This is due to the unpredictable behaviour of the ionizing radiation into space, and to the considerable number of variables therein involved: the primary proton beam brings about secondary neutron radiation and secondary gamma radiation, which start diffusing into space with a certain angular distribution – very burdensome to be predicted a priori. Such secondary radiation can then impinge onto other materials, by causing nuclear activation; a further beam of "tertiary" radiation is thereby generated, with another own angular distribution. Furthermore, because of the particle emission delay after activation [291], the influence of time shall be also contemplated. In view of the foregoing, it is blatant that an analytical approach for the shielding layout design is nearly unpracticable, and a computational one shall be adopted.

In a nutshell, the Monte Carlo Method is a tool which permits the estimation of unknown quantities by means of random samplings, which are ordinarily performed by non-human computational power. Although such definition may sound too reductive – owing to the high versatility and the multifariousness of applications offered by this tool – it ought to be mentioned that the difficulty of providing an exhaustive definition of Monte Carlo Methods has been already emphasized by several Authors [292].

The employment of Monte Carlo Methods in the field of radiotherapy has considerably growth in popularity over the past few decades, in particular since the 1970s onwards [293]. This is due to the great opportunity to predict outcomes of complex scenarios by means of a calculator, in place of manufacturing physical mock-up prototypes – which can be, sometimes, either expensive or unfeasible.

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[290] M. N. H. Comsan; "*Medical Proton Accelerator Project*" – Nuclear Research Centre, Atomic Energy Authority: Cairo (Egypt); published in 2019.
[291] When a material undergoes activation and becomes radioactive, it does not emit other particles immediately: the velocity of emission depends upon the *decay constant*, which is a nuclear propriety of the specific isotope – and it is independent on its physical and chemical state. The decay constant can be defined as the probability of particle emission per unit of time, and it is usually measured in [s^{-1}].
[292] For instance, as reported in the book "*Monte Carlo Principles and Neutron Transport Problems*" (Addison-Weskey, Reading, 1996), the authors J. Spanier and E. M. Gelbard state that «*it is difficult to construct a definition which characterizes the Monte Carlo method accurately, completely and concisely*».
[293] P. Andreo; "*Monte Carlo simulations in radiotherapy dosimetry*" – Radiation Oncology; published 27 June 2018.

Nowadays the most widespread packages in nuclear medicine for Monte Carlo simulations are GEANT4™ [294], MCNPX™ [295], PHITS™ [296] and FLUKA™ [297].

The particularity allowing the Monte Carlo Method application in radiotherapy (as well as in the nuclear science in general) is the *stochasticity* which governs many nuclear phenomena, like the behaviour of subatomic particles. For instance, it is oftentimes legit to assume that a spherical neutron source, which can be represented by a certain mass of a radioactive isotope, will emit neutrons in an isotropic way [298] – that is to say, each direction of emission has the same likelihood of the other ones, and it does not exist a preferential direction. This facet suggests the possibility of analysing the neutron behaviour by means of a computing simulation, instead of using a real physical source. By virtue of the isotropic emission, the placement of each neutron into the surrounding space can be determined with a random sampling: for every particle, the computer yields three random numbers, which correspond to three spatial coordinates (x, y, z) of its position. If the random sampling is repeated a huge number of times, the behaviour of the real source is thus reproduced.

The abovementioned experiment can be of interest in the field of radioprotection too: if the source were to be surrounded by an absorbing material, such simulation can be employed to determine the thickness of the layer above which a given shielding degree is guaranteed (for instance, so that the operators receive less than 20 mSv/year). Actually, this is the general approach through which the radiation shields are presently designed [299].

Arrangement of the shielding – mazes:

Instead of augmenting the degree of protection by realizing shields that are thicker and thicker, a valid alternative for radiation attenuation is the design of *mazes*.

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[294] S. Agostinelli, J. Allison *et al.*; "*Geant4: a simulation toolkit*" – Nuclear Instruments and Methods in Physics Research; published in 2003.
[295] L. Waters, G. Mckinney *et al.*; "*The MCNPX Monte Carlo radiation transport code*" – AIP Conference Proceedings 896; published 30 March 2007.
[296] T. Sato, K. Niita, N. Matsuda; "*Overview of particle and heavy ion transport code system PHITS*" – Annals of Nuclear Energy, Volume 82, Pag. 110-115; published in August 2015.
[297] F. Ballarini, G. Battistioni *et al.*; "The FLUKA code: an overview" – Journal of Physics Conference Series; published in May 2006.
[298] A. Jeffrey; "*The Solid Angle (Geometry Factor) for a Spherical Surface Source and an Arbitrary Detector Aperture*" – Nuclear Instruments and Methods in Physics Research A, Volume 813; published in March 2016.
[299] H. O. Tekin, M. Karahan, T. T. Erguzel *et al.* ; "*Radiation shielding parameters of some antioxidants using Monte Carlo method*" – Journal of Biological Physics; published 02 July 2018.

By way of example, the shielding layout of the Fukui Prefectural Hospital Proton Therapy Centre (Japan) [300] is shown in **Figure 25**.

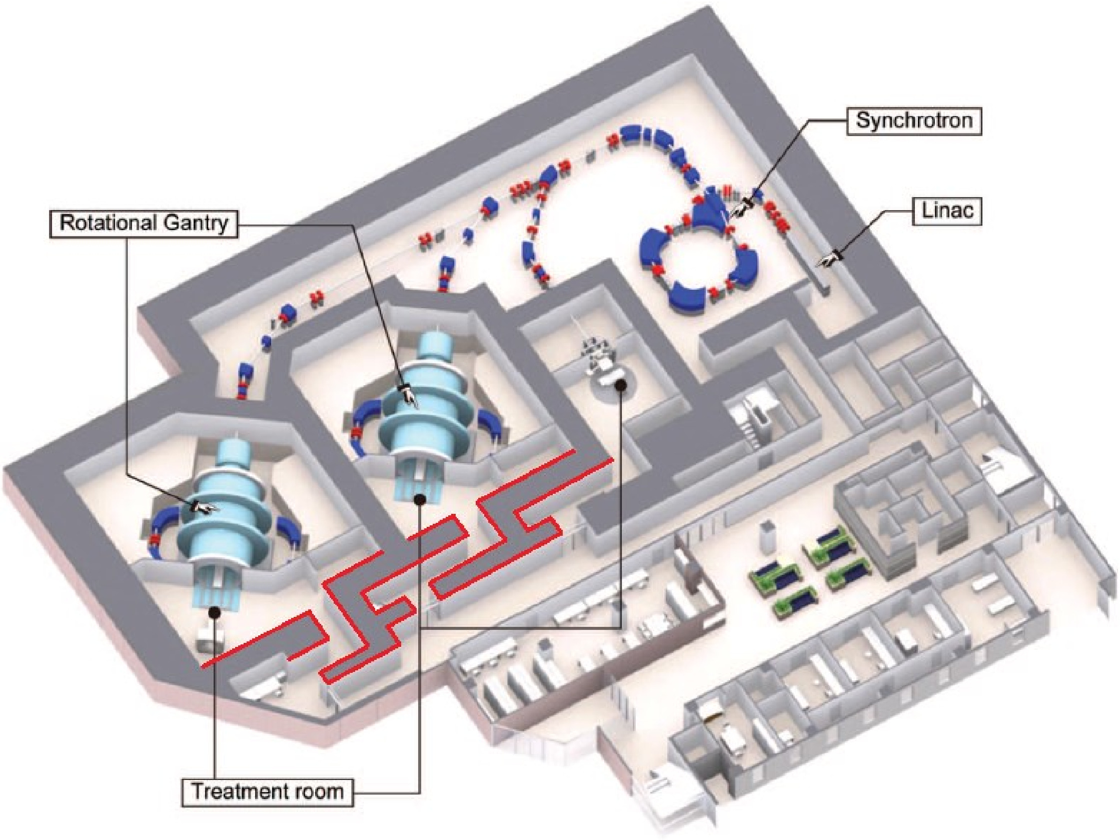

***Figure 25**: layout of Fukui Prefectural Proton Therapy Centre of Japan. One of the shielding mazes is highlighted in red lines.*

To enter each of the two gantry rooms, the person shall pass through the mazes highlighted in red. By the knowledge of the spatial radiation field distribution (which is ordinarily achieved by means of Monte Carlo simulations) it is possible to design a set of walls and shields with proper mutual orientations so as to make the scattered radiation passage more tortuous and unlikely. The mazes are a valid option to the only utilization of shielding doors, which are usually extremely weighty and difficult to be steered. Although a door is compulsory in certain areas of the facility (like the entry of the accelerator bunker, or in the walls facing outwards), the mazes allow a quick deambulation in the nearby of the protected areas with a degree of protection comparable to the shielding doors [301].

Once more, the maze disposition design is carried out with Monte Carlo codes, which allow the simulation of all the possible beam scattering directions against each portion of the maze, for a widespread range of scattering angles. This has been, for

[300] D. Satoh, Y. Maeda, Y. Tameshige, H. Nakashima; "*Shielding study at the Fukui Prefectural Hospital Proton Therapy Center*" – Journal of Nuclear Science and Technology; published in November 2012.
[301] *ibidem.*

instance, the kind of approach employed in the maze design of the Italian hadron therapy facility centre CNAO of Pavia [302].

Another crucial facet to be addressed is the presence of ducts through the walls of the mazes, which cause great discontinuities in the shielding material by acting as preferential pathways for the radiation passage. They can be the pipelines of the ventilation system, the raceways for electrical feeding, and all the hydraulic net for the cooling-down of some components; unfortunately their presence cannot be avoided. During the past, when the computational power for complex Monte Carlo simulations was not easily accessible, several Authors [303], [304], [305] endeavoured to analytically describe such problem: this is the case of K. Goebel *et al*. [306], which set forth, in the late seventies, a model for a first evaluation of the dose rate due to radiation leakage through the accessing ducts of the CERN Super Proton Synchrotron. The estimation passed through the plotting of the *universal transmission curves* (**Figure 26**): these charts report the dose attenuation factor as a function of a "corrected" distance, namely the ratio between the geometrical distance d from the tunnel entry and the square root $\sqrt{A}$ of the tunnel cross section.

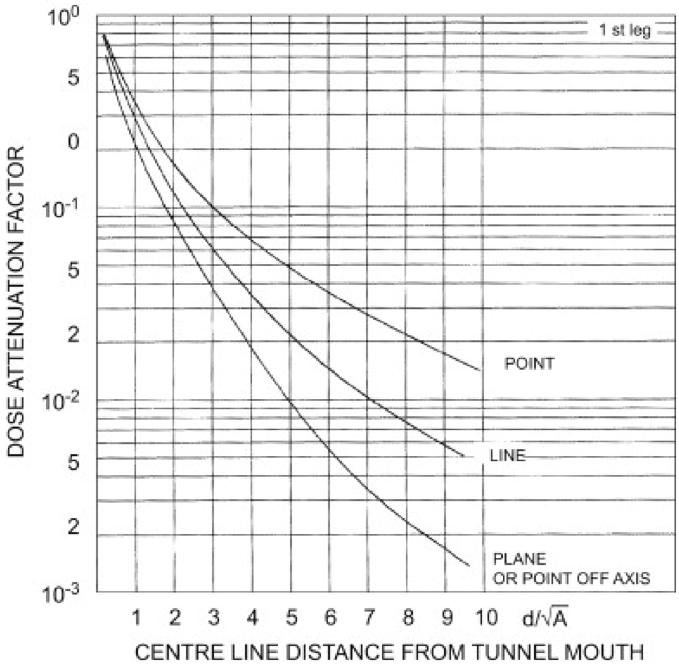

Figure 26*: universal transmission curves proposed by CERN for the estimation of the dose attenuation factor in a duct, as a function of the ratio between the geometrical distance from the entry and the square root of the duct cross section.*

[302] A. Porta, S. Agosteo, F. Campi; "*Monte Carlo simulations for the design of the treatment rooms and synchrotron access mazes in the CNAO Hadrontherapy facility*" – Radiation Protection Dosimetry, Volume 113, Issue 3; published 15 February 2005.
[303] T. Yamazaki, F. X. Massé, G. L. Fallon; "*A duct-streaming formula for neutrons in mazes*" – Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; Volume 248, Issues 2-3; ISSN 0168-9002; published in 1986.
[304] W. E. Selph, H. C. Claiborne; "*Methods for calculating effects of ducts, access ways, and holes in radiation shields*" – Oak Ridge National Laboratory; published 01 January 1968.
[305] K. Shin; "*Evaluation Formula for Radiation Duct Streaming*" – Journal of Nuclear Science and Technology, ISSN 0022-3131; published in December 1989.
[306] K. Goebel, G. R. Stevenson, J. T. Routti, H. G. Vogt; "*Evaluating dose rates due to neutron leakage through the access tunnels of the SPS*" – CERN Archives, Bldg. 61-S-001-O0229; published in 1975.

Some years later, as early as the computational power became more affordable, several studies questioned the accuracy of such curves [307], which show little consistency with the experimental results in a few specific scenarios (for instance, whenever the source is placed facing the duct).

Neutron shielding principle:

The neutron shielding principles, with respect to other particles, present a higher extent of complexity. As already mentioned, the neutron has no electric charge: it is thereby unfeasible to exploit the Coulombic interactions to halt them. Depending upon the energy of protons during a therapy treatment, which can span between 50 and 350 MeV [308], the energy of secondary neutrons is comprised in an even wider range, namely from some fractions of keV (the *thermal neutrons*) up to several hundred MeV (the *fast neutrons*) [309], [310] – even though the majority of them have energies lower than 10 MeV [311]. The capture of a fast neutron can be technically burdensome, because in its energetic state a scattering interaction is more likely than a capture interaction [312]: the likelihood of these two occurrences is dictated by the *neutron cross section* value (see the footnote [313]), which is strongly dependent upon the energy. Apart a few singularities, as a general rule the neutron cross section diminishes when the energy of neutrons augments: this is the reason why these particles are usually slowed down before being captured. Additionally, the absorber material might emit gamma radiation after a capture reaction, which requires further shielding too.

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[307] E. Mauro, M. Silari; "*Attenuation of neutrons through ducts and labyrinths*" – Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; Volume 608, Issue 1; published 01 September 2009.
[308] D. R. Grimes, D. R. Warren, M. Patridge; "*An approximate analytical solution of the Bethe Equation for charged particles in the radiotherapeutic energy range*" – Scientific Report; published in 2017.
[309] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility"* – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[310] H. Chen, W. Matysiak *et al.*; "*Dosimetric evaluation of hybrid brass/stainless-steel apertures for proton therapy*" – Physics in Medicine & Biology; ISSN 1361-6560; published in 2014.
[311] H. Paganetti; "*Range uncertainties in proton therapy and the role of Monte Carlo simulations*" – Physics in Medicine & Biology; published 07 June 2012.
[312] D. R. McAlister; "*Neutron Shielding Materials*" – PG Research Foundation, Inc. 1955 University Lane Lisle, USA; published 25 February 2016.
[313] The neutron cross section can be defined as a "probabilistic" area which quantifies the likelihood of interaction between an incident neutron and the nucleus of a targeted isotope. In the SI, its unit of measurement ought to be [m^2], but it is commonly expressed in [barn]. 1 [barn] = 10^{-28} [m^2]. The neutron cross section can be referred to the scattering probability (*scattering cross section*), to the capture probability (*capture cross section*) or both of them (*absorption cross section*). The summation of all the cross-section values related to each possible type of interaction is denoted as *total cross section*, which represents the overall probability of interaction. || Reliable data on the neutron cross section values can be found in the ENDF/B-VII.1 Library (ScienceDirect): "*Nuclear Data for Science and Technology: Cross Sections, Covariances, Fission Product Yields and Decay Data*", Volume 112, Issue 12, Pag. 2887-2996 – published in December 2011 by M. B. Chadwick *et al*.

The trend of the total neutron cross section as a function of neutron energy, for some typical isotopes employed in neutron shielding, is reported in **Figure 27**.

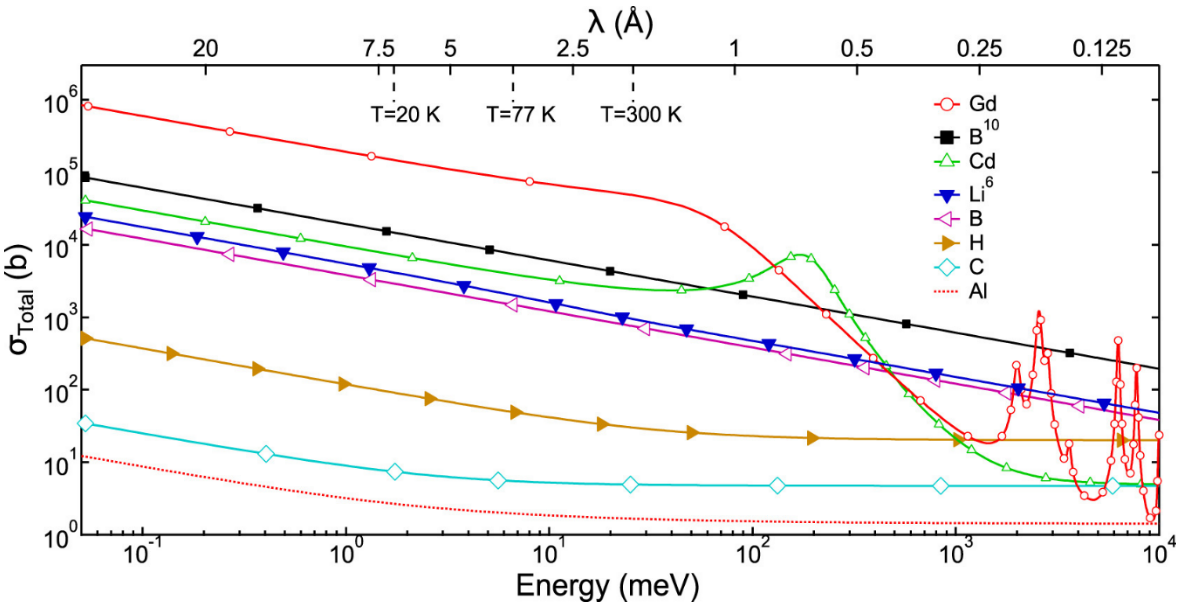

Figure 27*: trend of the total neutron cross section (in logarithmic scale) as a function of neutron energy for several isotopes used in neutron shielding.*

In this chart it is possible to appreciate the so-called *resonance region* of Gadolinium (Gd), represented by the swinging trend of the cross-section values for the highest neutron energies. For other isotopes, such as boron and lithium, the inverse proportionality is always respected.

In view of the foregoing, the design of a neutron shield passes through three different stages: the right isotope for the slowdown, the right isotope for the absorption and a proper one for gamma-ray shielding.

Slowdown phase:

As known from physics, in any collision (both elastic and inelastic) the total momentum must be conserved [314]: the greater is the momentum exchange, the higher is the neutron slowdown, and the smaller is the number of required collisions for the neutron to attain the thermal energies. In order to achieve a large momentum exchange, the masses of the two particles shall be alike: that is why the best materials for neutron slowdown are the ones with an elevated percentage of hydrogen – like it occurs in the moderator of many nuclear reactors [315] – since the mass of proton therein contained

[314] P. Mazzoldi, M. Nigro, C. Voci; "*Fisica",* Volume I, Edition II – EdiSES; ISBN 978-88-7959-137-9; published in 1998.
[315] In a nuclear reactor the *moderator* is the medium devoted to the slowdown of neutrons, which occurs because of a huge number of collisions within it. A few common examples of moderators are water and solid graphite.

is akin to the mass of neutron. The neutron slowdown material *par excellence* is water, in virtue of the high hydrogen percentage thereof [316]: on average, a neutron can drop almost 50% of its initial kinetic energy during a single collision with an atom of hydrogen [317]; this last one is actually the element requiring the least number of collisions for a neutron to reach the thermal energy state [318]. Anyhow, the selected material must offer particular mechanical proprieties too, since it shall fulfil given structural functions (like sustaining the weight of the roof): this is why the concrete is another good candidate, by virtue of its high-water content (averagely 10-20% by weight [319]).

In other scenarios the concrete-based shielding materials are too heavy to be manoeuvred; for instance, they are totally inadequate for personal protection devices, where lightweight and compactness are outright priorities [320]. This is why in recent times the focus has shifted towards the *polymers*, owing to their significant hydrogen content and many other qualities, such as environmental-friendliness, suppleness, high resistance to corrosion and a low degree of toxicity [321], [322]. A very effective shielding polymer is polyethylene (PE), one of the most common plastics all over the world [323]; this material can be also admixed with the concrete of the shielding walls, by enhancing the fast neutron slowdown in conjunction with hydrogen. Notwithstanding, polyethylene presents poor thermal and mechanical proprieties and, on account of its low atomic number, the total inadequacy in gamma-ray shielding. This facet can be partially overcome by incorporating high atomic number elements in its polymeric lattice, such as lead, wolframium, bismuth or barium [324].

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[316] X. Fu, Z. Ji, W. Lin, Y. Yu, T. Wu *et al.*; "*The Advancement of Neutron Shielding Materials for the Storage of Spent Nuclear Fuel*" – Science and Technology of Nuclear Installations, vol. 2021, Article ID 5541047, 13 pages, 2021; published 07 May 2021.
[317] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti – academic year 2019/2020.
[318] P. Rinard; "*Neutorn interaction with matter*" – Los Alamos National Laboratory; published in 1998.
[319] H. K. Hilsdorf; "*A method to estimate the water content of concrete shields*" – Nuclear Engineering and Design, Volume 6, Issue 3, Pages 251-263; ISSN 0029-5493; published in October 1967.
[320] O. Mehellia, M. Derradji *et al.*; "*Outstanding thermal neutrons shields based on epoxy, UHMWPE fibers and boron carbide particles*" – Applied Radiation and Isotopes, Volume 176; published in October 2021.
[321] M. I. Sayyed, M. M. Taki *et al.*; "*Fabrication, characterization of neutron and proton shielding investigation of tungsten oxide dispersed-ultra high Mw polyethylene*" – Chemical Physics, Volume 548; published 01 August 2021.
[322] D. Sariyer, R. Küçer, N. Küçer; "*Neutron Shielding Properties of Concretes Containing Boron Carbide and Ferro – Boron*" – Annals of Nuclear Energy, 53, Pag. 135-139; published in 2013.
[323] S. Hashmi, I. A. Choudhury; "*Encyclopedia of Renewable and Sustainable Materials*"; Elsevier, ISBN 978-0-12-813196-1; published in 2020.
[324] M. R. Kaçal, F. Akman; "*Evaluation of gamma-ray and neutron attenuation properties of some polymers*" – Nuclear Engineering and Technology, Volume 51, Issue 3; published in June 2019.

Absorbtion phase:

The ideal neutron absorbing material must have an elevated neutron capture cross section in the range of thermal energies: this is for instance the case of cadmium, lithium, gadolinium or boron [325], but also other minerals such as datolite, colemanite and galena, which are presently used as aggregates into the concrete shielding of many proton therapy facilities [326].

As regards boron, this element can be found in nature in the form of two stable isotopes, namely ^{10}B and ^{11}B (with percentage abundances of around 20% and 80% respectively [327]). Unlike ^{11}B, the isotope ^{10}B has a huge neutron capture cross section for the reaction ^{10}B(n,α)^{7}Li in the thermal energy range (about 3840 barns, *versus* 0,005 barns for ^{11}B [328]), which renders ^{10}B a first-rate neutron absorber.

(Parenthetically, ^{10}B is largely employed in many other areas of nuclear industry, like in the reactivity control of nuclear reactors [329]. In the oncologic field, this nuclide has been recently utilized in a very up-and-coming technique for the cure of tumour: the *Boron Neutron Capture therapy* [330].)

During the reaction ^{10}B(n,α)^{7}Li, the isotope ^{10}B captures a thermal neutron, by attaining the metastable state ^{11}B* for a short little while:

$$ {}^{1}_{0}n \ + \ {}^{10}_{5}B \ \longrightarrow \ {}^{11}_{5}B^{*} $$

Thereafter, ^{11}B* can decay in two different ways into its energy ground state [331]:

$$ {}^{11}_{5}B^{*} \ \longrightarrow \ \begin{cases} {}^{7}_{3}Li \ + \ {}^{4}_{2}\alpha \ + \ \gamma(2{,}79 \ MeV) \\ \\ {}^{7}_{3}Li^{*} \ + \ {}^{4}_{2}\alpha \ + \ \gamma(2{,}31 \ MeV) \end{cases} $$

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[325] D. R. McAlister; “*Neutron Shielding Materials*” – PG Research Foundation, Inc. 1955 University Lane Lisle, USA; published 25 February 2016.
[326] R. Mehrnejad; “*Improving Neutron Shielding Capacities of Datolite and Galena by Boron Carbide Additive for Nuclear Reactor Biological Shielding*” – Journal of Physical Chemistry & Biophysics, Volume 9, Issue 2, No. 278; published 08 December 2019.
[327] PubChem; “*National Library of Medicine: Boron*”, PubChem Element Summary for Atomic Number 5, Boron. Updated 02 October 2021.
[328] R. S. Carter, H. Palevsky *et al.*; “*Thermal Neutron Absorption Cross Sections of Boron and Gold*” – Physical Review Journals, Volume 92, Issue 3; published 01 November 1953.
[329] H. Yu, H. Ju *et al.*; “*Study of boron diffusion models and dilution accidents in nuclear reactor: A comprehensive review*” – Annals of Nuclear Energy, Volume 148; published 01 December 2020.
[330] T. D. Malouff, D. S. Seneviratne *et al.*; “*Boron Neutron Capture therapy: A Review of Clinical Applications*” – Frontiers in Oncology; published 26 February 2021.
[331] S. Devons; “*A note on the ^{10}B(n, α)^{7}Li reaction*” – Proceedings of the Physical Society, Section A; published in December 2002.

The first reaction, wherein ^7Li is in a stable configuration, eventuates only 6% of times [332]. The most common reaction (the remnant 94%) produces $^7Li^*$ in a metastable state, and it is thereupon ensued by a furthering gamma-ray emission:

$$^7_3Li^* \longrightarrow \ ^7_3Li \ + \ \gamma(0{,}478\ MeV)$$

The resulting α-particles of both reactions, easily halted by few micrometres of shielding material, do not pose any kind of concern [333]. The ultimate isotope of lithium is also a stable one, and the energy of the emitted photons is relatively low [334].

Although ^{10}B is very effective in neutron absorption, it is totally unfitted for gamma rays shielding [335]. This is why boron is ordinarily incorporated in the matrix of denser materials such as concrete, by constituting the so-called *borated concrete*. It can be also integrated into other elements, by forming the borated polyethylene, boron-aluminium alloy or boron carbide (B_4C) [336], [337]. The addition of ^{10}B into the concrete confers neutron absorbing proprieties to a material which already has slowdown proprieties; the high density of concrete offers gamma-ray shielding too, therewith fulfilling the three shielding phases all at once. Also, it ought to be remembered that each material receiving ionizing radiation can become radioactive, thereby being classified as a radioactive waste at the facility end-of-life. In this respect, several studies [338], [339] demonstrated how the addition of boron into the concrete markedly lessens the activation of the overall material, by capturing many neutrons which would have otherwise activated some additives and other aggregates (thence generating delayed photon emission too). Notwithstanding, the content of ^{10}B in the borated concrete cannot overtake a certain threshold (around 4% by weight [340]), since a high boron

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[332] W. A. Metwally, Y. A. Alharahsheh; "*Utilizing neutron generators in boron neutron capture therapy*" – Applied Radiation and Isotopes, Volume 174; published in August 2021.
[333] P. Lotti, D. Comboni *et al.*; "*Thermal stability and high-temperature behavior of the natural borate colemanite: An aggregate in radiation-shielding concretes*" – Construction and Building Materials, Volume 203; published 10 April 2019.
[334] D. R. McAlister; "*Neutron Shielding Materials*" – PG Research Foundation, Inc. 1955 University Lane Lisle, USA; published 25 February 2016.
[335] G. Tyagi, A. Singhal *et al.*; "*Radiation Shielding Concrete with alternate constituents: An approach to address multiple hazards*" – Journal of Hazardous Materials, Volume 404, Part B, ISSN 0304-3894; published in 2021.
[336] D. Gosset; "*Basic Properties of Boron Carbide*" – Comprehensive Nuclear Materials (Second Edition), Volume 7, Pag. 539-553; published in 2020.
[337] Z. Uddin, T. Yasin *et al.*; "*On the physical, chemical, and neutron shielding properties of polyethylene/boron carbide composites*" – Radiation Physics and Chemistry, Volume 166; published in January 2020.
[338] M. F. Kaplan; "*Concrete Radiation Shielding: Nuclear Physics, Concrete Properties, Design and Construction*" – Longman Scientific & Technical; ISBN 978-058-203773-1; published in 1989.
[339] G. Horitsugi, T. Fujibuchi *et al.*; "*Radiologic assessment of a self-shield with boron-containing water for a compact medical cyclotron*" – Radiological Physics and Technology; published in July 2012.
[340] A. Demirbaş, S. Karslioğlu; "*The effect of boric acid sludges containing borogypsum on properties of cement*" – Cement and Concrete Research, Volume 25, Issue 7; published in October 1995.

percentage can considerably undermine many mechanical proprieties, firstly the strength of the material.

Gamma-rays shielding phase:

After having captured one or more neutrons, the nucleus may not be in the minimal energy configuration yet: this is why a neutron capture reaction is often followed by the emission of other particles, usually photons. The optimum materials for photon shielding shall have a very high density and an elevated atomic number: this is the case of lead (Pb), which is one of the most adopted one. However, its usage poses a great deal of concern, chiefly its elevated toxicity – the lead has been claimed to be the second most perilous pollutant by the US Environmental Protectional Agency [341] – its low melting point and its modest mechanical resistance [342]. Additionally, great attention shall be paid during the handling and manufacturing of the lead: plenty of tiny lead particles, in the form of dust, can detach from the shielding surface during the installation phase, by starting hovering into the atmosphere for a very long time, with ensuing inhalation or ingestion [343]. Of course, this sounds quite inappropriate for a medical facility, wherein air purity and environmental neatness are paramount priorities.

This is not the case of iron and steel, which present a lower degree of toxicity [344] and a higher extent of robustness, albeit the average atomic weight is lower (and so it is their shielding capacity); however, they are not as costly as lead [345]. As a matter of fact, some studies mistrusted the existence of a single shielding material which could have all the requested shielding proprieties without any kind of disadvantage [346].

A coveted propriety of a neutron shielding material is, indeed, a limited emission of photons after the capture reactions. This stands for ^{6}Li, which is known for yielding little gamma radiation [347], but also ^{10}B, which produces a very lower amount of

[341] G. Tyagi, A. Singhal *et al.*; "*Radiation Shielding Concrete with alternate constituents: An approach to address multiple hazards*" – Journal of Hazardous Materials, Volume 404, Part B, ISSN 0304-3894; published in 2021.
[342] Lecture notes of the master's degree course "*Radiation Protection and Safety of Nuclear Plants*" of Politecnico di Torino, held by Prof. Massimo Zucchetti (slides by PhD. Student Luigi Candido) – academic year 2019/2020.
[343] M. Almurayshid, S. Alsagabi *et al.*; "*Feasibility of polymer-based composite materials as radiation shield*" – Radiation Physics and Chemistry, Volume 183; published in June 2021.
[344] L. Brewer, A. Fairbrother *et al*.; "*Acute toxicity of lead, steel, and an iron-tungsten-nickel shot to mallard ducks*" – Journal of Wildlife Diseases; published in July 2003.
[345] *ibidem.*
[346] F. Ozel, F. Akman *et al.*; "*Production of microstructured BaZrO3 and Ba2P2O7-based polymer shields for protection against ionizing photons*" – Journal of Physics and Chemistry of Solids, Volume 158; published in November 2021.
[347] M. B. Stone, L. Crow, V.R. Fanelli, J. L Niedziela; "*Characterization of shielding materials used in neutron scattering instrumentation*" – Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, Volume 946, ISSN 0168-9002; published in 2019.

gamma-rays with respect to the radiative capture of many other common elements (such as hydrogen, carbon or oxygen) [348].

■

There are two ways in which a neutron shield can be designed. The three aforesaid phases can be fulfilled either in three separate layers or within a single material – like it occurs, to a certain extent, in the borated-concrete.

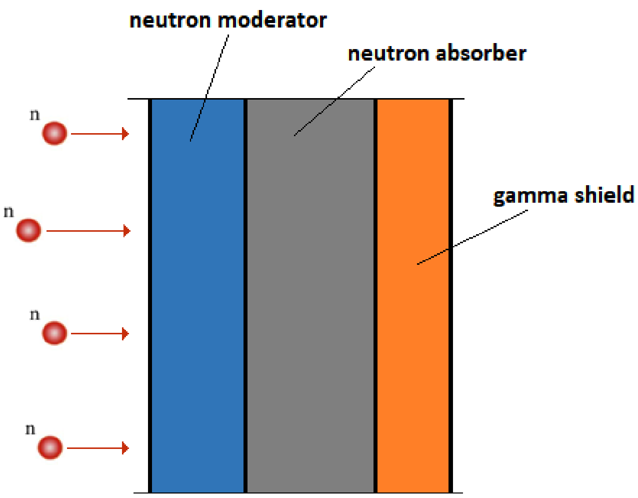

Figure 28: typical layout of a neutron shielding material with parted layers.

Figure 28 illustrates the typical arrangement of a neutron shielding material wherein the three layers are parted (oftentimes denoted as *multilayer shield*) [349]. However, in the majority of proton therapy facilities the adoption of a single material which can accomplish all the three shielding functions (designed as *composite shield*) is preferred.

Figure 29 and **Figure 30** seek to illustrate the shielding mechanism into a generic composite shield. The blue regions represent the moderator (for instance water), whereby the neutron beam is slowed down. Thence, the neutrons impinge on the nuclei of the absorber isotopes (for instance boron, denoted with the grey circles), where they get captured. In a few particular isotopes, instead of ensuing gamma-ray emission, the neutron can even split up the nucleus [350], whose fragments (symbolized in purple and yellow) release their kinetic energy into the surrounding medium [351].

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[348] D. R. McAlister; "*Neutron Shielding Materials*" – PG Research Foundation, Inc. 1955 University Lane Lisle, USA; published 25 February 2016.
[349] M. A. Sazli *et al.*; "*A review on multilayer radiation shielding*" – IOP Conference Series: Materials Science and Engineering; published in 2019.
[350] D. R. McAlister; "*Neutron Shielding Materials*" – PG Research Foundation, Inc. 1955 University Lane Lisle, USA; published 25 February 2016.
[351] W. D. Newhauser, R. Zhang; "*The physics of proton therapy*" – Physics in Medicine and Biology; published 21 April 2016.

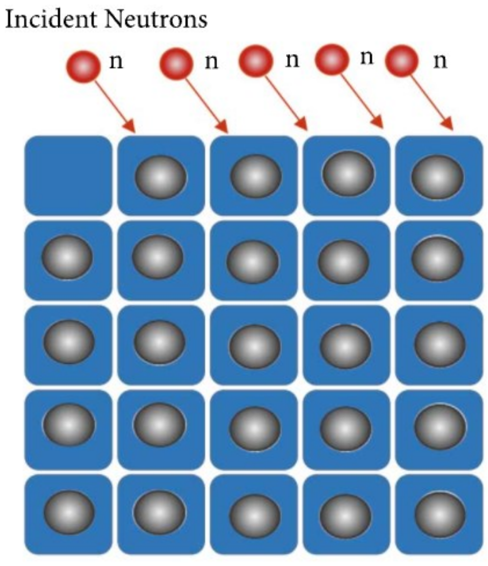

Figure 29: *graphical depiction of the neutron shielding principle in a mass of borated concrete – prior to neutron collision.*

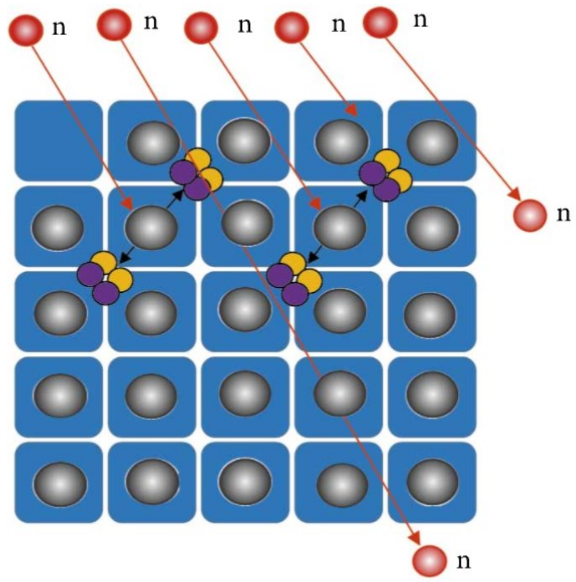

Figure 30: *graphical depiction of the neutron shielding principle in a mass of borated concrete – after the neutron collision.*

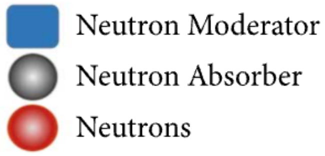

Figure 31: *legend of Figure 29 and Figure 30.*

The two shielding options (multilayer shield and composite shield) present advantages and disadvantages. As remarked by several Authors [352], an inaccurate amalgamation of the different chemicals within the composite shield – which is not so infrequent to occur [353] – can lead to the formation of peepholes in the solid matrix, which might act as preferential channel for the radiation passage [354]; such inconvenience cannot eventuate, of course, in a multilayer shield. Notwithstanding, the usage of a composite shield offers the possibility to operate a changeable dosing of the chemicals, whose percentages can be increased in order to augment the density for gamma shielding or other purposes [355].

[352] P. Wang, X. Tang, H. Chai, D. Chen; "*Design, fabrication, and properties of a continuous carbon-fiber reinforced Sm2O3/polyimide gamma ray/neutron shielding material*" – Fusion Engineering and Design; published in September 2015.
[353] A. Osman, M. A. El-Sarraf, A. A. Monem, A. E. Abdo; "*Studying the shielding properties of lead glass composites using neutrons and gamma rays*" – Annals of Nuclear Energy; published in April 2015.
[354] Y. Kim, S. Park, Y. Seo; "*Enhanced X-ray Shielding Ability of Polymer-Nonleaded Metal Composites by Multilayer Structuring*" – Industrial & Engineering Chemistry Research; published in May 2015.
[355] M. A. Sazli *et al.*; "*A review on multilayer radiation shielding*" – IOP Conference Series: Materials Science and Engineering; published in 2019.

The concrete is a first-rate neutron composite shielding material, since it can accomplish the three requirements (neutron slowdown, neutron absorption and gamma-rays shielding) within a single layer; actually it is one of the most adopted neutron shielding materials all over the world [356], in particular for the accelerator bunker walls. In addition to its higher hydrogen content for neutron dampening, several additives and aggregates can be admixed to increase its density, by rendering concrete an excellent gamma-ray shielding material too: this variant of concrete is denoted as *Radiation Shielding Concrete* [357]. Indeed, one of the weak points of the "traditional" concrete (*i.e.* the one utilized in construction) is a modest density value (ranging from 2200 to 2450 [kg/m^3] [358]) which can hamper the photon absorption. With the addition of minerals (such as magnetite, limonite, siderite, barite or hematite [359]) the density can be augmented up to 2900-6000 [kg/m^3] [360], which is habitually referred to as *heavy concrete*.

In general, the employment of heavy concrete is to be preferred in the areas with limited shielding space, whereas it would be too weighty for roof shielding or other suspended horizontal partitions. Indeed, also the lighter traditional concrete may pose an issue in this regard, whose thickness (and thus the weight) must be high anyhow: this is the reason why the roof shielding thicknesses are usually lower than walls [361], and the premises above roofs are flagged as *exclusion areas*, wherein the access is strictly interdicted during beam operation – actually the access can be also interdicted later on, in consequence of shielding activation. These last facets shall be taken into account in the protection from the skyshine effect too.

Neutron shielding design:

The early stages of the shielding design may be accomplished via an empirical approach. Indeed, the results analytically achieved may serve for a first substantiation of the ones obtained with a Monte Carlo simulation, which might be potentially implemented in the

[356] R. Li, Y. Gu, Z. Yang, M. Li, Y. Hou, Z. Zhang; "*Gamma ray shielding property, shielding mechanism and predicting model of continuous basalt fibre reinforced polymer matrix composite containing functional filler*" – Materials and Design, ISSN 0264-1275; published in 2017.
[357] B. Han, L. Zhang, J. Ou; "*Radiation Shielding Concrete*" – Smart and Multifunctional Concrete Toward Sustainable Infrastructures, Pag. 329-337, ISBN 978-981-10-4349-9; published 13 June 2017.
[358] E. G. Navy, "*Concrete Construction Engineering Handbook*" – CRC Press, Florida (US); Pag. 1-17; published in 1997.
[359] B. Aygün; "*Neutron and gamma radiation shielding properties of high-temperature-resistant heavy concretes including chromite and wolframite*" – Journal of Radiation Research and Applied Science, Volume 12, Issue 1; Pag. 352-359; published in 2019.
[360] E. G. Navy, "*Concrete Construction Engineering Handbook*" – CRC Press, Florida (US); Pag. 1-17; published in 1997.
[361] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

wrong manner – this is the reason why the knowledge of the analytical approach shall be always present in the expertise of any good designer.

The most credited analytical methods are the so-called *line-of-sight* methods: they commence with a hypothesis on the placement r of the beam loss, on the alleged shield thickness d_0, and on the beam angle θ with respect to a certain reference point. This scenario is depicted in **Figure 32**, whereby the dose into the point P is the subject of the estimation.

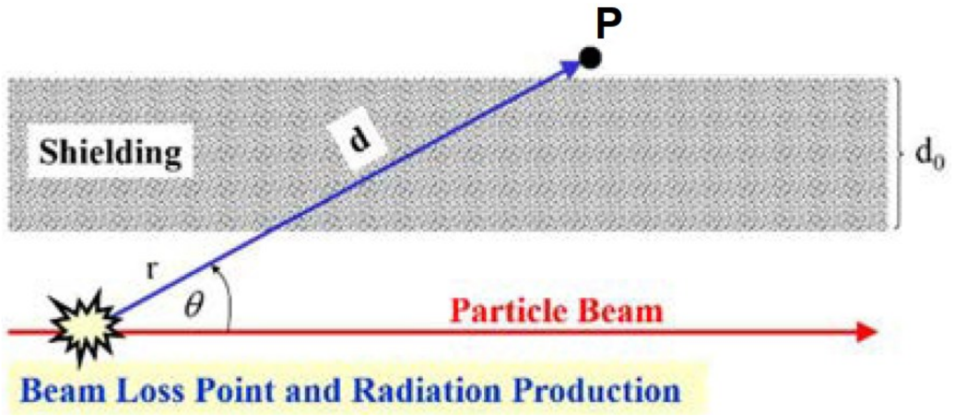

Figure 32*: example of application of a line-of-sight model for the dose estimation in point P (provided an assumption on the thickness d*$_0$*, on the distance d, on the angle* ϑ *and on the localization of the beam loss).*

As regards the analytical structure, in 1961 the scientist Moyer formulated a semi-empirical correlation to estimate the shield thickness enclosing a 6 GeV proton synchrotron [362]. For angles $\theta < 50°$:

$$H\left(E_{pr},\theta\right) = \frac{H_0\left(E_{pr},\theta\right)}{r^2} \cdot exp\left(-\frac{d_0}{sen(\theta) \cdot \lambda(\theta)}\right)$$

For angles $\theta > 50°$ a far more complex correlation shall be employed (not herein discussed).

The meaning of the geometrical variables, *i.e.* d_0, ϑ and r^2, can be understood by **Figure 32**. The output $H\left(E_{pr},\theta\right)$ represents the equivalent dose in point P, which is a function of the proton energy E_{pr} and the angular coordinate ϑ. The quantity $H_0\left(E_{pr},\theta\right)$ is the source term, namely the dose per particle in the point where the beam loss originates. The λ term designates the *attenuation length* (angular-dependent),

[362] C. Yamaguchi "*Shielding calculation using FLUKA – comparison with simple equations*" – National Laboratory of High Energy Physics, Japan; published in June 1988.

which represents the distance whereby approximatively 63% of the initial particles of the beam have been stopped [363].

One of the crucial hindrances in the Moyer's correlation applicability regards its limited validity for proton beam energies lower than 1 GeV [364], [365], which is actually the case of particle accelerators [366]: this is because each proton virtually takes part in a nuclear reaction whenever its energy overtakes 1 GeV, whilst this is not always true for lower energies, wherein the Coulombic interactions can still play a significant role (*i.e.* not all the protons are involved in non-elastic nuclear reactions).

Nevertheless, such restriction can be overcome. In a study published on the Journal of Nuclear Science and Technology [367] it has been demonstrated how the Moyer's correlation can be still applied in the energy range of therapeutical proton beams: it suffices to multiply the source term $H_0(E_{pr},\theta)$ of the equation for the nuclear interaction probability. The values of such probability (achieved by means of a FLUKA™ Monte Carlo simulation, in accordance with a report from CERN [368]) are shown in **Figure 33**. The chart reports the fraction of protons partaking in a nuclear reaction as a function of their energy, for a wide range of target materials.

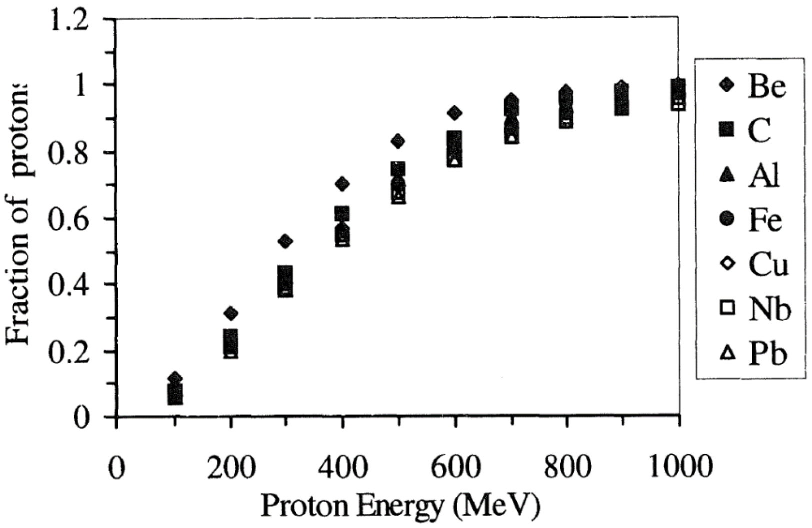

Figure 33*: fraction of protons undergoing a nuclear reaction as a function of their energy, for a wide range of target materials.*

It is possible to observe how a nuclear reaction occurs in the almost majority of protons approaching 1000 MeV.

The computation is precautionarily carried out with reference to the most critical conditions, *i.e.* a particle emission rate of approximatively 10^{10} protons per

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[363] Definition of *attenuation length* from ScienceDirect: "*Attenuation Length*" (taken by the article "*Subsea holography and submersible holocameras*" by J. Watson & N. M Burns, Pag. 294-326; published in 2013).
[364] L. E. Moritz; "*Using the Moyer Model at Energies less than 1 GeV*" – Journal of Nuclear Science and Technology, Supplement 1, Pag. 180-182; published in March 2000.
[365] G. R. Stevenson; "*Shielding High Energy Accelerators*" – Radiation Protection Dosimetry, Volume 96, Issue 4, Pag. 359-371; published 01 August 2001.
[366] E. Sengbusch, A. Pérez-Andújar *et al.*; "*Maximum proton kinetic energy and patient-generated neutron fluence considerations in proton beam arc delivery radiation therapy*" – Medical Physics; published in February 2009.
[367] L. E. Moritz; "*Using the Moyer Model at Energies less than 1 GeV*" – Journal of Nuclear Science and Technology, Supplement 1, Pag. 180-182; published in March 2000.
[368] A. Fasso *et al.*; "*CERN Report TIS-RP/97-05*", Pag. 158-170 – published in 1998.

second [369]. Indeed, another restraint of Moyer's Equation (as well as of the line-of-sight models in general) is its only applicability for a specific energy value of the beam [370]: accordingly, the equivalent dose should be always computed by using the highest value of the energy range, which unavoidably leads to the determination of the uppermost shielding thickness value. Indeed, when a considerable inconstancy of the energy beam is expected, and the highest energy values are not so likely to be employed, the Moyer's Equation may conduct to a substantial overestimation of the thickness.

Though the aforementioned restraints, the Moyer's correlation is mentioned in a publication from IAEA too, which formally recommends its employment for a first neutron shielding dimensioning in an ion therapy facility [371].

A thoroughgoing discussion about the line-of-site models, as well as on their strong limitations, can be retrieved in a paper from the peer-reviewed journal Radiation Protection Dosimetry [372].

[369] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility"* – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, No. 1891.
[370] *ibidem.*
[371] *ibidem.*
[372] G.R. Stevenson; "*Shielding High Energy Accelerators*" – Radiation Protection Dosimetry, Volume 96, Issue 4; pages 359-371; published 01 August 2001.

Conclusions and further insights

With a proper training of the personnel, the adoption of personal protective equipment, the right selection of the materials and a supposedly faultless shielding design, it can be concluded that the management of a proton therapy facility does not entail risk levels that are markedly higher than other medical installations (such as the ones devoid of ionizing radiation sources). Anyhow, the numerical quantification of the overall risk – in terms of, for instance, $\left[\frac{deaths}{year}\right]$ or $\left[\frac{mSv}{workload}\right]$ received by the personnel – as well as the ensuing comparison with the values of other similar facilities, can be only assessed with a thoroughgoing procedure of Safety and Risk Analysis (which was not the primary object of this dissertation).

One of the most hazardous areas in the facility is undoubtedly the degrader bunker, wherein the highest radiation levels can be measured [373]: great attention shall be paid during the maintenance therein, whose personnel must be properly qualified for the task. Furthermore, with a weak shielding design (or the non-compliance to the safety protocols from the workers), also the radiation production in other sites of the facility can be worrisome, either for direct exposure during beam operation or delayed exposure due to material activation [374]. In this regard, the related radioactive waste production can pose a jeopardy for the population even if an appropriate management *within* the facility is carried out, since the waste decommissioning is entrusted to third parties (and it can be accomplished even after decades).

Indeed, in this monograph the issue of decommissioning has been broached only incidentally – whilst this subject might deserve another entire dissertation. During the last decades the superintendence and the disposal of the radioactive wastes has become a real *vexata quaestio*, especially in Italy, wherein a National Repository for the long-lived radioactive wastes is still missing in 2022 [375]. As of today, the activated materials produced in the Italian medical facilities are stored in around 20 different temporary sites, waiting for being displaced to the permanent storage [376]. This is also the case of proton therapy facilities, each of which shall be equipped – as reported in the aforementioned IAEA publication [377] – with proper areas devoted to the safety storage (generally inside the accelerator bunker), pending for the transportation to the

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[373] V. Anferov; "*Energy degrader optimization for medical beam line*" – Indiana University Cyclotron Facility, Bloomington, Nuclear Instruments and Methods in Physics Research; published in 2003.
[374] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
[375] World Nuclear News; "Italy launches national debate on waste repository", published 08 September 2021.
[376] Official Website of Ispettorato Nazionale per la Sicurezza Nucleare e la Radioprotezione (ISIN); "Radioactive waste management" – Last update: 21 October 2019.
[377] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

final repository. Furthermore, the authorization for the commissioning of any proton therapy facility must be subordinated by a proper *waste management plan*, which shall be compiled during the design phase and delivered from the applicant licensee [378].

Eventually, it should be mentioned that the economical facet of the safety measures has not been broached whatsoever. As remarked by some Authors [379], a consistent share of the expense in an ion therapy facility is dependent upon the shielding outlay: this is why the shielding layout design, along with the choice of the proper materials, should be conducted in strict conjunction with the economic analysis – provided that the selection of cheaper materials could not prejudice their safety function, which is always the prevailing priority.

[378] IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.
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Figure 3 Official website of *Proteus®ONE – IBA proton therapy technology* (website cover picture). Last update: January 2022.

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Figure 14 *ibidem.*

Figure 15 *ibidem.*

Figure 16 J. A. Brennsæter; "*The Influence of the Energy Degrader Material for a Therapeutical proton Beam*" – Norwegian University of Science and Technology, Department of Physics; published in June 2015.

Figure 17 IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

Figure 18 *ibidem.*

Figure 19 I. S. Lagutina, V. P. Mashkovich *et al.*; "*Skyshine from photon radiation*" – Soviet Atomic Energy; published in February 1989.

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Figure 21 *ibidem.*

Figure 22 Lecture notes of the Master's Degree course "*Monte Carlo methods, safety and risk analysis*" of Politecnico di Torino, held by Prof. Nicola Pedroni and Prof.ssa Sandra Dulla – academic year 2020/2021.

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Figure 28 *ibidem.*

Figure 29 *ibidem.*

Figure 30 *ibidem.*

Figure 31 *ibidem.*

Figure 32 IAEA publication; "*Regulatory control of the safety of ion radiotherapy facility*" – Vienna, 2019; ISBN: 978-92-0-163119-0. Series: IAEA TECDOC series, ISSN 1011-4289, no. 1891.

Figure 33 A. Fasso *et al.*; "*CERN Report TIS-RP/97-05*", Pag. 158-170 – published in 1998.