LUISS

Department of Business and Management
Master of Science in Strategic Management

Chair of Healthcare Innovation

Proton Therapy in Non-Small Cell Lung Cancer (NSCLC): An Organizational, Cost-Utility, and Sustainability Analysis

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A Eleonora, Francesca e Veronica.
A chi affronta l'ingiustizia senza averne colpa alcuna.

INDICE

ABSTRACT

For patients with non-small cell lung cancer (NSCLC), choosing the right treatment can make a substantial difference in their future outcomes.

The present study analyses the differences between proton therapy and photon radiotherapy in terms of clinical efficacy and economic sustainability taking the National Centre for Oncological Hadrontherapy in Pavia as an organisational and technological reference point. It further examines the conditions under which proton therapy generates superior (or additional) clinical and economic value compared to photons, and how this facilitates its dissemination within the healthcare landscape.

An integrated methodological design was adopted. First, the framework of hybrid organisations and diffusion of innovation was applied to interpret governance, collaboration networks, and the trajectories through which technologies diffuse within the healthcare system. Concurrently, health economics tools were employed to evaluate costs, encompassing both capital expenditure (CAPEX) and operating expenditure (OPEX), and to assess the value generated using indicators such as QALY and ICER. Methodologically, patient selection was conducted using NTCP models in order to estimate the expected benefit at the individual level.

In clinical practice, protons have been shown to consistently reduce the radiation dose to the lungs, heart, and other vital organs while providing the same tumour coverage, with generally more favourable toxicity profiles in locally advanced stages and complex scenarios. From an economic perspective, the high capital and organisational intensity render the unit cost sensitive to patient volumes and productivity, directly influencing cost-effectiveness.

It is therefore evident that proton therapy is not superior in absolute terms, but is instead "more suitable for the suitable patients". The economic value of proton therapy is enhanced when patient indications are selective (ΔNTCP), techniques are contemporary (IMPT), and delivery is supported by economies of scale and hub-and-spoke models that stabilise flows.

CHAPTER I: THE NATIONAL CENTRE FOR ONCOLOGICAL HADRONTHERAPY

1.1. History

The National Centre for Oncological Hadrontherapy (CNAO), located in Pavia, is a leading global institution in the field of cancer radiotherapy employing beams of charged particles, known as hadrons.

Hadrons are subatomic particles that participate in the strong nuclear interaction, one of the four fundamental forces of physics. They belong to the family of composite particles, i.e., non-elemental, and consist of quarks. Hadrons are mainly divided into:

- Baryons (e.g., protons and neutrons, composed of three quarks);
- Mesons (e.g., pions, composed of one quark and one antiquark).

Hadrontherapy is a sophisticated form of cancer radiotherapy that uses beams of hadrons (primarily protons and carbon ions) instead of conventional X-rays. It is employed to treat tumours that are difficult to reach or resistant to conventional therapies.

The establishment of the National Centre for Oncological Hadrontherapy is the result of a long scientific, technological, institutional and organisational journey rooted in over half a century of research and innovation in the fields of particle physics, nuclear medicine and engineering applied to health. CNAO is not merely a clinical centre; rather, it is a true multidisciplinary scientific infrastructure, a point of convergence for physical, biological, engineering and clinical expertise.

The conceptual genesis of CNAO can be traced back to the 1990s; however, its scientific origins extend much further back in time, to 1946, when the American physicist Robert R. Wilson (1914-2000) published the article "Radiological Use of Fast Protons" in *Radiology*. In this pioneering work, Wilson first proposed the use of high-energy proton beams for the treatment of solid tumours, thus opening up the field for future hadrontherapy. He observed that high-energy protons exhibited a distinctive behaviour, characterised by the release of most of their energy at a specific point (the Bragg peak),

rendering them particularly well-suited for the precise targeting of cancerous cells while sparing healthy tissue.

Wilson's proposal initially went unheeded, as it matured in a post-war context strongly marked by the ethical responsibility associated with the military use of science, where he himself took part in the Manhattan Project and the development of the atomic bomb. The proposal thus became an emblematic example of scientific “sleeping beauty”: an innovative idea that lay silent for decades before finally being rediscovered and actualised in mature application contexts.

The revival of Wilson's vision took place in Europe starting in the 1980s and 1990s thanks to the efforts of prominent figures such as the Italian physicist Ugo Amaldi, who played a decisive role in spearheading and overseeing international research projects dedicated to hadrontherapy. In particular, Amaldi, in collaboration with Giampiero Tosi, proposed in 1991 an initial technical-scientific memorandum for the construction of an Italian Hadrontherapy Centre, suggesting the use of a synchrotron with a low magnetic field and high energy flux, capable of accelerating both protons and carbon ions. In support of this proposal, the TERA Foundation was established in 1992, a non-profit organisation dedicated to the promotion and development of the technical-scientific, political and institutional conditions necessary for the successful implementation of the project. The establishment of CNAO was an arduous process, far from straightforward. It underwent a protracted study and planning phase, culminating in participation in the PIMMS (Proton-Ion Medical Machine Study) project, coordinated at CERN in Geneva between 1996 and 1999. CERN, by virtue of its role as a major European scientific infrastructure devoted to fundamental research yet open to multidisciplinary collaboration, provided conducive environment for the refinement of the CNAO project, hosting scientists, engineers and doctors from various countries and concretely supporting the technical development of the future Italian accelerator. PIMMS was not a clinical project, but rather a theoretical and technical study aimed at defining a generic facility for oncological therapy with protons and ions. The results of PIMMS were then developed and adapted to Italian clinical needs thanks to the efforts of the TERA Foundation, which took charge of the engineering of the machine and related systems.

The realization of CNAO finally became possible in the early 2000s, when the Italian Ministry of Health, under the leadership of Umberto Veronesi, decided to fund the project,

recognising its innovative potential. The CNAO Foundation was established in 2001 with the participation of leading hospital and research institutions: the IRCCS Foundation Istituto Nazionale dei Tumori, the European Institute of Oncology, the Ospedale Maggiore of Milan, the Policlinico San Matteo Foundation of Pavia and the Carlo Besta Neurological Institute. The scientific and operational management was entrusted to a team of experts who had already gained relevant experience at CERN and in previous projects, including Director General Sandro Rossi and engineer Marco Pullia. The construction of the entire physical structure was undertaken between 2005 and 2010, with the involvement of over 400 companies, thus contributing to a significant technology transfer and the upskilling of the national industrial chain. The technological core of CNAO consists of a complex particle acceleration system based on a synchrotron, a type of circular accelerator capable of propelling protons and carbon ions to energies sufficient to penetrate deeply into human tissue and target cancer cells with extreme precision. The system comprises a linac (linear accelerator) that pre-accelerates the particles, a synchrotron that brings them to the desired energy, and a sophisticated system of beam transport lines to the treatment rooms. The latter are equipped with rotating gantries that allow the beam to be directed from different angles. The particles are controlled by advanced computer systems that integrate data from diagnostic imaging (CT, MRI, PET, etc.) and radiotherapy planning algorithms.

The construction of the facility was primarily facilitated by Italian technological expertise, with contributions from CNAO's collaborative efforts with the National Institute of Nuclear Physics (INFN), the University of Pavia, CERN itself, GSI (Helmholtzzentrum für Schwerionenforschung GmbH in Darmstadt, Germany) and LPSC (Laboratoire de Physique Subatomique et de Cosmologie de Grenoble, France).

The synchrotron at CNAO, unlike accelerators in physics laboratories, was designed and built specifically for the clinical treatment of patients. The construction of the centre involved 600 companies, 500 of which were Italian. The construction of the individual parts was entrusted to specialised companies, while assembly and commissioning were carried out by CNAO staff, in collaboration with the National Institute of Nuclear Physics, the Politecnico di Milano, the University of Pavia and CERN.

CNAO is now a world-leading facility, not only for its therapeutic capabilities, but also for its contribution to scientific and technological research. The centre actively

participates in clinical trials, European projects, training programmes and technological development activities in collaboration with academic and industrial entities.

Furthermore, it has sustained a persistent connection with CERN and other European infrastructures through the ENLIGHT network (European Network for Light Ion Hadron Therapy), contributing to the standardisation and dissemination of hadrontherapy practices on an international scale.

The infrastructure has been designed with a modular architecture that allows for future extensions and technological upgrades. For example, the implementation of new treatment rooms equipped with more compact technologies, such as single-room cyclotron sources, or the introduction of new particle types for non-oncological applications, including cardiovascular diseases, is being studied. This type of configuration enables the centre to maintain its alignment with the most recent advancements in precision medicine and state-of-the-art healthcare technologies.

Finally, it should be noted that access to treatment at CNAO is now guaranteed by the National Health Service, following the official recognition of hadrontherapy among the Essential Levels of Care (LEAs) in 2017. Consequently, all Italian citizens have access to the treatments provided by the centre without direct charges, thus making a therapeutic technology otherwise accessible only in a few countries in the world available to a wider audience.

1.2. What does CNAO do today

Hadrontherapy is a form of radiotherapy employed in the treatment of tumours that are often inoperable or resistant to traditional radiotherapy treatments.

In contrast to conventional radiotherapy, which relies on the use of X-rays or electrons, hadrontherapy uses protons and carbon ions. These subatomic particles, referred to as hadrons, (hence the name of the therapy) possess the advantage of being heavier and having more energy than electrons and are therefore even more effective in destroying cancer cells.

Globally, only six facilities are equipped to deliver hadrontherapy with protons and carbon ions, and one of these is CNAO, which makes it one of the most advanced

technological infrastructures internationally for oncological treatment using hadronic particles.

In order to be effective in targeting the tumour with extreme precision, the hadrons used in hadrontherapy must undergo extremely powerful acceleration by means of a particle accelerator inside the synchrotron.

Inside this synchrotron, the particle beam travels about 30,000 kilometres in half a second to reach the energy required for the therapy, after which it is directed towards the tumour. When cancer cells are hit, radiation produces a break in the DNA double helix, damaging their nuclei and causing the cell to lose its ability to replicate. The cells die and the immune system eliminates them. The primary benefit of hadrontherapy is that this cell death mechanism is extremely precise: it only affects the tumour mass and preserves healthy tissue.

The requisite number of hadrontherapy sessions depends on various factors, including the type of particle used, the type of tumour, its size and location. Typically, a session is conducted on a daily basis, across a period of between two and seven weeks.

The combination of these advantages, coupled with a very high degree of personalisation of the treatment at each stage, results in considerable destructive efficacy against tumour tissue. Consequently, the target, i.e., the tumour, must be located with millimetric precision significantly higher than that required in traditional radiotherapy.

As previously stated, hadrontherapy is mainly indicated for radio-resistant tumours, i.e., those tumours that respond poorly to the X-rays used in conventional radiotherapy, or for tumours that are located in particularly difficult sites. Hadrontherapy originally focused on tumours at the base of the skull, due to the need for high precision to avoid damage to nearby vital structures, nerves and vessels around the tumour mass.

To date, the pathologies that can be treated with hadrontherapy at CNAO are as follows:

Tumours of the brain, skull base and spinal cord

- Paragangliomas;
- Skull base chordomas;
- Intracranial chondrosarcomas;
- Malignant peripheral nerve sheath tumours;

- Hemangiopericytomas/intracranial solitary fibrous tumours;
- Intracranial meningiomas with special reference to meningiomas in critical locations (such as the skull base) and meningiomas with a high degree of aggressiveness;
- Retreatment of recurrences of encephalic neoplasms of any histological type in patients already treated with radiotherapy in the brain;
- Low-grade glial neoplasms;
- Craniopharyngiomas and pituitary macroadenomas;
- Cranial nerve neurinomas;
- Ependymomas of the adult and other rare neoplasms of the Central Nervous System;
- Neoplasms of the brainstem;
- Neoplasms of the spinal cord;
- Retreatment of tumours in already irradiated sites.

Tumours of the head, neck and upper respiratory tract

- Mucous melanomas
- Pleomorphic adenomas;
- Cystic adenoid carcinomas;
- Tumours of the salivary glands;
- Locally advanced tumours of the paranasal sinuses and nasopharynx;
- Ocular melanomas;
- Tumours of the orbit;
- Local recurrences of head and neck tumours (all histologies).

Tumours of the thorax

- Breast;
- Lung.

Pelvic tumours

- Malignant tumours of the prostate
- Recurrences of gynaecological tumours;
- Recurrences of neoplasms of the rectum;
- Vaginal and cervix melanomas;
- Lateral recurrences.

Limb and spine tumours

- Chordomas and chondrosarcomas;
- Sarcomas.

Paediatric solid tumours

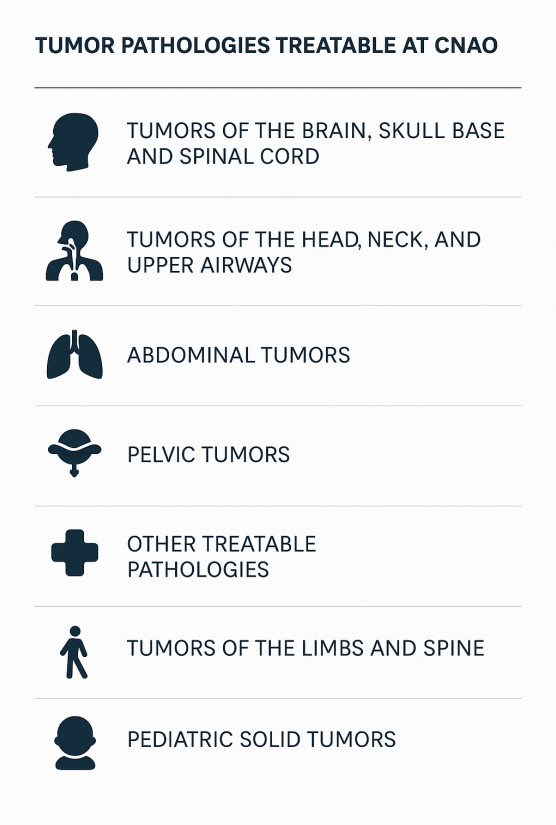

Figure 1: Tumours *treated with hadrontherapy at CNAO.*

Source: Author's own elaboration.

As mentioned earlier, the core of the process resides in the accelerator known as synchrotron. The accelerator is located within a 1,600-square-metre bunker, entirely shielded with reinforced concrete walls between two and six metres thick to guarantee effective protection from the ionising radiation produced during operation. The structure of the acceleration ring has a diameter of 25 metres and a circumference of approximately 80 metres, within which the path of the accelerated particles runs, directly connected to the treatment rooms where patients undergo therapy.

The synchrotron receives pre-accelerated beams of protons and carbon ions, generated by two separate hadron sources. In each source, the atom of the gas used (e.g., hydrogen or carbon dioxide) is ionised to a plasma state through magnetic fields and radiofrequency pulses, thereby separating the electrons from the atomic nuclei. The process isolates the protons and carbon nuclei, which are subsequently collected in packets consisting of billions of particles.

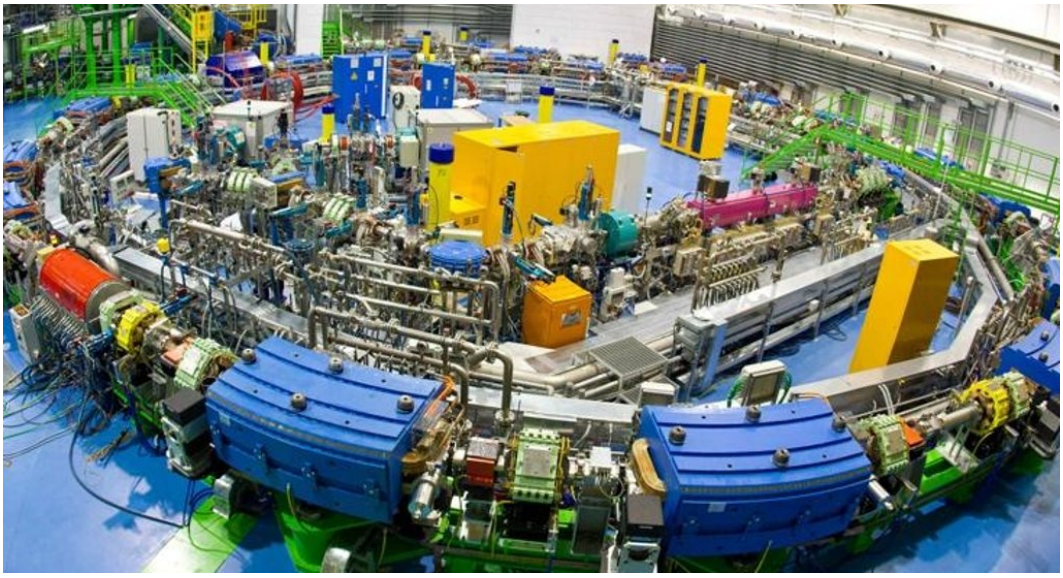

Figure 2: CNAO Synchrotron.

Source: Fondazione CNAO.

These packets are initially accelerated by a linear accelerator (linac) and then directed towards the synchrotron. Using dipolar and quadrupolar magnets arranged along the ring, the particles are accelerated to high kinetic energies: up to 250 MeV for protons and 4,800 MeV (or 400 MeV/u) for carbon ions. The energy is expressed in megaelectronvolts (MeV), a unit of measurement used in the nuclear field to quantify the energy of

subatomic particles. At these energies, the beams travel over 30,000 km/s before being directed towards the three treatment rooms, each equipped to deliver hadrontherapy with extreme precision.

The therapy beam is modelled as a “brush” of particles with a spatial precision of 200 micrometres, a feat made possible through an integrated surveillance and control system. The patient's spatial coordinates are monitored in real time by infrared cameras, capable of detecting three-dimensional movements with a high degree of accuracy. Concurrently, two scanning magnets modulate the direction of the beam, following the morphology of the tumour mass with millimetre precision. The penetration depth is adjusted by varying the energy of the particles, thus enabling selective, section-by-section irradiation of the neoplastic tissue. The number of sessions required for treatment with protons is typically 35, whereas for carbon ions it is approximately 16, depending on the type and location of the tumour. Hadrontherapy, particularly with heavy ions such as carbon, maximises the release of energy in the tumour area while minimising damage to surrounding healthy tissue.
As the charged particles penetrate the patient's body, they deposit minimal energy in the superficial tissues, and only at a certain depth (which depends on the initial energy of the particles) does the greatest release of energy occur.

This phenomenon is referred to as the Bragg peak, and hadrontherapy uses this selective release of energy to target only tumour cells.
It enables hadrons to behave like precise projectiles, facilitating the irradiation of tumours in challenging locations or close to healthy tissue.
By varying the energy of the particles, it is possible to release energy at the depth at which the tumour is located. For treating the entire tumour, particles of different energies with Bragg peaks at different depths are used.

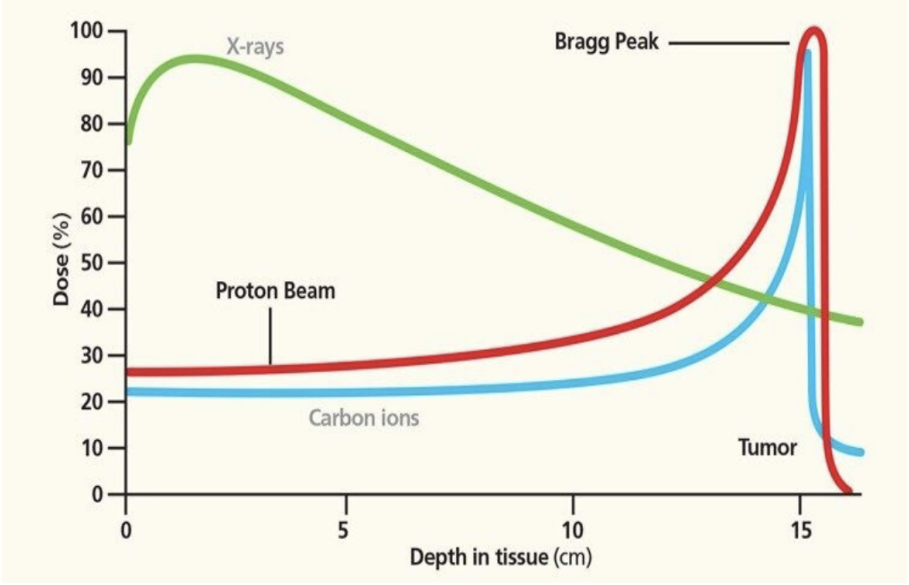

Figure 3: Bragg peak – differences between various types of technologies.
Source: Fondazione CNAO.

The advent of the INSpIRIT (Innovative Synchrotron for Particle Irradiation and Research in Ion Therapy) project, financed with a total budget of €10 million (of which €3.8 million was provided by the Lombardy Region) has enabled CNAO to implement a third hadronic source, capable of generating new ion species, such as helium, oxygen, and lithium, in addition to conventional protons and carbon ions. This technological enhancement, realised in collaboration with the HiFuture laboratory of the Teoresi Group and the National Institute of Nuclear Physics (INFN), significantly expands the centre's therapeutic and experimental capabilities.

The recently introduced ion species exhibit distinct radiobiological properties. For instance, helium ions possess a linear energy transfer (LET) ratio that exceeds that of protons but falls short of that of carbon ions. This offers a favourable trade-off between therapeutic efficacy and toxicity to healthy tissues. These characteristics render helium a promising candidate for the treatment of brain tumours, head and neck neoplasms, and uveal melanoma. The evaluation of clinical efficacy will be preceded by a physicochemical characterisation phase and preclinical studies on cell lines, with clinical trials scheduled to start in mid-2026.

Future integration of multi-ion mode treatments—i.e., sequential or simultaneous delivery of beams of different species—represents the frontier of personalisation in hadrontherapy. This approach has the potential to facilitate the selection of the most

suitable beam based on the individual biological profile of the tumour, which can be identified through blood biomarkers or advanced functional imaging techniques. The goal is to provide a bespoke treatment for each patient, which can also be integrated with systemic therapies such as chemotherapy and immunotherapy.

In addition to its intended application in the clinical field, the new hadronic source has also been designed for aerospace applications. Specifically, the generation of iron ion beams will be employed for irradiation testing on materials used in the fabrication of components for space missions, contributing to research into the resistance of materials in environments with strong exposure to cosmic radiation.

The INSpIRIT project also exemplifies a virtuous case of public-private collaboration and technology transfer. The HiFuture laboratory played a crucial role in the development of the source and the control systems for the linear accelerator magnets, as well as in the validation of the software for dose delivery with the new ion species. The INFN, through the Pavia and Southern National Laboratory sections, contributed to the design of a highly reliable and reproducible source, capable of doubling or tripling performance relative to existing sources.

With more than 5,000 patients treated since 2011, CNAO has established itself as an international centre of excellence in the field of oncological hadrontherapy, as well as an example of technological innovation applied to personalised medicine. The future outlook focuses on the further expansion of clinical indications and the introduction of new ionic species, thereby consolidating the role of applied physics in the fight against cancer.

1.3. Comparing technologies

Proton therapy, ion therapy, and hadrontherapy are all advanced radiotherapy techniques based on the use of charged particles for the treatment of solid tumours. However, there are significant differences in both physical and biological aspects, as well as in clinical application. The primary distinction between these methodologies concerns the type of particle used, the dose distribution, the biological effect on tumour cells, and the technological complexity required for their implementation.

Proton therapy employs protons, i.e., positively charged particles with a mass equivalent to that of a hydrogen atom. The principal benefit of this technique is its capacity to deposit

energy in a highly localised manner, attributable to the Bragg peak. This characteristic makes proton therapy particularly suitable in cases where the tumour is located in close proximity to critical organs, such as paediatric brain, eye, or skull base tumours. Furthermore, due to its high precision, proton therapy is associated with a lower incidence of late side effects, which is particularly relevant in young patients, for whom the preservation of healthy tissue is essential to ensure normal future development. From a biological standpoint, protons have an average linear energy transfer (LET) and relative biological effectiveness (RBE) of approximately 1.1, which is marginally higher than that of photons used in conventional radiotherapy. However, this value may vary within the beam, especially in the terminal regions, where the LET tends to increase.

Ion therapy, on the other hand, utilises heavy ions, particularly carbon ions (12C), which have a substantially higher mass and charge compared to protons. This results in reduced lateral beam scattering, more precise energy release, and, above all, a very high LET, which consequently leads to a significantly higher biological effect. In fact, the RBE of carbon ions can reach values between 2 and 3, rendering them particularly effective against radioresistant and poorly oxygenated tumours that do not respond satisfactorily to conventional radiotherapy or proton therapy itself. This is attributable to the fact that heavy ions induce complex and manifold DNA damage, which the tumour cell cannot effectively repair. Consequently, ion therapy is indicated for aggressive tumours located in difficult or inoperable sites, such as certain pelvic sarcomas or tumours at the base of the skull.

However, this increased biological efficacy is also accompanied by increased technological complexity, high operating costs, and increased sensitivity to dosimetric uncertainties, which require even more sophisticated planning to avoid damage to healthy tissue.

Finally, the term hadrontherapy is to be understood as a broader category that encompasses both proton therapy and ion therapy. The term derives from the Greek word *hadros*, meaning “heavy”, and is used in clinical and academic circles to denote any radiotherapy treatment carried out using hadronic particles, i.e., particles that interact via the strong nuclear force, such as protons, neutrons, and heavy ions. In practice, hadrontherapy is an umbrella term that encompasses the full range of technologies based on high-energy charged particle beams. However, while proton therapy is now an

established technology, with numerous clinical centres active in Europe, the United States, and Asia, ion therapy is still a more specialised and less widespread frontier, with only a few centres active worldwide. Examples include CNAO in Pavia, the HIMAC and Hyogo Centre in Japan, and the GSI in Germany.

Figure 4: Hadrontherapy treatment room.
Source: Fondazione CNAO.

1.4. Flash Therapy

Radiotherapy is a fundamental therapeutic tool in the fight against cancer, with approximately 50–60% of cancer patients eligible for treatment. In many cases, radiotherapy contributes significantly to curing the disease. However, despite considerable technological advances over the last two decades, its clinical effectiveness is still limited by toxicity to healthy tissues adjacent to the neoplasm. Reducing this toxicity would not only increase the dosage that can be safely administered, but also expand treatment options for resistant or locally advanced tumours, as well as reduce long-term side effects in patients with a more favourable prognosis.

In this context, FLASH radiotherapy (FLASH-RT) represents a new frontier in oncological radiotherapy. Preclinical studies have shown that, when administered at

significantly higher doses than current standards but for extremely short times (less than 100 milliseconds), irradiation can drastically reduce toxicity to healthy tissues while maintaining antitumour efficacy comparable to that of conventional radiotherapy. This phenomenon, known as the FLASH effect, is based on a radiobiological mechanism that is still being explored, but which shows great therapeutic promise.

The FLASH effect, documented in animal models, involves the ability to administer the therapeutic dose in fractions of a second, at rates up to 400 times higher than conventional ones. This method appears to achieve greater selectivity in radiation-induced damage, protecting healthy tissues and maintaining the cytotoxic action on the tumour unchanged. If these results are confirmed and translated into clinical practice, FLASH radiotherapy could represent a breakthrough in the treatment of currently difficult-to-treat cancers and in the optimisation of existing therapies.

At the national level, the Centro Pisano Multidisciplinare sulla Ricerca e Implementazione Clinica della FLASH Radiotherapy (CPFR), established within CISUP (Center for Instrument Sharing of the University of Pisa), aims to become a leading international reference centre on this increasingly important technique, both scientifically and in terms of clinical applications.

Rome recently hosted the FLASH Radiotherapy and Particle Therapy (FRPT) world conference, which brought together over 600 experts from more than 40 countries. One of the central issues highlighted was the need for a more in-depth understanding of the biological mechanisms underlying the FLASH effect. In particular, the role of long half-life proteins in healthy tissues is being investigated, as their absence in tumours could be a determining factor in therapeutic selectivity. Concurrently, the importance of precision in dose administration and measurement was reiterated as an essential requirement for ensuring safe and effective treatments.

The implementation of FLASH Radiotherapy requires the development of innovative technologies capable of generating beams with extremely high dose rates. Among the most promising solutions is the use of state-of-the-art lasers for plasma acceleration, awarded the Nobel Prize in Physics in 2018. This technology facilitates the acceleration of high-energy electrons through laser pulses of extreme intensity, capable of producing compact and highly directed beams. Work is underway at the CNR in Pisa to build

experimental facilities based on this technology, with the aim of developing systems compatible with the rigorous requirements of modern FLASH radiotherapy.

At the same time, solutions based on traditional medical accelerators, suitably upgraded to achieve the requisite dose rates, are also being explored. In particular, the Tuscany Health Ecosystem (THE) project is promoting the adoption of these technologies within the Pisa Centre for FLASH Radiotherapy, with the aim of launching the first clinical protocols, initially focused on superficial treatments.

Although the first evidence on the FLASH effect dates back to 2014, many of the underlying radiobiological dynamics remain unclear. Preclinical research is currently focused on mapping the tissues in which the effect is most effective, as well as defining safe protocols for clinical application. Concurrently, the first clinical trials have been launched to validate the experimental results and evaluate the effectiveness of the treatment according to rigorous statistical standards.

The large-scale introduction of FLASH radiotherapy requires a significant multidisciplinary effort involving physicists, physicians, biologists, and engineers. The accelerators currently in use in hospitals are not yet capable of generating the parameters required for FLASH-RT, especially for deep treatments. The development of new technological platforms will therefore be essential to overcome current limitations and make this therapeutic modality accessible clinically.

Looking ahead, FLASH radiotherapy has the potential to transform the entire paradigm of modern radiotherapy, offering more effective, less toxic, and significantly faster treatments. Furthermore, it could represent a concrete solution for particularly aggressive oncological diseases or those resistant to conventional treatments. However, the full development of this technology will require significant investment in terms of research, training and infrastructure.

1.5. CNAO' strategic role

The National Centre for Oncological Hadrontherapy is one of only six centres worldwide in which both proton therapy and carbon ion radiotherapy (CIRT) can be performed, thus positioning it as a leading centre in the field of hadrontherapy. Since it began clinical activity in 2011, CNAO has treated over 3,700 cancer patients, approximately 55% of

whom received CIRT. The centre's current operating capacity is around 600 patients per year, with an estimated potential increase of 20% to meet the growing national demand.

The centre treats a wide range of diseases, but the main indications include chordomas and chondrosarcomas of the skull base and spine, carcinomas of the head and neck, and adenoid cystic carcinomas. At present, ten of these diseases are eligible for reimbursement by the National Health Service under the LEAs, consolidating the role of hadrontherapy within Italian public treatment strategies.

The clinical results obtained to date indicate generally high local control rates, even in complex clinical conditions. Approximately 25-30% of treated patients underwent re-irradiation, while 15% had large tumours. Notwithstanding this, clinical outcomes remained consistent with those documented in the international scientific literature, with predominantly low-grade toxicity. In certain instances, the safety profiles observed proved to be more favourable than those described for conventional radiotherapy techniques.

In terms of clinical research, CNAO stands out for its substantial contribution to the development of evidence on the efficacy and tolerability of hadrontherapy. However, there is still a paucity of direct comparative studies between hadrontherapy and advanced photon radiotherapy, despite some clinical trials currently underway in selected oncological fields, including low-grade gliomas, oropharyngeal, and oesophageal tumours.

In the case of chordomas, chondrosarcomas, and salivary gland neoplasms, CIRT has shown particular effectiveness in controlling the disease, as evidenced by several studies. A retrospective analysis conducted at CNAO and published in 2020 analysed the outcomes of 135 patients, 70 of whom underwent proton therapy and 65 received CIRT. Patients treated with carbon ions had more complex neoplasms. The median follow-up was 44 months. At five years, the local control rate was 71% in the CIRT group and 84% in the proton therapy group, while overall survival (OS) was 82% and 83%, respectively. Acute or late toxicity of grade ≥3 was observed in 11% of patients, highlighting the favourable safety profile of the therapy.

According to epidemiological estimates, limited to the diseases included in the LEAs, approximately 5,000 patients per year in Italy could benefit from proton therapy and approximately 1,000 from carbon ion therapy. Consequently, it is essential to establish a

national network of centres dedicated to hadron therapy, in which CNAO can act as a reference hub. Such a network structure would optimise patient care, facilitate recruitment into clinical protocols, enhance translational research, and strengthen synergies between hospitals, universities, and research institutes.
The adoption of a multidisciplinary collaborative model, based on the integration of clinical, physical, and biological expertise, is essential for consolidating the role of hadrontherapy in modern oncology and ensuring equitable access to highly complex technological and scientific treatments.

1.6. Agreements between centres and regions: the case of Emilia-Romagna

We have seen how proton therapy represents one of the most advanced forms of cancer radiotherapy. However, its technological complexity and the high cost of the necessary infrastructure have constrained its dissemination in Italy, causing inconvenience and delays in treatment for potential patients.

In light of the limited geographical distribution of these centres, it has become necessary to develop interregional cooperation tools to ensure access to treatment even for patients residing in regions without dedicated facilities. In Italy, this cooperation is grounded in Article 8-sexies of Legislative Decree 502/1992, which governs compensation for assistance provided to citizens in regions other than their region of residence. Additionally, the 2010-2012 and Health Pact 2014-2016 further promote agreements between neighbouring regions to regulate healthcare mobility and foster economies of scale in the management of highly complex services.
Interregional agreements on proton therapy have a dual function: firstly, they guarantee patients access to innovative treatments, and secondly, they optimise the use of public resources through a tariff compensation mechanism.
The agreements stipulate clinical eligibility criteria, procedures for referring and authorising patients, and rules for reimbursement and pricing. In this regard, a key aspect concerns the authorisation process. Indeed, access to treatment by patients from outside the province must be validated by their regional health service, through a process involving the relevant radiotherapy department and the health management of the local

health authority. Only after formal authorisation can the patient be admitted for treatment at the specific proton therapy centre, in order to avoid unregulated healthcare mobility.
A clear example of such agreements is the agreement between the Emilia-Romagna Region and the Autonomous Province of Trento, initially signed in 2019 and renewed several times in subsequent years up to the most recent renewal in February 2025. This agreement provides a precise delineation of the conditions for delivery and the categories of eligible patients. These categories include, for example, chordomas and chondrosarcomas of the skull base and spine, radioresistant sarcomas, high-grade intracranial meningiomas near the optic pathways, paediatric tumours, and recurrences necessitating re-irradiation. These pathologies, characterised by anatomical complexity and distinct radiosensitivity, benefit significantly from the physical characteristics of proton therapy.

From an economic perspective, the agreement stipulates a 20% reduction in the standard rates established by the Autonomous Province of Trento for proton therapy treatments, with direct billing to the patient's local health authority. This mechanism enables the Emilia-Romagna Regional Health Service to absorb the high cost of treatment in a sustainable manner. Patients are therefore referred through a regulated process that ensures clinical appropriateness and economic sustainability. The prescription must be issued by the National Health Service, validated by the public radiotherapy department and the health directorate, and then communicated to the Provincial Health Services Agency of Trento. This agreement can be regarded as a virtuous model of interregional cooperation, aimed at combining clinical needs and managerial efficiency. It facilitates access to highly specialised treatment for patients in Emilia-Romagna suffering from complex neoplasms, treatment that is not available within their region. Concurrently, the Trento centre consolidates its role as a national reference centre, with a sufficient patient volume to ensure operational continuity and clinical-scientific development. Agreements of this kind are therefore genuine strategic healthcare planning tools, capable of strengthening the cohesion of the national healthcare system and promoting the widely discussed equity in access to innovative treatments.

CHAPTER II: HYBRID ORGANISATIONS BETWEEN ECONOMICS AND BUSINESS

2.1. Traditional organisational types and institutional logics

Business organisations can be defined as structured systems of resources and activities designed for the production of goods or services to meet specific needs, following a given organisational structure and an economic logic oriented towards sustainability over time. Conventionally, such organizational structures have been situated along a continuum between two opposite poles: the market, wherein regulation occurs through price and competition, and the hierarchy, wherein coordination is internal to the enterprise and exercised by a central authority.

In the field of business economics, organisations are typically classified into three broad categories:

1. For-profit enterprises;
2. Public entities;
3. Non-profit organisations.

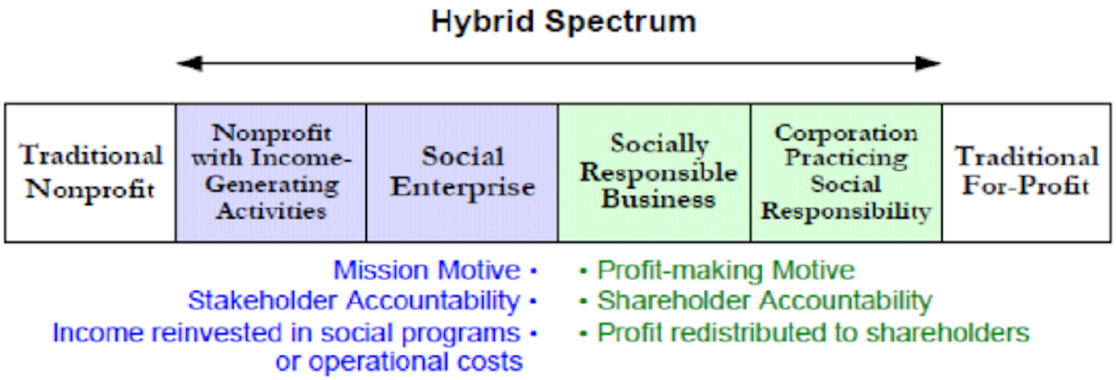

Figure 5: Social enterprise hybrid spectrum.

Source: Alter K.

Each of these types reflects a dominant institutional logic. Private enterprises are primarily driven by market logic, with the objective of maximising profit and generating

economic value for their stakeholders. Conversely, public organisations are guided by the logic of the state, pursuing collective and social ends, often independently of economic efficiency criteria. Finally, the non-profit sector is historically associated with the principles of solidarity and active citizenship, aiming to address unmet social needs often overlooked by the state and the market.

Nevertheless, these three established forms have proved inadequate to cope with the growing social and economic complexities, leading to deficiencies in both the market and public institutions. Consequently, there is an increasing necessity for organisational structures capable of integrating multiple logics in a flexible and efficient manner.

2.2. Hybrid organisations

Hybrid organisations can be regarded as a response to this need. They combine distinctive elements of two or more institutional logics, merging elements of both the market and the hierarchy. They also introduce mechanisms for joint coordination between actors that simultaneously maintain asset-related and managerial independence. Battilana and Lee (2014) define hybrid organisations as "entities that are configured as a vehicle of convergence between economic rationality and social rationality", capable of operating across the blurred boundaries between the public, private, and third sectors. This capacity to operate across diverse domains enables them to pursue the dual mission of economic sustainability and social impact, frequently resulting in innovations in process and governance.

From an economic-institutional perspective, hybrid organisations are institutional structures situated in an intermediate zone between the market and hierarchy, which use mixed coordination mechanisms, where two or more partners share strategic decision-making rights and, in some cases, property rights over common goods. This results in the coexistence of incomplete contracts, trust, and shared forms of governance.

2.2.1. Theoretical examples

Hybrid models take the form of numerous organisational arrangements observable in practice. Among these, the main ones include:

a) Joint ventures: independent legal entities formed by two or more companies that contribute assets, expertise, or capital. The partners share decision-making rights over common activities while retaining autonomy in other areas of operation. JVs are particularly prevalent in knowledge-intensive sectors, such as pharmaceuticals and technology, where they mitigate innovation costs and share risk;

b) Strategic alliances: agreements between independent companies that choose to cooperate to achieve shared objectives without establishing a separate legal entity. They are based on shared resource flows and decision-making processes, as in the case of airlines that cooperate on routes and loyalty programmes while maintaining their own identity and autonomy;

c) Franchises and consortia: in franchising, the franchisor grants the franchisee the right to use the company's brands and formats in exchange for royalties. The partners operate independently but are bound by shared control mechanisms and standards. Consortia similarly allow small companies to join together to gain advantages of scale while retaining their independence;

d) Co-operatives and business networks: co-operatives, especially agricultural or artisanal ones, constitute hybrid forms par excellence. Members are co-owners and users of the service, and the organisation functions according to the democratic principle “one person, one vote”, thereby maintaining a democratic governance structure oriented towards the benefit of members. In contrast, business networks are established through more or less formal connections between entities that coordinate specific activities by sharing resources, knowledge, or markets. In the field of healthcare, the clinical directorate model analysed by Correia and Denis (2016) shows how a clinical directorate in a public

hospital can integrate managerial and professional logics, while preserving doctors' strong operational autonomy;

e) Social Enterprises: represent the archetype of hybridisation, as they are designed to fulfil a social mission through the economic instruments of private enterprise. They are characterised by a continuous tension between the need to generate profitability and the need to maintain their founding social commitment.

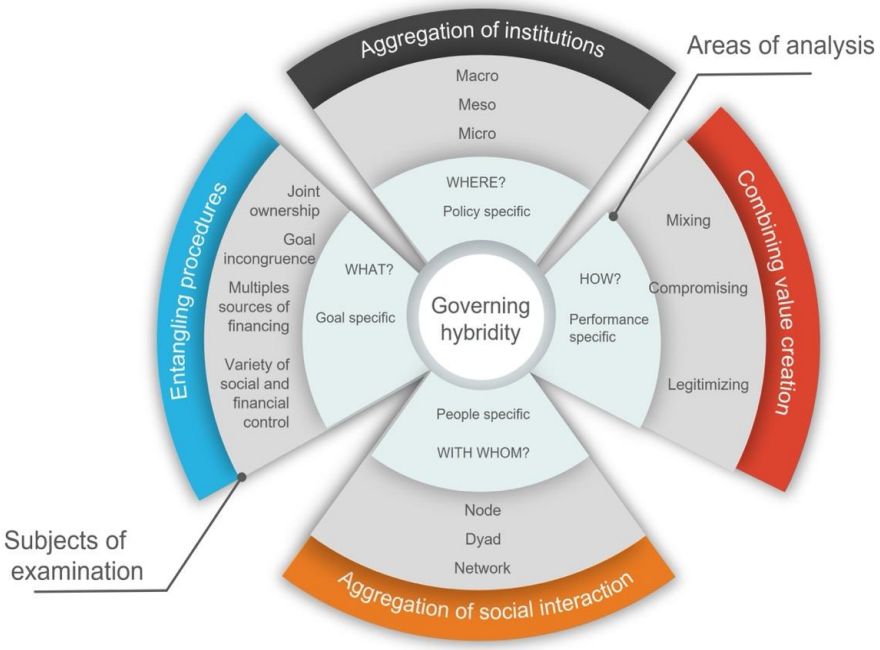

Figure 6: Governing hybridity.
Source: IRSPM.

Public-private partnerships, particularly in the energy, transport, or health domains, also represent hybrid forms. They are often governed by complex contracts and fiduciary agreements, with the objective of generating public goods through market instruments.

2.2.2. Advantages

One of the primary strengths of hybrid organisations lies in their remarkable organisational flexibility and capacity to integrate economic, social, and institutional logics within a single operational structure. The integration of diverse resources, competencies, and perspectives enables hybrid organisations to respond in innovative and adaptive ways to complex problems, often characterised by high uncertainty and multiple stakeholders. This capacity for integration enables the development of long-term sustainable solutions that generate economic value without sacrificing social and environmental objectives related to impact.

A further distinctive element is the institutional resilience that hybrid organisations demonstrate in the face of changing environments. By operating in environments that are frequently unstable, poorly regulated, or subject to rapid change, these entities can adapt their structures and strategies with greater agility than traditional organisations, while maintaining consistency with their founding mission. The combination of practices and values from different institutional systems enables them to withstand environmental pressures, and to redefine their organisational boundaries dynamically.

Some of the primary benefits of hybridisation can be categorised as follows:

- Risk sharing: in sectors characterised by high volatility, such as technological innovation or social entrepreneurship, the collaborative nature of hybrid organisations facilitates the distribution of financial, operational, and reputational risks among different partners. This sharing incentivises investment in initiatives with high potential impact, which would otherwise be considered too risky by individual actors;
- Access to complementary expertise: thanks to cooperation between organisations from different sectors (public, private, third sector), hybrid organisations can access a broader portfolio of tangible (e.g., financial capital, infrastructure) and intangible (e.g., managerial expertise, technical knowledge, relational capital) resources. This complementarity fosters innovation and the achievement of objectives that no actor, in isolation, could pursue alone;
- Cost and process efficiency: by avoiding rigid vertical integration and opting for networked forms of cooperation, hybrid organisations significantly reduce

transaction, coordination, and monitoring costs. The use of flexible arrangements, strategic partnerships, and shared governance models facilitates economies of scale and scope without the burden of traditional hierarchical structures;

- Greater adaptability and learning capacity: hybrid organisations, due to their composite nature, are endowed with a strong organisational learning capacity. Through continuous interaction with different actors, they develop more sophisticated sensemaking mechanisms, which enable them to interpret and respond to environmental changes with greater timeliness and creativity than standard organisations;
- Institutional innovation: hybrid organisations not only respond to existing logics, but often contribute to redefining the institutional frameworks in which they operate, proposing new ways of collaboration between sectors and introducing innovative organisational practices that can subsequently be adopted on a wider scale.

From a managerial perspective, the management of hybrid organisations requires the implementation of complex leadership models, capable of balancing and integrating different operational logics and values. Conventional management skills that prioritise economic efficiency are in fact insufficient: it is imperative to develop mediation skills between economic, social, and environmental objectives, as well as advanced relational skills to manage the multiplicity of stakeholders involved.

In this context, the concept of selective coupling assumes strategic relevance: hybrid organisations purposefully select elements and practices from different logics, combining them in a way that is functional for the objectives pursued and dynamically adapting them to the operational context. This is not a mere sum of different practices, but rather a synergistic combination capable of generating new organisational configurations well-suited for resolving multidimensional problems.

A further benefit of hybrid organisations is multi-stakeholder accountability, which extends beyond traditional financial accountability to encompass forms of social, environmental, and ethical reporting. This approach fosters an organisational culture based on transparency, widespread accountability and the creation of shared value, enhancing the institutional legitimacy of the organisation and improving its ability to attract resources and support from a variety of actors.

2.2.3. Criticalities and challenges

Notwithstanding the numerous advantages, the dual nature of hybrid organisations entails significant risks and contradictions. Firstly, they are subject to internal conflicts between different value and operational dimensions. Consequently, the coexistence of a social mission and economic objectives may generate tensions in decision-making processes, personnel recruitment, and financial reporting practices.

From a legal perspective, hybrid organisations may find themselves in a regulatory grey area, especially when they combine elements of not-for-profit and for-profit entities. The case of US health foundations owning private insurance companies is an emblematic example: they risk losing their privileged tax status if they sacrifice their social mission for commercial purposes.

It is also important to emphasise the inherent challenge in maintaining legitimacy with different stakeholders, who may have divergent expectations regarding the prioritisation of economic or social objectives. As noted by Zollo et al. (2022), organisational identity is often fragmented, and the management of external legitimacy becomes a critical process that requires integrated or compartmentalised organisational structures depending on the circumstances.

Other critical issues may include:

- Risk of opportunism: partners may adopt free riding strategies or other opportunistic behaviour;
- Coordination difficulties: the absence of a strong central authority may impede the ability to reach consensus and implement decisions quickly;
- Monitoring and control costs: it is often necessary to establish committees, auditing systems, or costly governance mechanisms to prevent deviant behaviour;
- Uncertain durability: many hybrid organisations are unstable and can readily dissolve if trust, economic interest, or strategic alignment is lost.

2.2.4. Governance

A distinctive feature of hybrid organisations is the centrality of governance, understood as the set of formal and informal mechanisms that regulate the allocation of rights, the coordination of activities, and the resolution of conflicts. Hybrid forms of governance can vary in:

- Centralised governance: characterised by a strong strategic centre, which coordinates and regulates common activities;
- Decentralised or shared governance: based on contracts, joint committees, or established social norms among partners;
- Relational governance: based on mutual trust, reputation, and long-term relationships rather than binding legal norms.

As Williamson (1996) suggests, hybrid organisations occupy an intermediate position between market and hierarchy, requiring governance systems that are sufficiently robust to ensure cooperation, yet sufficiently adaptable to respect the autonomy of participants.

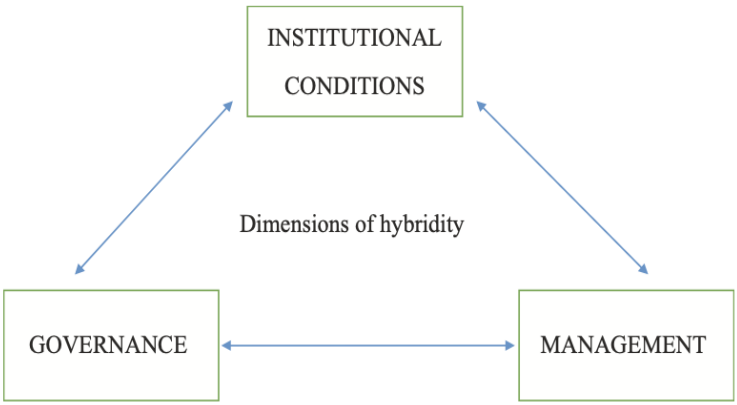

Figure 7: Managing hybrid organizations.

Source: Alexius S. – Furusten S.

2.3. CNAO Organisational Model

The National Centre of Oncology Hadrontherapy in Pavia is a paradigmatic case of hybrid organisation in the health sector. The coexistence of divergent missions is made possible by a flexible legal structure, an ambidextrous organisational configuration, and governance oriented towards integration. This demonstrates how clinical excellence, and scientific advancement can be combined, offering valuable insights into the design of hybrid infrastructures in the health and research sectors.

Established as a foundation under private law with public participation, CNAO combines clinical activity—oriented towards the treatment of oncological patients through advanced techniques—with a mission of frontier scientific research in the fields of medical physics, biomedical engineering, and applied health technologies.

2.3.1. Legal structure and institutional purposes

CNAO Foundation was formally acknowledged in 2001 by the Ministry of Health as a non-profit organisation with the institutional task of "designing, building and managing a national centre for oncological Hadrontherapy". Its legal nature reflects that of a foundation with public participation, where the Ministry of Health, the Ministry of Education, Universities and Research (MIUR), the Lombardy Region, and the INFN (National Institute of Nuclear Physics) play key roles in strategic governance, representing the intersection between public and private, which is typical of hybrid organisations.

The dual aims of CNAO—namely, the highly specialised treatment of cancer patients refractory to conventional radiotherapy and scientific and technological innovation—necessitate an organisational structure capable of supporting multiple and sometimes divergent objectives. Therefore, the internal structure of CNAO draws inspiration from ambidextrous organisational models, which balance operational efficiency and innovative adaptability.

2.3.2. Internal organisational set-up

The internal structure of CNAO is divided into two major functional poles/areas:

1. Clinical-Assistance Pole: includes the operating units dedicated to patient reception, therapeutic planning, treatment administration, and follow-up. Radiotherapists, medical physicists, nurses, medical technicians, and administrative staff work here. Clinical activities are managed in accordance with hospital protocols and quality standards similar to those of public cancer centres;
2. Technological-Scientific Pole: includes the medical physics laboratory, the team of engineers responsible for the maintenance and updating of the synchrotron, and

the research groups dedicated to the development of new applications of hadrontherapy. European projects (such as the aforementioned INSPIRE and HITRIplus) and collaborations with universities and research centres are promoted here.

The two souls, clinical and scientific, are interdependent yet autonomous, linked by horizontal coordination mechanisms. Unitary governance is ensured by the general management and the board of directors, while the two poles operate according to distinct logics: evidence-based medicine for the former, exploratory research and experimentation for the latter. This configuration is indicative of the structural hybridisation model, in which organisational units oriented towards different logics coexist under a single governance.

2.3.3. Coordination mechanisms and performance evaluation

CNAO's approach to innovation governance has also been described as an “innovation-driven hybrid”, an organisational model in which the coexistence of different professions (physicists, physicians, engineers, administrators) requires a high degree of cultural and regulatory mediation. In this context, leadership plays a crucial role in the management of hybrid tensions, i.e., the conflicts between economic efficiency, ethics of care, and free research.

Coordination between the two areas is facilitated by:

- Cross-functional teams for the management of clinical protocols and research projects;
- Shared information systems for the collection and analysis of clinical and experimental data;
- Regular meetings between clinicians and researchers to validate new therapies or technologies;
- An organisational culture based on responsible innovation, in which the ethical value of care is integrated with the objective of generating knowledge applicable to public health.

Performance is assessed at multiple levels:

- Clinical indicators such as treatment success rates, patient safety, waiting times;
- Scientific indicators, including number of publications, patents, and funded projects;
- Economic-financial indicators concerning the sustainability of the infrastructure.

These dimensions reflect a logic of multiple accountability, according to which the organisation is simultaneously held responsible before a plurality of stakeholders, each with different objectives, evaluation criteria, and expectations. In particular, CNAO is accountable:

i. to the national and regional health system, regarding the efficiency and effectiveness of the clinical treatments provided;
ii. ii. to the scientific and academic community, in terms of the production and dissemination of scientific knowledge;
iii. to public funding bodies, in terms of transparent and sustainable use of economic resources;
iv. to civil society, as a non-profit foundation with an ethical mission oriented towards care and fair access to therapeutic innovation.

The coexistence of these accountability obligations requires CNAO to carefully manage organisational tensions and adopt governance and control systems capable of balancing efficiency, innovation, and social responsibility. This configuration, characteristic of hybrid organisations, also requires ongoing reflection on the boundaries of its mission and on the coherence between its stated aims and operational practices.

2.4. Future challenges of hybrid organisations

It has been observed that hybrid organisations are becoming increasingly relevant in the contemporary economy, facing significant evolutionary challenges. These include digitisation and artificial intelligence, which require innovative mechanisms of coordination and shared control; sustainability and social responsibility, which call for

governance capable of integrating economic objectives with social and environmental goals; and finally, institutional regulation, as many hybrid forms remain difficult to frame legally, raising issues of competition, taxation, and accountability.

Finally, the primary challenge remains long-term viability: hybrid organisations must be able to adapt their governance mechanisms to internal and external changes, maintaining the balance between autonomy, cooperation, and shared control within an increasingly complex and heterogeneous society.

CHAPTER III: INNOVATION AND EFFECTIVENESS OF PROTON THERAPY

3.1. Diffusion of innovation

The diffusion of innovations is a process through which a new idea, technology, practice, or product is gradually adopted within a social system. This phenomenon is a fundamental aspect of organisational change and management studies, as it allows scholars to analyse the mechanisms through which innovations achieve mass adoption or, conversely, fail to take root in the market.

The analysis of diffusion is based on a multidisciplinary perspective, integrating concepts from economics, social psychology, communication, and strategic management. In this context, diffusion should not be confused with individual adoption, as the former is a collective process characterised by social interactions and network influences.

The theoretical model—arguably the most influential theory in the literature—was developed in 1962 by Everett M. Rogers (1931-2004), who defines diffusion as *"*the process by which an innovation is communicated through certain channels over time among the participants in a social system*"*.

In fact, any idea, when accompanied by an effective business model, has the potential to become an innovation. The Innovation Diffusion Theory posits that ideas for innovative products and services can, over time, gain momentum and disseminate within a given population or social system. This diffusion prompts individuals, as part of the system, to adopt new ideas, behaviours, products, and services. Adoption usually involves a change (or replacement) of previous behaviours.

The diffusion of new technologies is best understood as the result of competition among rival alternatives for achieving certain goals. This competition takes place between companies that seek to enhance the profitability of their investment in innovation and choose the most efficient alternative to this end, creating a circular relationship between diffusion and profitability.

Rogers' model relies on four key elements:

- Innovation: an idea, good, or service perceived as new by an individual or adoption unit;
- Communication channels: formal and informal tools through which information about innovation is disseminated;
- Time: the temporal dimension influences the speed and sequence of adoption;
- Social system: the set of interacting units within which innovation is disseminated.

Specifically, Rogers identifies five categories of adopters, each representing a demographic group with distinctive socio-psychological characteristics and a different level of acceptance of new ideas:

1. Innovators (2.5%) → they are individuals with a high propensity for risk, open to experimentation, and often possessing substantial economic and cultural resources;
2. Early Adopters (13.5%) → they are opinion leaders within the community, capable of translating innovation into terms that are understandable and attractive to others;
3. Early Majority (34%) → they adopt innovation after observing the positive experience of others, showing a pragmatic attitude;
4. Late Majority (34%) → they are more sceptical and adopt only when the innovation has become standard and the perceived risks are minimal;
5. Laggards (16%) → they are tied to traditions, with a low propensity for change and poor access to innovative information channels.

The aforementioned segmentation is commonly represented by the bell-shaped Innovation-Adoption Curve, with a corresponding cumulative S-shaped (sigmoid) trend of penetration over time.

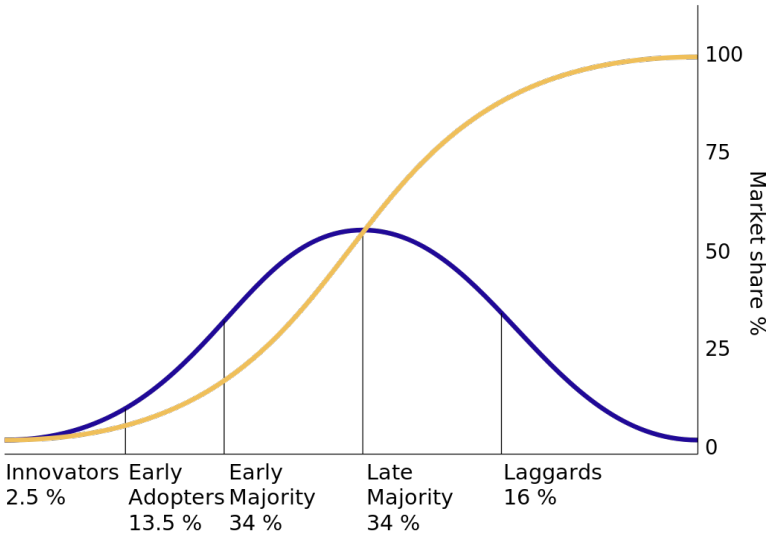

Figure 8: Rogers' Curve.

Source: Rogers E.

According to Rogers, five perceived factors of innovation significantly affect the speed and breadth of diffusion:

- Relative advantage: the degree to which the innovation is perceived as better than the previous practice;
- Compatibility: the level of consistency with the values, experiences, and needs of potential adopters;
- Complexity: the ease with which an innovation can be understood and used;
- Trialability: the possibility of experimenting the innovation on a small scale before full adoption;
- Observability: the degree to which the benefits of the innovation are visible to others.

In addition to these objective and subjective dimensions, the structure of the social system is also believed to play a decisive role: norms, communication networks, and the position of opinion leaders can accelerate or slow down adoption. Formal and informal communication channels also profoundly influence the speed with which information about innovation spreads and is accepted. Finally, the time factor—encompassing the

sequence in which diverse groups of adopters (innovators, early adopters, early and late majority, laggards) come into play—dictates the pace of diffusion, underscoring the dynamic and progressive nature of adoption, shaped by the continuous interaction between the characteristics of innovation, the social context, and communication processes.

In the field of healthcare, a growing number of empirical studies and meta-analyses have demonstrated that the adoption and diffusion of digital innovations are the result of a complex interaction between individual, organisational, and systemic factors. Beyond the desire to innovate, variables such as organisational capacity, leadership commitment, the effectiveness of internal communication structures, staff training, and regulatory and infrastructural preparedness are crucial to the successful implementation of new technical and healthcare solutions.

For decades, the Diffusion of Innovation (DOI) model developed by Rogers (2003) has served as a key theoretical reference point for analysing technological adoption processes in healthcare, at both the level of healthcare professionals, and organisations as well as patients. However, this interpretative framework has recently been criticised for its predominantly linear and "actor-centric" approach, which tends to underestimate the impact of structural, institutional, and political factors, particularly relevant in highly complex and regulated sectors such as healthcare.

In this context, the most recent literature emphasises the need for multi-level approaches capable of capturing the dynamic interaction between micro, meso, and macro factors. At the micro level, elements such as individual perceptions, cognitive patterns, digital skills, and professional identity directly influence the propensity to adopt. At the meso level, organisational practices, leadership behaviour, and internal policies act as mediators between the actions of end users and pressures from the wider healthcare system. Finally, at the macro level, political will, regulatory frameworks, national strategies, and the availability of digital infrastructure determine the overall context for diffusion.

This standpoint is consistent with the Consolidated Framework for Implementation Research (CFIR), which integrates individual, organisational, and external context dimensions to analyse and optimise implementation processes. Furthermore, Liang

(2012) proposed a multi-level gap model for eHealth, which distinguishes between awareness, availability, and actual use of technologies, thereby highlighting the frequent misalignments between the introduction of digital solutions and their full integration into healthcare processes.

However, adoption challenges are not limited to the initial phase: healthcare innovation pathways are often characterised by non-linear dynamics, interrupted by institutional inertia, exogenous shocks (e.g., health crises), political resistance, and changing policy priorities.

A recent paradigmatic example of how exogenous shocks can reshape the trajectories of healthcare innovation is the COVID-19 pandemic and the subsequent development of mRNA and viral vector vaccines. Conventionally, the processes of research, clinical trials, regulatory approval, and vaccine production follow a multi-year timeline, characterised by rigidly structured phases. However, the global urgency of the health emergency has led to a profound reorganisation of these pathways:

- Development overlap, with concurrent preclinical studies, clinical trials and industrial production preparation;
- Accelerated regulatory procedures, facilitated by the use of tools such as rolling reviews by the EMA and FDA, which allowed for continuous evaluation of data as it became available;
- Unprecedented multi-level coordination, with the simultaneous involvement of actors at the micro level (researchers and healthcare professionals), meso level (pharmaceutical companies, hospitals, clinical laboratories), and macro level (governments, international organisations such as the WHO, supranational regulatory bodies);
- Global digital and data-sharing infrastructures, which enabled the near real-time sharing of genomic sequences, research protocols, and preliminary results, accelerating innovation and adoption.

This has demonstrated how the combination of political pressure, financial mobilisation, organisational capacity, and technological availability can drastically reduce innovation times. However, it has also revealed critical issues, including the initial unequal

distribution across countries, vaccine refusal among specific social groups, and challenges related to logistics and the management of the cold chain, which have negatively affected distribution in certain areas of the world.

This prompts a reconsideration of conventional sequential models and underscores the potential for the utilisation of integrative theoretical frameworks.

An example of such an approach is the STAD-HC (Socio-Technical Adoption and Diffusion in Health Care) model, which combines the process logic of DOI with a multi-level perspective. This model allows researchers to analyse not only the individual determinants of adoption, but also strategic alignment, governance, and policy coherence at the healthcare system level. The strength of this approach lies in its ability to integrate contextual dynamics with implementation processes, rendering it particularly useful for understanding the spread of emerging technologies such as artificial intelligence, blockchain, and the Internet of Things in healthcare.

3.2. Innovation and adoption

Innovation has been identified as a fundamental component in economic and social development processes. Joseph Schumpeter (1934) was among the first to emphasise its role in creative destruction, highlighting how technological and organisational renewal can radically transform economic sectors, stimulating growth and redefining competition. The development of new products and services, whether radical or incremental innovations, is therefore the arena in which companies seek to consolidate their market leadership or, in some cases, simply to ensure their survival.

The contemporary economic scenario is characterised by an exponential acceleration in technological progress, which has resulted in a substantial increase in the number of innovative concepts introduced to the market. Shorter product life cycles and the growing incidence of internal cannibalisation have made innovation both indispensable and risky. It has been observed that innovation and commercial success are not necessarily linearly

correlated, as a technologically advanced idea may encounter cultural, economic, or organisational obstacles that compromise its large-scale diffusion.

In this context, one of the most significant challenges facing statistical and economic research is the development of *ex ante* forecasting methodologies capable of estimating innovation diffusion models even before their commercial launch. The objective is twofold: to reduce the business risk associated with the introduction of a new product; to provide management with analytical tools for planning marketing strategies, resource allocation and production management. Forecasting models, such as those derived from Bass's paradigm (1969), are based on the analysis of the adoption curve over time, understood as the probabilistic distribution of sales or overall adoptions. However, the application of these models is complex due to the scarcity of data in the early stages and the multiplicity of variables involved: consumer heterogeneity, macroeconomic conditions, the effectiveness of communication strategies, the role of the media and social networks, competitive pressure, and, last but not least, technological progress, which can quickly render a product obsolete.

The Bass model, developed by Frank Bass, seeks to describe the process of adoption of new durable products in a population using a simple differential equation. The model elucidates the interaction between current users and potential users of a new product. The basic premise is that future consumers can be classified as innovators (who use the product because they appreciate its features) or imitators (who adopt the product because they imitate current users). Consequently, according to this model, the growth rate of new users will depend on the size of the target market, the number of current users who can be imitated, and the number and degree of imitation among adopters. The Bass model has been extensively used in forecasting, particularly for sales forecasts and technological forecasts for new products.

In contrast to Rogers' approach, Bass reduces the number of adopter categories from five to two and specifies that the distinction is based on purchasing influence. Consequently, innovators are not influenced at the time of initial purchase by the number of individuals who have already purchased the product, while imitators are influenced. The importance of innovators is more significant at the beginning, then tends to gradually decrease over

time. The author thus posits that the speed and timing of adoption depend on their degree of innovation and the propensity of potential buyers to emulate.

As a matter of fact, it is one of the most widely used quantitative approaches for describing and predicting the temporal trend of new product adoptions.

The model is based on two key parameters:

- innovation coefficient (p), which represents the probability of adoption independent of social influence;
- imitation coefficient (q), which represents the influence exerted by word of mouth, observation, and interactions between consumers.

The conditional probability function describing adoption in a time interval *t* is as follows:

$$f(t) = \frac{F(t)}{1 - F(t)} = p + qF(t)$$

where *F(t)* represents the cumulative fraction of adopters up to time *t*.

Developing the formula, the number of new adopters at time *t* can be expressed as:

$$\frac{dN(t)}{dt} = \left[p + q\ \frac{N(t)}{m}\right][m - N(t)]$$

where:

- *N(t)* is the cumulative number of adopters at time *t*;
- *m* represents the maximum potential number of adopters (market potential);
- *p* is the innovation coefficient;
- *q* is the imitation coefficient.

The analytical solution of the differential equation provides the cumulative adoption curve, which takes on the typical S-shape: slow in the early stages, accelerated in the growth phase, and finally decreasing upon reaching market saturation. In quantitative terms, the cumulative function is expressed as:

$$N(t) = m \frac{1 - e^{-(p+q)^t}}{1 + \frac{q}{p} e^{-(p+q)^t}}$$

while the distribution of periodic adoptions (i.e., sales or new adoptions in each period) is given by:

$$n(t) = N(t) - N(t-1)$$

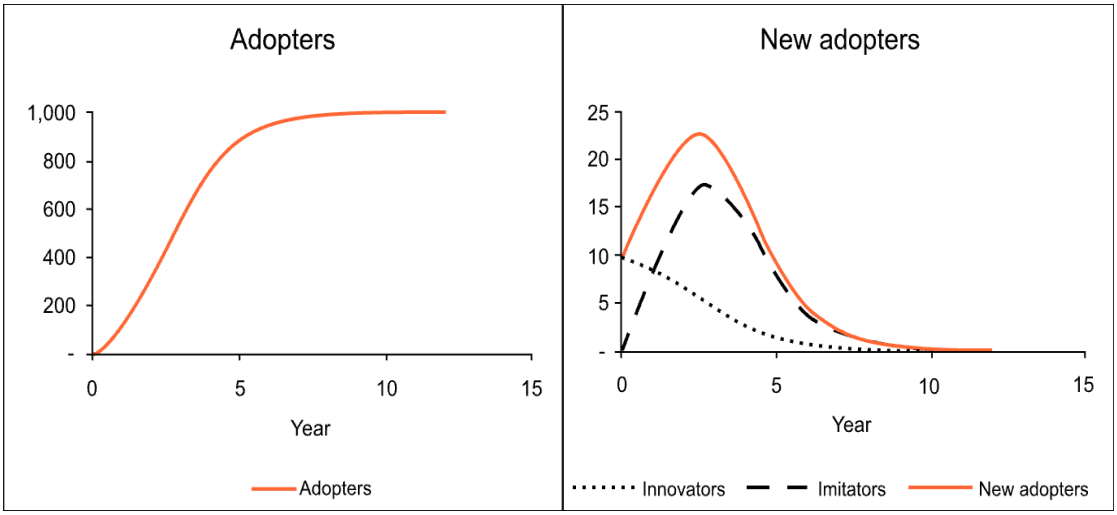

Figure 9: Innovators and imitators' behaviour.
Source: Rogers E.

Several studies have demonstrated the empirical validation of the Bass model, which has proved particularly useful in the field of strategic management, as it allows future demand to be estimated and supports decisions concerning launch policies, pricing strategies, and investments in communication. Moreover, its ability to distinguish between the effect of innovation and imitation enables companies to better understand adoption dynamics and plan targeted interventions based on the product life cycle.

The literature also highlights how forecasts can diverge significantly from actual market trends: overestimating demand leads to risks of overproduction, high storage costs, and rapid depreciation of inventories. Conversely, an underestimation of demand can result in product shortages, lost sales, and reduced overall profitability. Accurate forecasting, on

the other hand, allows management to optimally plan the product life cycle, efficiently allocating resources and capital.

A further line of research, developed since the 1990s, has focused on the international dimension of innovation diffusion. It has been observed that cross-country processes accelerate the adoption curve in secondary markets: consumers in one country positively influence potential adopters in other contexts through interpersonal communication and indirect observation, reducing their perceived uncertainty and encouraging consumption. This explains why, in many cases, innovations introduced later in a market experience a faster take-off phase than in the original context. However, even this process is not uniform, as cultural differences, heterogeneity of consumer preferences, economic disparities, and different levels of technological infrastructure contribute to shaping highly heterogeneous diffusion trajectories even between geographically and culturally close countries.

3.3. The effectiveness of proton therapy

As discussed in the first chapter of this study, proton therapy represents a structural innovation in oncological radiotherapy, thanks to the unique physical ability of protons to deposit the maximum dose in a selected area, known as the spread-out Bragg peak, while minimising the irradiation of surrounding healthy tissues. This optimal dosimetric profile facilitates both enhanced local tumour control in cases where an increase in dose is indicated and a significant reduction in toxicity to healthy tissues, rendering proton therapy particularly useful in oncological situations where preserving quality of life is imperative.

The distinctive benefits of ion beams for cancer therapy are attributed to their macroscopic and microscopic energy deposition pattern, which differs from conventional photon radiation used in standard radiotherapy. On a macroscopic scale, the dose profile with a Bragg peak at greater depths and modest lateral dispersion allows for better dose conformation to the tumour. At the microscopic level, the localised energy deposition around the particle trajectory results in high biological effectiveness, typically expressed in terms of clinically relevant relative biological effectiveness. Numerous experimental

investigations have also revealed complex dependencies of RBE on various physical and biological parameters, including ion type, dose, position in the field, and cell or tissue type.

The effectiveness of proton therapy has already been demonstrated in a variety of oncological contexts by numerous studies, and many more are still ongoing. In the case of head and neck paragangliomas, which are rare diseases often located in proximity to critical structures such as cranial nerves and blood vessels, proton therapy has shown local control rates of 100% with a favourable toxicity profile and a positive impact on patient symptoms. In a cohort treated at the Institut Curie, no cases of acute toxicity above grade 2 were reported, and neurological and otolaryngological symptoms were stabilised or improved in most patients, confirming the high tolerability and functional efficacy of the technique.

Another crucial field of application is paediatric tumours, particularly medulloblastoma. This central nervous system neoplasm, which is the most prevalent brain tumour in children, is conventionally treated with surgery, chemotherapy, and craniospinal radiotherapy. However, the late side effects of photon radiotherapy (e.g., endocrine deficits, impaired bone growth, cognitive decline, and the onset of secondary tumours) represent a significant clinical challenge. For this reason, the use of proton therapy enables a substantial reduction in the dose to healthy tissues, particularly the pituitary gland, thyroid, inner ear, and brain parenchyma, helping to preserve neurocognitive development and quality of life of survivors. Systematic reviews have demonstrated that, while maintaining high survival rates, proton therapy reduces the likelihood of endocrine dysfunction and cognitive deficits compared to traditional techniques. This is particularly relevant in children, as radiation at an early age has permanent consequences that affect their entire lifespan.

Proton therapy has also shown efficacy in more complex oncological contexts, such as recurrent gynaecological tumours. In a retrospective study of patients with recurrent epithelial ovarian cancer, proton therapy achieved local control of 91.5% at one year and 71.3% at two years, with no grade ≥3 toxicity. These data are particularly significant given that these patients, who are often platinum-resistant and have already undergone multiple lines of therapy, have limited treatment options. The effectiveness of proton therapy in

this context confirms its potential role as a loco-regional salvage treatment, capable of prolonging progression-free survival and enhancing quality of life without severe side effects.

From a radiobiological point of view, proton therapy is conventionally characterised by an average RBE of 1.1 in comparison to photons. However, microdosimetric and experimental research has shown that this value is not uniform along the beam path, but rather tends to increase in the distal region of the spread-out Bragg peak (SOBP), where the energy of the protons is lower and the linear ionisation density (LET) is higher. This variability has significant clinical implications, as in regions close to critical structures, the actual distribution of the biologically effective dose may differ from the planned dose. This observation paves the way for the integration of microdosimetry into treatment systems.

At the same time, innovative approaches have been developed to further enhance the biological effectiveness of protons. These include proton–boron capture therapy (PBCT), a promising strategy based on the nuclear reaction $p + {}^{11}B \rightarrow 3\alpha$ (pB), which generates high LET α particles in the tumour region. Experimental studies have shown that the presence of boron-containing compounds, such as borocaptate sodium (BSH), amplifies the cytotoxic efficacy of protons, increasing cell lethality and the complexity of chromosomal aberrations. Experiments involving low-energy proton beams have yielded analogous outcomes, demonstrating a substantial increase in DNA damage in tumour cells treated with BSH. This development signifies a pivotal advancement in proton therapy towards enhanced forms of hadron therapy, which combine the ballistic precision of protons with the radiobiological efficacy characteristic of heavy ions.

3.3.1. Coordination mechanisms and performance evaluation

Photon radiotherapy has been the standard treatment in oncology for decades, based on the use of high-energy X-rays capable of passing through tissue and gradually depositing the dose along their path, with inevitable exposure of adjacent healthy tissues.

Conversely, proton therapy uses proton beams, which, due to the physical property of the Bragg peak, release their maximum energy at a specific depth with minimal dose beyond

the tumour target. This peculiarity enables a significantly more conformal dose distribution, thereby sparing surrounding organs at risk to a considerable extent.

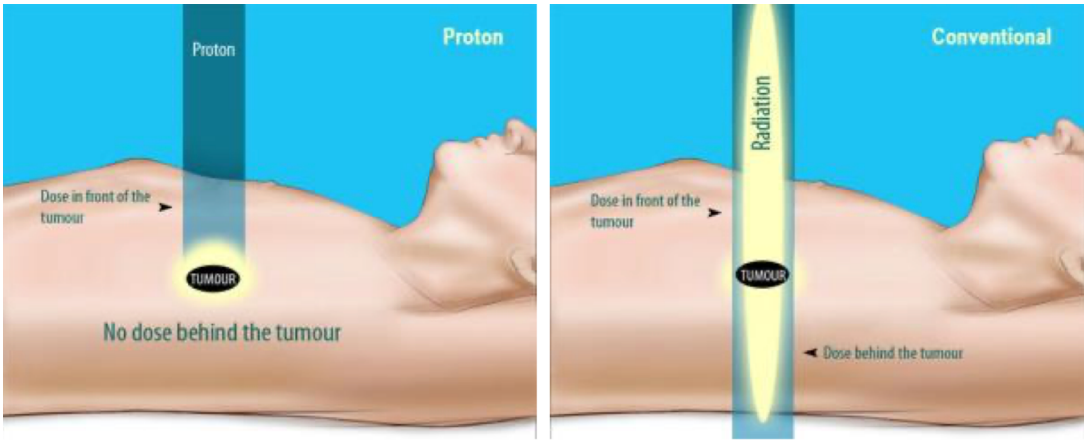

Figure 10: Differences in irradiation between proton and conventional radiotherapy
Source: European Institute of Oncology.

A substantial body of clinical and dosimetric research has validated the efficacy of proton therapy in reducing long-term toxicity. For example, in left breast cancer with lymph node involvement, proton therapy has shown a significant reduction in the dose to the heart and lungs compared to photon radiotherapy, lowering the risk of cardiovascular events and pulmonary complications. Similarly, in paediatric craniospinal treatments, protons have reduced the average dose to critical organs such as the thyroid, heart, pancreas, and oesophagus by more than 10 Gy, resulting in a decrease in the incidence of late effects and secondary tumours. Recent studies on Ewing's sarcoma and cases of mediastinal lymphoma have highlighted similar advantages: compared to photons, protons have achieved lower exposure of the rectum, bladder, testicles, and anal canal.

From a neurological perspective, proton therapy has been shown to reduce the loss of grey and white matter volume in the brain in patients with glioblastoma compared to photons, suggesting a potential benefit in preserving cognitive function. Finally, in skull base tumours, such as chondrosarcomas, the combination of surgery and proton therapy has significantly reduced local recurrences compared to surgery alone, despite the occurrence of specific side effects, including sensorineural hearing loss.

This demonstrates how proton therapy may be preferable to conventional radiotherapy in all situations where it is essential to reduce the dose to critical organs close to the tumour.

In fact, in such cases, the superior dosimetric profile of protons results in a lower incidence of acute toxicity and, most significantly, late effects, thereby ensuring a better quality of life for patients and reducing the indirect costs associated with the management of chronic complications.

CHAPTER IV: SUSTAINABILITY OF PROTON THERAPY

4.1. Sustainability in economics

The notion of sustainability occupies a pivotal position in contemporary economic debate, assuming multiple meanings that extend beyond the mere environmental dimension. In economics, sustainability refers to the capacity of a productive, social or institutional system to preserve its balance over time, ensuring continuity of resources and benefits for present and future generations. This concept, which originated in the ecological and environmental fields, has gradually spread to macroeconomic, microeconomic, and sectoral analyses, becoming a guiding criterion in policy choices and corporate strategies.

One of the most frequently cited references is the definition contained in the United Nations Brundtland Report (1987), according to which sustainable development is "development that meets the needs of the present without compromising the ability of future generations to meet their own needs". This definition has been instrumental in situating sustainability within the framework of economic policy, thereby underscoring the interconnectedness between economic, social, and environmental dimensions.

In economics, the concept of sustainability can be examined through at least three distinct lenses:

1. Economic sustainability, understood as a system's capacity to ensure long-term economic growth and stability without generating unsustainable imbalances, such as excessive debt, persistent inflation, or inefficient use of resources;
2. Social sustainability, understood as the necessity to preserve cohesion, equity, and collective well-being, thus preventing economic development from producing exclusion or unmanageable inequalities;
3. Environmental sustainability, understood as the rational use of natural resources and the mitigation of the ecological impact of economic activities, so that growth does not compromise the natural systems on which human life depends.

Economic literature has emphasised that sustainability is not a static condition, but rather a dynamic process of adaptation and balancing between often conflicting objectives: growth and environmental protection, efficiency and equity, innovation and stability. Consequently, sustainability analysis requires methodological tools that integrate conventional economic indicators (e.g., GDP or productivity) with a more comprehensive assessment of well-being and quality of life, encompassing natural, social, and human capital indicators.

From a theoretical standpoint, the debate also revolves around two opposing viewpoints:

- the weak sustainability perspective, according to which natural capital can be partially replaced by economic and technological capital, provided that the overall level of well-being is not reduced;
- the strong sustainability perspective, which considers certain natural resources to be irreplaceable and requires their absolute preservation for future generations.

In the contemporary debate on healthcare system management, the evaluation of new technologies is progressively adopting a multidimensional approach that considers not only clinical effectiveness, but also economic sustainability and the allocative efficiency of available resources. The introduction of innovations such as proton therapy therefore requires a theoretical framework that analyses their impact not only in therapeutic terms, but also in economic and social terms.

In healthcare, the concept of sustainability refers to a system's ability to ensure access to effective and equitable care while concurrently safeguarding long-term economic stability. Sustainability implies, on the one hand, the compatibility of healthcare expenditure with available resources and, on the other, the maintenance of high-quality standards without reducing accessibility for patients. In other words, a healthcare intervention can be considered sustainable when its economic impact is justified by the benefits it generates, both in terms of health and social value.

Closely linked to this concept is that of efficacy, which in health economics is understood as the ability of a technology to produce an expected clinical benefit under ideal or experimental conditions. Efficacy provides the scientific basis for the justification of the adoption of a technology. In the absence of a proven therapeutic advantage, any

assessment of cost or economic impact would be unwarranted. However, efficacy alone is not sufficient to determine the legitimacy of an investment; a comparison must be made with the results obtained in terms of health in real contexts—i.e., with effectiveness—and with the system's ability to finance such services in a fair and continuous manner.

Conversely, the concept of efficiency refers to the principle of optimal use of limited resources, a fundamental principle of health economics. This notion can be divided into three main dimensions:

- allocative efficiency, which concerns the distribution of resources across health sectors and programmes in order to maximise collective well-being;
- technical efficiency, understood as the ability to achieve maximum output (health outcomes) from a given input (resources);
- cost-effectiveness efficiency, which assesses the relationship between the costs incurred and the benefits obtained in terms of health, often expressed through standardised measures such as Quality-Adjusted Life Years (QALYs) or Disability-Adjusted Life Years (DALYs).

The application of these concepts to a technology such as proton therapy necessitates a detailed analysis. Economic sustainability must fully consider the high initial investment required to build the centres, the operating and maintenance costs, and the volume of patients that can be treated. Clinical effectiveness, although supported by growing evidence, must be weighed against alternative treatments, such as conventional radiotherapy. Finally, efficiency requires a comparative assessment that compares the cost-benefit ratio of proton therapy with other treatment options, taking into account not only clinical outcomes but also the reduction of side effects, patients' quality of life and the impact on the national health system.

4.2. Sustainability of proton therapy

It is evident that proton therapy has firmly established itself as a major innovation in the field of oncology in recent decades. This is primarily due to its capacity to deliver high

doses of radiation to tumours with extreme precision, significantly reducing exposure of healthy tissue. This feature renders this technology particularly attractive for the treatment of paediatric cancers and tumours located near critical organs.
However, alongside the clinical enthusiasm, the issue of economic sustainability has emerged strongly. Indeed, the high initial investment required to build a proton therapy centre (estimated at between €60 and €150 million) and the recurring operating costs, such as those related to energy and specialised personnel, give rise to concerns regarding the cost-effectiveness of introducing and disseminating this technology within national healthcare systems.

4.2.1. Fixed costs (CAPEX)

When considering the comprehensive cost estimate for the construction of a proton therapy centre, it is necessary to differentiate between initial investments—known as fixed or capital costs (CAPEX)—and variable and recurring operating costs (OPEX).

When a healthcare institution initiates a proton therapy project, the investment mainly comprises four fixed cost items:

- bunker rooms with shielding and technical systems (HVAC, electrical, safety systems);
- the accelerator (cyclotron/synchrotron or compact synchrocyclotron);
- transport lines and treatment rooms (rotating gantries or fixed lines);
- clinical/digital equipment (imaging, TPS, QA).

In the early 2000s, a benchmark analysis by Goitein and Jermann estimated the construction cost of a centre with two turnkey gantries at €62.5 million, in comparison to approximately €16.8 million for a centre with two photon linacs: a ratio of ≈3–4:1, which explains the intense economic debate from the outset of proton therapy implementation.
Today, the ranges are wider because there are “compact” single-room configurations and multi-room systems with 3-5 rooms. Economic evaluation and HTA documents place the total investment between approximately $25 million and $200 million, with lower values typical of a single room added to existing facilities and higher values for multi-room greenfield centres. An updated clinical review indicates that modern single rooms

frequently fall within the $40–50 million range, consistent with recent trends (miniaturisation of sources and simplified civil layouts).

The following section will present concrete examples that will help to determine the scale. In Italy, the National Centre for Oncological Hadrontherapy (CNAO in Pavia) reports a total investment of €180 million for construction and clinical trials (2001–2013), largely financed by public funds. The construction of the Proton Therapy Centre in Trento amounted to a cost of €100–104 million, as confirmed by local press sources and provincial records. Still in Italy, smaller projects are significantly lower in scale: the CRO in Aviano reports a total investment of around €32 million, while the IEO in Milan has indicated an expected investment of around €40 million for its Proton Center.

In the United Kingdom, the government has committed £250 million to launching two large NHS centres in Manchester and London, which gives an indication of the impact of a national multi-site programme.

This range therefore reflects technological choices (e.g., cyclotron vs. synchrotron; 360° rotating gantries vs. fixed lines; pencil beam scanning, which is now almost universal), scale (one compact room vs. three to five rooms with dedicated lines), the degree of reuse of existing infrastructure, as well as local building and regulatory variables. Not surprisingly, the main methodological revisions in health economics emphasize that evidence on the "true" costs of centres is often incomplete or heterogeneous and that assessments must explicitly state assumptions about CAPEX and depreciation.

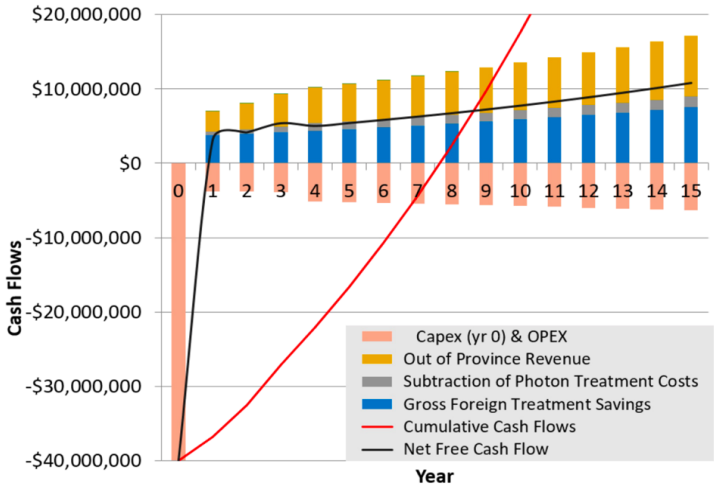

Figure 11: What conditions make proton beam therapy financially viable in Canada. Source: Smith et al.

4.2.2. Variable costs (OPEX)

The structure of operating costs for centres is relatively consistent across the literature and covers areas such as vendor-supported maintenance and servicing of the facility, personnel (doctors, physicists, RTTs/therapists, dosimetrists, nurses, service and engineering technicians, administrative staff), energy costs, consumables and related clinical services. A Canadian business case by Smith et al., which analyses a centre with a single beam line integrated into an ongoing hospital project, provides a clear overview. The estimated annual OPEX at full capacity is almost equal to $4.81 million, broken down into approximately $2.13 million in salaries, $2.0 million in supplier service contracts, $0.2 million for electricity, plus minor items for clinical services and consumables. During the ramp-up (years 1–3), costs are lower as staff numbers increase gradually. The same analysis quantifies the incremental CAPEX at ~$40 million (≈$30 million for the single-line system + ~$10 million for construction and ancillary systems), demonstrating that integration into an existing cancer centre reduces duplicate expenses.

The item “service and maintenance” is crucial. In tenders and business plans, it is often modelled as an annual percentage of the facility’s value. Reference values cited in two technical/managerial documents are around 10–15% of the equipment cost per year, consistent with the levels observed for complex, highly specialised systems. Independent economic models of particle therapy also introduce annual maintenance quotas (4–7%) and renewal/updates quotas (1–2% for proton components) to simulate scheduled replacement cycles over the system’s lifetime. The combined effect is that operating costs in hadrontherapy centres far exceed capital costs (≈87% vs. 13% in a comparative study by Maastricht University), with costs per fraction remaining highly sensitive to assumptions about staffing, QA and workloads.

Direct measurements of energy are now available: a technical study of a compact system (Mevion) from 2023 by Dvorak et al. reported an annual consumption of ~490 MWh, with an average of ~52 kWh per patient (significant differences appear depending on the cancer location and number of fractions). Once again, the economic weight of energy remains lower than that of personnel and maintenance, but it is not negligible in contexts with high electricity prices.

The “personnel” item depends on the organisational model and the mix of functions covered internally (clinical physics, site engineering, QA, data management for protocols and registries) versus those covered externally. The aforementioned Canadian business case offers a realistic FTE profile during ramp-up and at full capacity (RTT, physicists, dosimetrists, nurses, administrative staff). This can be used as a benchmark for the size of a single-room facility treating approximately 300–350 patients/year. The transition from one to three years to four to fifteen years results in an increase in FTE and payroll, stabilising costs at full capacity. More recent multicentre surveys in the US confirm that multi-room proton centres employ more staff than photon departments, with marked differences in physics/engineering and therapy figures, although the numbers vary with rooms and schedules.

Finally, “consumables” are relatively limited in cost, particularly in installations that use pencil beam scanning (PBS) only, as the use of patient-specific hardware is reduced compared to passive scanning. However, there remain non-negligible expenditures for QA (phantoms, cameras, detectors), immobilisation devices, small materials and spare parts not covered by the service contract. A summary of the technological and organisational trade-offs and their cost implications can also be found in major contemporary clinical and methodological reviews.

In the absence of public price lists, many administrations use updated guide coefficients for the two items that have the greatest impact on the income statement: the service/maintenance contract and personnel. For the former, management and tender documents often report a range of 10–15% of the facility's value per year (with variations depending on the guaranteed uptime levels, parts included, software/hardware upgrades, and QA coverage). For instance, if we assume $30 million worth of equipment for a single room, 10–15% per annum would correspond to $3–4.5 million/year in service costs. This explains why maintenance is often the first OPEX item to be fully operational, as evidenced by the Canadian case (2 million per annum in a single-beamline scheme). In terms of staffing, realistic plans call for multidisciplinary teams that grow over the three-year start-up period. The same FTE profile as in the Canadian case is a good starting point for scheduling, waiting lists and QA, bearing in mind that proton centres (with the same number of patients) tend to require more technical and physics/engineering FTEs than photon departments. Finally, the electricity consumption measured on compact systems

(≈490 MWh/year total; ≈52 kWh/patient in mixed cases) allows the power consumed to be converted, at local prices, into a verifiable and comparable budget item over time (also useful for environmental sustainability programmes).

In light of the above, it should be noted that the literature insists on one point: for a given technology, operational scale (i.e., the number of patients treated and the speed at which full capacity is reached) has a greater impact on the unit cost than CAPEX. This is because maintenance and personnel count more than the capital share on the cost per fraction and per patient.

In this regard, a study conducted in the Netherlands (Chen et al., 2023) estimated the costs per patient using the time-driven activity-based costing methodology. Costs ranged from €12,062 for ocular melanoma to approximately €89,716 for head and neck tumours. Indirect costs (depreciation, operating costs, and interest) accounted for over 80% of the total costs. Scenario analysis showed that increasing the number of patients treated significantly reduces unit costs. Moving from 244 treatments per year to full capacity (800 treatments), the cost per patient is reduced by about one-third compared to the start-up phase. This highlights that the economic sustainability of proton therapy (PT) is closely linked to the centres reaching full capacity, as it reduces the impact of fixed costs by spreading them over a larger number of treatments.

Year	0	1	2	3	5	10	15
Year		**2024**	**2025**	**2026**	**2028**	**2033**	**2038**
Estimate of Incremental Gross Savings							
Savings from avoided treatments in the USA		$3,780,000	$3,971,268	$4,172,214	$4,605,125	$5,894,248	$7,544,237
Photon RT costs avoided (Table 2)		$473,850	$604,159	$770,302	$1,052,519	$1,236,846	$1,448,140
Total Incremental Net Savings		**$4,253,850**	**$4,575,427**	**$4,942,517**	**$5,657,643**	**$7,131,093**	**$8,992,378**
Estimate of Initial and Incremental Costs							
Capital Expense	-$40,000,000						
Operating expense: low throughput adjustment during ramp-up		$1,068,845	$1,090,222	$1,112,026	$0	$0	$0
Annual operating expense		-$4,808,584	-$4,904,756	-$5,002,851	-$5,204,966	-$5,746,703	-$6,344,824
Total Costs	**-$40,000,000**	**-$3,739,739**	**-$3,814,534**	**-$3,890,824**	**-$5,204,966**	**-$5,746,703**	**-$6,344,824**
Out of province cost recovery							
Out of province revenue		$2,700,000	$3,442,500	$4,389,188	$5,017,073	$6,421,514	$8,219,102
Net Free Cash Flow	**-$40,000,000**	**$3,214,111**	**$4,203,393**	**$5,440,880**	**$5,469,750**	**$7,805,904**	**$10,866,656**
NPV	$42,348,599						

Figure 12: Estimate of the costs of a proton therapy project.
Source: Smith et al.

4.3. Cost-utility in healthcare

In the field of health economics, one of the most challenging aspects concerns the evaluation of medical technologies and treatment programmes. Every healthcare system must address the critical issue of how to use limited resources to maximise public health benefits. No matter how substantial they are, financial and organisational resources are never unlimited. For this reason, a tradition of studies and methods has developed over the decades to evaluate the economic impact of healthcare choices, with the aim of making the decision-making process more transparent and equitable.

Among the various forms of economic evaluation, cost-utility analysis plays a central role. It belongs to the broader family of cost-effectiveness analyses, but is distinguished by the use of a particular outcome measure: Quality-Adjusted Life Years (QALYs). Before delving into the details, it is helpful to define cost-utility and explain why QALYs are an innovative and powerful tool for measuring the value of care.

4.3.1. Quality Adjusted Life Years

The concept of QALY was introduced to integrate two fundamental dimensions of health experience into a single indicator: quantity of life (i.e., survival, or how long a person lives) and quality of life (perceived well-being during that period).

In simple terms, a QALY corresponds to one year of life lived in perfect health, representing a kind of unit of measurement. If a patient lives for a year with a condition that reduces their quality of life—for example, chronic pain or functional limitations—that year will be "weighted" with a value lower than 1, for example 0.7. In this case, the year would not be worth 1 QALY, but 0.7 QALYs. Similarly, if a person lives for ten years with a quality of life of 0.5, the total amount will be:

$$10 \text{ years} \times 0{,}5 = 5 \text{ QALY}$$

The QALY is therefore calculated by weighting the years of life by a coefficient that represents the perceived quality of that state of health.

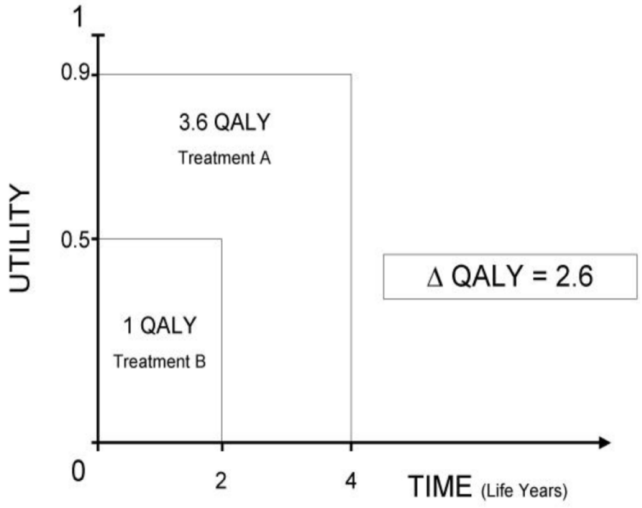

Figure 13: Example of QALY calculation between two therapies.
Source: Siponen J.

These coefficients are not arbitrary, but are estimated using validated measurement tools, such as standardised questionnaires (e.g., the EQ-5D, widely adopted internationally), or through stated preference methodologies (such as Time Trade-Off, in which individuals are asked to express how many years of healthy life they would be willing to trade for years lived in worse conditions).
In this way, QALYs translate the complexity of human life into comparable numbers, enabling the evaluation of diverse scenarios. For example, a treatment that extends life by five years in moderate health may generate the same number of QALYs as another treatment that extends life by three years, but in optimal health.

4.3.2. Cost-utility analysis

Cost-utility analysis (CUA) uses QALYs as a measure of health outcomes and relates them to the costs incurred to achieve them. In other words, it is a comparison between the resources used and the benefits obtained, where the benefits are not just “raw” years of life, but years of life lived with a satisfactory quality.

This methodology differs from other forms of economic analysis. Traditional cost-effectiveness analysis, for instance, measures results in specific clinical units (e.g., “deaths avoided” or “cases diagnosed”), which makes it difficult to compare different

interventions. Thanks to the use of QALYs, cost-utility analysis allows even very different interventions—such as an oncological drug and a cardiovascular prevention programme—to be compared on a common scale, since both produce gains (or losses) in terms of QALYs.

The general formula for the calculation is as follows:

$$CUA = \frac{C}{QALY}$$

where:

- C = total cost of treatment (in euros, dollars or other currency);
- QALY = quality-adjusted life years gained by the patient with that treatment.

Another strength of CUA is that it provides public decision-makers with a clear framework. Governments, regulatory bodies and national health systems (such as UK's National Institute for Health and Care Excellence – NICE) use CUA as a basis to determine whether a technology should be funded by the public system.

4.3.3. The Incremental Cost Effectiveness Ratio

The primary outcome of a cost-utility analysis is the incremental cost-effectiveness ratio (ICER). This indicator measures the additional cost of obtaining one more QALY when switching from a standard treatment to a new treatment.
Mathematically, the ICER is calculated as the ratio between the difference in costs and the difference in QALYs of the two alternatives:

$$ICER = \frac{C_n - C_s}{QALY_n - QALY_s}$$

where:

- C_n = mean cost of the new treatment/technology per patient;
- C_s = mean cost of the standard treatment/technology;
- $QALY_n$ = QALYs expected with the new treatment/technology;
- $QALY_s$ = QALYs expected with the standard treatment/technology.

If, for example, a new treatment costs €20,000 more than the standard treatment, yet it concomitantly yields a gain of 2 QALYs per patient, the ICER will be €10,000 per QALY. This value has no absolute meaning but must be interpreted in light of an acceptability threshold. That is to say, the willingness of a healthcare system to bear the cost to obtain an additional QALY. In the United Kingdom, the historically adopted threshold is between £20,000 and £30,000 per QALY. Other countries have developed different parameters, although the threshold value is often not formally stated.

In Italy, no official threshold exists at present. However, the Italian Health Economics Association (AIES) suggests an indicative range of between €25,000 and €40,000 per QALY. A study on price negotiations with the AIFA reveals that an ICER ≥ €40,000 per QALY exerts considerable influence on the outcome of the negotiation, while economic studies (e.g., COVID-19 vaccines) frequently employ a reference WTP (willingness to pay) threshold ranging from €30,000 to €35,000 per QALY.

Moreover, if the new treatment is more expensive and less effective, it will be said to be "dominated". If, on the other hand, it is less expensive and more effective, it will be said to be "dominant".

4.3.4. Cost-utility of proton therapy

To assess the sustainability of proton therapy, scientific literature has adopted health economics tools, with particular reference to cost-utility analyses. The main indicator employed is the quality adjusted life year (QALY), which measures the years of life gained by weighting them for quality of life. Based on this metric, the incremental cost-effectiveness ratio (ICER) is calculated, which indicates the incremental cost for each QALY gained compared to a reference treatment, which in this case is usually represented by conventional photon radiotherapy. The sustainability of proton therapy is therefore defined by comparing the cost per QALY with the willingness-to-pay thresholds adopted in different countries.

The evidence currently available in the literature presents a complex picture that is not without contradictions. In the treatment of breast cancer, for example, recent studies have

demonstrated that the use of protons, due to the drastic reduction in the dose to the heart, can prevent late cardiac events and generate clinical benefits, especially in younger patients and those with cardiovascular risk factors. An analysis by Li et al. (2022) estimated that, for women under 60 with diabetes or hypertension, proton therapy can be cost-effective with ICERs below $50,000 per QALY, a threshold commonly accepted in the international literature. Conversely, in the absence of significant comorbidities, the cost difference compared to conventional radiotherapy is not fully justified, rendering the intervention less sustainable.

Another area of application concerns head and neck cancers, particularly oropharyngeal carcinomas. Brodin et al. (2021) demonstrated that proton therapy leads to a significant decrease in late complications such as dysphagia, xerostomia, or hypothyroidism, resulting in benefits in terms of quality of life. However, the cost-utility analysis demonstrated considerable inter-individual variability, with ICERs ranging from approximately $54,000 to over $1.5 million per QALY, with a median of over $360,000. Proton therapy was relatively more sustainable in patients with p16-positive tumours, which are known to be characterised by longer survival and therefore a greater probability of benefiting from reduced side effects in the long term. These results therefore confirm that the sustainability of the technology cannot be generalised, but depends heavily on the clinical and prognostic characteristics of the patient.

In the field of paediatrics, the literature is generally more favourable. Studies on childhood medulloblastoma have shown that the use of protons, due to the dosimetric savings on the endocrine and central nervous systems, produces average gains of over 2.5 QALYs per patient compared to conventional radiotherapy. In Brazil, Fernandes et al. (2019) calculated an ICER of approximately $34,590 per QALY, a value considered cost-effective in relation to gross domestic product per capita, albeit only on condition that the centre treated a minimum of 150 patients per year. A recent Japanese study (Yoshimura et al., 2025) also confirmed the cost-effectiveness of paediatric proton therapy, with an ICER of around ¥887,000 per QALY, well below the ¥5 million threshold set by the government. These analyses suggest that, particularly in paediatrics, proton therapy can represent an efficient use of healthcare resources, as it avoids late complications that have a profound impact on quality of life and long-term care costs.

By contrast, data on adult brain tumours appear to be more controversial. A prospective study conducted in Sweden (Sampaio et al., 2024) showed that, despite a higher average cost of approximately $1,300 per patient, proton therapy did not produce a significant increase in QALYs compared to photon radiotherapy, resulting in a cost-effectiveness probability of less than 30% at any willingness-to-pay threshold. Analogous uncertainties also emerge for prostate tumours, where systematic reviews have highlighted the paucity of comparative data and the absence of evidence of clinical superiority in terms of survival or quality of life.

A critical determinant across the literature is the role of economies of scale. As demonstrated above, proton therapy is characterised by notably high fixed costs, which weigh disproportionately when the number of patients treated is limited. The analysis by Rao and Vadrucci (ENEA, 2016) showed that the cost per treatment can be drastically reduced with an increase in the annual number of cases, reaching values that are competitive with conventional radiotherapy. Not surprisingly, studies on medulloblastoma have emphasised that the technology only becomes cost-effective above certain volume thresholds, estimated at approximately 150–200 patients per year per centre. It is evident that, to ensure the sustainability of a proton therapy facility, it is insufficient to merely demonstrate its clinical advantage. Instead, it is also necessary to guarantee its intensive and continuous use, thereby averting the risk of underutilisation of a very high-cost infrastructure.
According to the same authors, conventional radiotherapy has significantly lower construction and operating costs. The study estimated that the costs of establishing a proton therapy centre are approximately 2.5 times higher than those of radiotherapy (€62.5 million vs. €16.8 million), with annual operating costs also more than double. However, a comparison using the levelized cost of health (LCOH) indicator, similar to the levelized cost of energy but applied to QALYs, shows that the difference between PT and PHT narrows considerably as the number of patients treated rises.

For example, in the case of prostate cancer with a risk of radio-induced secondary neoplasia, the cost gap per QALY between the two technologies is 84% if only 10% of the estimated patients (approximately 1,000 patients per year) are treated. However, this falls to 17% if 50% of patients are treated, and to 3% if all eligible patients are treated

with proton therapy. When the costs of long-term care (related to toxicity and side effects) are also included in the calculation, PT may even be more advantageous than conventional radiotherapy.

Proton therapy cannot therefore be evaluated solely on a static basis; rather, it must be considered from a long-term dynamic perspective, in which economies of scale, technological innovations, and the appropriate selection of eligible patients are key factors in transforming it into a strategy that is not only clinically superior but also economically sustainable.

CHAPTER V: APPLICATION TO THE CASE OF NON-SMALL CELL LUNG CANCER

5.1. Non-small cell lung cancer (NSCLC)

At this point, the analysis focuses on the oncological case that is the subject of this study, namely non-small cell lung cancer (NSCLC).

Among malignant lung tumours, non-small cell lung cancer is the most prevalent form, accounting for approximately 85% of diagnosed clinical cases. The neoplasm is of epithelial origin, developing from the tissues lining the bronchi and lung parenchyma. Its aetiopathogenesis is strongly associated with tobacco consumption, although other significant risk factors include exposure to ionising radiation and environmental and occupational contaminants.
In the early stages of the disease, NSCLC may remain asymptomatic and be diagnosed incidentally following radiological investigations performed for other clinical conditions. However, in advanced stages, symptoms such as dyspnoea, chest pain, persistent cough, and episodes of haemoptysis or haemorrhage may occur. The progression of the neoplasm can lead to the formation of masses that obstruct normal lung ventilation, as well as bronchial haemorrhages and metastasis, which mainly affect the mediastinal lymph nodes, adrenal glands, liver, bones, and central nervous system.

From a histopathological perspective, non-small cell lung cancer comprises three main variants:

- Adenocarcinoma: represents approximately 50% of all NSCLCs and is typically located in the peripheral regions of the lung, originating in the smaller bronchi. It is the most common form in non-smokers and can occur in areas of fibrosis or pulmonary scarring;

- Squamous cell carcinoma: represents approximately 30% of cases and develops from the epithelium of medium-large airways. It is associated with a relatively more favourable clinical course than other histotypes;

- Large cell carcinoma: less common (about 10% of cases), is characterised by high biological aggressiveness and rapid progression.

At the molecular level, NSCLC results from the uncontrolled proliferation of respiratory epithelial cells that accumulate multiple genetic mutations, estimated at 10–20 at the time of clinical diagnosis. The alterations involve oncogenes (KRAS, c-Myc), signal transduction factors (EGFR, HER2/neu), and anti-apoptotic genes (Bcl-2). Inactivating mutations of tumour suppressor genes, such as p53, further contribute to neoplastic progression.

In addition to cigarette smoking, several occupational risk factors have been identified, including exposure to asbestos fibres, ionising radiation, heavy metals (nickel, chromium, arsenic, beryllium), and substances such as silica and coal dust. Air pollution, with particular reference to radon, is also considered a relevant aetiological agent. Furthermore, previous lung diseases (tuberculosis, fibrosis, COPD) and parenchymal scarring are predisposing conditions for the development of adenocarcinomas.
From a clinical perspective, symptoms depend on the extent and location of the tumour mass. In addition to chronic cough, chest pain, haemoptysis, hoarseness, and dysphagia, unintentional weight loss, asthenia, persistent low-grade fever, and recurrent respiratory infections may be observed. Specific complications include bronchial obstruction, pleural effusion, superior vena cava syndrome, bone metastases with pain and pathological fractures, and brain metastases with complex neurological symptoms (headache, motor deficits, cognitive impairment).

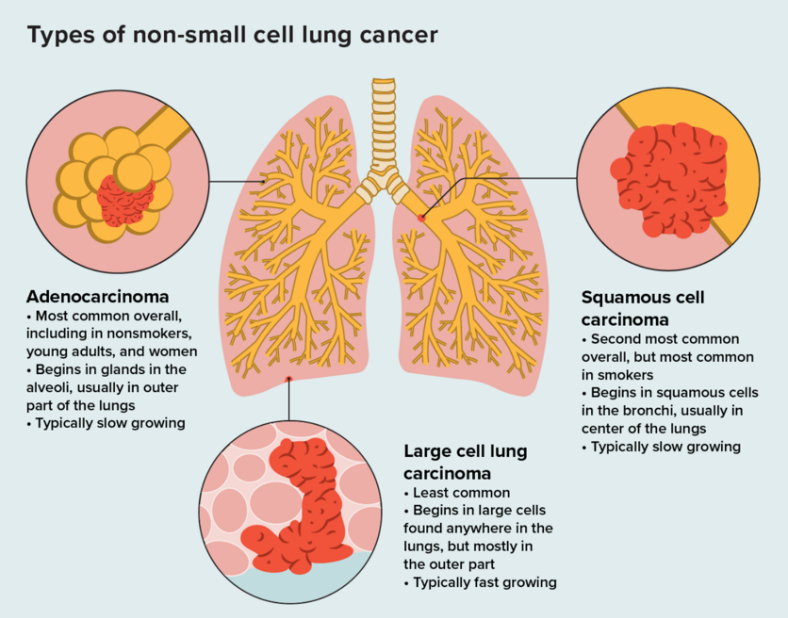

Figure 14: Types of NSCLC.

Source: Hoffman J.

The diagnosis of non-small cell lung cancer is based on an integrated approach that includes medical history, physical examination, radiological investigations (such as chest X-ray, computed tomography, magnetic resonance imaging, PET), and histological confirmation by biopsy (fine needle aspiration, bronchoscopy, thoracoscopy). Tissue samples permit not only histological characterisation but also molecular analysis to identify genetic mutations (KRAS, EGFR, ALK, MET, BRAF, HER2, ROS1, RET, NTRK), which are essential for determining the therapeutic pathway.

Treatment depends on the stage of the disease, the patient's general condition and the presence of specific molecular mutations. In the early stages, surgical resection is the standard approach, possibly combined with adjuvant chemotherapy. In locally advanced or metastatic cases, multimodal treatments combining surgery, chemotherapy, radiotherapy, immunotherapy (anti-PD-1/PD-L1), and targeted therapies are indicated. In the terminal stages, however, the objective of palliative therapy is to control symptoms and improve quality of life.

Despite advances in diagnostics and treatment options, the prognosis for non-small cell lung cancer remains poor, with five-year survival rates of 16% in men and 23% in women.

Consequently, public health strategies must focus on primary prevention (for example, encouraging smokers to quit and on the reduction of occupational and environmental exposure), early screening and the development of innovative therapies capable of improving clinical outcomes and long-term survival.

Among the recent advancements in the field of therapy for non-small cell lung cancer, proton therapy is emerging as a promising radiotherapy strategy, thanks to its capacity to deliver the dose with high precision by exploiting the Bragg peak phenomenon, thereby minimising exposure of surrounding healthy tissues such as the oesophagus and heart. Accordingly, the present thesis focuses on this application.

5.2. Proton therapy applied to NSCLC: efficacy, advantages and limitations

Radiotherapy represents a fundamental element of the therapeutic approach for non-small cell lung cancer, covering both the early inoperable stages and the locally advanced stages (II–III). Experience over recent decades has shown that the simple escalation of the photon dose does not necessarily translate into better clinical outcomes, as toxicity to critical thoracic organs ultimately becomes the limiting factor. As seen in the RTOG 0617 trial by Bradley et al. (2015), escalation from 60 to 74 Gray (the unit of measurement of the absorbed dose in radiotherapy) was detrimental, with a negative impact of the cardiac dose on overall survival, highlighting the urgent need for techniques that enable better preservation of the lung, heart, and oesophagus. In view of this, proton therapy was developed precisely to improve the therapeutic ratio substantially.

The Bragg peak ensures that protons release maximum energy at a defined depth with a substantial absence of exit dose, thus reducing the irradiation of tissues downstream of the target. This dosimetric profile is particularly relevant in the chest region, where structures at risk are adjacent to the tumour volume. However, the use of protons in the chest requires careful management of range uncertainties, respiratory motion and anatomical variations. Moreover, high-level comparative clinical evidence is still evolving. These considerations are at the heart of the consensus guidelines for the lung issued by the Particle Therapy Co-Operative Group, which develops consensus statements and clinical recommendations on the use of particles in oncology.

From an organisational perspective, the prevailing strategy for locally advanced unresectable NSCLC involves the concurrent administration of chemoradiotherapy at a radical dose (approximately 60–70 Gy equivalent) followed by consolidation immunotherapy with durvalumab in eligible patients. Regardless of the type of radiation, planning should aim to minimise the dose to organs at risk. Proton therapy fits into this paradigm when the dosimetric profile allows for a clinically significant advantage in terms of organ sparing.

For inoperable peripheral tumours, stereotactic body radiation therapy (SBRT) with photons remains the standard treatment option, with local control rates > 90%. Dosimetric studies show that protons reduce the dose to the lung, heart, oesophagus and bone marrow while ensuring robust target coverage. However, comparative clinical evidence on hard outcomes, such as overall survival and local control, has not yet demonstrated a clear superiority of proton therapy over SBRT in typical stage I cases. Consequently, the use of protons in this setting is more selective.

A systematic meta-analysis by Chen et al. (2023) of nineteen studies (with a total of 851 patients) on particle therapy (protons and carbon ions) in inoperable stage II–III NSCLC reported very encouraging aggregate rates. The 2-year overall survival (OS) was 61.3% with a 95% confidence level, in which the actual 2-year survival in the population of patients treated with particle therapy was between 54.7% and 68.7% (95% CI 54.7–68.7), 2-year progression-free survival (PFS) was 37.9% (33.8–42.6) and 2-year local control (LC) was 82.2% (78.7–85.9). At 5 years, OS was 41.3% and LC was 61.5%. In subgroup analyses, the regimen with concomitant chemoradiotherapy and protons was associated with the most favourable survival outcomes. Cumulative ≥G3 toxicity remained low, with oesophagitis and dermatitis at 2.6% and pneumonia at 3.4%. These data suggest that proton particle therapy may offer competitive efficacy with a favourable tolerability profile in locally advanced (II-III) stages compared to stage I cases.

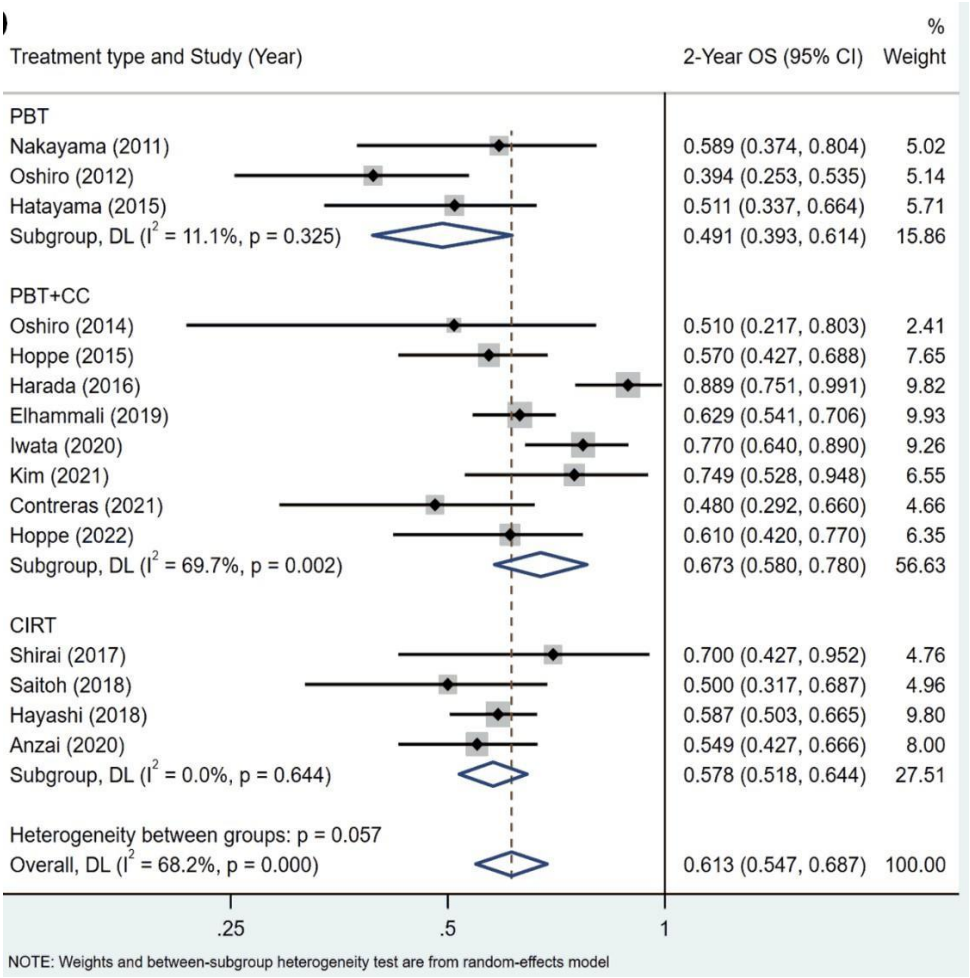

Figure 15: Meta-analysis of the 2-year overall survival rate (OS): subgroup analysis stratified by treatment type. Source: Chen et al.

In addition to the aggregates, there are several individual prospective studies that offer useful details. In a multicentre phase II trial of hypofractionated protons with concomitant chemotherapy (total dose 60 Gy in fractions of 2.5–3.53 Gy) by Hoppe et al., the 1-year and 3-year OS were 89% and 49%, respectively. No acute oesophagitis ≥G3 was observed, while 14% of patients developed pulmonary toxicity ≥G3. These results indicate the clinical feasibility of shorter regimens with reduced oesophageal toxicity, leveraging protons' typical sparing effect.

A review focused on NSCLC by Qiu et al. (2021) summarises other contributions: in cohorts treated with radical dose protons and chemotherapy, the median OS was around 26–33 months, with 2-year OS of ~57% and 5-year LC of ~72% being reported. In a retrospective multicentre comparison with 3D-CRT and IMRT, the proton group showed

lower rates of ≥G3 pneumonia and oesophagitis (2% and 5% with protons vs. 30% and 18% with 3D-CRT and 9% and 44% with IMRT), albeit with all the caveats about the methodological limitations of non-randomised comparisons.

Finally, in a recent comparative meta-analysis by Tan et al. (2025), which compared HDR brachytherapy, SBRT and hypofractionated proton therapy in locally advanced NSCLC, the 2-year OS for protons was ~56% (95% CI 42–70) and 2-year LC was ~84% (68–100), with no acute events ≥G3 but a late toxicity rate ≥G3 of 14% (4–24%), confirming that the safety profile is generally favourable in the acute phase but not without selected late risks.

Thus, the dosimetric savings offered by protons become of even greater strategic importance in cases where reirradiation of the chest is required or where post-operative radiotherapy must cover a complex field. A number of studies on re-irradiation with protons report the possibility of completing treatment in the majority of patients, with median OS ~15 months from the end of re-irradiation and a relatively low incidence of ≥G3 toxicity, albeit with rare severe events in high-risk sites, such as massive pulmonary haemorrhages. This finding underscores the critical importance of meticulous case selection and thorough planning in ensuring the efficacy of interventions. In post-operative radiotherapy, preliminary dosimetric and clinical studies suggest that intensity-modulated proton therapy reduces doses to the bone marrow, lung and heart more than intensity-modulated radiation therapy and passive scattering proton therapy, with lower rates of ≥G3 oesophagitis (IMPT = 3.7% vs. IMRT = 11.8%).

Overall, numerous planning comparisons show marked reductions in the average dose and low/medium dose volumes to the lungs, heart and oesophagus with the same clinical volume coverage. In selected analyses, IMPT reduced the average lung dose by 40% and the heart dose by 60% compared to photon radiotherapy. In scenarios with elective lymph node irradiation, pulmonary V20 (percentage volume of the lung, excluding the tumour, receiving at least 20 Gy) and mean lung dose were reduced by up to 18% and 36%, with decreases in oesophageal dose and cardiac V25 (percentage volume of the heart receiving at least 25 Gy) of up to 63%. These signals appear consistent with the physical mechanism of the absence of an exit dose.

In cohorts compared with 3D-CRT/IMRT, lower rates of radiation pneumonitis and ≥G3 oesophagitis are observed with protons; in concomitant hypofractionated regimens, ≥G3

oesophagitis may be virtually absent, while ≥G3 pneumonitis remains non-zero but contained. The reduction in the low-dose bath to the lung and the limitation of the cardiac dose contribute to these profiles.

This is how dosimetric sparing can render hypofractionation, combination with chemotherapy doublets or immunotherapy, and re-treatment feasible, with a greater likelihood of completing programmes without interruption, which is crucial for the effectiveness of treatment.

Radiation cardiotoxicity is an area of growing concern in thoracic tumours, and reducing the cardiac dose is plausibly useful for improving long-term outcomes, as suggested by the dose-heart/survival relationship observed with photons and the expanding corpus of literature on radiation-induced heart disease. It is imperative to emphasise that, given the substantial resources and financial implications involved, the optimisation of benefits should be prioritised in subgroups exhibiting elevated risk of toxicity or compromised anatomical characteristics.

However, it should be noted that protons are sensitive to tissue density, range and respiratory motion. In pencil-beam scanning (IMPT), the interplay effect between spot and tumour motion can worsen dose robustness and homogeneity, which is why 4D CT, repainting and robust optimisation are effective mitigation strategies. Anatomical variations during treatment require stringent adjustments and quality control.

Although reduced in the acute phase, severe late toxicity can emerge in high-risk sites (bronchial fistulas, oesophageal stenosis, pulmonary haemorrhages in re-irradiation). The clinical studies report late ≥G3 events in a minority of patients, demonstrating that the clinical advantage of protons is not universally guaranteed but depends on the case, technique and quality of planning, requiring careful selection, stringent dosimetric constraints and close follow-up.

Last, but certainly not least, is the issue of costs and access. Proton therapy requires dedicated infrastructure and higher initial costs. Although evidence suggests cost-effectiveness in specific indications (thanks to fewer adverse events and hospitalisations), sustainability remains a matter of health policy and appropriateness of indication.

5.3. The sustainability of proton therapy in cases of NSCLC

The evaluation of the sustainability of a healthcare technology involves medium- to long-term economic convenience for the system and for patients (including the so-called financial toxicity), the capacity to generate measurable clinical value (survival and quality of life), and the feasibility of effective scaling up of delivery in relation to anticipated patient volumes.

In the context of proton therapy for non-small cell lung cancer, the debate—which is also addressed in this thesis—centres on the higher costs of investment and treatment compared to advanced photon therapy (IMRT/VMAT) and the potential downstream savings due to reduced acute and late toxicity and, in selected scenarios, enhanced clinical outcomes.

The standard measure for comparing alternatives is the ICER, expressed in €/QALY. The decision is contingent upon a comparison with a willingness-to-pay (WTP) threshold defined at the system level. A classic systematic review has already reported that, although not cost-effective in the early stages, PT may be favourable in locally advanced cases when there is a substantial and clinically relevant reduction in toxicity.

Currently, specific evidence for NSCLC shows heterogeneous results that are difficult to analyse due to the influence of various factors, including technology (passive scattering vs. IMPT), the stage of the disease (stage I vs. III), and the method of patient selection.

A systematic review by Verma et al. in 2016 concluded that proton therapy is not cost-effective in the early stages of the disease, but it becomes so in locally advanced cases due to a reduction in severe adverse events (radiation pneumonia, oesophagitis) that have a significant impact on healthcare costs and patients' quality of life.

A study of the most recent models for locally advanced NSCLC, conducted in the Netherlands (Aldenhoven et al 2023), revealed that the “Proton for All” (PT_All) approach was not cost-effective in comparison to photons. Conversely, individualised selection using the NTCP model (which directs patients with a high expected risk of clinically relevant toxicity to proton therapy) significantly improves the economic profile. In particular, under the assumption of equivalent treatment times between intensity-modulated proton therapy and intensity-modulated radiation therapy, the ICER of the individualised strategy fell to around €76,300/QALY, close to European thresholds and

therefore proved to be potentially cost-effective. In the least favourable base-case scenario, the ICER exceeded €160,000/QALY, indicating that individualised proton therapy may be cost- effective for stage III, while its indiscriminate use is not.

The impact of the type of proton therapy should also be emphasised. A 2023 review by Li et al., dedicated to economic studies in the lung, found that, with passive scattering, proton therapy is generally more expensive and less cost-effective than photons, while the new IMPT technology (which further reduces the dose to the lung, oesophagus, and heart) could lead to different conclusions.

Sustainability also depends, if not primarily, on the actual reduction in future adverse events. As evidenced in the preceding paragraph, PT has shown fewer side effects on vital organs than photon therapy. These differences have the potential to yield healthcare cost savings (hospitalisations, artificial nutrition, treatment interruptions) as well as gains in terms of QALYs.

A number of other studies have shown that proton therapy in non-small cell lung cancer appears to be economically justifiable in certain selected settings (stage III, high risk of toxicity) and with IMPT techniques, particularly if model-based criteria (NTCP) are adopted for referral. In the remaining scenarios, however, a high degree of uncertainty remains and assessments are sensitive to assumptions about costs, productivity and tariffs. This underscores the rationale behind the focus of decision-makers on randomised trials such as RTOG-1308, which completed enrolment in September 2023 and is poised to offer further insights into the impact on survival and cardiotoxicity, with inevitable economic repercussions.

5.3.1. Brief micro- and macroeconomic analysis

At the microeconomic level, proton therapy incurs high fixed costs and higher variable costs per fraction than photons. A very recent analysis by Sugden et al. estimated average fixed costs per patient of approximately €11,200 for protons versus €9,650 for photons, with variable costs per fraction of €930 versus €265, resulting in a total PT/PH cost ratio of approximately 2.8–3.5 depending on assumptions (time/fraction, efficiency). The study argues that the predominant drivers are capital and overhead costs, while the duration per fraction exerts a substantial influence on the variables. Consequently, productivity and throughput (fractions/hour, sessions/shift) emerge as decisive factors. Consistent results,

albeit older, have also emerged from other comparative costing analyses between particles and photons.

At the macroeconomic level, Health Technology Assessments confirm that systemic cost-effectiveness depends on the balance between investment and patient volumes that can be realistically treated locally, and on the mitigation of toxicity (and related expenses) in well-selected cohorts. A 2021 Ontario Health Assessment estimated that starting a four-room centre would cost an additional CAD 125 million over five years, with expected benefits mainly in paediatric indications and selected adult subgroups. However, for lung cancer, cost-effectiveness remains uncertain and is influenced by candidate selection.

For predominantly fixed-cost technologies, such as proton therapy, sustainability is optimised by increasing both patient volume and room utilisation (gantry time). In practice, the more patients/fractions that are treated in the same amount of time (by optimising setup, imaging and delivery times), the more the fixed costs per patient are diluted.

It is no coincidence that model-based selection focuses on patients with high expected NTCP, increasing their marginal value, achieving more QALYs, and reducing toxicity avoidance costs per treatment, thereby improving ICERs. Numerical examples from the Netherlands show how the proton/photon cost ratio improves by reducing the time per fraction (e.g., from 20 to 10 minutes) and increasing daily productivity. Conversely, underutilisation and fragmented waiting lists have been demonstrated to negatively affect sustainability.

5.4. CNAO as a hub-and-spoke model

In this research, the results suggest that proton therapy for NSCLC can achieve sustainability if:

1) the volumes of eligible patients, identified through NTCP models, are adequately consolidated through structured referral networks, as is the case in the agreement between the Trento Proton Therapy Centre and the Emilia-Romagna Region discussed above. These networks function as a sort of hub-and-spoke model;

2) clinical delivery ensures a high utilisation rate of the rooms, minimising downtime and unplanned retreatment, thereby limiting the incidence of variable costs.

In Italy and around the world, hub-and-spoke networks have become the prevailing standard in oncology and radiotherapy. The Italian Association of Radiotherapy and Clinical Oncology's guidelines for organisational quality reiterate the role of regional networks, and national documents advocate the hub-and-spoke model as the optimal structure for facilitating equitable access to sophisticated technologies.
From this standpoint, the aforementioned National Centre for Oncological Hadron Therapy in Pavia represents a natural hub for proton therapy. As stated in the 2024 management report, which was produced by the centre itself, the total number of patients treated had exceeded 5,360 by the end of that year. In addition, 542 patients had travelled from all over Italy in 2024 alone.

A possible application of the hub-and-spoke model to the CNAO could be structured as follows:

- Hub → CNAO: responsible for the management of high-value cases (i.e., eligible patients), IMPT planning, treatment delivery, and referral back to the original spoke for shared follow-up and management of late toxicity;
- Spokes → Medical clinics: IRCCS and regional radiotherapy centres responsible for activities such as early identification and staging of non-small cell lung carcinomas in eligible patients, with standardised calculation of normal tissue complication probability (NTCP) for pneumonitis, oesophagitis and cardiac events on photon treatment plans, and subsequent automatic referral to CNAO when the NTCP difference exceeds pre-established thresholds;
- Backup and Alliances: establishment of inter-centre operational agreements with national centres equipped with proton therapy (such as the Proton Therapy Centre in Trento) in order to balance and optimise workloads, maximise available sessions, and reduce waiting times.

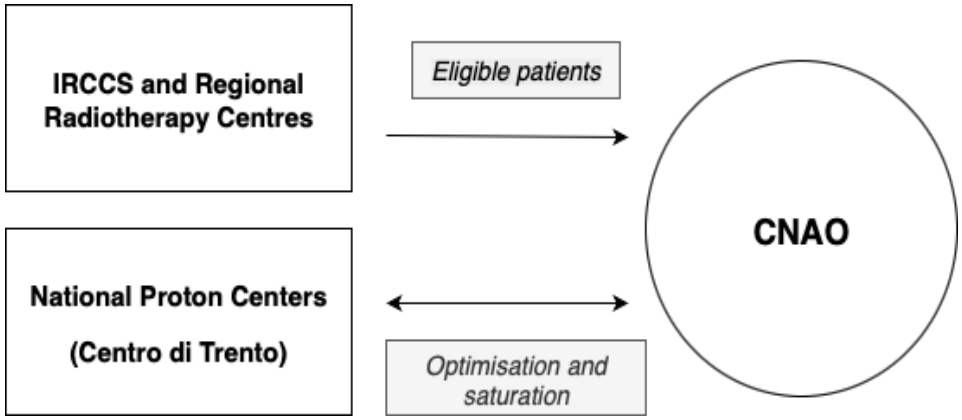

Figure 16: CNAO model hub-and- spoke.

Source: Author's own elaboration.

This would create a network that channels selected cohorts with a high-risk reduction using protons (ΔNTCP) to the CNAO. This would result in:

- the stabilisation of annual patient volume, reducing variability;
- greater utilisation of proton therapy rooms, reducing the average fixed cost per patient;
- the maximisation of QALYs and the minimisation of toxicity costs, improving the programme's ICER.

Therefore, assuming an unchanged tariff regime, the transition from fragmented delivery to the concentration of patient volume in high-activity contexts, with optimisation of time per fraction and operational flows, would be a decisive lever for the sustainability of proton therapy. Greater resource saturation would allow for the dilution of fixed costs per treated case and the containment of variable costs related to downtime and retreatment, thereby bringing the programme closer to—and in some scenarios beyond—commonly adopted cost-effectiveness thresholds.

5.5. The diffusion of innovation of proton therapy in NSCLC

The dissemination of proton therapy depends not only on its clinical efficacy, but also on its capacity to align with Rogers' five attributes—relative advantage, compatibility,

complexity, trialability, and observability—within healthcare systems operating under well-established economic and organisational constraints.

In terms of relative advantage, it has been demonstrated that modern techniques enable proton therapy to significantly reduce the dose to critical organs, with a favourable signal on toxicity, especially in locally advanced cases. It is precisely this main perceived value that is believed to fuel its adoption, rather than clear differences in hard endpoints that have not always been evident in historical comparative studies. The dedicated reviews analysed in this work illustrate this profile clearly: the dosimetric data are consistent, the clinical data show fewer complications and feasibility in appropriate settings, while the scenario of absolute superiority in outcomes remains in evolution.

With regard to compatibility, coverage decisions and HTA assessments have favoured selective adoption: in the lung, cost-effectiveness is considered uncertain if use is indiscriminate, while it improves when selection is targeted at subgroups at high risk of toxicity. This "cautious but enabling" position encourages centres to integrate PT into care pathways that prioritise appropriateness and value, rather than expanding it to all patients.

The complexity aspect should not be underestimated. Thoracic proton therapy requires specific high-level skills and workflows (motion management, robust optimisation, QA, integration with chemo-/immunotherapy). In addition to this technical complexity, there are administrative frictions (authorisations and timings) that are comprehensively described in the thoracic oncology literature. This suggests that, in terms of diffusion, adoption grows where there are experienced teams and standardised procedures that reduce operational barriers.

Trialability is a decisive factor. Indeed, a key factor that facilitates diffusion is model-based selection, in which photon and proton plans are compared for each patient and the ΔNTCP (expected reduction in complications) is calculated. Should the ΔNTCP exceed the predefined thresholds, then PT is justified; otherwise, it is not considered as such. The capacity of "testing" the innovation at an individual level lowers the perceived risk, thereby making its adoption more palatable to clinical and economic decision-makers.

The credibility of the innovation depends on comparative results and up-to-date economic evidence. This is where observability comes into play. Two messages affect the adoption curve. The first is that a systematic review of economic evaluations in the pulmonary field

shows that the old passive scattering was generally more expensive and not cost-effective compared to photons, which has led to a shift towards modern studies with IMPT techniques. The second concerns the latest models for stage III, which suggest that the individualised (ΔNTCP-based) strategy is potentially cost-effective, while “protons for all” is not. This evidence highlights the areas where proton therapy is advancing along the Rogers curve, creating real value and directing its adoption towards the “right patients”.

From a diffusion perspective, three conditions are believed to determine the outcome:

1) the standardisation of NTCP selection (trialability + compatibility);
2) the concentration of eligible patient volumes and the optimization of fraction time in order to reduce the average cost per patient (room productivity is a direct economic determinant of adoption). Dutch costing analyses show that PT has higher fixed costs per patient and variable costs per fraction than photons. Without adequate throughput, cost-effectiveness—and therefore the propensity to adopt—is weakened;
3) the creation of organisational networks (hub-and-spoke) that stabilise flows and make access times predictable.

CONCLUSION

The present study has examined, from an integrated and multidisciplinary perspective, the differences in terms of clinical efficacy and economic sustainability between proton therapy and photon radiotherapy technologies in the specific case of non-small cell lung cancer.

The conceptual framework combined elements of hybrid organisation theory and diffusion of innovation with health economics, connecting three interdependent levels: what technology makes possible, what organisations can reliably deliver, and what healthcare systems can sustain over time. In this sense, the National Centre for Oncological Hadrontherapy in Pavia emerges as a paradigmatic case of clinical-scientific infrastructure capable of combining treatment, research, and technology transfer, as well as acting as a national hub in cooperative care networks, aspects that directly influence the efficient diffusion of proton therapy.

In terms of clinical efficacy, the results collected confirm that the physical-dosimetric advantage of protons leads to a consistent reduction in the exposure of the lungs, heart, oesophagus and other vital organs while maintaining the same tumour coverage, in selected thoracic settings. In particular, in locally advanced NSCLC, the evidence analysed shows competitive local control rates and a favourable toxicity profile, particularly when proton therapy is integrated into concomitant regimens or in complex scenarios such as re-irradiation. Despite the limitations of the available literature, these outcomes do not equate to a generalised superiority over hard endpoints compared to the best photon techniques. However, they delineate a clinical perimeter in which the expected benefit is greater: patients with unfavourable anatomies, high risk of cardiopulmonary toxicity, and the need to comply with stringent constraints on organs at risk. Under these conditions, the lower low-dose bath to healthy tissues and the reduction in cardiac dose are plausibly relevant to long-term survival, given the known dose-heart/outcome relationship in thoracic tumours.

However, the picture changes when moving from clinical efficacy alone to economic sustainability. Proton therapy is a technology that is both capital-intensive and organisation-intensive. The initial investment required is significant, and ongoing operational support is necessary. Unit costs are sensitive to patient volume and room productivity. The data cited in the thesis project show that, for the same technology, it is

workload and speed of access to the treatment regimen—rather than CAPEX alone—that determine the cost per patient, since maintenance and personnel weigh more significantly than the capital share on the cost per fraction. Consequently, the ICER of proton therapy in NSCLC improves when its use is selective and targeted (model-based selection on ΔNTCP) and when centres achieve and maintain adequate saturation and throughput. The application of "protons for all" is not cost-effective. Conversely, "protons for the right patients" can be cost-effective, particularly with contemporary techniques (IMPT) and in cohorts with a high risk of complications. Accordingly, continuous innovation in proton techniques is expected to further strengthen this aspect.

This conclusion on the conditional value of proton therapy is consistent with the hybrid nature of the organisations that deliver it and with the mechanisms for disseminating innovations in healthcare. Concurrently, the effective and sustainable diffusion of proton therapy requires collaborative channels that mitigate access friction and consolidate clinical demand, such as hub-and-spoke networks with clear eligibility criteria, standardised referral processes, data sharing, and selection tools.

The work also demonstrates that current technological trajectories—from IMPT to the multi-ion perspective and FLASH radiotherapy—can further expand the therapeutic scope of hadron radiotherapy. However, this growth is contingent upon the development of organisational and regulatory frameworks that are sufficiently robust to absorb it. The history and evolution of CNAO, with its roots in the European hadrontherapy network and its openness to new ion species, illustrate the trajectory of an innovation that remains both a social and a technical construct.

From a methodological perspective, the primary limitation that emerges concerns the quality and heterogeneity of the comparative evidence available in the case of NSCLC. Much of this evidence is observational or non-randomised, and the variability of techniques (PSPT vs. IMPT), dose patterns, and selection criteria require caution in extrapolating results and call for the completion and critical reading of ongoing or recently completed randomised trials, as well as prospective registries with clinical outcomes, patient-reported outcomes, and economic evaluations conducted with real-world data. At the same time, at the economic level, ICERs are sensitive to assumptions about service/maintenance costs, productivity per fraction, tariffs and time horizons. For

this reason, the allocation decision should be based on transparent and replicable scenarios, with extensive sensitivity analyses.

In summary, the conclusions reached are clear in their conditionality. At the present time, proton therapy is not “absolutely better”, but it is “more suitable” for “suitable patients”. Looking ahead, the recommendation that emerges from the work is that NTCP models should be formally integrated into the diagnostic, therapeutic and care pathways for NSCLC. Furthermore, interregional agreements should be consolidated to stabilise referral flows. In addition, investment in skills, quality assurance and optimisation of times per fraction is recommended, as well as the continuation of comparative studies and transparent and up-to-date cost-utility analyses. Finally, the adoption curve should be sustained with reimbursement policies consistent with the willingness to pay for the QALYs obtained.

In future studies, a systematic and comparative evaluation of at least four complementary guidelines is recommended:

- at the clinical level, pragmatic (ideally randomised) trials comparing IMPT and IMRT in NSCLC with hard endpoints and patient-reported outcomes, including late cardiopulmonary toxicity and major adverse cardiovascular events at 5–10 years, re-irradiation cohorts and combinations with chemo-immunotherapy;
- at the methodological level, the use of model-based selection on ΔNTCP reinforced by predictive models and machine learning techniques, and local validation of cardiopulmonary NTCP models;
- at the economic-organisational level, prospective micro-costing on real-world data with extended sensitivity analyses and reimbursement thresholds for regional and national levels, study of productivity determinants (learning curve, throughput per room, fraction times, failure-to-start rates) and evaluation of hub-and-spoke models in terms of equity of access and resource saturation;
- in terms of technological trajectories and sustainability, comparative explorations of proton FLASH and multi-ion therapies, alongside assessment of the environmental footprint per treatment, operational safety and ethical and data governance implications (national registries, federated learning, quality standards and audits).

In order to successfully complete the proposed research agenda, particular attention should be directed towards Radiation Therapy Oncology Group RTOG-1308, a phase III randomised study comparing proton therapy and photon radiotherapy in locally advanced NSCLC in a chemoradiotherapy setting. The final results, which are eagerly awaited, will be decisive in clarifying the effect of treatment on key clinical outcomes and long-term cardiopulmonary toxicity, as well as providing key input—credible, comprehensive and with reduced uncertainty—to enable the construction and validation of cost-effectiveness/cost-utility analyses and budget impact assessments for NSCLC treatment.

Looking ahead, the primary analysis should incorporate pre-registered sub-analyses on high-risk populations (based on ΔNTCP, cardiac dose, comorbidities and the need for lymph node irradiation), as well as the distinction between proton (e.g., IMPT) and photon (IMRT/VMAT) techniques, and a systematic collection of patient-reported outcomes. It is also desirable that the study provides harmonised datasets for the purposes of meta-analysis and cost-utility modelling. This will facilitate the swift translation of the results into clinical guidelines, NTCP-based eligibility criteria, and reimbursement policies consistent with social willingness to pay.

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