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TECHNOLOGICAL ADVANCES IN EXTERNAL BEAM RADIOTHERAPY. STUDY OF NEW TREATMENT STRATEGIES.

Presentata da: Carlo Algranati

Coordinatore Dottorato

Igor Diemberger

Supervisore

Gastone Castellani

Co-supervisore

Lidia Strigari

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A Cinzia e Davide

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«Ho sempre pensato che la prima carità che l'ammalato
deve avere dal medico è la carità della scienza.
È la carità di essere curato come va.
Senza di questo è inutile parlare delle altre carità.
Senza di questo si fa del paternalismo e del pietismo soltanto».

Giancarlo Rastelli *(1933-1970)*

Abstract

This research covers the use of advanced technologies in external beam radiotherapy (EBRT), such as proton therapy for thoracic tumors, a central issue with significant implications for radiation oncology. By combining motion management, adaptive planning, and radiobiological modeling, my Ph.D. work aims to better understand the issue and prospect of proton therapy optimization. The primary objectives of this research are to evaluate the image-guided proton therapy (IGPT) procedures, determine the efficacy of online adaptive proton therapy (oAPT), and estimate secondary cancer risk using mechanistic models. To reach these objectives, my study uses a mixed-method approach involving systematic literature review, dosimetric simulation, and collaborative clinical research by leveraging multicentric scientific collaborations.

Through the use of probabilistic robustness evaluation tools, computational-based secondary malignancy risk models, and comparative case studies, the study explores dose conformity, plan adaptation, and long-term biological outcomes. Key findings include the identification of persistent uncertainties in thoracic IGPT and evidence supporting the superiority of pencil-beam scanning proton therapy in mitigating secondary cancer induction in ultra-fractionated radiation therapy. These findings suggest that enhanced motion management and radiobiological modeling enhance the therapeutic index of proton therapy, indicating broader utility to treatment personalization. Findings from this research are expected to advance medical physics and radiation oncology, offering new knowledge on IGPT application particularly relevant for hybrid proton and photon therapy approaches. My Ph.D. work investigated how to develop hybrid

treatments with radiobiological modeling for risk computation that identifies a solid basis for future studies in next-generation personalized Radio-oncology .

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List of Abbreviations

4DCT — Four Dimensional Computed Tomography

4D-DECT — Four Dimensional Dual-Energy Computed Tomography

CBCT — Cone Beam Computed Tomography

DVH — Dose–Volume Histogram

EAR — Excess Absolute Risk

EBRT — External Beam Radiotherapy (photon-based)

FLASH — Ultra-high Dose-rate Irradiation Technique

GPU — Graphical Processor Unit

Gy — Gray (unit of absorbed dose)

HFPV — High-Frequency Percussive Ventilation

IGPT — Image-Guided Proton Therapy

IMPT — Intensity-Modulated Proton Therapy

IP — Interstitial Pneumonia

LET — Linear Energy Transfer

M-LASSO — Multivariable Logistic Regression Model with a Minor Absolute Shrinkage and Selection Operator

NSCLC — Non-Small-Cell Lung Cancer

NTCP — Normal Tissue Complication Probability

OARs — Organs at Risk

OED — Organ Equivalent Dose

PBS — Pencil Beam Scanning

PSPT — Passive Scattering Proton Therapy

PT — Proton Therapy

RBE — Relative Biological Effectiveness

RD — Radiation Dermatitis

RE — Radiation-Induced Esophagitis

SBRT — Stereotactic Body Radiation Therapy

SCLC — Small-Cell Lung Cancer

SMN — Secondary Malignant Neoplasm(s)

SPArc — Spot Scanning Arc Therapy

SVM — Support Vector Machine

TCP — Tumor Control Probability

TPSs — Treatment Planning Systems

TVB — Thoracic Vertebral Bodies

VMAT — Volumetric Modulated Arc Therapy

1.Introduction: Advances in Proton Beam Radiotherapy

1.1 Background and Ratio

Radiotherapy has been used for over a century as an important part of cancer treatment. It works by causing lethal damage to cancer cells, impairing their ability to live and grow [1].

Traditional photon-based radiotherapy techniques have evolved significantly, incorporating technological innovations such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic body radiotherapy (SBRT). These techniques allow for highly conformal dose distributions that maximize tumor control while minimizing toxicity to surrounding normal tissues [2].

Despite these technological developments, photon radiotherapy is limited by its intrinsic physical characteristics, i.e., the absence of a specific range in biological tissues. The basic principles of photon physics mandate that energy is distributed along their whole trajectory, leading to substantial doses of exit to normal tissues outside the target region. This limitation has driven interest in alternative particle-based modalities such as proton beam therapy (PBT), which offers a unique advantage in dose distribution due to the Bragg peak phenomenon. Unlike photons, protons deposit most of their energy at a well-defined depth, allowing for precise tumor targeting while sparing adjacent organs at risk [3].

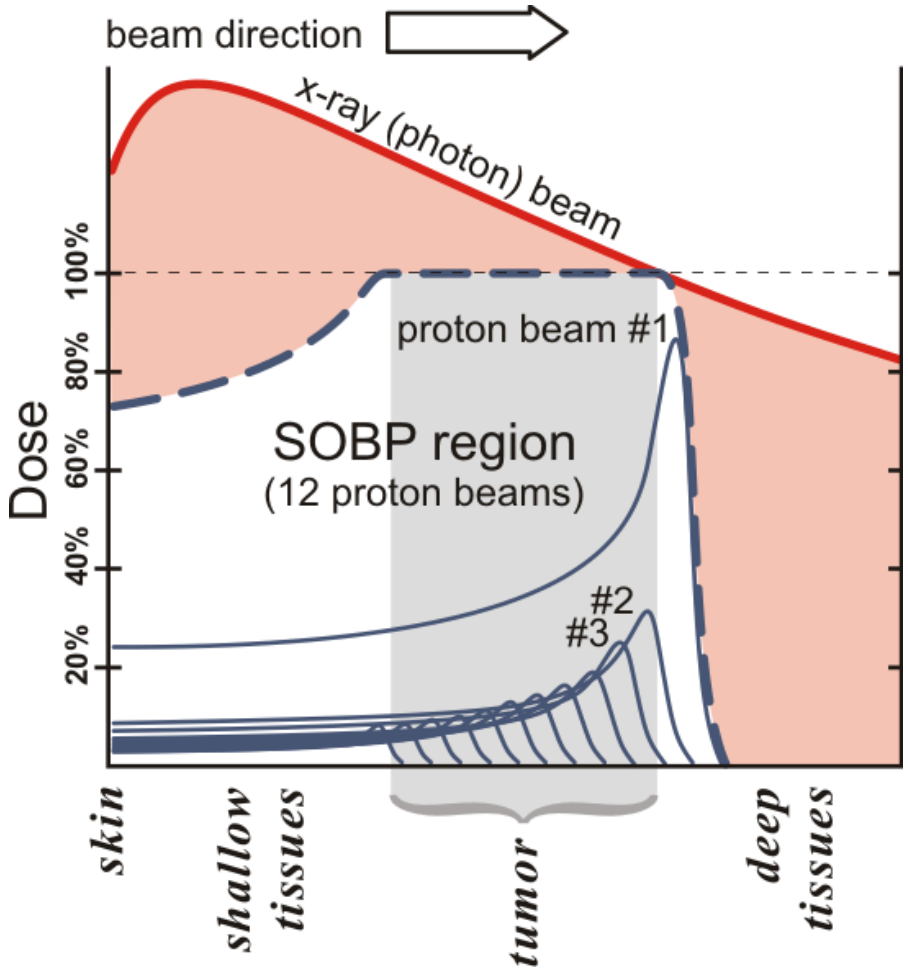

Figure1. In a typical treatment plan for proton therapy, the spread out Bragg peak (SOBP, dashed blue line) shows how the radiation is distributed. The SOBP is the sum of several individual Bragg peaks (thin blue lines) at different depths. Note that most of the proton radiation is delivered to the tumor, not to the skin and shallow tissues in front of the tumor or to the deep tissues behind the tumor. The red line shows the depth-dose plot of an X-ray beam (photon or conventional radiation therapy) for comparison. The pink area represents additional doses of X-ray radiotherapy in front and behind the tumor – which can damage normal tissues and cause secondary cancers, especially of the skin. Redrawn by the author based on MarkFilipak, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=27983203

The emergence of proton therapy represents an important step forward for radiation oncology, particularly in anatomically complex disease sites where normal tissue sparing is essential. One such challenging anatomical region is the thorax, where tumors of the lung and mediastinum present significant dosimetric and biological complexities. The presence of heterogeneous tissue densities—ranging from low-density pulmonary parenchyma to high-density bony structures—introduces uncertainties in proton range calculations, necessitating sophisticated treatment planning and delivery strategies [4]. Furthermore, the moving of thoracic organs, influenced by respiratory motion, cardiac pulsation, and gastrointestinal peristalsis, poses additional challenges to the precision of proton therapy.

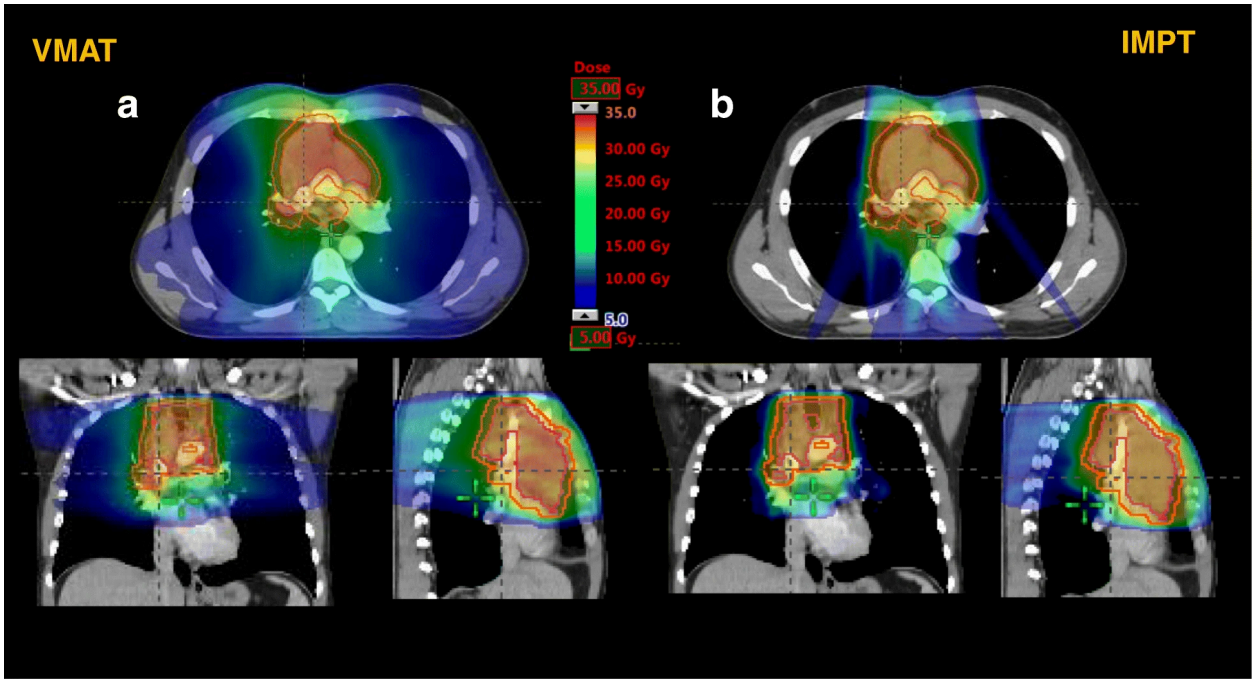

Figure 2. In a) Volumetric arc treatment of a patient with large mediastinal mass with a considerable low dose bath (blue). b) Intensity modulated proton therapy with a significant reduction of low dose bath [27].

Interest in proton therapy for thoracic malignancies has grown considerably in the last years, driven by the potential for reduced radiation-induced toxicity to critical structures such as the lungs, heart, and esophagus. Traditional photon-based techniques, despite their conformality, still result in non-negligible doses to these organs, leading to complications such as radiation pneumonitis, cardiac morbidity, and esophageal stricture formation [4]. The dosimetric advantage of protons suggests a theoretical reduction in such toxicities. Yet, the practical implementation of proton therapy in this setting remains challenging, including motion management, robustness of treatment planning, and the integration of advanced imaging techniques for real-time adaptation [5].

Beyond the technological considerations, there exists a fundamental biological question regarding the impact of proton therapy on long-term carcinogenesis, particularly the risk of radiation-induced secondary malignancies. While proton therapy reduces integral dose exposure to normal tissues, concerns remain regarding the potential contribution of secondary neutrons, particularly with passive scattering proton therapy (PSPT). Unlike conventional photon therapy, where secondary cancer risk is primarily attributed to low-dose scatter, proton therapy introduces additional complexities in radiobiological modeling due to differences in relative biological effectiveness (RBE) and neutron contamination [6]. As such, the study of secondary malignancies in the context of proton therapy represents a critical area of investigation, with implications for patient selection, treatment optimization, and long-term survivorship [7].

This thesis is designed to address these fundamental issues by considering the status of proton therapy in treating thoracic malignancy and its implications for secondary cancer risk. Based on a comprehensive literature review and new clinical and dosimetric analyses, this work outlines the opportunities and challenges involved in advancing proton therapy as a mainstream oncological modality. Learning from technological advancement and biological understanding, this investigation aims to contribute to the evolution of radiation oncology so that proton therapy can realize its maximum potential to augment patient care with fewer unwanted consequences.

1.2 Technological Status of conventional radiotherapy

Photon radiotherapy has undergone outstanding developments in the last decades, from essential two-dimensional (2D) to sophisticated three-dimensional (3D) and four-dimensional (4D) technologies [8]. All such developments have significantly enhanced photon-based cancer

treatment's accuracy, efficacy, and safety to emerge as the most common radiotherapy technique worldwide.

Among the main pillars of modern photon treatment is Intensity-Modulated Radiotherapy (IMRT), which enhances dose distribution through inverse treatment planning and dynamic multileaf collimation. IMRT enables highly conformal radiation delivery, allowing tumor dose escalation while minimizing irradiation of adjacent healthy tissues. The advent of VMAT has further refined this approach by enabling continuous dose modulation throughout 360-degree gantry rotation, thereby improving treatment efficiency and target conformity [8].

Incorporating image-guided radiotherapy (IGRT) has improved photon therapy by increasing precision of localization and reducing geometric uncertainties. Cone-Beam Computed Tomography (CBCT) has become a standard part of IGRT, allowing daily confirmation of patient anatomy before each treatment session, thus guaranteeing proper tumor targeting. This is particularly crucial for tumors in mobile regions, such as the lungs and abdomen, where organ motion can lead to significant spatial deviations.

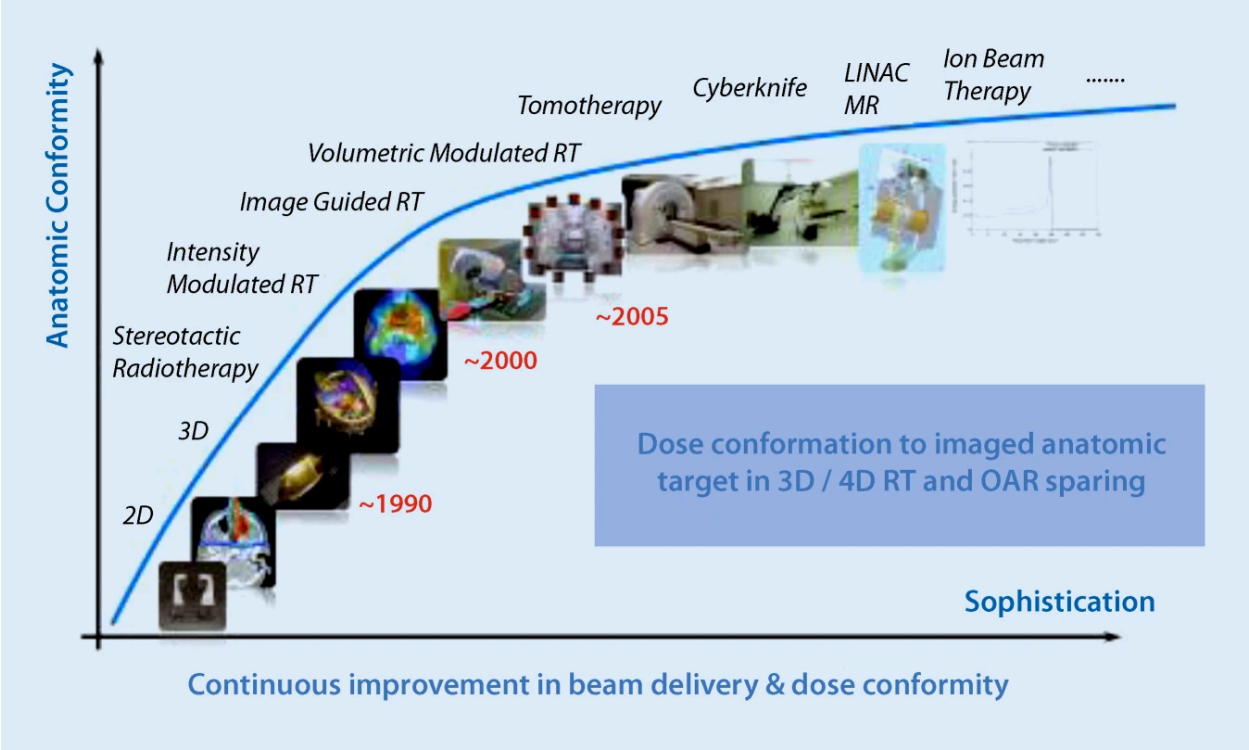

Figure 3. Improvement in radiotherapy (RT) during the past decades. MR magnetic resonance, OAR organ at risk [8].

Further refinements in motion management techniques have been driven by the introduction of 4D-CT imaging, which captures tumor motion throughout the respiratory cycle. This has enabled the development of respiratory gating and tumor tracking strategies, wherein radiation is delivered only during specific phases of the breathing cycle. Approaches such as Deep Inspiration Breath Hold (DIBH) and Respiratory-Gated Radiotherapy (RGRT) have demonstrated efficacy in reducing cardiac and pulmonary toxicity in thoracic malignancies [9].

Outside of IGRT, the advent of MRI guided radiotherapy (MRIgRT) has enormously enhanced soft tissue visualization. Hybrid MRI-Linac systems provide high-quality real-time imaging, allowing for adaptive radiotherapy techniques that respond to anatomical variation during the course of treatment. This technology is especially valuable in the scenario of tumors located in

mobile or deformable areas because it provides real-time radiation application adjustments, which enhances the accuracy of treatment [10].

Alongside imaging progress, the incorporation of Artificial Intelligence (AI) and Machine Learning (ML) algorithms has transformed photon therapy processes. AI-powered auto-segmentation tools enable more uniform and precise definition of target volumes, minimizing inter-observer variability among radiation oncologists. Additionally, algorithms for predictive modeling and adaptive radiotherapy are in development to foresee anatomical alterations and adjust dose distributions, accordingly, improving both treatment precision and efficacy [11].

Another significant breakthrough in photon radiotherapy is the advent of Stereotactic Body Radiotherapy (SBRT) and Stereotactic Radiosurgery (SRS). These high-precision techniques deliver ablative radiation doses in a limited number of fractions, leveraging advanced immobilization and image guidance to achieve outstanding tumor control. SBRT has demonstrated exceptional efficacy in treating early-stage lung cancer, oligometastatic disease, and primary tumors in the central nervous system, often rivaling surgical interventions in selected cases [12].

"**FLASH is not photon-specific;** it refers to **ultra-high dose-rate irradiation** and is in principle independent of beam quality (photons, electrons, protons), pending modality-specific delivery constraints." Photon therapy has experienced groundbreaking advancements in FLASH radiotherapy, a technique that administers radiation at ultra-high dose rates much quicker than traditional therapy. Initial preclinical investigations indicate that FLASH radiotherapy could selectively protect healthy tissues while preserving tumor-killing properties, likely diminishing

radiation-related toxicities. Nonetheless, additional clinical validation is necessary before broad clinical application can be achieved [13].

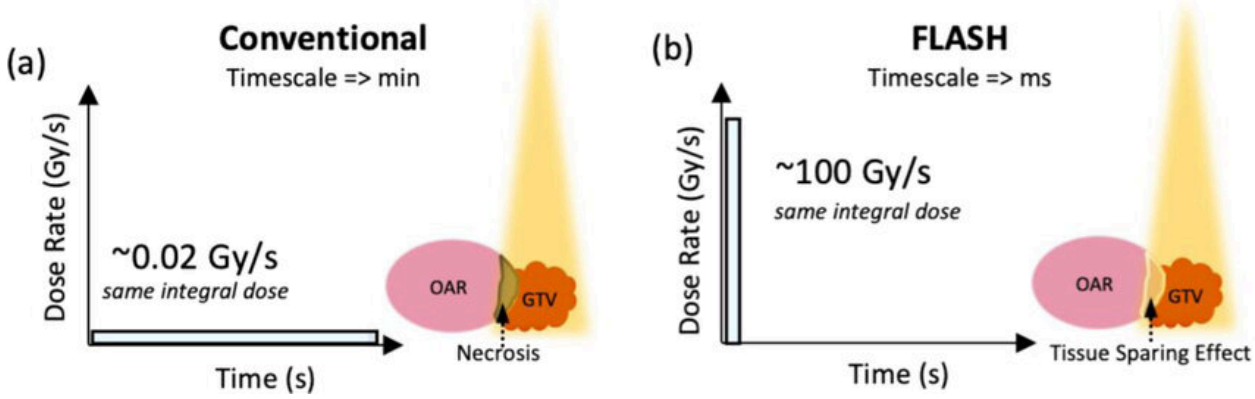

Figure 4. Comparison of observed effects using conventional versus FLASH irradiation techniques. (a) Higher incidences of tissue necrosis (in skin, intestinal crypt cells, etc) have been observed as a side effect of conventional dose rate, compared to certain tissues receiving (b) FLASH dose rates, which appear to have a normal tissue sparing effect [14].

Even with these developments, photon therapy is still limited by its fundamental physical characteristics. The ongoing accumulation of radiation throughout the beam trajectory causes inevitable exit doses, which heightens the likelihood of radiation-induced damage to neighboring organs. This constraint has prompted the investigation of other methods like proton therapy, which provides enhanced dose conformity via the Bragg peak effect.

Finally, photon radiotherapy has seen unprecedented technological advancement that has introduced cutting-edge imaging, motion management, artificial intelligence-based automation, and novel dose delivery methods to outcome optimization. Even as such advances accumulate toward improved tumor control with reduced side effects, inherent limitations in photon treatment continue to inspire interest in alternative modalities like proton treatment.

The future of radiation therapy will see sustained enhancement of adaptive, image-guided, and AI-enhanced methods, securing its ongoing applicability in contemporary radiation oncology.

1.3 The Emerging Role of Proton Beam Therapy.

The dosimetric benefits of proton therapy have resulted in its rising use in treating cancers where organ movement, radiosensitivity, and normal tissue limitations present considerable therapeutic difficulties. PBT has shown clinical advantages in pediatric cancer, head and neck tumors, central nervous system cancers, and situations needing re-irradiation. Nonetheless, its possibilities reach well beyond these applications, especially in thoracic oncology, where lung and mediastinum tumors pose intricate anatomical and physiological difficulties.

A major advantage of proton therapy is its ability to reduce integral dose, which is particularly important for pediatric patients, as lowering late toxicities is essential. Unlike photons, protons allow for accurate control of dose administration. This method has shown to reduce the risks of radiation pneumonitis, cardiac problems, and secondary cancer concerns especially relevant in the radiotherapy for thoracic and breast cancers, where long-term toxicity can significantly impact patients' quality of life [15].

Expanding Applications of Proton Therapy

Beyond traditional indications, recent technological advances have expanded the range of proton therapy uses. Advances in Pencil Beam Scanning (PBS) have revolutionized proton delivery through spot-by-spot dose painting with millimetric precision. PBS bypasses the need for passive scattering techniques based on higher secondary neutron production—a variable associated with increased risk of radiation-induced secondary cancers [16].

Furthermore, the advent of FLASH proton therapy, that uses ultra-high dose rate administration, has shown the ability to protect normal tissues while ensuring tumor-killing effectiveness. Preclinical research indicates that FLASH could provoke varying biological responses in normal

versus cancer cells, yet the fundamental radiobiological mechanisms are still being actively explored. If successfully translated into clinical practice, FLASH proton therapy could further reduce treatment-related toxicities and redefine the therapeutic window for radiation oncology.

Comparative Efficacy and Cost Considerations

Despite its dosimetric and clinical advantages, proton therapy has faced significant barriers to widespread adoption, largely due to the high cost and infrastructure requirements associated with proton beam facilities. A single PBT center requires extensive capital investment, including the construction of large-scale cyclotrons or synchrotrons capable of accelerating protons to therapeutic energies. The financial burden of proton therapy has led to concerns regarding cost-effectiveness, particularly when compared to modern photon-based modalities such as IMRT, VMAT, and SBRT—all of which have achieved substantial technological refinements in recent years [17].

However, emerging evidence supports the long-term cost savings associated with proton therapy, particularly for pediatric and re-irradiation cases, where the reduction in late toxicities can lead to decreased healthcare expenditures over a patient's lifetime. Ongoing health economic analyses are increasingly incorporating quality-adjusted life years (QALYs) and other patient-centric outcomes into cost-effectiveness models, reinforcing the value proposition of proton therapy beyond simple upfront costs.

Future Opportunities and Integration with Multi-Modal Treatment

Looking to the future, the incorporation of proton therapy into multimodal cancer treatment plans shows great promise. The use of PBT in combination with immunotherapy, chemotherapy, and targeted agents is a new horizon for the management of cancer. Early-stage clinical trials are examining the possibility of synergistic immune modulation by proton therapy, with an emphasis

on how the changes in the tumor microenvironment created by protons can augment systemic anti-tumor activity [18].

Furthermore, the utilization of proton arc therapy, which is tantamount to VMAT in photon therapy, is being studied as a mean to enhance dose conformity and accelerate treatment times. Proton arc therapy can potentially improve tumor coverage and minimize organ-at-risk exposure by irradiating protons along uninterrupted arc trajectories, further optimizing the therapeutic ratio [19].

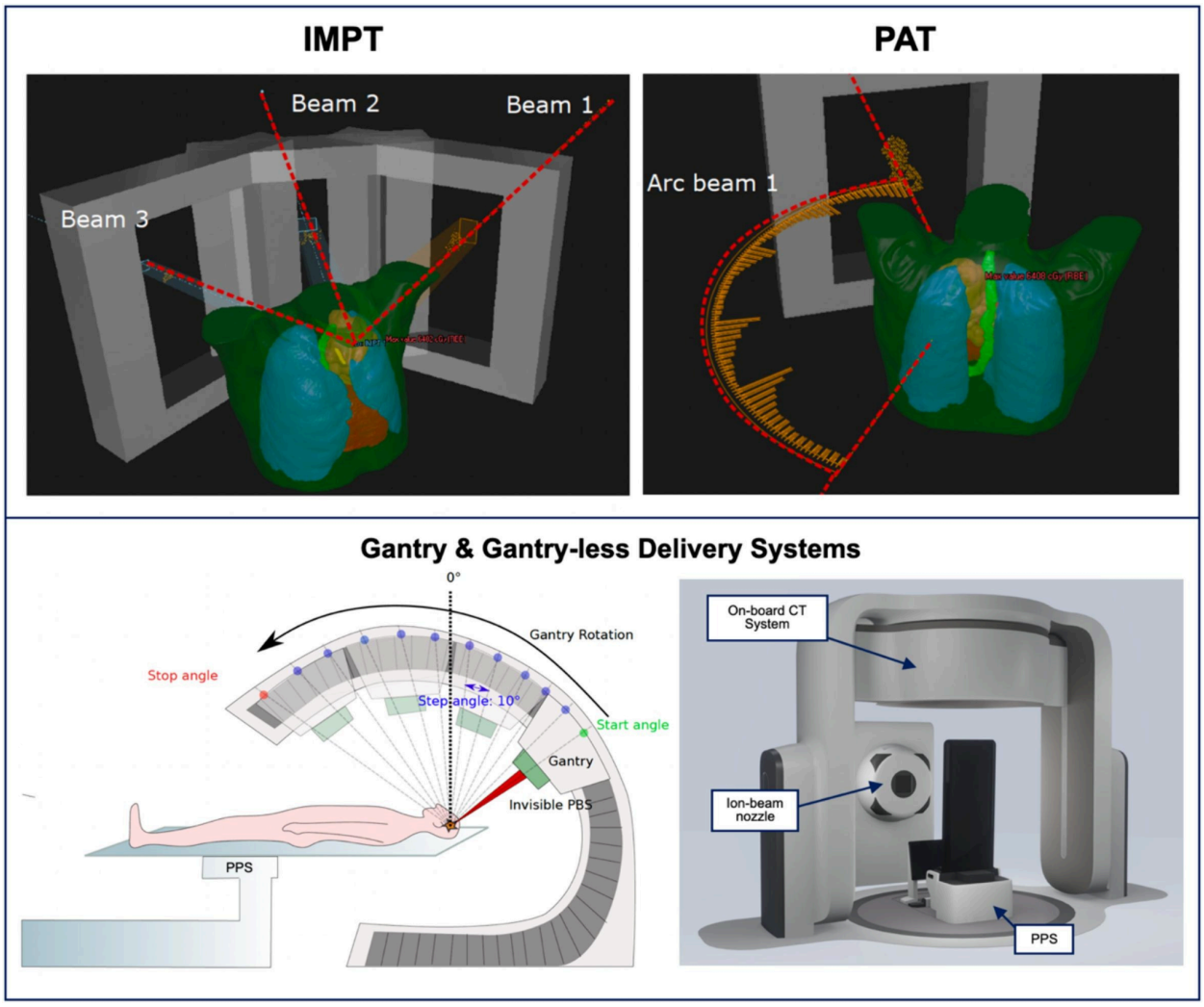

Figure 5. IMPT versus particle arc therapy (PAT) planning and delivery techniques. PAT involves rotational motion of a gantry and/or patient position system (PPS) using protons, carbon and/or novel ion beams, e.g., spot-scanning proton and hadron arc therapy [19].

Proton beam therapy has emerged as a technologically advanced and clinically rewarding mode of radiation with an unparalleled degree of precision in dose delivery and lower normal tissue toxicity. Continued research into PBS, adaptive therapy, FLASH, and proton arc techniques will continue to expand the role of PBT clinically to be used for even more forms of malignancy. As

financial challenges still occur, ongoing advancement in cost-effectiveness modeling and treatment optimization will likely drive increased access to proton therapy throughout the world. As radiation oncology progresses towards personal, adaptive, and biologically guided treatment approaches, proton therapy will play a significant role in shaping the future of precision radiotherapy. Research and new technology will be crucial to unleashing the complete therapeutic potential of protons, at last improving outcomes and quality of life for patients with cancer globally.

1.4 The Gap: Image-Guided Proton Therapy (IGPT) and Thoracic Cancer

Image guidance for protons is challenged not only by historically slower clinical integration of imaging technologies but also by intrinsic physical factors: range uncertainties due to stopping-power conversion, motion (intrafraction and interfraction), and density heterogeneities that modify proton path length and distal fall-off. These aspects make on-board verification and adaptive strategies particularly relevant compared with photons.[5].

Motion Management and Density Heterogeneities

Motion (respiratory and cardiac) and tissue heterogeneities alter proton range and dose deposition. Mitigation includes robust optimization, 4DCT-based planning, gating/breath-hold, rescanning, and adaptive replanning. One of the main drawbacks of proton therapy in thoracic oncology is motion-related uncertainty sensitivity. In contrast to photon therapy, where small spatial motion has little impact, protons have steep dose gradients and are thus very sensitive to intrafraction motion with delivery. The problem is acute in lung cancer because respiratory motion of the tumor results in dose misregistration, which degrades the efficacy of treatment. To deal with this issue, several motion management strategies have been investigated, such as

4D-CT imaging, respiratory gating, and live tumor tracking. Four-dimensional computed tomography (4D-CT) allows the evaluation of tumor motion throughout the respiratory cycle, allowing clinicians to tailor treatment plans in order to account for motion-related uncertainties. Gating of respiration, with the proton beam synchronized to a given phase of the respiratory cycle, has been shown to reduce dose variability caused by motion. Additionally, real-time tumour tracking methods including fiducial marker systems and electromagnetic tracking have shown potential to enhance motion compensation methods. These methods, however, are still technically complex and need further advancement for widespread clinical application [5].

In addition to motion, density variations within the thoracic area add additional challenges to proton range calculations. The existence of air, soft tissue, and bone results in sudden variations in relative stopping power (RSP), causing uncertainties in the estimation of proton beam range. In contrast to photons, which experience minimal impact from density changes, protons lose a considerable amount of energy as they pass through various tissues. This leads to range uncertainties that need to be carefully considered in treatment planning.

To mitigate this challenge, dual-energy CT (DECT) imaging has been introduced as a means of improving proton range calculations. Motion Management and Density Heterogeneities

DECT enables better tissue characterization by differentiating materials more accurately, thereby reducing range prediction errors. Also, Monte Carlo simulations have been increasingly employed to model complex heterogeneities and refine dose calculations. While such developments are encouraging, continuous clinical validation and deployment in the everyday setting are matters for further research.

The Growing Interest in Proton Therapy for Lung Cancer

Despite these challenges, there is growing interest in the application of proton therapy for lung cancer because it has the potential to reduce pulmonary toxicity and improve long-term survival. Traditional photon-based approaches, such as IMRT and SBRT, have been highly effective in lung cancer management, yet they continue to deliver substantial radiation doses to surrounding normal lung tissues, the heart, and the esophagus. Given that many lung cancer patients present with pre-existing pulmonary conditions, minimizing radiation exposure to healthy lung tissue is paramount [20].

Proton therapy is distinctly advantageous in this regard, as it significantly reduces integral dose outside the tumor volume. Proton and photon therapy comparisons in lung cancer have demonstrated a significant reduction in radiation pneumonitis and cardiac toxicity, leading to improved treatment tolerability. Furthermore, the ability to escalate tumor dose while sparing critical structures makes proton therapy particularly appealing for locally advanced non-small cell lung cancer (NSCLC), where dose escalation has been associated with better disease control.

A major area of research in lung cancer proton therapy is the development of adaptive strategies to address daily anatomical variations. Anatomical and tumor volume changes over the course of treatment can significantly impact proton range, necessitating adaptive proton therapy (APT). Emerging techniques such as daily onboard imaging, CBCT-guided adaptation, and MRI-integrated proton systems are being explored to refine proton delivery in response to real-time anatomical shifts.

These technologies can potentially enhance the accuracy of treatment and minimize dose uncertainties [21].

In addition, hypofractionated and ultra-hypofractionated proton therapy regimens are investigated for lung cancer. The use of fewer, higher-dose fractions aligns with the principles of

biological dose escalation, potentially leading to improved tumor control while reducing overall treatment duration. Early-phase clinical trials are exploring the efficacy of proton-based SBRT in early-stage NSCLC, with preliminary findings suggesting comparable or superior outcomes to conventional photon SBRT [22].

In summary, while proton therapy clearly has dosimetric and biological advantages in thoracic oncology, its clinical use remains technology challenging with uncertainties due to motion and density heterogeneities. Technologies such as 4D-CT, real-time tumor tracking, DECT, and adaptive planning have potential for such challenges, but further research and standardization are required for generalized clinical application. Despite these challenges, growing interest in proton therapy in lung cancer is its potential to reduce treatment-associated toxicities and improve long-term patient outcomes. With advances in technology, continued investment in image-guidance and motion management technologies will be key to achieving the full therapeutic potential of proton therapy in thoracic malignancies.

1.5 The Radiobiology of Secondary Cancers: A Critical Factor in Proton Therapy

The most significant issue of radiation oncology is secondary cancers caused by radiation, particularly in survivors of cancer. While radiation therapy is a key curative and palliative therapy, its impact on the normal tissue and potential carcinogenicity need an appreciation of radiobiological principles. PBT possesses a unique place in reducing radiation-induced secondary cancers because of its physical and biological features.

The Risk of Radiation-Induced Secondary Malignancies

Radiation-induced secondary cancers are the outcome of genomic instability, oxidative stress, and ongoing damage in the DNA of the exposed normal tissue. The probability of secondary

malignancies is influenced by factors such as radiation type, dose distribution, age at exposure, and underlying genetic predisposition. In conventional photon radiotherapy, scattered radiation leads to significant low-dose exposure beyond the target region, increasing the likelihood of long-term carcinogenic effects. Epidemiological data from Hodgkin's lymphoma and pediatric cancer survivors have demonstrated a clear correlation between radiation dose and secondary malignancy risk, particularly for solid tumors and hematologic malignancies [23].

In contrast, PBT reduces the integral dose to normal tissues due to the Bragg peak phenomenon, leading to a theoretical reduction in secondary cancer risk. However, passive scattering proton therapy (PSPT), an early method of PBT delivery, introduces additional neutron scatter, which has been associated with increased stochastic effects and potential carcinogenesis. Neutrons, which have a high linear energy transfer (LET), can induce complex DNA damage that is more difficult for cells to repair, thereby increasing mutagenic potential. This has caused concern that secondary neutrons in proton therapy can contribute to carcinogenic risk despite total dose reduction.

To mitigate these concerns, modern proton therapy techniques, particularly PBS, have significantly reduced neutron contamination. Unlike PSPT, which uses scattering foils that generate neutron byproducts, PBS employs magnetically controlled proton spots to minimize neutron production. Recent Monte Carlo simulations and retrospective cohort analyses suggest that PBS may offer a significantly lower risk of secondary malignancies compared to both PSPT and conventional photon therapy. However, long-term clinical data remain limited, and ongoing prospective studies are needed to validate these findings [24].

Impact of Proton Therapy on Secondary Cancer Development

The impact of PBT on second malignancies also goes beyond physical dose distribution and into the realm of radiobiological response. There is emerging evidence that protons' biological effectiveness—usually parameterized with an average relative RBE of 1.1—can be modified by tissue type, LET spectrum, and microdosimetric variations. This has challenged the true radiobiological effect of proton irradiation on normal tissues, particularly with regards to carcinogenesis.

Recent in vitro studies have explored the effects of proton irradiation on DNA repair pathways, oxidative stress responses, and cellular senescence. Findings indicate that while proton-induced DNA damage is generally less diffused compared to photon exposure, the complexity of double-strand breaks may be higher in high-LET regions, leading to potential long-term genetic instability. Additionally, studies on bystander effects—where irradiated cells induce damage in adjacent, non-irradiated cells—have shown differences in proton versus photon-mediated intercellular signaling, further complicating secondary malignancy risk assessment [25].

Clinically, secondary malignancy incidence following pediatric and young adult proton therapy has been an area of active investigation. Longitudinal cohort studies have reported lower rates of secondary cancers in proton-treated patients compared to photon-treated cohorts. This has been particularly important in brain tumors, sarcomas, and childhood leukemias, where preservation of maturing tissues of critical value is a must. However, long-term follow-up is essential, since latency periods for second cancers may be over two decades [26].

Moreover, advances in FLASH proton therapy, which can provide ultra-high dose rates, have been promising in differentially sparing normal tissues with tumoricidal effect retention. Preliminary reports indicate that FLASH irradiation may elicit a protective biochemical response in normal tissues, possibly at the expense of reduced carcinogenic risk. While such findings are

encouraging, more mechanistic and clinical research will be required prior to the use of FLASH treatment as an extensively used risk-reducing modality for secondary cancers.

Thus, the radiobiological implications of proton therapy in secondary malignancy development remain an active area of study. While PBT affords substantial advantages in reducing integral dose and scattered radiation, neutron exposure issues, high-LET effects, and microdosimetric uncertainties necessitate continued research. Advances in PBS, adaptive proton therapy, and FLASH radiation hold potential for further mitigating these risks, but comprehensive long-term clinical data will be essential in shaping future guidelines. As proton therapy becomes increasingly integrated into oncologic treatment paradigms, ensuring a robust understanding of its radiobiological impact on secondary malignancies will be paramount to optimizing patient outcomes in the era of precision radiation oncology.

1.6 Purpose of this Thesis

The rapid advancements in proton beam radiotherapy (PBT) have opened a new horizon in the field of radiation oncology. Since proton therapy continues to advance, it becomes mandatory to critically examine its potential, limitations, and future direction. This thesis attempts to contribute to the ever-growing body of knowledge on proton therapy treatment modalities, with specific reference to overcoming the technological, clinical, and radiobiological limitations in its performance. Through an in-depth analysis of image-guided proton therapy (IGPT), motion management strategies, and the radiobiological implications of secondary malignancies, this work seeks to bridge the gap between theoretical advancements and clinical implementation.

The primary objectives of this thesis are triple.

First, evaluate the state of IGPT today, identifying the most significant technological deficiencies and indicating potential corrections towards improved tumor tracking and adaptive planning.

Secondly, discuss the use of proton therapy in thoracic cancers, i.e., lung cancer, where organ motion and heterogeneity present significant dosimetric challenges.

Third, examine the risk of radiation-induced secondary malignancies, exploring how recent advances in proton therapy delivery, such as PBS, may mitigate long-term carcinogenic risks while maintaining therapeutic efficacy.

Finally, discuss possible new treatment strategies that arise from our work.

Bridging the Gap in Image-Guided Proton Therapy

One of the major shortcomings of proton therapy compared to photon-based modalities is the relative lack of robust image-guidance techniques. While IGRT has revolutionized photon radiotherapy, similar levels of integration and accuracy have not yet been widely achieved in proton therapy. The uncertainties in proton range calculations, particularly in highly mobile regions like the thorax, highlight the urgent need for advanced motion management and real-time imaging solutions. Comprehensive analysis of current motion mitigation techniques, including respiratory gating, fiducial marker tracking, and Monte Carlo-based adaptive planning, will be undertaken to assess their feasibility in routine clinical applications.

Optimizing Proton Therapy for Thoracic Cancer

The treatment of thoracic malignancies, particularly lung cancer, represents one of the most technically challenging applications of proton therapy. The presence of heterogeneous lung densities, respiratory-induced tumor motion, and variations in patient anatomy significantly

impact proton range accuracy. Despite the theoretical advantages of protons in sparing normal lung and cardiac tissue, these challenges must be carefully addressed to fully realize their potential in thoracic oncology.

This thesis will investigate current and emerging strategies for mitigating motion-related uncertainties in lung cancer treatment with protons. This includes a systematic review of 4D-CT simulation, robust treatment planning approaches, and adaptive radiotherapy protocols.

Radiobiological Considerations and Secondary Cancer Risk

While the dosimetric advantages of proton therapy are well-established, its long-term radiobiological impact remains an area of active research. This thesis will review the actual radiobiological models for estimation of secondary cancer formation in proton therapy, comparing it with conventional photon radiotherapy. A key area of focus will be the potential of hypofractionation and dose escalation, evaluating whether these approaches, when combined with PBT, can lead to superior clinical outcomes compared to conventional photon-based regimens.

Towards the Future of Proton Therapy

By means of such research areas, this thesis aims to offer a blueprint for extending proton therapy as an oncologic modality in the mainstream, so that technological progress can be easily translated to hard clinical benefits. By eliminating the current gaps in IGPT, maximizing motion management in thoracic cancers, and elucidating the radiobiologic risk of secondary cancer, this research aims to contribute valuable inputs to the development of the next generation of precision proton therapy.

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2. Literature Review

2.1 Overview of Proton Therapy in Clinical Practice

The goal of this chapter is to show the work done in the last year to report the main recent technological improvements in proton therapy. Our goal was to highlight the current challenges and prospects of treatment, to identify new treatment strategies potentially helpful for improving the outcome and reducing their related toxicity. As the outcome of this chapter, we identify crucial aspects that need further investigation and choose among them for a research path that goes in a hopefully fruitful direction in the next few years. In that sense this work was fundamental in our doctoral research to plan future efforts of our resources in the best direction.

2.2 Literature search strategy

A PubMed/Medline search was performed using the appropriate query string to identify the publication related to PT in thoracic tumours, mainly represented by small-cell-lung-cancer (SCLC) and non-small-cell-lung-cancer (NSCLC), mesothelioma, thymoma, and esophageal cancer. These thoracic malignancies are challenging from the treatment point of view because of relevant tissue heterogeneities, moving organs and targets, and the limited availability of onboard soft tissue imaging devices.

We included the following keywords/strings in the PubMed query search: ("PT" AND "thoracic") OR ("PT" AND "non-small-cell-lung-cancer") OR ("PT" AND "small-cell-lung-cancer") OR ("PT" AND "mesothelioma") OR ("PT" AND ("thymoma" OR "thymic malignancy")) OR ("PT" AND "esophageal cancer").

Filters: from 2018/07/01–2022/06/30. The research was restricted to the last four years to include only the title and/or abstract keywords. The search was also extended, including Scopus and Embase results.

The search was done on the 20th of September, 2022.

2.2 Study selection

Two authors independently reviewed titles and abstracts to decide on study inclusion. Full articles were retrieved when the abstract was considered relevant. Only papers or abstracts published in English were considered.

Papers were selected if they contained information about the treatment of thoracic tumours with PT and gave answers or inside view on the following medical physics issues:

1. Planning. Which are the emerging methods, techniques, and technologies for simulation, planning, setup, adaptation, motion monitoring, and delivery in PT for thoracic tumours?

2. Motion. Which devices and technologies are used for motion management, patient fixation, and immobilisation for thoracic tumours?

3. Imaging. Which is the planning approach and techniques for handling complex, heterogeneous, and moving thoracic tumours?

4. Delivery. Which are the technological advances for motion management, treatment delivery, and adaptation.

5. Radiobiology & Clinical Outcomes. Which are the advances in radiobiology and clinical outcomes reported for tumours and organs at risk (OARs) in the thoracic district?

6. Cost-effective analysis and economics. What are the results of optimising resources of the PT facility when the thoracic district is treated?

The data were summarised in a database with the following issues: first author, journal, year, and title. Data analysis and interpretation rely on Bogner and Menz's [3] related Expert interviews.

2.3 Results

Description of included studies and inclusion criteria

Based on the reported PubMed/Medline search, 164 papers and abstracts were identified. The results are represented in Fig.1. Substantial growth was observed by looking at the included papers through the years.

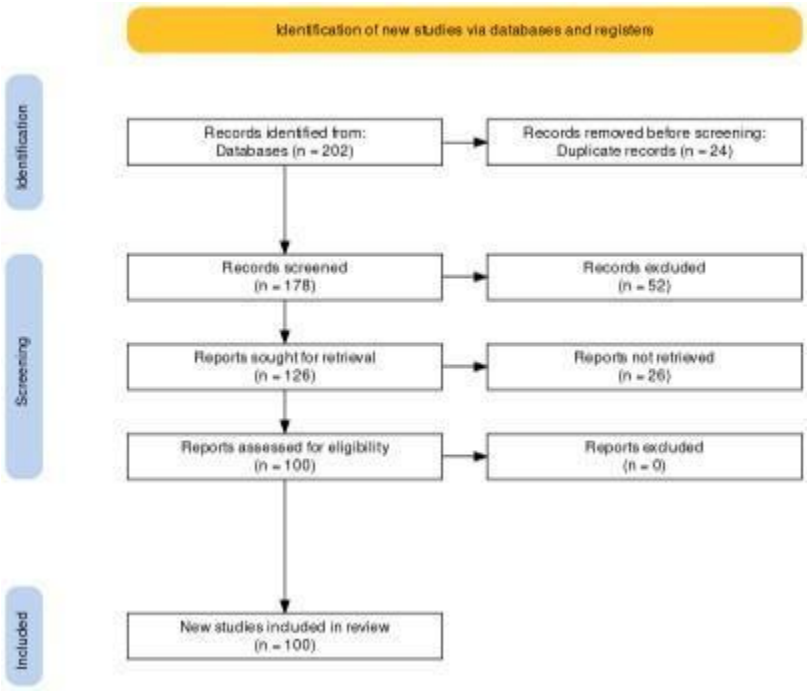

Figure 1. Numbers of included and excluded papers from the PubMed search related to PT in thoracic tumours. PRIMA2020 flow diagram.

Out of the 164 records, 31 were excluded as duplicates. 133 papers identified focus on the following disease:

- "Thoracic Cancer" 62 (46.6%)
- NSCLC 46 (34.6%)

● "mesothelioma" 5 (3.8%)

● "thymoma"/"thymic malignancy" 4 (3.0%)

● "Esophageal cancer" 16 (12.0%)

43 papers of 133 records screened were excluded for the following reasons: Not inherent to the addressed questions. 96 full-text articles were selected according to medical physics-related questions 1 to 5 described in paragraph study selection in Material and Methods.

The identified papers addressed the following categories (obtained according to the addressed issues 1 to 5 identified in Tab.1): Planning [4–22](#19), Motion [23–30](#8), Delivery [31–41] (#11), Clinical outcome and radiobiology [2,26,42–92](#54), Economics [93–96](#4). Papers containing information were counted in the group more representative of the study purpose.

Fig.2 shows the distribution of the papers per category and year of publication.

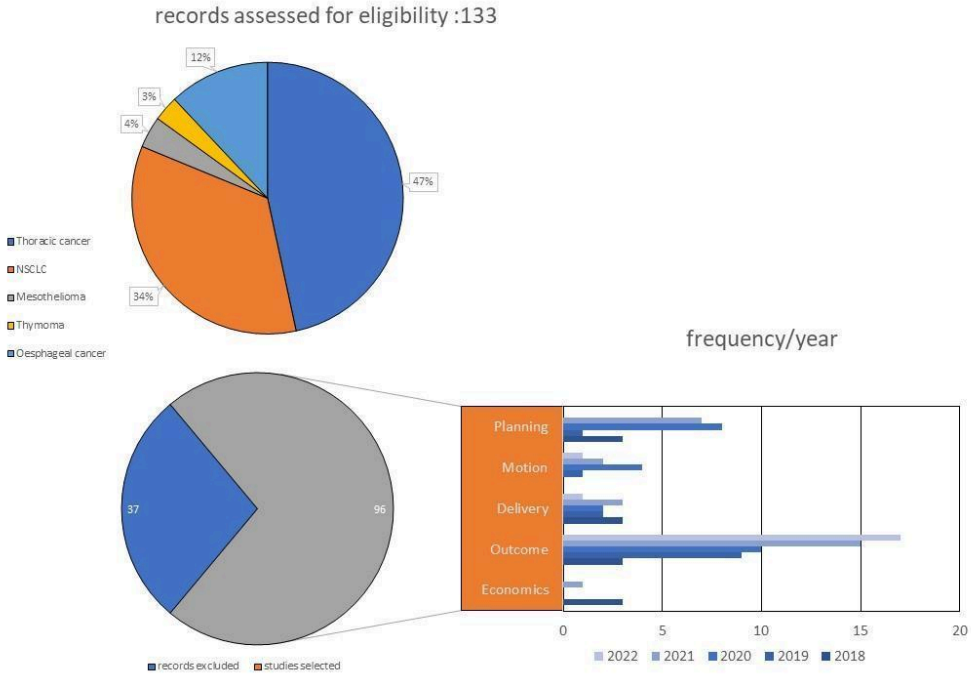

Figure 2. Distribution of the papers per category and year of publication: there is a trend of

augmenting the number of papers that contain information on the medical physics issues posed in this study over the years.

2.3. THE PAST: solved questions

We start our discussion with the issues that we considered solved in the research of the past years for improved treatment precision in proton therapy.

Dose calculation and verification issues

At the state of the art, proton dose calculation engines allow accurate and efficient calculation of absorbed dose in lung tissues [6,11–13,19,21,22]. In general, Monte Carlo dose calculation is the standard method to ensure more accurate dose computations to improve target coverage and the sparing of OARs in PT [6]. In addition, dose calculation speed is substantially reduced using Graphical processor Unit (GPU)-based solutions [6]. GPU-based solutions are already implemented in commercial Treatment Planning Systems (TPSs).

Anthropomorphic thorax phantoms, such as in [4,98], are suitable for imaging and dosimetric studies in a thoracic geometry closely matched to lung cancer patients under realistic motion conditions.

Studies on field ballistics for improved robustness

Several Authors [28–30] used the specific field ballistic to improve the robustness of absorbed dose distributions. In particular, the study of Gu et al. [28] suggested the routine use of the S-I oblique posterior beams for the treatments of distal esophageal carcinoma, while that of Moller et al. [30] recommended the use of PBS posterior beam angles, resulting in being the more robust to anatomical changes and respiration during IMPT delivery. To mention in this paragraph is also the consensus guideline [99].

Breath-Hold Techniques

Many authors reported that the breath-hold techniques were both dosimetrically robust and feasible to deliver with acceptable treatment time.

Fracchiolla et al. [24] report on the implementation, validation, and results of the first two PT PBS treatments of limited amplitude moving targets performed at their centre.

Recently, there has been a consensus that in the thoracic regions, having a peak-to-peak motion of less than 5mm, there is no necessity to adopt a motion management technique, as highlighted in [1].

Delivery, imaging, technologies and adaptive techniques

In the delivery category, we select eight papers [31–41]. We look at the motion mitigation techniques and image-based technologies reported over the last few years. We point to our previous work to have a systematic review of the imaging techniques used in PT [1] and the work of Molitoris [36]

In-room, Cone Beam CT(CBCT)-based synthetic CTs were reported in [33] to enable accurate proton dose calculations for lung cancer patients' requiring adaptive planning. This approach solves accuracy problems related to proton beam dose calculation on CBCT in the thoracic district and allows an online adaptive therapy approach without in-room CTs.

Breath Hold techniques are currently used also for PT delivery using different commercial devices, as reported by [24,39].

4D-CBCT reconstruction patients treated with PT are reported by [40]. Moreover, the 4D-CT approach is used to treat PT patients, mainly free breathing, when small movements of the target are registered [32,34]. The free-breathing techniques are often used with beam delivery improvements, such as repainting [24] or unique beam add-ons such as ridge filters [37] to

improve the interplay effects -typical for PBS delivery systems - thus avoiding cold and hot spots in the target. In addition, Gut et al. reported that volumetric rescanning and respiratory gating might effectively and efficiently mitigate dose degradation due to tumour movement [41].

In the paper of Li et al. [31], the evaluation of the range uncertainties that arise from daily CBCT images for proton dose calculation was compared to one based on CT images, thus supporting its use for daily dose validation in selected proton patients.

In the study of Visser et al. [27,61], the daily position verification allowed for optimising target dose coverage of oesophageal cancer using a diaphragm position correction. The approach permits achieving adequate target dose coverage in case of minor deviations in diaphragm position and best mitigating the loss of coverage in case of significant deviations of the diaphragm through daily online imaging.

In the study of Huang et al. [35], 4DCT ventilation imaging is incorporated into functional PT in functional IMPT plans to further preserve high-functioning lung regions without degrading the PTV coverage.

Sala et al. [38] report that High-Frequency Percussive Ventilation (HFPV) employs high-frequency low tidal volumes (100–400 bursts/min) to provide respiration in awake patients while simultaneously reducing respiratory motion. HFPV may provide thoracic immobilisation during RT, particularly for Stereotactic Body Radiation Therapy (SBRT) and PBS-PT.

Of note, no studies are reporting online PT adaptation in thoracic tumours.

<u>Clinical outcome issues</u>

PBS provides good target coverage and local control while reducing radiation dose for OAR compared with advanced photon RT [42, 48, 59, 61, 62, 68, 75, 76, 77, 78, 79, 84, 85, 86, 88, 87, 90, 92, 93].

Hoppe et al. [49, 73] reported that fractionated PT delivered at 2.5 to 3.53 Gy per part for 60 Gy with concomitant chemotherapy offers good survival. In advanced NSCLC, reduction of toxicity rates is generally prohibited for photon therapy.

Moreover, PT may be a relatively safe treatment for NSCLC patients with Interstitial Pneumonia (IP) [50] or lung cancer patients with poor pulmonary function without compromising the quality of life or pulmonary fibrosis [51]. Moreover, optimally coupled proton-photon planning improves treatment planning quality compared to IMRT alone, potentially reducing toxicity risk while enhancing PT access for NSCLC patients [52].

In esophageal cancer, other authors [55,56] found that proton beams were superior to intensity-modulated radiotherapy (IMRT) in sparing OAR and reducing reported toxicity and postoperative complications. Kato et al. [53] for oesophageal cancer emphasize that many factors can influence the distribution of IMPT versus VMAT doses, such as the physiological curvature of the spine and the wide range of variation from the neck to the trunk. Oonsiri et al. [26] reported that the IMPT plan significantly reduced radiation dose to surrounding organs when treating thoracic regions due to its specific and site-dependent proton beam profile. Tumour is relative to the heart. McGuinigal et al. [58] reported improved clinical data from patients with thymic malignancies treated with PT and accurately calculated with a Monte Carlo-based plan.

2.3 THE PRESENT: Almost solved questions

In this paragraph, we continue our discussion with issues that we considered almost in proton therapy.

<u>Image-based technologies</u>

Time-resolved single-source dual-spiral dual-energy computed tomography named 4D-Dual-Energy-CT(4D-DECT) for proton treatment planning within the thoracic region was

evaluated by Wohlfahrt et al. [14]. The 4D-DECT technology reduces range uncertainties to less than 2mm, which is a big step forward in improving the accuracy of range calculation.

Dose comparison and robustness

As reported by [15], IMPT provides some incremental dosimetric improvements beyond cardiac-optimised photon-based Volumetric Modulated Arc Therapy (VMAT), despite the high quality of VMAT plans incorporating cardiac substructures into the optimisation process.

Similar works from[9,18,20] and [10,16,19]show the reduction of absorbed doses to the OARs of the thoracic district.

Notable is the development of the first type of proton arc technique, such as Spot scanning Arc therapy (SPArc), that could further improve the dosimetric results [8].

Nevertheless, the clinical advantage of dose sparing remains to be determined due to the limited clinical follow-up.

The term robust planning has emerged from the literature over the last few years. Often it is used as a generic term to identify mitigation strategies to conserve dose distribution of target and OARs inside a specific boundary for minor positioning errors of the patient, energy changes of the PBS beam, and anatomical changes of the irradiated tissues [10]

The data in-silico study suggests that IMPT could be significantly advantageous in treating thymoma patients with particular emphasis on substantially reducing the risk of cardiac failure and secondary cancer induction. Robust planning is a technical prerequisite for the safety of the Delivery [7].

In another planning study, robust PBS plans were achievable in carefully selected patients. Considerable dose reductions to the lung, heart, and thoracic vertebra were possible without

compromising target coverage. Sparing these lymphopenia-related organs may be particularly important in this era of immunotherapy [17].

Teoh et al. recently proposed a probabilistic approach to this concept [10].

Planning evaluation tools

Several authors adopted comprehensive plan robustness evaluation tools inside commercial treatment planning systems [20,23–25,27] for plan robustness evaluation in the presence of interplay effect, setup, and range uncertainties.

Technologies

Rescanning technologies are still a topic of debate.

2.4 THE FUTURE Issues to solve and research directions

Finally, we discuss issues that are still open in proton therapy that request attention in the future

Radiobiology models

Based on radiobiology modelling, PT currently shows advantages in improving treatment parameters compared to advanced photon techniques in lymphoma, thymic malignancies, malignant mesothelioma, and craniospinal irradiation.

In the last few years, few works have been published on radiobiological models of PT in the thoracic district. They can be divided into these groups:

- Studies on cardiac toxicity /cardiovascular disease and Normal Tissue Complication Probability (NTCP) models.
- Studies on Secondary Malignant Neoplasms (SMN) proton irradiation compared to photon treatment.
- Studies on variable Relative Biological Effectiveness (RBE)
- Studies on FLASH

Studies on cardiac toxicity /cardiovascular and oesophagus

Garant et al. [64] report that heart dose significantly predicts cardiac toxicity in patients undergoing curative treatments for oesophageal cancer.

Defrane et al. [69] point out that tumour volume is strongly related to mortality risk in the first two years after chemoradiotherapy for NSCLC. Modelling indicates reduced cardiac dose and smoking habitus may affect survival in small-tumours patients.

NTCP models ([66]) show a linear radiation dose-response relationship between the mean absorbed dose to the heart (Dheart, mean) and the risk of dying for cardiac disease, particularly when the Dheart, mean exceeds 5 Gy. This goal can be feasible using Depth inspiration breath hold. Limited data on dose-volume predictors for heart substructures and cardiac toxicity are available.

Other authors [60] suggest that PT enables dose escalation on patient-specific radio-resistant regions of tumour hypoxia in NSCLC, increasing Tumour Control Probability (TCP) while reducing NTCP compared to non-escalated treatments delivered with state-of-the-art photon techniques.

In addition, Ntentas et al. [63] reported that in patients with Hodgkin lymphoma, PT might reduce the risk of radiation-related cardiovascular disease compared with photon RT.

One is related to Lyman–Kutcher–Burman NTCP modelling for radiation-induced esophagitis in NSCLC patients receiving PT [71].

Chen et al. [70] compared the predictive performance of different modelling methods in developing NTCP models for predicting radiation-induced esophagitis (RE) in NSCLC patients receiving PT. The multivariable logistic regression model with a minor absolute shrinkage and selection operator (M-LASSO) provided the best predictive results for radiation-induced

esophagitis. The standard Lyman-Kutcher-Burman modelling had similar or better predictive performance than the most complex Support Vector Machine (SVM) modelling. The advanced machine learning approaches (M-LASSO and SVM) might have limited applicability in clinical settings with a relatively small amount of data, likely due to the risk of overfitting the training data.

Monti et al. [44] developed two NTCP models for predicting radiation-induced esophagitis in thoracic treatment, including the proton and photon RT modality and a dosimetric factor: V55Gy. The cross-validated performance showed good predictions for both models (ROC-AUC of 0.70 and 0.73, respectively)

Apart from radiation-induced cardiovascular disease and esophagitis, only a few publications were found for the NTCP applied to the other endpoints.

Palma et al. [89] was the only study investigating the incidence of acute radiation dermatitis (RD). The work describes NTCP models for severe RD in thoracic cancer patients treated with IMRT or PSPT.

Cao et al. [45] reported that IMPT significantly reduced the dose to the thoracic vertebral bodies (TVB), the lung, the heart, the oesophagus, and the spinal cord compared to VMAT. Tumour distance to TVB was significantly associated with a reduction of NTCP, predicting the risk of grade ≥ 3 acute hematologic toxicity higher than 10%. For the patients with tumour distance $\leq$ 0.7 cm to TVB, the absolute reduction of dose (mean, V30 and V40) to TVB was significantly lower than that in patients with tumour distance > 0.7 cm.

Yang et al. [47] evaluated the toxicity associated with curative re-irradiation in patients with thoracic recurrence of NSCLC who underwent hypofractionated RT or concurrent chemotherapy.

Yang et al. [67] reported that fistulas or severe airway obstruction occurred in patients with

tumours adjacent to the proximal bronchial tree and oesophagus due to the high doses delivered to the oesophagus, irrespective of using photon or proton beams.

McNamara et al. [72] point out the importance of uncertainties of the NTCP models predicting radiation pneumonitis in the design of clinical trials. McNamara et al. demonstrated that NTCP differences between proton and photon therapy treatments might be too small to support a model-based trial approach for specific treatment sites, such as lung cancer, depending on the chosen normal tissue endpoint.

Studies on Secondary malignant neoplasms (SMN)

Few studies have been found on SMN modelling in thoracic regions.

Vogel et al. [100] reported that treatment with PT can achieve comparable target coverage but significantly reduced doses to OARs, leading to fewer predicted SMNs than IMRT. By decreasing expected late complications, PT may improve the therapeutic ratio of adjuvant radiation therapy for patients with stage II thymic malignancies.

Using the PBS technique, Lideståhl et al. [57] compared the calculated risks of radiation-induced SMNs for patients treated for thymic tumours with 3D-CRT, IMRT, or single-field uniform dose PT. A cancer-induction model based on the organ equivalent dose concept was used. In conclusion, PBS potentially reduces the risk of SMNs compared to 3D-CRT and IMRT in treating thymic tumours.

Similarly, Koenig et al. [43] reported that PT for patients with thymic malignancies could yield dramatic dose reductions to absorbed doses to adjacent thoracic OARs. Using radiobiological estimations based on Dasu and Schneider models, Koenig et al. demonstrate that PT halves the risk of secondary malignancies of the lung, breast, and oesophagus relative to X-ray-based techniques, including IMRT, in particular in young female patients.

In addition, Ntentas et al. [46] reported that proton beam therapy might reduce the risk of second cancers compared with photon RT in patients with Hodgkin lymphoma. The predicted benefit of PT in terms of predicted 30-year absolute mortality risks was not universal and limited to specific categories of patients with lymphoma and lowered mediastinal or axillary disease. Smoking cessation was strongly encouraged in smokers necessitating thoracic RT.

Variable RBE

The variable-RBE models predict increased doses of various OARs, suggesting that strategies to reduce high-dose linear energy transfer in critical structures should be developed to minimise possible toxicity associated with IMPT [83]. In addition, Rørvik et al. [82]out the difficulties in predicting the RBE of different models. There were considerable variations between the other models' RBE and RBE-weighted dose estimations. These variations resulted from fundamental differences in experimental databases, model assumptions, and regression techniques.

New paradigm

Due to the FLASH-sparing effect of normal tissues at both the proximal and distal side of tumours, IMPT plans can meet current constraints, limited by the RBE values that can be avoided using the shoot-through FLASH PT. In this context, in the shoot-through FLASH PT, the proton beams have sufficient energy to reach the distal exit side of the patient, thus enabling an attractive treatment modality to explore further [2].

Economics, patient selection

In this category, we select four papers [93–96]. Dosimetry studies have indicated that PT can significantly reduce the doses for normal organs, especially the lung, heart, and oesophagus while maintaining similar robust target volume coverage in both early and advanced NSCLC compared with photon therapy. However, as pointed out by [93], most studies have been

single-arm and concluded no significant changes in the efficacy for early-stage NSCLC by PT over SBRT with photons.

Ntentas et al. [84] attempt to find subgroups of patients with Hodking Lymphoma who could benefit the most from dosimetrically PT based on the pre-chemotherapy disease characteristics. These findings facilitate the selection of patients who should be considered a priority for PT.

Liao et al. [95] explored strategies for accelerating the development of trials aimed at measuring meaningful clinical endpoints and maximising the value of PT by personalising its use for individual patients. The comparison between [42,94] proton and photon/X-ray radiation therapy for NSCLC must consider both the up-front cost of treatment and the possible long-term cost of complications. In the analysis from Smith et al. [96], current costs favour X-ray therapy. However, relatively small reductions in the price of PT may result in a shift to the preference for PT.

In summary, we show in Table 1 the results of our evaluations.

Solved	Almost solved	Still open
● Dose calculation and verification ● Motion management ● Clinical outcome	● Image-based technologies ● Dose robustness ● Planning evaluation tools ● Rescanning	● Radiobiology ● Economics, patient selection

Table 1: Summary of the literature overview on the state of the art and identified open questions

2.5 Conclusions

The analyzed papers highlighted those numerous aspects regarding the PT planning, including beam technologies, field ballistics and calculation engines for thoracic tumours, are mainly solved due to the capability of taking into consideration the density heterogeneity of tissues

around and into the target, while other such as the planning methodologies and technological solution are "almost solved" and requires further development and validation.

All the essential critical aspects of Imaging for Simulation and Planning of thoracic tumours treatment with PT are solved. At the same time, the setup images are "almost solved", depending on the available technology and the type of treatment performed.

The appropriate planning margins are "almost solved" due to the recent introduction of systems for online imaging and motion management. This ongoing technological improvement led to “almost solved” issues in treatment delivery and opened critical issues for off-line/online adaptation.

Numerous Authors attempt to estimate the NTCP risk for the primary OARs using ad hoc proposed models, including exploring the added value of artificial intelligence-based models. However, the number of cases of toxicity and the uncertainties of NTCP models demand additional efforts to be used for a safe guide of prospective trials.NTCP models for secondary malignancy cancers still represent an open issue.

Despite the number of patients and pathologies treated, cost-effectiveness evaluations have yet to reach adequate maturity to be considered as a solved problem.

2.6 Advances in knowledge

Our overview analyses the technological, planning, and breath monitoring aspects before and during PT treatments in the thoracic region, including the frontier radiobiological elements at this time. This analysis clarifies the solved, almost solved and open issues considering the state of the art of PT technology applied to the thoracic target treatments. The highlighted “almost solved” and "still open" issues need more scientific, technological and socio-economic efforts. Among these issues we choose to concentrate our effort in the following 2 fields:

- Online adaptive proton therapy (oAPT) and
- Studies in radiobiology of secondary cancers related to proton therapy

The following chapter will focus on those two fields and explain the research and development work that will continue from our side in the next years.

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3. Online Adaptive Proton Therapy (OAPT)

3.1 Introduction

Online Adaptive Proton Therapy (OAPT) is an evolving technique aimed at improving the accuracy and effectiveness of proton therapy treatments by adjusting the treatment plan in real time based on anatomical and positional changes. This summary compiles the latest research from the last five years, covering workflow implementation, imaging technologies, dosimetric impact, and clinical outcomes.

3.2 Workflow of Online Adaptive Proton Therapy

The standard proton therapy workflow involves pre-treatment imaging, treatment planning, and quality assurance prior to therapy initiation. In contrast, OAPT introduces a dynamic adjustment mechanism, where a new 3D image (typically CT or CBCT) is acquired daily, and predefined structures are transferred onto the newly collected image. The treatment plan is then adapted to account for anatomical changes, ensuring more precise dose delivery [1].

A key challenge in OAPT is the time constraint; the workflow must be automatically completed within the typical duration of a patient appointment. Therefore, pre-delivery patient-specific measurements are often replaced with automated physical and clinical quality assurance checks [1].

3.3 Imaging Technologies for Daily Adaptation

Imaging modalities currently used for OAPT include in-room CT, CBCT, and integrated MRI. CT-based planning is the gold standard due to its accuracy in proton range calculation, but frequent imaging increases radiation doses. Researchers are developing low-dose CT protocols to partly address this issue [3].

In head and neck cancer, studies have also compared adaptation based on CBCT with adaptation using in-room CT, and it has been observed that in-room CT provides higher fidelity in identifying anatomical changes, thereby enhancing the precision of dose delivery [4].

3.4 Automated Planning and Dose Calculation

To make OAPT more efficient, automation is crucial. Automation-driven planning strategies, such as plan-library-assisted adaptive treatment and Monte Carlo-based simulations, have been developed for intensity-modulated proton therapy (IMPT). These strategies facilitate near real-time adaptation, particularly for prostate and cervical cancer treatments [3].

The development of IMPT plan generation algorithms with high speed, achieving optimization in under ten seconds, has also been reported. These developments are critical for real-time adaptive therapy [5].

3.5 Clinical Implementation and Dosimetric Impact

Recent clinical studies highlight the benefits of daily adaptive proton therapy (DAPT) in improving dose accuracy. Anatomic changes, such as tumor shrinkage, variations in organ filling, and weight loss, can significantly impact the proton dose distribution. Studies comparing weekly versus daily adaptation have demonstrated that daily adaptation provides superior target coverage while reducing unnecessary doses to normal tissues [6].

Dosimetric studies have also explored the impact of different contouring techniques on online adaptation. While automated organ-at-risk (OAR) contouring methods yield minor dosimetric variations, automated target contouring remains challenging, requiring manual verification [7].

3.6 Future Perspectives and Challenges

Despite its potential, OAPT faces several challenges, including:

Computational Requirement: Heavy processing capability is required for real-time dose recalculation.

Quality Assurance: Treatment safety must be ensured by automated verification without intruding upon therapy.

Clinical Adoption: Training for general clinical staff and standardization of practice are required for general implementation.

Existing research studies, such as the RAPTOR (Real-time Adaptive Proton Therapy Optimized for Radiotherapy) study, are tackling these issues by integrating machine learning and real-time imaging with clinic workflow (https://raptor-consortium.com).

Overall, online adaptive proton therapy is an exciting technology that enhances treatment precision, particularly in anatomically complex cases. We think that as research goes on and technology continues to evolve, OAPT will be the standard in proton therapy in the years to come.

3.7 Workflow of the Trento Proton Therapy Facility

To understand where the conventional treatment process can improve with OAPT, we summarize the treatment workflow in the following figure.

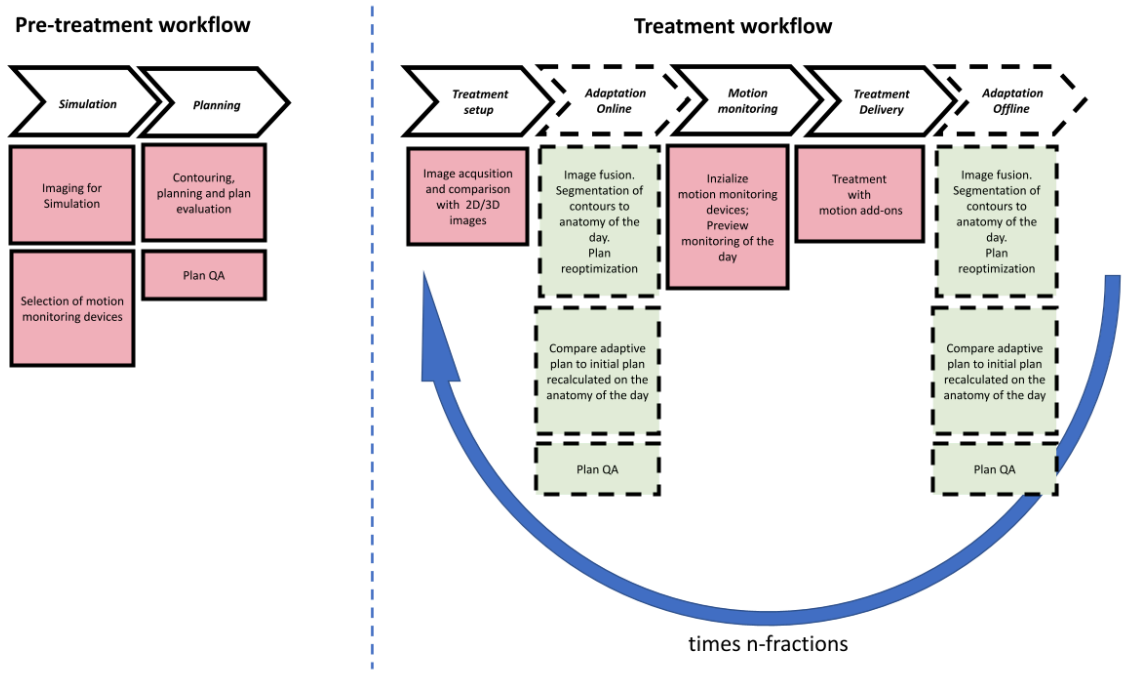

Figure 1: Treatment workflow of Trento proton therapy facility.

In the following list, we summarize the process of the boxes in red in figure 1.

Pre-treatment workflow

- **Imaging for simulation:**
    - **CT Simulation:** A planning CT scan is acquired with the patient in the treatment position using immobilization devices.
    - **MRI and PET/CT Fusion:** For better soft tissue contrast and tumor delineation, MRI and/or PET scans are co-registered with the planning CT.
    - **CT with breath-hold:** Used for tumors affected by respiratory motion (e.g., lung, liver).
- **Contouring:**
    - **GTV, CTV:** The radiation oncologist delineates the Gross Tumor Volume (GTV) and clinical Target Volume (CTV).

    - **Organs at Risk (OARs):** Critical structures are contoured to minimize radiation exposure.
- **Planning (Medical Physics Role):**
    - **Beam Arrangement:** Selection of beam angles to optimize dose distribution.
    - **Robust Optimization:** Considering setup uncertainties and range uncertainties specific to proton therapy.
    - **Monte Carlo Simulations:** Employed for complex cases to enhance dose calculation accuracy.
    - **Plan Evaluation:** Dose-Volume Histograms (DVHs) are reviewed to ensure coverage and OAR sparing.
- **Plan QA (Medical Physics Team):**
    - **Phantom Measurements:** Dosimetric verification using ion chambers, film, or 3D dosimetry phantoms.
    - **Range Verification:** Ensures the proton beam range matches the planned depth.

Treatment workflow

- **Treatment setup:**
    - **Image-Guided Radiation Therapy (IGRT):** Daily orthogonal X-rays CT on rail for accurate positioning.
    - **Surface-Guided Radiation Therapy (SGRT):** Used for some anatomical sites to monitor patient movement in real-time.
- **Motion monitoring:**
    - **Real-Time Position Verification:** Ensures the patient remains in the correct position during irradiation.
    - **Motion Management:** Techniques such as breath-hold for mobile tumors.
- **Treatment Delivery:**
    - **Pencil Beam Scanning (PBS):** The Trento facility uses PBS for high-precision dose painting.
    - **Adaptive Techniques:** Adjustments are made for anatomical changes over the treatment course.

Additional dashed groups of boxes are highlighted in green relative to offline and online adaptive therapy. Both procedures are similar, even if online adaptive therapy is done before and offline

adaptive therapy is done after the treatment delivery phase. What is changing is the timescale. In offline adaptation, this work can be done from one treatment fraction day to the next. In online adaptive, the following procedure must be done in the order of some minutes just before the treatment delivery:

- **Adaptive procedure**
    - **Image fusion:** Image acquired through CT-on rail is fused to reference images.
    - **Segmentation:** automatic propagation of the contours to the anatomy of the day and check of the medical staff.
    - **Plan re-optimization: the plan is readapted to the actual CT-on rail image**
    - **Comparison** of the adapted plan to the reference plan
    - **QA of the plan**

In addition, the new plan must be sent to the treatment system and scheduled correctly for the treatment fraction. At first glance, this seems a minor detail, but it has been revealed as time-consuming in a system not specifically designed for online adaptive therapy.

Figure 2: The CT-on rail (right side) of the Trento facility in gantry room 1.

3.8 Daily Adaptive Proton Therapy: the PSI approach.

To develop an in-silico QA, we describe an online adaptive approach developed by the Paul Scherrer Institute of Switzerland facility at their Gantry n.2 treatment room. Figure 2 shows their Daily Adaptive Proton Therapy (DAPT) workflow.

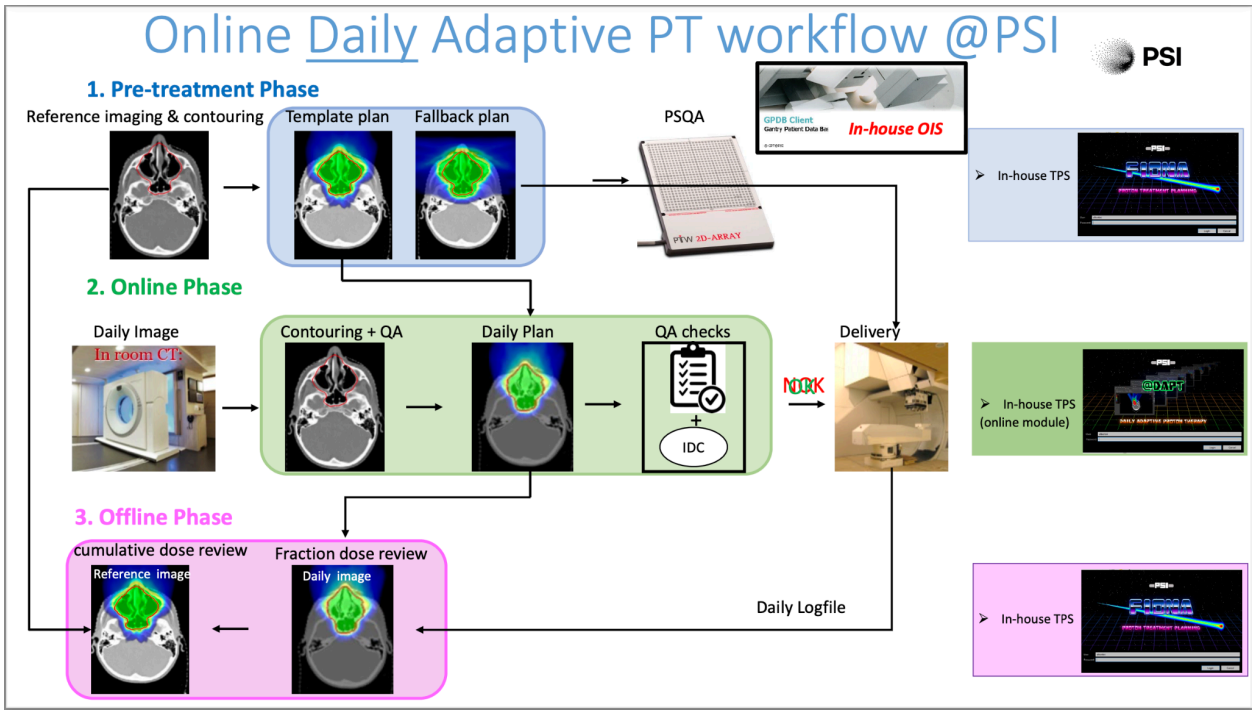

Figure 3. Daily Adaptive Proton Therapy at Gantry2 in PSI. Courtesy Francesca Albertini

The workflow is based on a "daily-upfront" adaptation. The advantages of this approach are:

- Faster daily setup procedure.
- There is no extra time to compare plans and decide whether to adapt or not adapt
- Automatic execution of all adaptive steps. From contouring to the comparison of the independent dose calculation, without waiting for the approval of previous steps.

The workflow is divided into three steps:

- Pre-treatment phase in blue
- Online phase in green
- Offline phase in magenta

In the pre-treatment phase, reference imaging and contouring of the tumor and OAR are performed in a standard simulation phase. Two plans are generated. One so-called fallback plan ensures that a standard of care plan can be applied to the patient at each treatment fraction, even if the online adaptation workflow fails for some reason. For this conventional plan, QA is performed with typical QA devices, such as an array of ionization chambers, as shown in figure 3.

The second plan is called the Template Plan. This is the plan that will be optimized in the online session. The optimization process must be fast enough to generate the adapted plan. PSI uses in this position a speedy optimization algorithm based on GPU that does this process in seconds.

At this point, a daily QA plan is generated. This plan goes through an in-silico QA process even before the medical doctor checks the contours and absorbed dose distribution of the fraction delivered the day before by the "yesterday" plan. In this way, the daily plan is ready to be applied as soon as the physician validates the contours and dose distribution. If this check is passed, the daily plan will be applied to the patient who, in the meantime, is positioned correctly in the treatment position.

If the check fails, the Fallback plan is applied to the patient.

In the offline phase, the machine's steering files produced after the treatment fraction will be used to recalculate the fraction's dose on the daily CT-on rail more accurately but time-consumingly.

They will also be stored inside the TPS to track the dose per fraction given to the patient. The cumulative dose will be reviewed and considered for the following fraction.

3.9 Ongoing works: Online plan QA and evaluation of OAPT on thoracic tumors.

The major bottleneck in a system like Trento is that it was not explicitly designed for OAPT. New radical software upgrades would be necessary, which would be challenging to implement and, therefore, costly.

So why further investigate "online adaptation" research? Mainly for 2 reasons:

The patient plan QA for online adaptation could, to some extent, improve the efficiency of the actual workflow. The idea of replacing cumbersome patient QA that requires beamtime with fast "in silico" QA is attractive, but it needs to be done in a way that ensures the same accuracy as physical patient QA verification done with dosimetry devices.

Before investing in upgrading our system, we need to quantify the advantages of OAPT in clinical practice by making specific studies of the tumor sites we treat. Our work hypothesis is that those advantages are particularly important in thoracic tumor treatments. We have to assess by comparative TPS studies among standard-of-care treatments and "virtual" online adaptive procedures the gain of such procedures.

This part of the chapter summarizes the research and development work that I developed and implemented. A comparative study among the standard of care in Trento and OAPT in thoracic tumors. The aim is to replan already treated patients with thoracic tumors in Trento to highlight the gain of APT.

3.10 Comparative case studies among the standard of care and virtual OAPT.

We made several case studies to compare standard care of Trento simulated OAPT in the case of patients with moving targets. Here we present the most significant studies analyzed.

<u>Case A: external change</u>

A 70-year-old female initially presented with repetitive lung lesions of colon adenocarcinoma, previously operated and chemo-treated. The patient received a biological equivalent dose of 60 cobalt Gy delivered over 20 treatment fractions of proton radiation over 4 weeks.

- **Imaging for simulation:**
    - **CT Simulation:** A planning CT in inhale with breath hold system (ABC Elekta) was acquired with the patient in the treatment position using conventional immobilization devices such as windboard and knee fix on a radiotransparent carbon fiber treatment table.
        - N. 5 Breath hold planning CT where acquired. 3 for tumor delineation and intrafraction tumor movement evaluation and 2 for infra-fractional movement evaluation redoing the scan to the patient after a pause simulating the difference positioning between two fractions.
    - **PET/CT Fusion:** For better tumor delineation, a PET scan is co-registered with the planning CT.

- **Contouring:**
    - **GTVs, CTV and ITV:** The radiation oncologist delineates the Gross Tumor Volume (GTV) and clinical Target Volume (CTV) on different CTs. ITV was generated on one of the five breath hold CT.
    - **Organs at Risk (OARs):** Critical structures are contoured to minimize radiation exposure.
- **Planning:**
    - **Beam Arrangement:**3 of beam direction where selected for the plan dose distribution.
    - **Robust Optimization:** 5mm geometrical uncertainties and 3.5% range uncertainties used in the robust optimization of TPS Raystation. Monte Carlo dose engine was used to enhance dose calculation accuracy.
    - **Plan Evaluation:** Dose-Volume Histograms (DVHs) are reviewed to ensure coverage and OAR sparing in the nominal case and in the robustness evaluation tool implemented in the TPS.

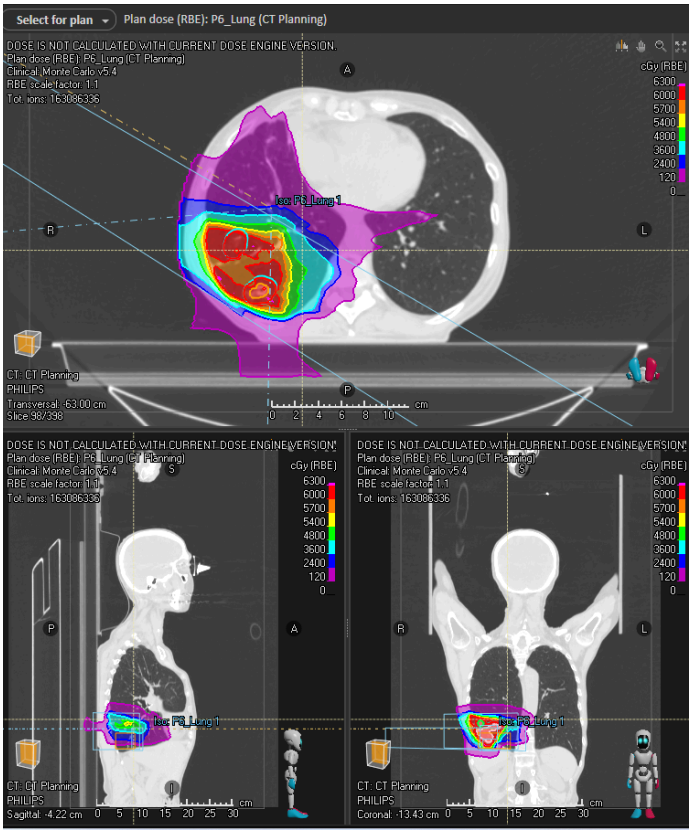

Figure 4: Dose distribution on case A.

Treatment workflow

- **Treatment setup:**
    - **Image-Guided Radiation Therapy (IGRT):** Daily orthogonal X-rays CT on rail for was used,
    - **Surface-Guided Radiation Therapy (SGRT):** Used for anatomical sites to monitor patient movement in real-time.
    - **Motion Management:** breath-hold ABC Elekta.
- **Treatment delivery:**

Patient was treated in 20 fractions and received 9 CT-on rails for plan calculation. In one plan recalculation showed consistent differences of dose to the target ITV due to different entrance surface (see orange arrow **Figure 4**) of the posterior field. The plan was adapted offline and delivered from the 13 to 20 fractions.

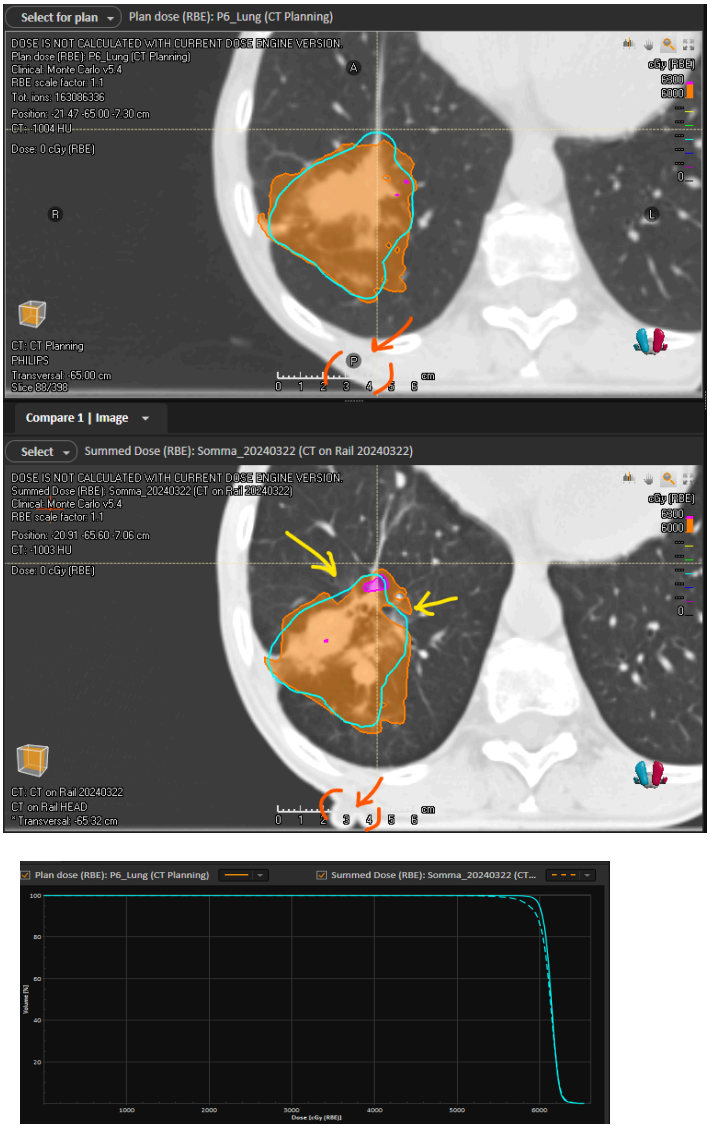

Figure 5: Dose distribution comparison with difference in dose distribution of ITV. Lack of coverage in image (yellow arrow) and different entrance surface (orange arrow) of posterior field and DVH of ITV.

To analyze the dose distribution associated with the total treatment (**Figure 5**), we focused on the following steps:

1. calculation of the delivered plans on each CT-on rail, interpolating the data for the fractions where CT was not available. A plan was generated summing up all dose contributions deformed to the planning CT and called a deformed plan.
2. Calculation of a virtual online adaption for all CT on rail available with reduction to 3mm of the geometrical uncertainties and interpolating the data for the fractions, where CT was not available. A plan was calculated summing up all dose adapted plans for each CT-on rail and called adapted.

The result was that the DVHs of ITV of the deformed to the adapted plan of the whole treatment are difficult to distinguish and not worth showing. We instead show a boxplot of deformed vs adapted plans in which we can appreciate the difference among the fraction of the value D95 of the ITV ROI (**Figure 6**). Clearly, the virtual online adapted plan is more conformal, but the absolute difference of the two boxplots is minimal. Similarly, the overall reduction of OAR DVH at risk among deformed and adapted plans is systematically, as foreseen, lower.

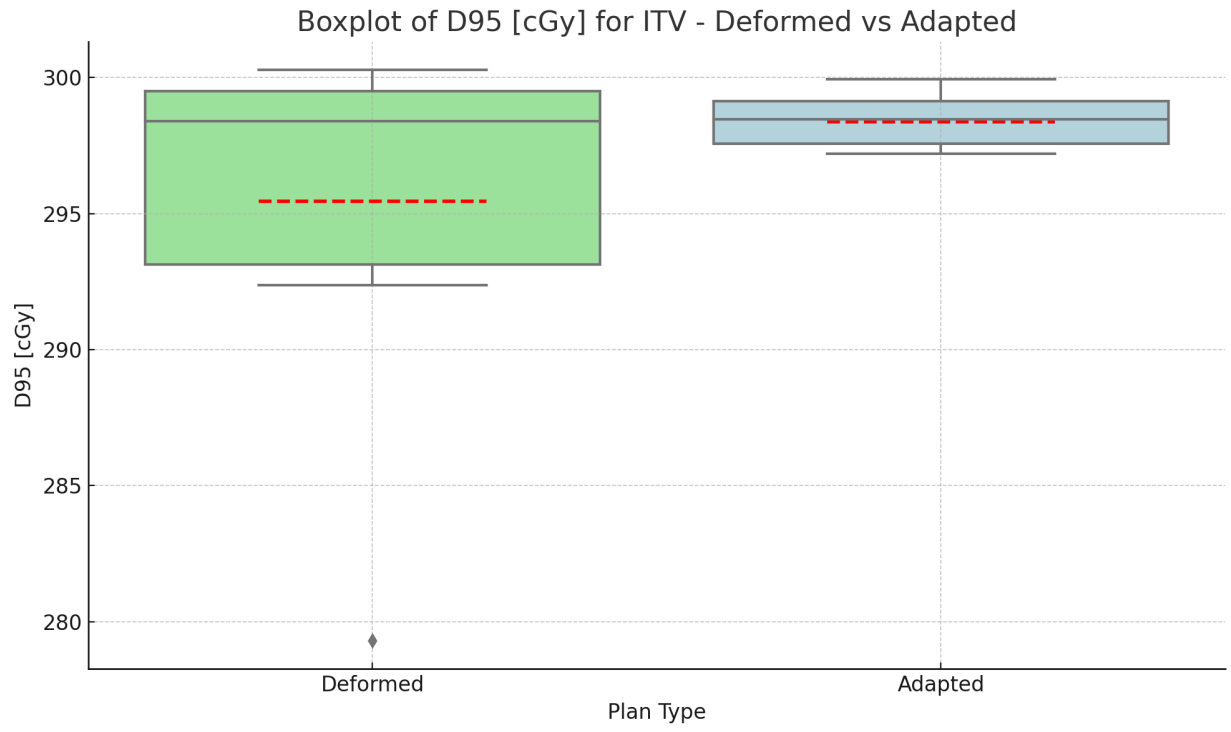

Figure 6: Boxplot D95 of the ITV Deformed vs Adapted plan.

Case B: internal change

A 77-year-old male initially presented with multiple liver lesions. The patient received a biological equivalent dose of 67.5 cobalt Gy delivered over 15 treatment fractions of proton radiation over 4 weeks.

- **Imaging for simulation:**
    - **CT Simulation:** A planning CT in exhale with breath hold-hold system (ABC Elekta) was acquired with the patient in the treatment position using conventional immobilization devices such as wing board and knee fix on a radiotransparent carbon fiber treatment table.
        - Two Breath hold planning CT images were acquired for tumor delineation and intra and infra-fractional movement evaluation, re-acquiring the scan to the patient after a pause simulating the difference positioning between two fractions.
- **Contouring:**
    - **GTVs, CTV and ITV:** The radiation oncologist delineates the Gross Tumor Volume (GTV) and clinical Target Volume (CTV) on different CTs. ITV generated both breath hold and free breathing CT.
    - **Organs at Risk (OARs):** Critical structures are contoured to minimize radiation exposure.
- **Planning:**
    - **Beam Arrangement:** 2 of beam directions were selected for the plan dose distribution.
    - **Robust Optimization:** 6mm geometrical uncertainties and 3.5% range uncertainties used in the robust optimization of TPS Raystation. Monte Carlo dose engine was used to enhance dose calculation accuracy. To take in acute inter-factional and infra-fractional motion both CT were included in the robust optimization function of TPS Raystation.
    - **Plan Evaluation:** Dose-Volume Histograms (DVHs) are reviewed to ensure coverage and OAR sparing in the nominal case and in the robustness evaluation tool of TPS.

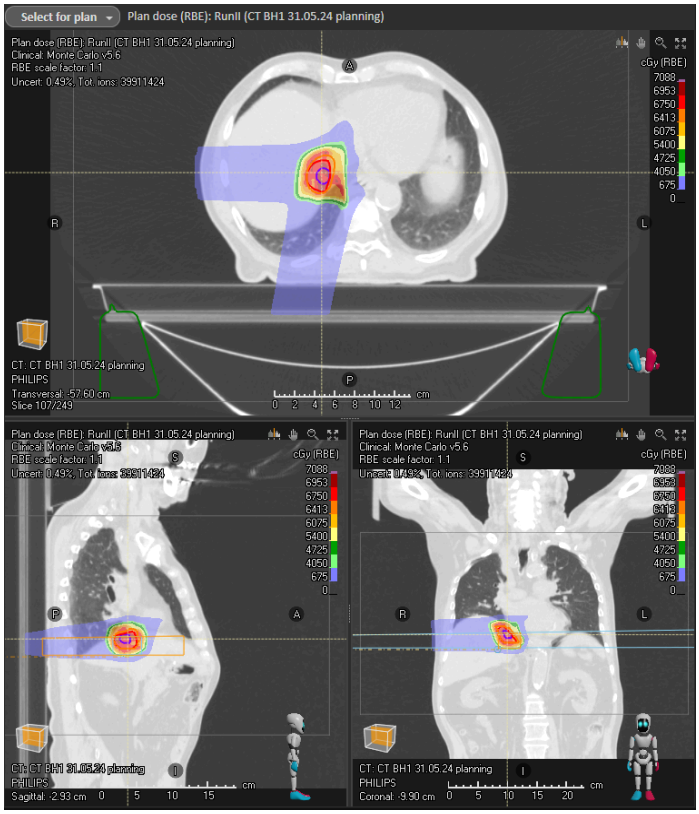

Figure 7: Dose distribution on case B.

Treatment workflow

- **Treatment setup:**
    - **Image-Guided Radiation Therapy (IGRT):** Daily orthogonal X-rays CT on rail for was used.
    - **Surface-Guided Radiation Therapy (SGRT):** Used for anatomical sites to monitor patient movement in real-time.
    - **Motion Management:** breath-hold ABC Elekta.
- **Treatment delivery:**

Patient was treated with 15 fractions and received 15 CT-on-rails for plan recalculation on the daily basis. In one fraction recalculation was seen a consistent difference of dose to the OAR IVC (inferior vena cava) due to the differences revealed by the image fusion (see red arrow **Figure** 8), particularly on the ITV. OAR IVC changes maximum value by 5 Gy if considered that this change is applied to all fractions.

In the subsequent fraction the problem was not any more present and the patient was treated without any change till the end.

Figure 8: Dose distribution comparison with a difference in dose distribution of ITV for the specific fraction normalized to the whole treatment. Minor differences were observed in the ITV DVH. OAR: IVC maximum value changes by 5 Gy, assuming that this change was expected at each fraction.

To analyze the absorbed dose distribution associated to the entire treatment, we followed the following steps:

- calculation of the delivered plans on each CT-on rail. A plan was generated summing up all dose contributions deformed to the planning CT and called a deformed plan.
- calculation of virtual online adaptation for all CT on rail with reduction to 4 mm of the geometrical uncertainties. A plan was calculated summing up all dose adapted plans for each CT-on rail and called adapted.

Figure 8 shows that the DHV of ITV and IVC of deformed to the adapted plan, which resulted in comparable. The D1 of IVC is around 1 Gy less for the adapted vs the deformed plan. Clearly, we can see the washout effect that reduces the IVC maximum dose over fifteen fractions.

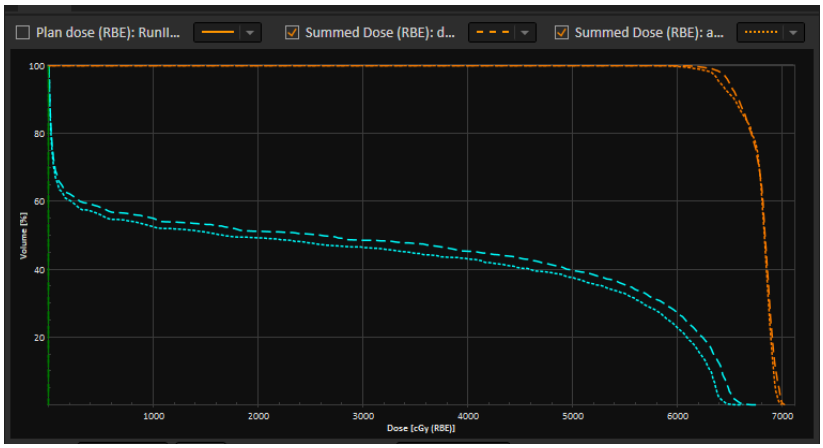

Figure 9: DVH of ITV and IVC of the Deformed vs Adapted plan.

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4. Radiobiology of Proton Therapy: Implication for Secondary Malignancies

4.1 Introduction

The physical properties of proton therapy have established it as a highly effective approach in contemporary radiation oncology, providing enhanced dose distribution and minimizing exposure to surrounding healthy tissues when compared to traditional photon therapy. Nevertheless, the possibility of radiation-induced secondary malignancies (SMs) continues to be a subject of ongoing research. The unique linear energy transfer (LET) characteristics, variations in relative biological effectiveness (RBE), and the generation of secondary neutrons associated with proton therapy lead to distinct radiobiological outcomes, highlighting the need for a comprehensive assessment of its long-term carcinogenic risks [1].

Radiation-induced secondary malignancies arise from persistent DNA damage, genomic instability, and oxidative stress following exposure to ionizing radiation. Multiple factors, including radiation modality, dose distribution, patient age, and genetic predisposition influence the risk of SMs. Due to its characteristic Bragg peak phenomenon, proton therapy significantly reduces the integral dose to surrounding normal tissues, thereby theoretically lowering the risk of SMs compared to photon-based approaches [2].

Despite these dosimetric advantages, proton therapy is not entirely exempt from secondary malignancy risks. One of the primary concerns is neutron contamination, particularly in passive scattering proton therapy (PSPT). Secondary neutrons, produced during beam interactions with beamline components and patient tissues, possess high LET properties and can induce complex, difficult-to-repair DNA damage. In contrast, pencil beam scanning (PBS) proton therapy, which eliminates the need for scattering foils, has significantly reduced neutron dose deposition, thereby mitigating the risk of neutron-induced carcinogenesis [3].

Another key aspect in the radiobiology of proton therapy is the variation in RBE across different tissues and dose distributions. While the conventional assumption of an RBE of 1.1 is widely applied in clinical practice, emerging evidence suggests that RBE is heterogeneous and dependent on LET, with values increasing in regions of higher LET near the distal end of the proton beam. This elevated RBE has implications for both tumor control and normal tissue toxicity, as higher LET radiation induces more complex DNA double-strand breaks (DSBs), which are less efficiently repaired. Consequently, uncertainties in LET-dependent RBE modeling present challenges in risk assessment for secondary malignancies following proton therapy [4].

4.2 Comparative Risk Assessment: Proton Therapy vs. Photon Therapy

Epidemiological research and retrospective evaluations have studied the occurrence of secondary malignancies among patients undergoing proton therapy in comparison to those receiving photon therapy. These studies suggest that proton therapy has a reduced overall risk of secondary malignancies, especially in pediatric cancer patients [5].Investigations involving pediatric cases of medulloblastoma, rhabdomyosarcoma, and Ewing sarcoma have shown a significantly lower incidence of secondary tumors following proton therapy when compared to intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) [6].

In adult oncology, proton therapy has been increasingly utilized for head and neck cancers, central nervous system (CNS) tumors, and thoracic malignancies, where precise dose delivery is critical for reducing normal tissue exposure. Longitudinal cohort studies have suggested that proton therapy confers a statistically significant reduction in the occurrence of radiation-induced sarcomas and solid tumors compared to photon-based treatments. However, challenges remain in interpreting these data due to variations in follow-up duration, patient selection biases, and evolving proton delivery techniques [7].

4.3 Emerging Strategies to Minimize Secondary Malignancy Risk in Proton Therapy

Advancements in treatment planning, delivery techniques, and radiobiological modeling are actively being pursued to reduce the risk of secondary malignancies associated with proton therapy. Key strategies include:

- Transition from Passive Scattering to Pencil Beam Scanning: The adoption of PBS has decreased secondary neutron exposure, mitigating a radiation-induced carcinogenesis. Clinical studies have demonstrated lower neutron doses in PBS-treated patients than those receiving PSPT, reinforcing the importance of treatment modality selection in risk reduction [8].
- LET and RBE Optimization in Treatment Planning: The development of LET-based treatment planning algorithms aims to more accurately model RBE heterogeneity of different tissues, thereby refining dose calculations and reducing unexpected toxicities. Advanced Monte Carlo simulations and biologically weighted dose optimization strategies are being integrated into proton therapy workflows to improve RBE predictions and limit excessive radiation exposure to normal tissues [2].
- FLASH proton therapy. Preclinical studies indicate that ultra-high dose rate irradiation may induce a distinct radiobiological response with sparing of normal tissues while maintaining tumor control. However, the effect on radiation-induced secondary malignancies is not demonstrated clinically and remains an open research question. In this thesis, FLASH is therefore cited only as a future perspective, not as an established strategy for reducing secondary-cancer risk.[9].
- Genomic and Biomarker-Guided Risk Assessment: Advances in genomic profiling and biomarker discovery are enabling personalized risk stratification for radiation-induced secondary malignancies. Identifying genetic predispositions to radiation-induced DNA

damage and repair deficiencies may inform individualized treatment plans that minimize long-term secondary malignancy risks in susceptible patient populations [10].

While proton therapy offers substantial advantages in minimizing normal tissue exposure and reducing secondary malignancy risks compared to conventional photon therapy, challenges persist in fully elucidating its long-term radiobiological effects. The adoption of PBS, RBE-optimized treatment planning, and emerging technologies such as FLASH therapy hold promise for further risk reduction. Ongoing clinical trials and longitudinal follow-up studies will be critical in defining the definitive risk-benefit profile of proton therapy concerning secondary malignancies. As precision medicine continues to evolve, integrating radiogenomic insights, AI-driven adaptive planning, and real-time dosimetric monitoring will be pivotal in ensuring the safest and most effective application of proton therapy in oncology [11].

4.4 Risk Estimation for Radiation-Induced Secondary Cancers

The risk of radiation-induced secondary cancer was estimated using two distinct, well established, radiobiological models, initially described by Dasu et al. [12] and Schneider et al. [13]. The Dasu model is also known as the "competition model", as it describes the competition between the induction of carcinogenic mutations and cellular survival and further considers both treatment dose fractionation as well as non-uniformity of the dose distribution across the irradiated organ. The Schneider model is based on the calculation of the organ equivalent dose (OED). The OED concept postulates that any two dose distributions in an organ are equivalent if they result in the same radiation-induced SM incidence. In the Schneider model, besides the induction of carcinogenic mutations and cellular survival, repopulation and repair are also taken into account to calculate the risk for inducing SM [14].

Data extracted from the dose–volume histograms (DVHs) for each treatment modality can be used for risk calculation of radiation-induced SM.

Dasu model

We estimated secondary cancer risk using the Dasu "competition" model, which couples mutation induction and cell survival within a linear–quadratic (LQ) framework. For each organ of interest, the risk contribution is accumulated over **differential DVH bins**, where **vi** is the f**ractional organ volume** represented by the **i-th bin**, receiving a **mean dose Di** delivered in **n fractions.** Model **coefficients α_1 ,α_2 ,β_1 ,β_2** were taken in accordance with **ICRP Publication 60 (1990)**. We report **Total risk** and, where available, **Fatal risk** endpoints.

In short, the Dasu model is a linear-quadratic (LQ)-based model:

$$\text{Total risk}_{\text{organ}} = \frac{1}{\sum_i v_i} \sum_i v_i \times \left\{ \left(\alpha_1 D_i + \frac{\beta_1 D_i^2}{n} \right) \times exp\left[-\left(\alpha_2 D_i + \frac{\beta_2 D_i^2}{n} \right) \right] \right\}$$

where *vi* is the fractional organ volume represented by the i-th differential DVH bin, receiving a mean dose *Di* delivered in n fractions. The risk coefficients α1,α2 and β1, β2 and are taken from the ICRP publication according to [14]. For the Dasu model, the term "total risk" comprises the risk for development of any cancer, while the term "fatal risk" only includes secondary malignancies resulting in death.

Table 1. Risk coefficients (α_1, second and third column) and the linear quadratic model parameter (last column) used for risk assessment for the different organs at risk.

Organ	α_1 (Gy^{-1}) Fatal Risk	α_1 (Gy^{-1}) Total Risk
Lung	0.0101	0.0144
Breast	0.0028	0.0144
Esophagus	0.0014	0.0015
Thyroid	0.0028	0.0144

The risk coefficients were taken from ICRP 103 according to Mondlane et al. [17].

Table 1. Risk coefficients (α1, second and third column) and the linear quadratic model parameter (last column) used for risk assessment for the different organs at risk.

Schneider Model

The risk of inducing SM was also estimated utilizing the Schneider model, which is based on determination of OED. The OED concept postulates that any two dose distributions in an organ are equivalent if they result in the same radiation- induced SM incidence.

$$\mathrm{OED} = \frac{1}{N}\sum_{i=1}^{N} D_i e^{-\alpha_{org} D_i}$$

where vi and Di are defined as in the Dasu model above and the sum is taken over N dose calculation points, which represent the same constant volume of the organ.

Based on the OED, the incidence of a secondary malignancy Iorg was calculated using the equation Schneider suggested. Here, **I0org** is the organ specific cancer incidence 0 rate and **αorg** is the specific sterilization parameter.

$$I^{org} = I_0^{org}\ \mathrm{OED}\ e^{-\alpha_{org}\ \mathrm{OED}}$$

Organ Equivalent Dose (OED) was computed from **differential organ DVHs**; for each bin, the **mean dose Di** and fractional volume **vi** entered the summation. Organ-specific parameters **I0org** and **αorg** were **taken from the literature** for the same organ/site and endpoint. **No parameter fitting** was performed on our data. Instead, we conducted **deterministic sensitivity analyses** by varying **αorg** within published ranges and propagated the resulting uncertainty to OED-based risk estimates.

Age model for EAR (conservative assumption).

In the pediatric case study, adult EAR coefficients were used due to the lack of robust pediatric-specific data aligned with our endpoints and fractionations. This approach is **conservative**, since absolute EAR values are likely underestimated, but the main objective was the **relative comparison** across modalities (photons, electrons, protons).

Risk estimation of proton therapy in pediatric patients: Breast-Leukemia Case

Using the Schneider model we publish a poster with the following abstract:

Introduction

Acute lymphoblastic leukemia (LAL) is undoubtedly the most common pediatric patient disease and has peripheral recurrence characteristics, including solid lymphatic organs. We study an 11-year-old girl with LAL recurrence in the right mammary parenchyma that underwent proton therapy using active breath control.

Material and Methods

3 CT imaging studies in treatment position were acquired in deep inspiration breath-hold (DIBH) with Active Breathing Coordinator ABC system (Elekta Instrument AB, Stockholm). The treatment plan was done on the Raystation Treatment Planning System (RaySearch Laboratories AB,Sweden). The physician contoured the target volumes in all studies. Based on that ITV, PTV was generated, and all principal organs at risk were contoured for CTs. A pencil beam scanning proton therapy plan was defined with two fields (see figure). Both fields were optimized with Single Field Optimization (SFO) technique and range robust optimized with the TPS tools. The prescribed dose was 1.8 GyRBE for 20 fractions (total dose 36GyRBE).

The patient alignment was performed with Align-RT (Vision RT Ltd., UK) and orthogonal kilovolt X-rays before each treatment fraction. The beam delivery was performed synchronizing

the DIBH of the patient with the machine using the ABC system together with an optical tracking system (Gate-RT, Vision-RT Ltd., UK) as safety control during the treatment.

To evaluate the radioprotection and local control of the patient, two comparative plans with electrons and high conformal partial breast photons were created (see Fig.1). The Excess Absolute Risk (EAR) of radiation-induced solid cancer were calculated for all plans.

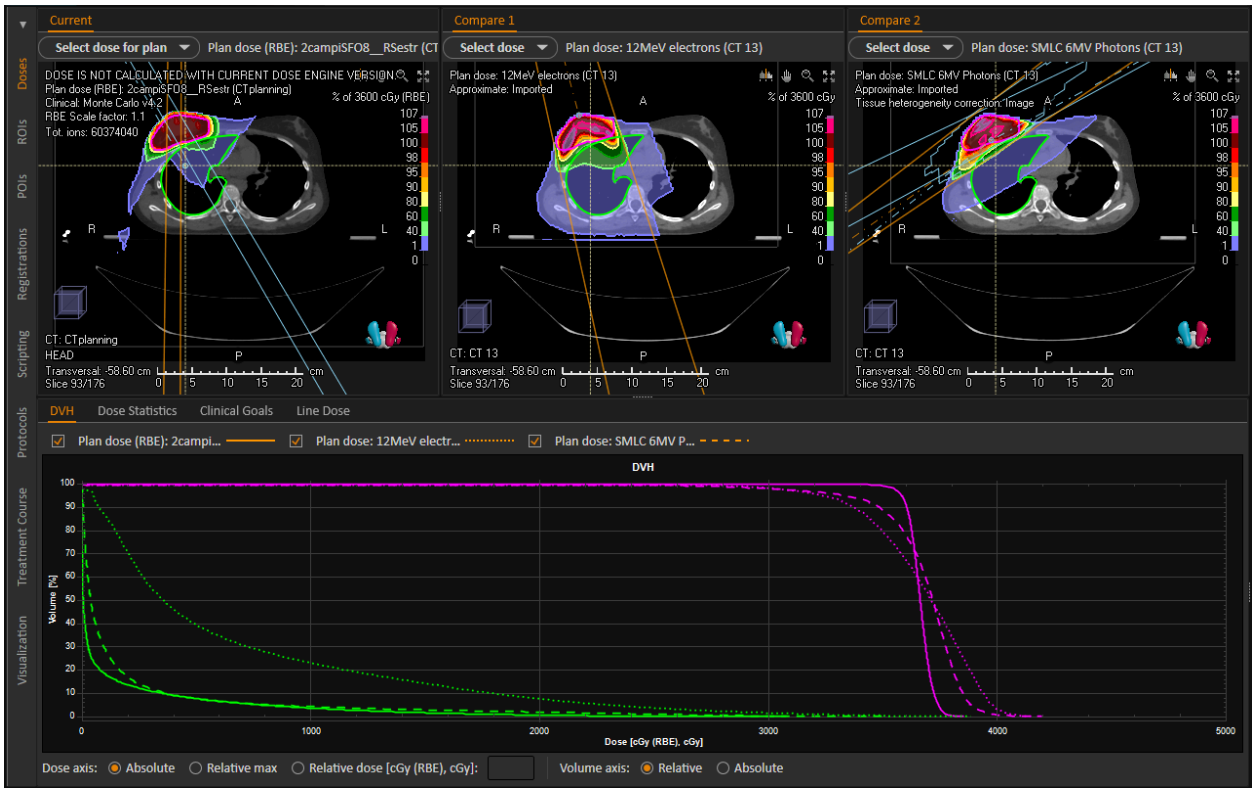

Figure 1: plan comparison among proton plan, 12MeV electron and 6MV photon plan.

	Excess Absolute Risk	
	Right breast	Right lung
Protons	6.0	***34.0***
Electrons	5.4	176.6
Photons	5.7	48.0

Table 2: Excess Absolute Risk (EAR) for right breast and right lung. Lower number means lower risk.

This treatment technique in an atypical localization due to a LAL recurrence proved to be feasible and safe in a collaborative pediatric patient. A comparison shows the superiority of the proton plan over the photon and electron plan.

Risk estimation of different fractionation scheme

Using the Dasu model the total risk of different fractionation schemes were calculated for the Bladder OAR in a radiation therapy of the prostate.

The three regimes compared are

Low fraction dose regime of 39 fractions at 2Gy for a total dose D of 78Gy.

Moderate hypofractionation regime of 20 fractions at 3Gy for a total dose of 60 Gy.

Ultra-high hypofractionation regime of 7 fractions at 6.1Gy for a total dose of 42.7 Gy.

As input values for the different $\alpha 1$,$\alpha 2$ and $\beta 1$, $\beta 2$ the data from the original publication of Dasu05 were used.

The results of the calculation are tabbed in table 3

	Fractionation regimen	Ratio of Total risk bladder Relative to low fractionation regimen
Low dose fractionation	38 fractions x 2Gy=78Gy	1
Moderate hypofractionation	20 fractions x 3Gy = 60 Gy	39
Ultra-high hypofractionation	7 fractions x 6.1Gy =42.7Gy	187

Table 3: comparison of risk for different irradiation schemes

The surprising result of this elementary calculation, the Dasu model, finds that risk of secondary cancer in the bladder is orders of magnitude higher in hypofractionation treatments of the prostate. Only small portions of OARs are irradiated with this dose and, as we see form the formula of the Dasu model, the total effect is obtained integrating over the hole volume of the ROI Bladder.

To simulate a realistic case, we developed a plan for an irradiation prostate and lymph nodes as shown in figure 2. The plan was done with VMAT photon technique following the prescription described by [15] and the proton arc technique implemented in Trento [16].

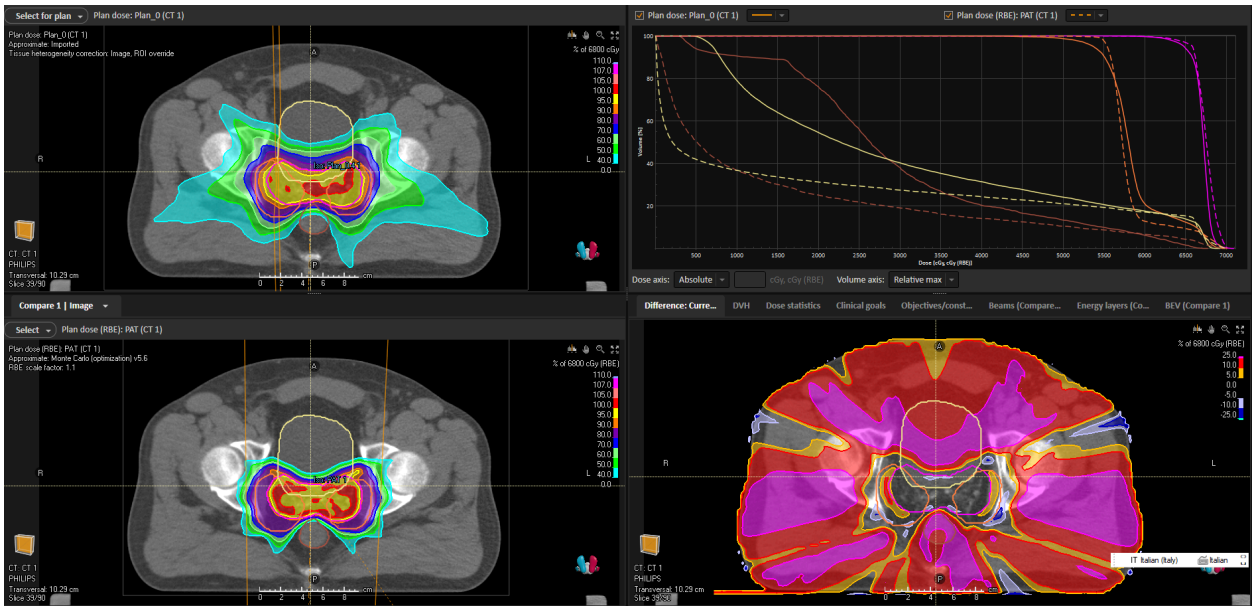

Figure 1: plan comparison among photon arc and proton arc plan on a prostate cancer patient with lymph node involvement.

Accordingly, with this plan we exported the DVH of the bladder and calculated the total risk for the photon and proton plan with a prescription dose of 34 fractions for a total of 56 Gy to lymph nodes and 68 Gy to the prostate bed. To simulate the case undergoing an hypofractionated regime, we rescaled the same DVH to a dose with 5 fractions for a total of 25 Gy to lymph nodes and 30.36 Gy to prostate bed.

	photon	proton
Low dose fractionation	1.95‰	2.5‰
Ultra-high hypofractionation	3.93‰	2.12‰

Table 5: Calculation of the total risk of secondary cancer of the bladder with Dasu Model in case of low dose fractionation and Ultra high hypofractionation.

The results are unexpected considering the clinical approaches. The photon with normal fractionation has the lowest risk on the bladder. The ultra-high fractionation with photons has the highest risk, around 2 times the previous case. Proton plans are not better than the normal fractionation photon plan, but surely better than the ultra-high fractionation, even here the difference is a factor of 2.

The explanation of this is related to the combination of fraction dose and differential dose volume histogram

Limitations (model dependence)

Model-based estimates depend on parameter choices (e.g., αorg\alpha_{\mathrm{org}}αorg, RBE, LET) and baseline incidence. Our analyses are derived from **single-patient** DVHs; cohort-level conclusions require dedicated datasets. Future work will (i) incorporate **pediatric-specific** risk coefficients where available, (ii) extend to **cohort studies** with uncertainty quantification, and (iii) explore **range- and LET-aware** planning strategies to mitigate secondary-cancer risk.. In this work Both frameworks are **parameter-dependent** and rely on literature values that may vary across populations and endpoints. Uncertainties related to **RBE/LET** and **neutron dose** are not fully captured. Our dose inputs are **single-patient DVHs**, which preclude cohort-level inference. Therefore, results should be interpreted as **model-based estimates** rather than direct clinical risks.

Organ	Model	Parameters	Reference/ Note
Bladder	**Dasu**	α1,α2,β1,β2	**ICRP 60 (1990)**
Bladder	**Schneider**	I0,org, αorg [low,high]	**Schneider 2005, Organ specific ref.**
Lung	**Dasu**	α1,α2,β1,β2	**ICRP 60 (1990)**
Lung	**Schneider**	I0,org, αorg [low,high]	**Schneider 2005, Organ specific ref.**

Table 5. Parameters used in risk estimation (draft). For each organ, we list: (A) Dasu coefficients α1,α2,β1,β2 (ICRP60,1990),(B) Schneider parameters I0,αorg with literature source and range used in sensitivity, (C) Endpoint (Total/Fatal/EAR).

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5. Discussion and Conclusions

In recent years, radiotherapy has undergone profound changes as regards the technological aspects for the release of the therapeutic dose (such as photon beams with Flattened Filter Free beam and Proton therapy), imaging systems for patient centering and alignment, for the management of tumor movement and the adaptation of treatment along the course of therapy. The treatment adaptation pones several challenges in radiotherapy particularly in proton therapy due the uncertainties in deformation matrixes of calculated absorbed doses per fraction, OAR deformation and several radiobiological issues of treatment effect at the voxel level per each fraction.

Last but not least, particular attention is being paid to using artificial intelligence and radiomics techniques for the planning, quality assurance, and personalization of the treatment itself. In this context, I worked on combining the existing technologies with the implementation of radiobiological models acquired to further improve the quality of life (in terms of efficacy and efficiency) of the patient's undergoing radiotherapy. The quality of the optimized treatments was evaluated in terms of disease control and toxicity. Overall, patient radiation protection was measured in terms of reducing radio-induced secondary effects.

The first activity of my Ph.D. has been a review of the literature of the last years regarding the technological development and innovation of proton therapy to identify trends and open issues in the field.

Based on this analysis, I focused on the treatment of moving targets in proton therapy, which is the most technologically challenging approach, particularly for thoracic lesions and critical treatment sites (such as head and neck cancer).

Solved	Almost solved	Still open
● Dose calculation and verification ● Motion management ● Clinical outcome	● Image-based technologies ● Dose robustness ● Planning evaluation tools ● Rescanning	● Radiobiology ● Economics, patient selection

Table 1: Summary of the literature overview on the state of the art and identified open questions in proton therapy for challenges sites.

During our period abroad at the PSI in Switzerland, we focused on online Adaptive Proton Therapy (oAPT), which is related to the "Almost solved" row in the table. During the last period of study, we dedicated our efforts to the last row, "Still open," of the table. I worked on radiobiological models related to new treatment comparisons and strategies for radiotherapy using protons and photons, with a particular focus on different fractionation schemes.

Discussions and Conclusions

Online Adaptive Proton Therapy oAPT

Chapter 3 summarizes the outcome of my work at PSI, collaborating on the implementation of recent techniques using oAPT. Patients treated with this modality typically have treatment sites in the head and neck cancer. In collaboration with the proton therapy center in Trento, I implemented and tested the oAPT leveraging our dataset of patients with lung and liver tumors treated with proton therapy using pre-treatment CT-on-rail imaging devices and respiratory gating over the past few years.

The discussion of the results of my analysis can be summarized in the following points:

1. Firstly, the work demonstrates a good correlation between the planned and the adapted dose distributions for each treatment fraction, indicating that the treatment technique with respiratory gating effectively matches the original plan in most cases.
2. In cases with larger differences from the planned cases, adaptive online therapy can address the problem. However, given many fractions, the final results, even without online adaptation but with adaptation triggered by the clinical decision, are good throughout the entire treatment course. Of course online adaptation is useful, supposing it in a streamlined workflow within a reasonable timeframe, as there may be situations related to incorrect positioning of the patient or external changes in the patient's anatomy where triggered adaptation could be ineffective.
3. In the case of treatments with few fractions, such as ultra-hypofractionated prostate treatments, the online adaptive mode seems necessary, because the "wash-out" effect of fractionation is no longer present.

In conclusion, during my period abroad at the PSI in Switzerland, I focused on identifying new solutions for oAPT and I implemented and tested this approach for thoracic and liver tumors. Thus, the feasibility and technical efficacy of this strategy lead to the conclusion that the oAPT is an "almost solved" issue, also in thoracic and liver tumors based on my results (under publications).

<u>Radiobiological models for secondary cancers in radiotherapy: single and hybrid treatments of protons and photons</u>

Patients receiving radiotherapy for prostate cancer are at risk of developing secondary malignancies such as gastrointestinal cancer, bladder cancer, and rare secondary sarcomas. Such risks underscore the importance of follow-up over a prolonged period.

Radiation exposure to the bladder during prostate treatments correlates with an increased incidence of bladder cancer, especially at higher doses. Studies estimate that the risk can rise significantly following treatment, with patients facing this risk as they reach longer follow-up periods after the initial therapy [1,2,3] emphasized that late complications following radiotherapy often manifest years after treatment, which further substantiates the connection between radiotherapy and subsequent bladder malignancies.

During the last period of Ph.D., I dedicated my efforts to "still open" questions of table 1.

Hybrid proton-photon treatment is a new and evolving treatment option in radiotherapy. It combines the advantages of proton and photon therapy, aiming to achieve maximum tumor control with minimal side effects. Recent studies have yielded several significant findings on the biological and clinical aspects of hybrid treatments.

One of the central advantages of hybrid proton-photon therapy is its potential to improve treatment planning quality. Studies demonstrate that hybrid therapy can enhance target coverage and spare OAR more effectively than traditional photon or proton-only therapies. For instance, Li et al. discuss how hybrid methods can optimize both the number of fractions delivered by protons and photons, leading to better overall plan quality and robustness against uncertainties in treatment delivery [4,5]. Gao also emphasizes that a well-designed hybrid inverse optimization can yield superior tumor coverage while minimizing OAR exposure, suggesting a clear clinical benefit of combining the two modalities [6].

The accessibility of proton therapy is often limited due to resource constraints; therefore, hybrid proton-photon therapy offers a practical solution. Torelli et al. present a novel approach that utilizes most treatment fractions with photon beams while reserving proton fractions for high-dose applications, thereby expanding the availability of proton therapy for patients with

metastatic cancer [7]. Similarly, Amstutz et al. provide evidence that optimizing the combination of photon and proton therapies can address the challenges faced by patients with advanced non-small cell lung cancer (NSCLC) [8]. This demonstrates the potential of combined modalities to increase the population that can benefit from scarce proton therapy resources.

Hybrid treatment also addresses challenges related to fractionation. Several authors explore fractionation strategies that leverage both proton and photon modalities to maximize therapeutic ratios [9]. For instance, research indicates that combining fractionation techniques with hybrid planning can improve the overall biologically effective dose (BED) to the tumor while reducing damage to normal tissues [10].

I applied and calibrated existing radiobiological models (Dasu, Schneider) to clinical scenarios and planning comparisons, specifying assumptions and parameter sources. The results of my study, using the radiobiological model of Dasu, on different fractionation schemes are surprising:

1. The photon with normal fractionation has the lowest risk of secondary bladder cancer.
2. The ultra-high fractionation with photons poses the highest risk, approximately twice that of the first case.
3. Proton plans are not superior to the standard fractionation photon plans in terms of secondary cancer risk of bladder; however, they are certainly better in ultra-high fractionations setting compared to photons. Even in this case, the difference is a factor of 2.

The explanation of this is related to the combination of fraction dose and differential dose volume histogram. The study has several limits.

First of all, the secondary tumor model checked is only one (i.e., bladder cancer). Only a prostate case study was studied with proton arc and VMAT irradiation techniques. Therefore, this intriguing result must be carefully verified in a prospective observational study. However, it

remains a warning flag for high fractionation schemes and opens the door to various research paths in radiobiology and treatment planning optimization of combined strategy. The results are under publication.

Limitations and Future Directions

I applied and calibrated existing radiobiological models (Dasu, Schneider) to clinical scenarios and planning comparisons, specifying assumptions and parameter sources, with sensitivity analyses where appropriate. Model-based estimates of secondary cancer risk are inherently dependent on parameter values (e.g., αorg, RBE, LET) and baseline incidence rates. The present work is restricted to single-patient DVHs, which prevents statistical generalization to larger cohorts. Absolute risk values should therefore be interpreted with caution.

Future research will focus on:

(i) inclusion of **pediatric-specific risk coefficients**,

(ii) **cohort-level analyses** with uncertainty quantification, and

(iii) integration of **range- and LET-aware planning strategies** and **FLASH irradiation** into comparative studies

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My Ph.D. work identified the key aspects that require further steps of knowledge in the proton and photon radiotherapy field focusing on technical challenges and radiobiological approaches. It is not always that proton therapy is better when we consider all possible issues related to radiation therapy. During my work, I investigated a new type of treatment strategies applicable to both photon and proton external beams and their combination, thus opening new possibilities to develop future research.

In conclusion, based on the investigations during my Ph.D., hybrid proton-photon therapy is emerging as a promising new strategy in cancer treatment, combining the advantages of both modalities to maximize therapeutic gain. However, secondary cancer risk is potentially limiting the benefit of hybrid approaches. My Ph.D. identified possible approaches to adopt hybrid solutions while reducing secondary cancer risk for treated patients, based on combined absorbed doses using an appropriate metric for plan optimization.

Future research will undoubtedly play a crucial role in enhancing our understanding and exploring the full potential of the optimal hybrid modalities, using the tools and methods developed during my Ph.D.

References Chapter 5

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