BABEȘ-BOLYAI UNIVERSITY

Faculty of Physics

Doctoral School of Physics

Ph.D THESIS

SUMMARY

Creation of a Novel Glycerin Bolus for Optimized Surface Dose in Skin and Breast Radiotherapy

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Cluj-Napoca

2025

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Introduction

Radiotherapy remains a cornerstone in the multimodal management of breast cancer, offering curative and palliative potential, particularly in the postoperative setting and for patients presenting with locally advanced disease. The advent of modern techniques and a deepened understanding of radiobiology and dosimetry have enabled personalized and more effective treatment strategies, yet unique technical challenges persist—particularly when malignancies exhibit significant involvement of superficial tissues.

A clinically significant subset of breast cancers, namely those classified as T3 and T4 according to the TNM system, are defined by their large size (>5 cm) and/or direct extension into contiguous skin and chest wall structures, respectively. Tumor invasion of the dermal and subdermal planes increases the risk of local recurrence and portends a worse prognosis, underscoring the imperative for meticulous local control. In these complex scenarios, a critical goal of therapeutic planning is the assurance of adequate and homogeneous radiation dose deposition to the most superficial layers, where the tumor may abut or even ulcerate the skin. Achieving this requires consideration of the distinct physical interactions between high-energy photon and electron beams and biological tissues, as well as the clinical deployment of adjunct materials to modulate dose build-up[1].

The impetus for the research presented in this thesis arose directly from clinical experience with a patient suffering from advanced-stage, skin-invasive breast cancer. During the radiotherapy planning phase for this individual, it became clear that delivering the prescribed dose to the skin and superficial subcutaneous tissue was essential not merely for palliation, but as a fundamental component of curative therapy. However, this task was hindered by the technical inadequacies inherent to conventional bolus materials — specifically, limitations in conformality, reproducibility, patient comfort, and radiological properties. Such challenges highlighted the need for a bolus material that could be easily adapted to the patient's anatomy, provide predictable radiological equivalence, and improve overall treatment robustness.

Consequently, this doctoral thesis was conceived to address these significant gaps, together with the lack of standard operation procedures as well as national and international guidelines for the use of bolus materials. The principal aim has been the development, characterization, and clinical evaluation of a novel, patient-adaptive bolus composed of biocompatible and FDA-approved materials. Throughout the project, interdisciplinary approaches were employed, spanning materials science, dosimetry, and clinical practice, to produce a solution more closely tailored to the demands of contemporary breast cancer care. A secondary objective of this thesis was to emphasize the critical need for the establishment of standardized protocols and evidence-based guidelines regarding bolus positioning in radiation therapy. Such standards would facilitate reproducibility, enhance dose accuracy, and contribute to the overall quality and safety of clinical practice.

The structure of this thesis is organized as follows to comprehensively address both the theoretical and applied aspects of the research problem:

Chapter 1 provides a foundational overview of radiotherapy as a medical discipline. The interaction mechanisms of photon and electron beams with matter are elucidated, emphasizing how these processes determine dose distributions in biological tissues. Key physical principles, such as photoelectric effect, Compton scattering, and pair production for photons, as well as scattering and energy deposition characteristics of electrons, are discussed in relation to their practical implications for clinical dose delivery. Additionally, the chapter explores the current landscape of clinical radiotherapy, including advances in treatment planning systems and beam customization, setting the stage for understanding the role and modification of surface dose.

Chapter 2 shifts focus on the clinical and pathological aspects relevant to the patient population motivating this research. The epidemiology and biological behavior of skin cancer and skin-invading breast cancer, particularly T3 and T4 lesions, are reviewed with attention to the challenges of achieving local control. Contemporary codes of clinical practice are summarized, with special reference to the use of bolus materials in ensuring adequate surface dose. Here, a critical appraisal of currently available bolus technologies is presented, encompassing an evaluation of their physical properties, dosimetric performance, and practical considerations such as daily positioning and patient comfort. This analysis is supported by evidence from my publication on daily bolus positioning, underscoring the need for innovation in this area.[2]

Chapter 3 outlines the radiotherapy workflow, spanning simulation, planning, delivery, and quality assurance, and serves as the technical heart of the thesis. This chapter introduces the application and challenges of synthetic computed tomography (sCT) for radiotherapy planning, referencing my published work on this emerging modality[1]. The chapter's central section details the systematic development and evaluation of the novel bolus material, including its composition, manufacturing process, and extensive characterization. The methods employed range from physical and dosimetric testing—such as PDD measurements and CT-based HU analysis—to clinical implementation with breast cancer patients. Furthermore, the workflow for integrating the novel bolus into conventional and advanced planning paradigms is described, providing insights into both the opportunities and the barriers encountered. The results and the need for standardization are supported by part of the guideline paper on the use of bolus.[4]

Chapter 4 synthesizes the experimental results, emphasizing the clinical and technological gains attributable to the novel bolus solution. The limitations of the present work are considered candidly, along with potential implications for broader clinical adoption. Concluding remarks highlight the contributions of this research to the field and articulate future avenues for study, including further optimization of material properties, large-scale clinical trials, and integration with patient-specific manufacturing techniques such as 3D printing.

The **Discussion chapter 5** delineates how these insights have directly informed the development of a comprehensive guideline. Ultimately, our findings provide actionable recommendations for clinical practice, contributing toward improved consistency and quality in radiotherapy protocols. The concluding chapter puts all the findings in the context of the current literature and provides a comprehensive discussion of the current achievements and challenges.

This thesis integrates fundamental physical science with practical clinical application, aiming to translate laboratory innovation into tangible improvements for patients treated with advanced breast cancer. It is anticipated that the standardization of the use of boluses and the development and validation of a novel bolus materials will not only enhance surface dose delivery and therapeutic outcomes for this challenging cohort but also inform future innovations in radiotherapy for a broad spectrum of malignancies requiring precise surface dose modulation.

I. Chapter Fundamental Principles and Mechanisms of Radiation and its Interactions with Matter: Ionizing and Non-Ionizing Effects

Radiation is a foundational concept in physics, denoting the process by which energy is emitted or transmitted through space or a material medium, either as waves or particles. This phenomenon broadly encompasses electromagnetic radiation—including, but not limited to, radio waves, microwaves, infrared radiation, visible light, ultraviolet radiation, X-rays, and gamma rays—as well as particulate forms of radiation, such as alpha particles, beta particles, and neutrons [1-7]

The study of radiation is pivotal due to its dual wave-particle nature, a cornerstone of quantum theory, which reveals that radiation exhibits both wave-like propagation and particle-like interactions with matter. [6]

In physics, radiation is classified broadly into ionizing and non-ionizing categories based on the energy carried by particles or waves. Ionizing radiation possesses sufficient energy to remove tightly bound electrons from atoms, thus creating ions, a process fundamental to many natural and technological phenomena [8-11].The stability of atomic nuclei and the nature of radioactive decay underpin much of the behavior of ionizing radiation, which emits particles and photons such as alpha particles, beta particles, X-rays, and gamma rays during nuclear transformations [12]

Understanding radiation physics is crucial not only for elucidating the fundamental interactions between radiation and matter but also for its extensive applications across various fields including medical imaging, radiation therapy, and environmental science [13]. This chapter aims to provide a comprehensive introduction to the physical principles governing radiation, its classification, interaction mechanisms with matter, and the implications of these interactions in both natural and applied contexts.

I.1 Ionizing Radiation

Ionizing radiation is defined as energy, transmitted either as electromagnetic waves or as subatomic particles, that possess sufficient energy per photon or particle to dislodge tightly bound electrons from atoms or molecules, thereby resulting in ionization. This process generates charged species (ions), which can disrupt molecular structures and induce a range of physicochemical changes. Of particular concern are the biological consequences of ionizing radiation, as the resultant molecular disruptions can lead to significant cellular damage, including the induction of DNA lesions and other genotoxic effects [1-9].

I.1.1 Types of Ionizing Radiation

Electromagnetic: X-rays and gamma rays are the primary forms of electromagnetic ionizing radiation. They occupy the high-frequency, short-wavelength end of the electromagnetic spectrum [1-4]

Understanding the distinction between these sources is crucial for radiation protection and public health initiatives.

I.1.2 Biological Effects of Ionizing Radiation

Ionizing radiation exerts its biological effects primarily by damaging molecular structures within cells, with DNA being especially susceptible to disease. This damage can manifest as single- or double-strand breaks, base modifications, and chromosomal aberrations. The consequences of such molecular disruptions are diverse and depend on the extent of the damage and the cell's ability to repair it.

I.2 Non-Ionizing Radiation

Non-ionizing radiation encompasses all forms of electromagnetic radiation that lack the energy per photon to ionize atoms or molecules. Instead, these radiations can only excite electrons to higher energy states without causing ionization [22-30].

I.2.1 Types of Non-Ionizing Radiation:

Non-ionizing radiation does not directly damage DNA or cause mutations, so the risk of cancer or genetic effects is much lower compared to ionizing radiation.[22-26]

I.3 Interaction of the radiation with the matter

I.3.1 Compton Scattering

Compton scattering is a fundamental interaction mechanism between high-energy photons (typically X-rays or gamma rays) and matter, specifically with electrons that are only loosely bound to atoms or essentially free. When a photon of sufficient energy collides with such an electron, it imparts a portion of its energy to the electron, causing the electron to be ejected from its atomic shell. The photon itself is deflected from its original trajectory, emerging with reduced energy in a new direction. This process is governed by the conservation of energy and momentum [31-38].

This mechanism is crucial in medical imaging and radiation therapy, as it affects the attenuation of X-rays and gamma rays in tissues and contributes to image contrast and dose distribution. The scattered photons, having lower energy and altered direction, can contribute to background noise in imaging systems and increase the dose outside the primary beam in radiotherapy [36-40].

I.3.2 Photoelectric Effect

The photoelectric effect is a photon-matter interaction in which an incident photon is completely absorbed by a bound atomic electron, typically from an inner shell (such as the K-shell). The entire energy of the photon is transferred to the electron, which is then ejected from the atom if the energy exceeds the electron's binding energy. The kinetic energy of the emitted photoelectron is given by:

$E_{photon} = hf = \frac{hc}{\lambda}$ [1]

where we have used the wave relation c = fλ, the constant h is called Planck's constant

The atom, now ionized, is left with a vacancy in its inner shell, which is rapidly filled by an electron from a higher energy level. This transition releases energy, often in the form of characteristic X-rays or Auger electrons, further contributing to the ionization process [1-3,43-50].

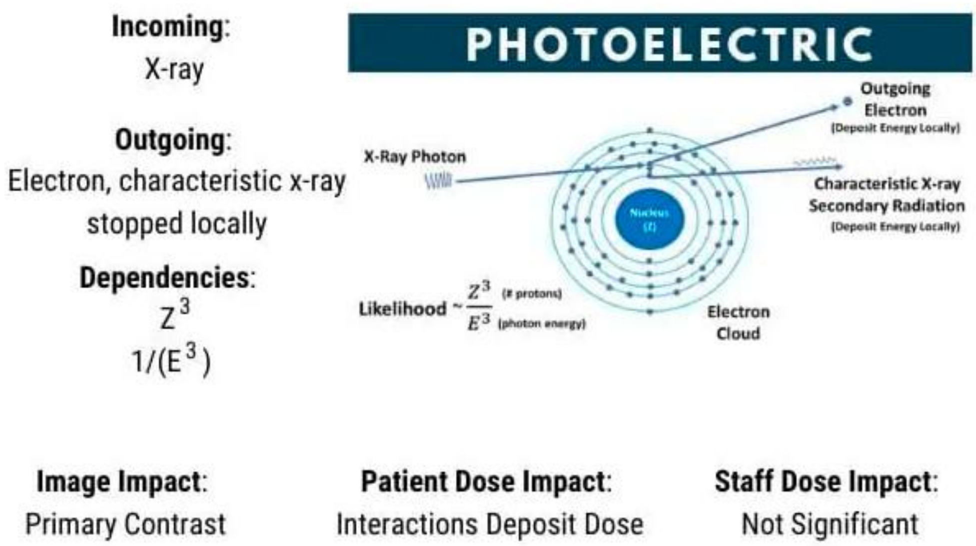


Figure I-1Illustration of Photoelectric effect, showing possible resulting interactions and effects[20]

1.3.3 Rayleigh (Coherent) Scattering

Rayleigh scattering, also known as coherent scattering, occurs when photons interact with bound electrons in atoms or molecules whose size is much smaller than the wavelength of the incident photon. In this process, the photon is scattered elastically: it changes direction but retains its original energy (wavelength) [51-67].

Rayleigh scattering is most significant for low-energy photons and in materials with low atomic numbers. In the context of X-rays and gamma rays, its contribution to overall attenuation is generally minor compared to the photoelectric effect and Compton scattering, but it can influence imaging quality by contributing to background scatter. [53-58]

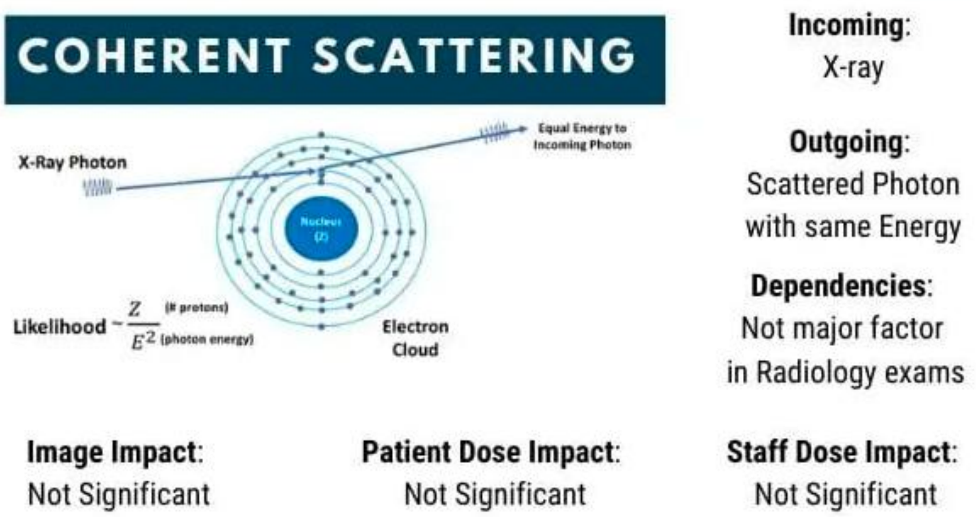


Figure I-2Illustration of coherent scattering, showing possible resulting interactions and effects [20]

I.3.4 Attenuation of Radiation in Matter

In practical applications, attenuation determines the effectiveness of shielding, the dose delivered in medical imaging and therapy, and the design of protective barriers in radiation environments. The exponential nature of attenuation means that even small increases in material thickness can lead to substantial reductions in transmitted intensity.

I.3.5 Treatment Planning system

The core of contemporary radiotherapy is the treatment planning system, which integrates imaging, beam modeling, and optimization algorithms to generate highly individualized plans.[1]

II. Chapter Radiotherapy Applications and Anatomical Considerations in Skin and Breast Cancer: Clinical Benefits and the Role of Bolus Materials

Cancer is a devastating disease that affects millions of individuals worldwide, causing significant morbidity and mortality. Among the various types of cancer, skin cancer has appeared as a growing public health concern, with its incidence steadily increasing over the past few decades. Skin cancer encompasses a range of malignant growths that originate from the cells within the skin, and it is broadly classified into three main types: basal cell carcinoma, squamous cell carcinoma, and melanoma.

In radiation therapy for skin cancer treatment, bolus materials play a critical role in ensuring the best delivery of radiation to the targeted tumor while minimizing exposure to healthy surrounding tissues. Bolus refers to a material, typically made of water-equivalent or tissue-equivalent substances, that is placed on the patient's skin or surface to increase the radiation dose at the surface and within the first few millimeters of the underlying tissues. The presence of bolus alters the depth-dose distribution of the radiation beam, allowing for a more uniform and targeted delivery of the radiation to the tumor. The composition, thickness, and placement of the bolus material can significantly affect the radiation dose distribution and the overall treatment outcome.[2]

II.1 Radiotherapy and its benefits

Radiotherapy, also known as radiation therapy, is a widely used modality in the treatment of various types of cancer. It employs high-energy radiation, such as X-rays, gamma rays, or charged particles, to target and destroy malignant cells while minimizing the impact on healthy surrounding tissues. Radiotherapy plays a crucial role in the comprehensive management of cancer, often used in combination with other treatment modalities, such as surgery, chemotherapy, and immunotherapy.

II.2 Skin anatomy

The skin, the largest organ of the human body, forms the protective interface between the organism and its external environment and is comprised of three principal layers: the epidermis, dermis, and hypodermis (subcutaneous tissue). This multilayered structure ensures a dynamic array of functions spanning protection, sensation, thermoregulation, immune defense, and metabolic activities such as vitamin D synthesis.

II.2.1 Skin Cancer and risk factors

Skin cancer is a prevalent and growing health concern worldwide, with its incidence steadily increasing over the past few decades. This malignant condition encompasses a range of cancers that originate from the various cell types within the skin, including basal cell carcinoma, squamous cell carcinoma, and melanoma. Understanding the characterization, causes, effects, and treatment of skin cancer is crucial for effective management and improved patient outcomes.

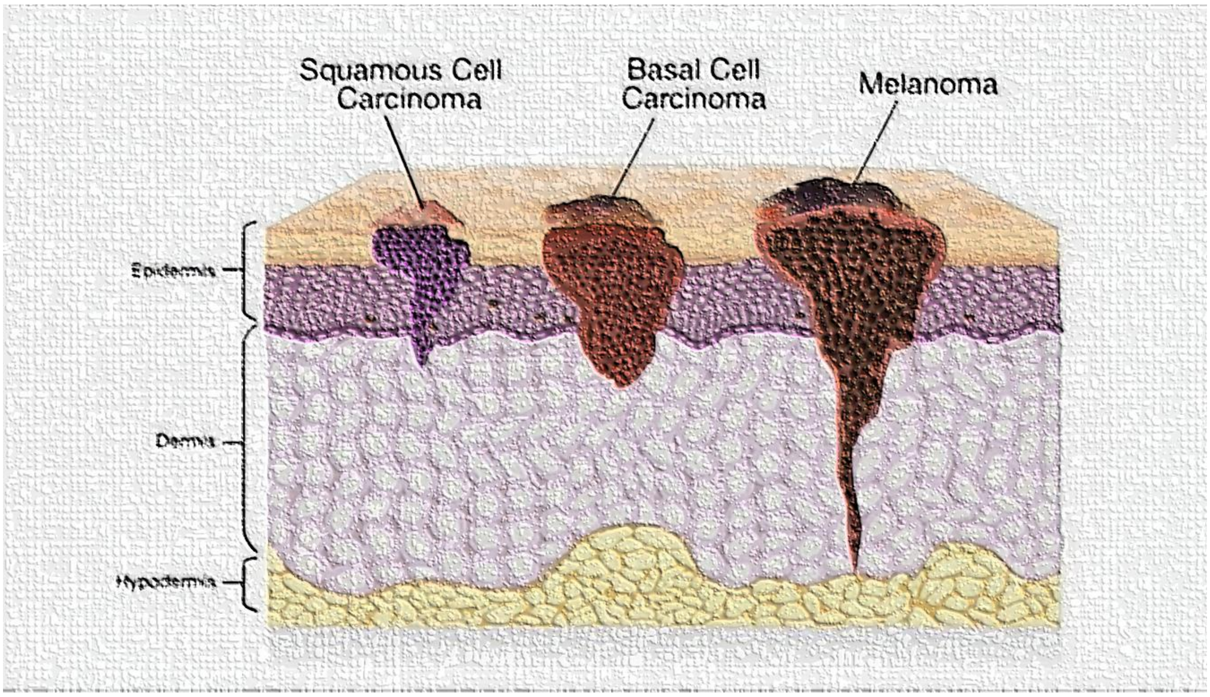


Figure II-1 Anatomical depiction of different skin cancer types and their invasion into distinct skin layers.

II.3 Breast anatomy

The human breast represents a bilaterally paired, morphologically dynamic organ situated on the anterior thoracic wall, whose primary physiological function is the production and secretion of milk in the postpartum period, as well as providing structural and aesthetic contributions to the body contour. Its intricate anatomy is designed to fulfill endocrine, exocrine, and supportive roles, each underpinned by coordinated microanatomical, vascular, lymphatic, and neural networks. The following overview presents a comprehensive academic analysis grounded in contemporary anatomical and histological research.

II.3.1 Breast Cancer

Skin-invading breast cancer represents an especially challenging entity within the spectrum of breast malignancy, with T3 and T4 lesions characterized by their substantial size and/or demonstrable extension into the dermal and subdermal tissues. T3 tumors are defined as those larger than 5cm, while T4 tumors are classified by direct invasion of the skin and/or chest wall, regardless of primary tumor size. According to contemporary cancer registries, cutaneous involvement occurs in approximately 1–10% of metastatic breast cancer cases, with breast cancer accounting for roughly 30% of all cutaneous metastases. [102-105]

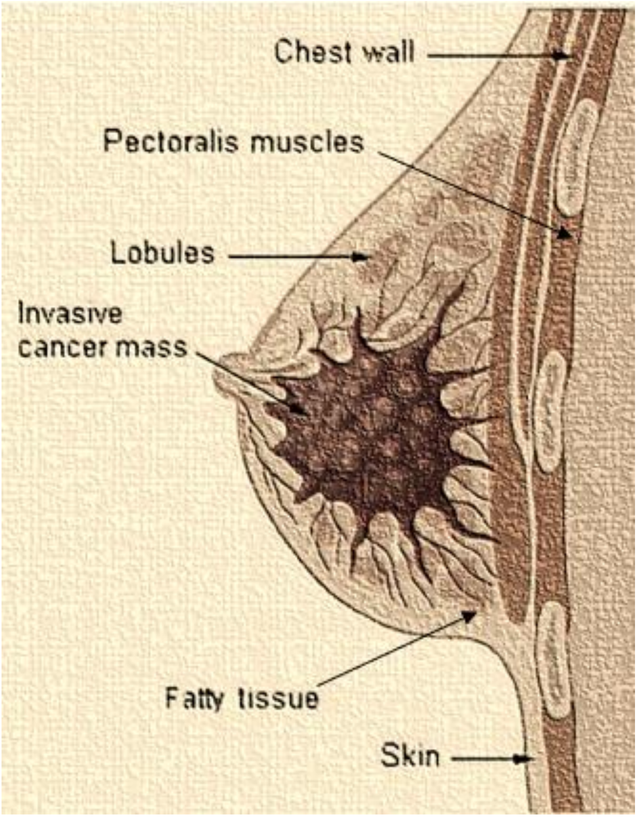


Figure II-2Depiction of breast cancer progression involving cutaneous tissue infiltration.

Current guidelines for the management of T3 and T4 breast cancer emphasize a multidisciplinary approach, combining surgery, systemic therapy, and radiotherapy.

Radiotherapy is a mainstay for ensuring local control, particularly in the postmastectomy setting and when cutaneous margins are involved. However, photon beams exhibit a 'skin-sparing' effect due to their depth-dose characteristics; without modification, this leads to suboptimal dosing of the most superficial tissues, precisely where residual tumor risk is highest in T4 disease.

For this reason, clinical practice guidelines—and recent peer-reviewed studies—endorse the use of bolus materials on the skin for breast cancer patients with dermal involvement [102-107]

II.4 The Role of Bolus Materials

Bolus materials, which simulate tissue equivalence and are placed directly on the patient's skin during radiation therapy, serve to eliminate the surface-sparing effect of megavoltage photons, increasing the dose delivered to the skin and subcutaneous tissues. This is particularly vital for T4 tumors or cases with ulcerative or infiltrative skin involvement. Various bolus materials are in clinical use—ranging from standardized commercial products (such as Superflab or thermoplastics) to customized 3D-printed devices for improved fit and reproducibility [110-115]

The materials used as bolus are generally soft, pliable, and water-equivalent—properties that facilitate both patient comfort and physical dose conformity. By positioning the bolus in direct contact with the skin, the surface dose is increased via scattering and the promotion of dose build-up. As a direct consequence, the maximum radiation dose, or D_{max}, is translocated toward the skin surface, enabling therapeutic dose levels to be delivered more superficially compared to treatments where no bolus is used. In the absence of a bolus, the highest dose deposition for megavoltage photon beams typically occurs at a depth of several millimetres to centimetres below the skin—a phenomenon termed the 'skin-sparing effect'.

Optimization of bolus thickness is a key consideration in clinical practice and is determined by several factors, including the type of radiation beam, its energy, and the desired depth of dose build-up. The determination of optimal bolus thickness is made during the radiotherapy planning process, commonly within the Treatment Planning System (TPS), and is performed by the medical physicist in consultation with the radiation oncologist. Where an elevated surface dose is clinically required, a bolus of 1 cm thickness is frequently selected; however, when the intent is to balance surface dose enhancement with the mitigation of potential toxicities such as radiodermatitis, a thinner bolus (e.g., 0.5 cm) may be preferable.

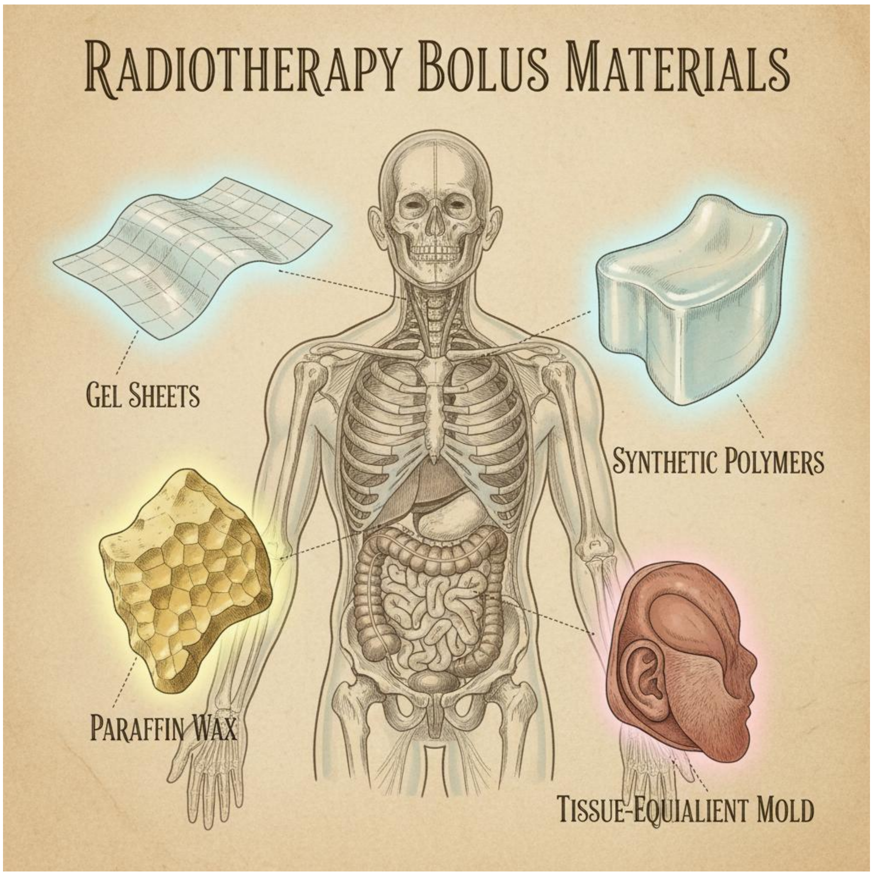


Figure II-3 Visual representation of commonly used bolus materials in radiation therapy.

The scientific literature underscores the clinical relevance of several types of bolus materials, from standard silicone-based commercial products to moldable thermoplastic compounds and highly sophisticated, patient-specific 3D-printed boluses. Notably, in low-resource settings, commercially available bolus sheets remain most accessible, though their efficacy is maximized only on flat or gently contoured surfaces. For irregular or highly contoured anatomical sites, more adaptable or moldable bolus materials are required to minimize the formation of air gaps, which can significantly undermine dose delivery quality. Therefore, rigorous characterization of any bolus material is essential, particularly in relation to its radiological response and physical integrity[128-129].

The primary objective of the present study is to develop and characterize a cost-effective, home-fabricated bolus material composed of glycerin and adhesive agents. This novel bolus is designed to be reusable, user-friendly, and economically viable, with properties tailored to ensure clinical acceptability and reproducibility in superficial radiotherapy applications.

Table II.1Properties of Selected Clinical Bolus Materials

Bolus Material	**Composition**	**Properties**	**Safety**	**Transparency**
Superflab – Gel	**Water-based gel with acrylic polymer**	**Flexible gel, uniform thickness, ρ = 1.02 g/cm³**	**FDA-approved**	**Semi-transparent**
Aquaplast Thermoplastic pellets	**Hydrophilic organic polymer**	**Powder mixed with water, ρ = 1.02 g/cm³**	**FDA-approved**	**Transparent (moldable form); opaque after hardening**
Waxes	**Hydrocarbon wax**	**Inflexible; economical natural wax**	**FDA-approved**	**Opaque**

Together with my colleagues we accentuate the critical role that consistent and accurate placement of bolus material plays throughout the course of daily radiotherapy (RT) fraction.[2A] The research provides clear evidence that variability in bolus positioning can lead to significant discrepancies between the planned dose distribution calculated during treatment planning and the actual dose ultimately delivered to the anatomical target. Such differences have important clinical implications, as unintended variations in surface and target dose could compromise the overall efficacy of radiotherapy and potentially impact patient outcomes.

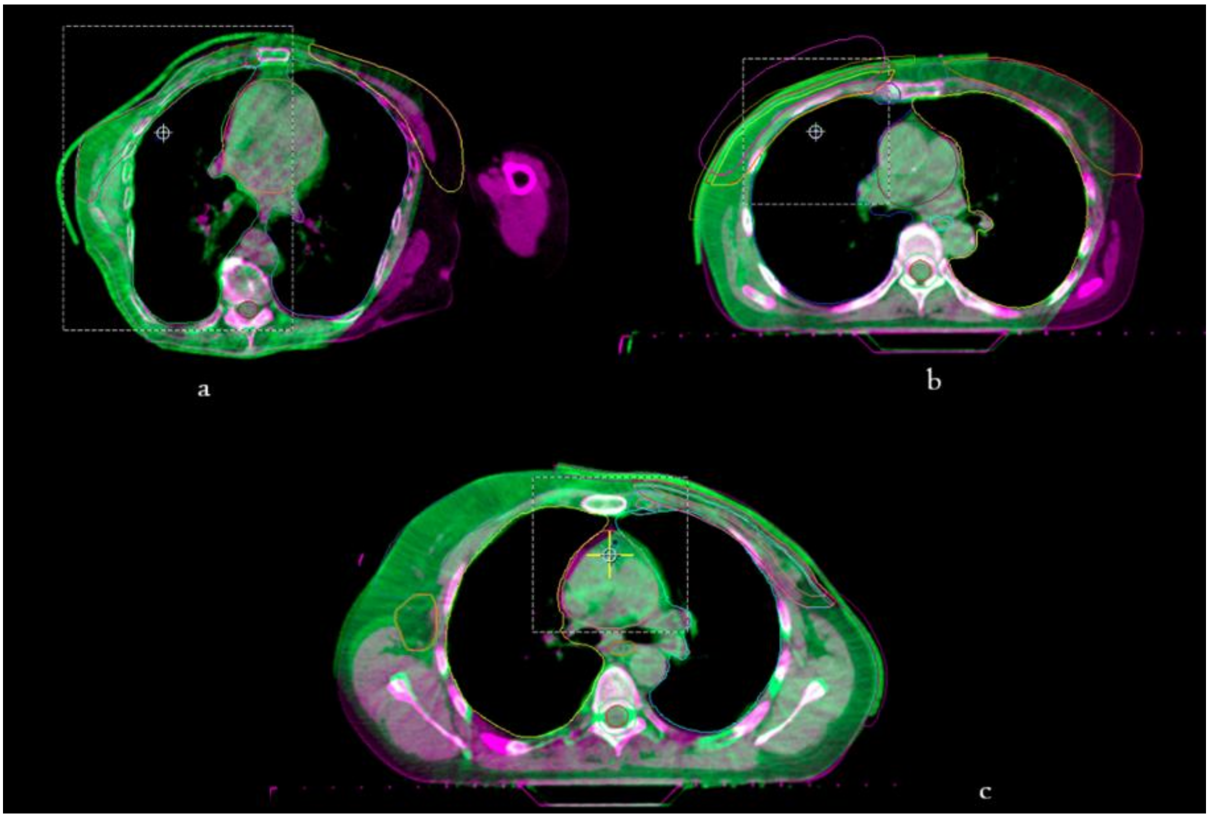


Figure II-4 Fused CBCT and CT clinical images demonstrating the significance of maintaining a regular contour and planar surface in the patient's exposed region.
(a) *The patient's chest wall with a non-planar surface results in the formation of air-gaps;*
(b, c) *A planar surface allows for optimal adherence of the bolus material to the skin, minimizing air gaps and ensuring effective dose delivery.*

These results underscore the necessity for meticulous verification and adjustment of bolus placement with each treatment fraction. Routine assessment protocols should be implemented to detect and correct any deviations in bolus positioning, thereby assuring that the intended dose distribution is faithfully reproduced across all sessions. Ensuring accurate contact between the bolus material and the patient's skin surface is particularly essential in treating superficial or irregularly contoured lesions, where air gaps or misalignments are more likely to occur, increasing the risk of underdosing critical areas.

The findings suggest that enhanced attention to bolus management could substantially improve both treatment quality and patient safety in daily clinical practice. Moreover, this study highlights the importance of developing advanced technologies or workflow strategies aimed at standardizing bolus applications. Such innovations may include imaging-based verification, patient-specific molds, or automated positioning solutions that further reduce inter-fraction variability.

In conclusion, maintaining optimal bolus placement during each radiotherapy fraction is fundamental for achieving the planned therapeutic objectives. Ongoing research and technological improvements are recommended to support healthcare professionals in this endeavor, ultimately maximizing the clinical benefits of bolus use in external beam radiotherapy and contributing to improved patient care and local disease control.[2A]

III. Chapter Innovations in Bolus Materials and Dosimetric Practices for MRI-Based Radiotherapy: Guidelines, Limitations, and Novel Developments

The clinical workflow for radiotherapy treatment is underpinned by a series of well-defined, interdependent stages designed to ensure the highest standards of accuracy, safety, and therapeutic efficacy (Figure III-.1.).

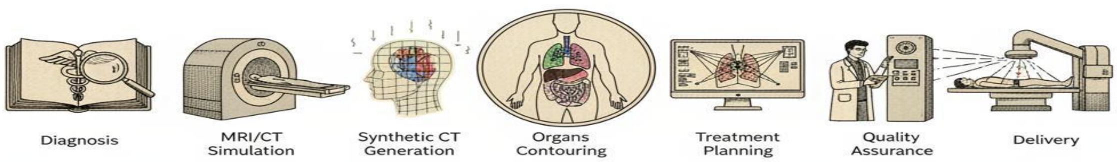


Figure III-1Workflow schematic illustrating the radiotherapy process for cancer diagnosis and treatment.

Implementing sCT generation within a radiotherapy workflow, especially when based on MRI, offers several advantages. MRI provides superior soft-tissue contrast compared to CT, enabling more accurate tumor and OAR delineation, which is crucial in anatomical regions with poor CT definition (e.g., brain, prostate, and head and neck). The use of sCT bridges the gap by providing the necessary electron density map for accurate dose calculation without exposing patients to additional ionizing radiation from a second CT scan. This approach streamlines the workflow, improves target delineation accuracy, and enhances patient comfort, ultimately contributing to more precise treatment delivery and better clinical outcomes. Synthetic computed tomography (sCT) images derived from magnetic resonance imaging (MRI) have emerged as a viable alternative to conventional CT scans for radiotherapy treatment planning. This approach enables the elimination of registration errors inherent to multi-modality imaging, thereby enhancing spatial accuracy in target delineation. Moreover, the exclusive use of MRI for anatomical visualization and dose calculation reduces the costs and ionizing radiation exposure to patients resulting from additional CT scans. Currently, CE- and FDA-approved sCT solutions are clinically available for specific anatomical regions, including the pelvis, brain, and head and neck. Meanwhile, the development and validation of more sophisticated deep learning (DL) methodologies to generate sCT for other anatomical sites are actively underway in ongoing research. [89-100]

III.1 Advantages of sCT in MRI-Only Radiotherapy

Synthetic computed tomography (sCT), particularly those generated via artificial intelligence for MRI-only radiotherapy, offers several distinct advantages that address key clinical and operational limitations of conventional CT-based workflows.

By removing the requirement for both MRI and CT, sCT simplifies logistics, reduces patient appointments, and may decrease overall costs by avoiding duplicate scanning and associated resources. Additionally, it supports faster patient throughput and less waiting time.

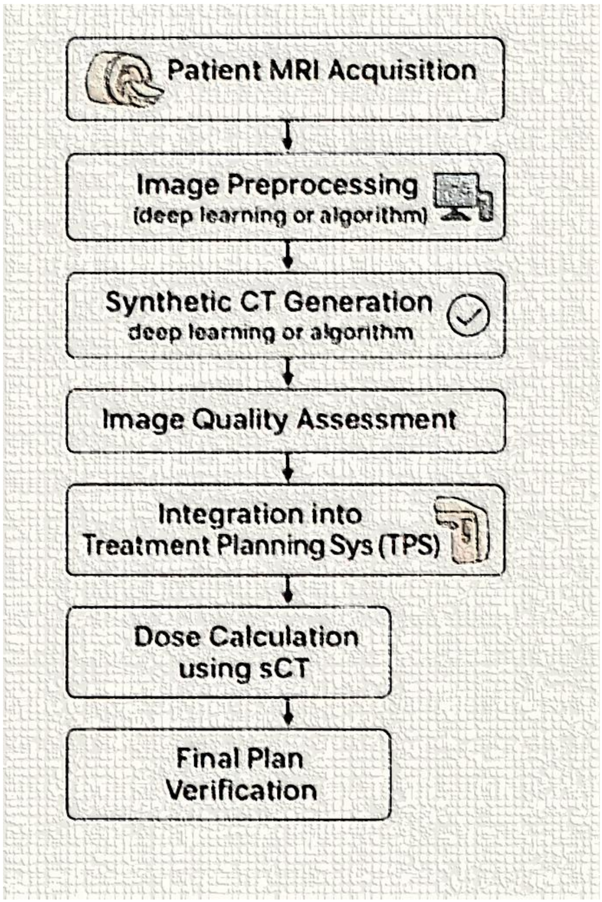


Figure III-2 Diagrammatic representation of the process for generating synthetic CT (sCT) from MRI.

III.2 Bolus guideline and Standard of practice

The application of bolus materials in postmastectomy radiotherapy (PMRT) represents a critical aspect of optimizing surface dose distribution and enhancing local tumor control. The clinical rationale for bolus usage has been extensively discussed in recent literature and highlighted by Kaidar-Person et al., whose collaborative Delphi study assembled a multidisciplinary cohort of international experts to systematically evaluate existing evidence and achieve consensus on the indications and protocols for bolus application in PMRT[44]. This landmark initiative underscored the heterogeneity of practice patterns across institutions, as well as the significant disparities concerning bolus thickness, schedule, and material selection. The absence of randomized prospective trials addressing these variables has, to date, precluded the development of definitive international guidelines, thereby contributing to variability in clinical outcomes and the potential for increased treatment-related toxicities.

III.3 The Build-Up Region and Surface Dose Challenge

In megavoltage photon beam radiotherapy, one of the inherent physical characteristics is the phenomenon known as the dose build-up effect. Unlike kilovoltage beams which deposit their energy near the surface, megavoltage photons (e.g., 6 MV or higher) have a relatively low surface dose, with maximal dose deposition occurring several millimeters beneath the skin surface, typically at a depth referred to as D_{max}. This behavior, while advantageous for sparing overlying healthy skin in deep-seated tumors, poses significant challenges when the target volume includes superficial or cutaneous tissues.

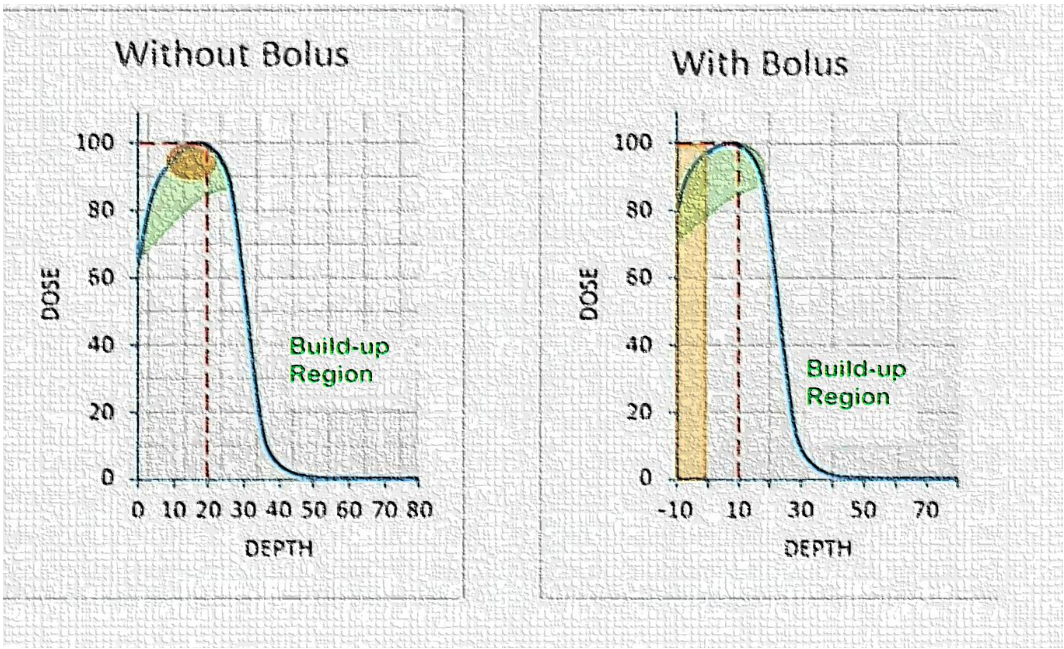


Figure III-3Illustration of the build-up region and the alteration of the maximum dose (Dmax) location after bolus application.

To address this limitation, a tissue-equivalent material known as a bolus is employed in clinical practice. A bolus effectively acts as a surrogate tissue layer, shifting the build-up region towards the skin surface. By placing it directly on the patient's skin, the radiation build-up occurs within the bolus, ensuring the maximum dose is delivered precisely at or near the dermal layers. This technique improves both the tumoricidal effect and the homogeneity of the dose distribution across the treatment area.

III.5 Conceptualization of a Novel Bolus Material

The development of this material was guided by a set of practical and clinical requirements:

- Tissue equivalency, ensuring appropriate radiation attenuation characteristics.
- Flexibility and moldability, allowing for accurate conformation to irregular body surfaces.
- Reusability or ease of fabrication, promoting efficient clinical implementation.
- Biocompatibility and non-toxicity, to allow direct contact with human skin.
- Economic feasibility, ensuring accessibility within a variety of clinical institutions.

III.5.1 Glycerin as a Key Component

Glycerin (or glycerol) is a hygroscopic, trihydroxy alcohol with extensive applications in the pharmaceutical industry due to its non-toxic, hydrating, and plasticizing properties. Density-wise, glycerin closely approximates that of soft biological tissue (~1.26 g/cm^3), making it an excellent candidate for tissue equivalency in bolus fabrication. Furthermore, glycerin maintains flexibility and viscosity over a wide range of temperatures, which is advantageous for shaping and patient comfort.

Polyvinyl acetate (PVA) is a synthetic polymer with strong adhesive and film-forming properties. In aqueous dispersion (e.g., white glue), it exhibits good elasticity while retaining form.

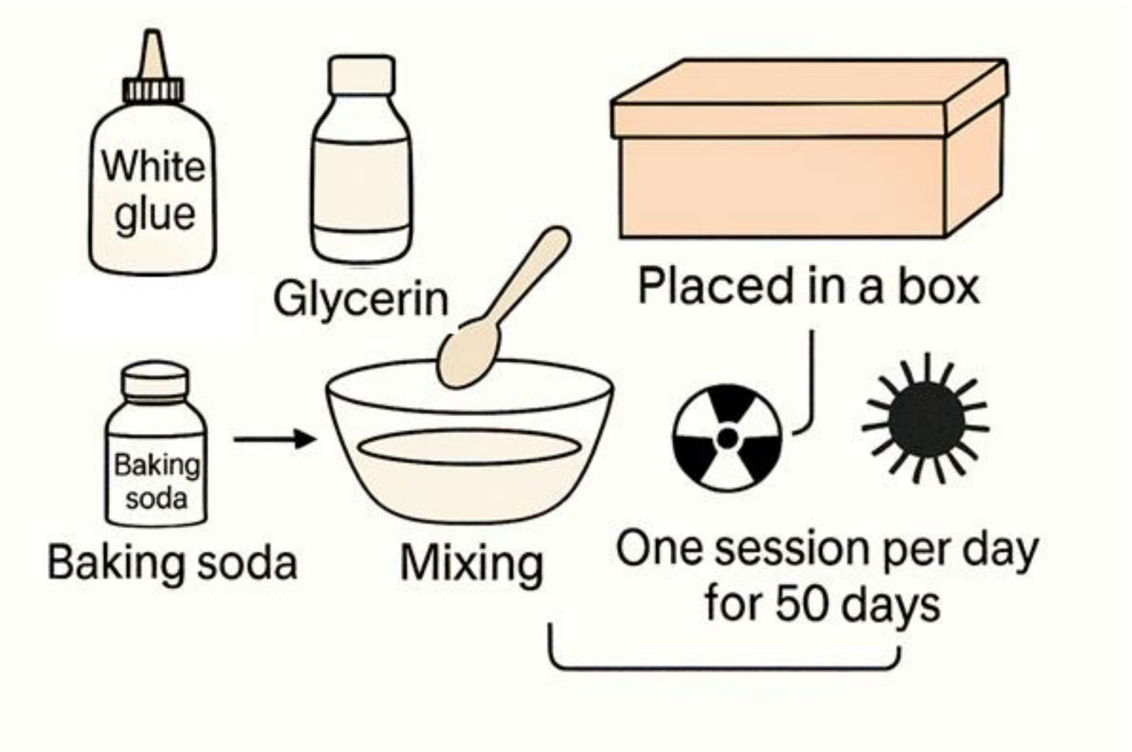


Figure III-4Schematic illustration of the preparation process for moldable bolus material and irradiation process.

III.6 Research Objectives and Scope

The central goal of this research is to develop, characterize, and evaluate a glycerin-PVA-based bolus material that overcomes the conformity and air gap issues observed in conventional bolus systems. The study is divided into the following key objectives:

- Material Development: To formulate and optimize a mixture of glycerin and PVA adhesive suitable for clinical use as a radiation therapy bolus.
- Physical and Mechanical Characterization: To assess the elasticity, density, transparency, and surface adherence properties of the fabricated bolus.
- Radiological Evaluation: To conduct dosimetric testing—including percent depth dose (PDD), surface dose analysis, and dose homogeneity assessments—in clinical photon and electron fields.

- Comparative Analysis: To benchmark the performance of the novel bolus against conventional commercial products in both uniform phantoms and anthropomorphic phantoms simulating clinical geometry.
- Clinical Implementation and Feasibility Study: To evaluate potential applications in real-world treatment planning scenarios, focusing initially on post-mastectomy breast cancer cases with superficial invasion.

III.7 Significance of the Study

By addressing the key limitations of existing bolus technologies, this research aims to contribute with a practical and clinically superior solution that enhances dose conformity, treatment reproducibility, and overall patient outcomes in radiotherapy. The novel bolus is expected not only to demonstrate greater adaptability to complex anatomical sites but also to offer potential advantages in terms of production flexibility, cost, and patient comfort.

The results of this chapter were partially published in the paper (10.1016/j.radonc.2024.110387) and at national and international conferences (1 -6)).

IV. Chapter Dosimetric Techniques and Imaging Metrics in Radiotherapy: Beam Characterization, Depth Dose Assessment, and Hounsfield Unit Measurements for Bolus Material Evaluation

This chapter presents the methodology and results of a comprehensive dosimetric evaluation of the glycerin–PVA-based bolus material, focusing specifically on absolute dosimetry, percent depth dose (PDD) testing, and Hounsfield Unit (HU) analysis. These tests were designed to benchmark the novel bolus against standard commercial bolus material and to ascertain its suitability for clinical use in external beam radiotherapy.

IV.1 Linear Accelerator and Beam Parameters

All dosimetric measurements were conducted using an Elekta Infinity medical linear accelerator equipped with photon energies of 6 MV, 10 MV and with electron energies of 4 MeV, 6 MeV, 9 MeV, 12 MeV and 15 MeV. For testing, a standard 10×10 cm² field size was used, with the source-to-surface distance (SSD) set at 100 cm.

The novel bolus was prepared in custom-molded slabs of varying thickness (0.5 cm, 1.0 cm, and 1.5 cm) for comparative testing with a commercial Superflab,Klarity Gel Bolus KSR-3005, bolus of equivalent sizes.

IV.2 Absolute Dosimetry

To evaluate the attenuation properties and dose transmission of the novel bolus compared to a known standard under reference conditions absolute dose measurements were performed in a solid water phantom using a 0.6 cc Farmer-type ionization chamber (PTW 30013) connected to a PTW UNIDOS electrometer according to IAEA TRS-398 protocol.

The difference in absorbed dose was used to calculate the relative attenuation introduced by the bolus materials.

The attenuation factor is expressed as the fraction of the initial X-ray beam that is absorbed or scattered per unit thickness of the material. It is typically denoted by the μ and is measured in units of inverse length, such as per centimeter (cm^-1) or per millimeter (mm^-1).

Table IV.1Attenuation factor measurements were conducted for three different types of bolus materials using 6 MV photon radiation. Repeated measurements were performed at a source-to-surface distance (SSD) of 100 cm with a 10 × 10 cm² square field.

Bolus Type	no Bolus	Superflab bolus material	Aquaplast bolus material	Glycerin based bolus material
Electric Charge	**electric charge(nC)**	**electric charge(nC)**	**electric charge(nC)**	**electric charge(nC)**
	18.15	**17.9**	**17.89**	**17.81**
	18.15	**17.9**	**17.89**	**17.8**
	18.16	**17.89**	**17.89**	**17.81**
	18.16	**17.9**	**17.89**	**17.82**
	18.16	**17.91**	**17.88**	**17.82**
	18.15	**17.89**	**17.9**	**17.83**
	18.16	**17.9**	**17.88**	**17.82**
	18.16	**17.9**	**17.9**	**17.82**
	18.16	**17.91**	**17.9**	**17.82**
	18.18	**17.89**	**17.9**	**17.83**
Average	**18.16**	**17.90**	**17.89**	**17.82**
Attenuation factor	**1**	**1.005**	**1.004**	**0.996**

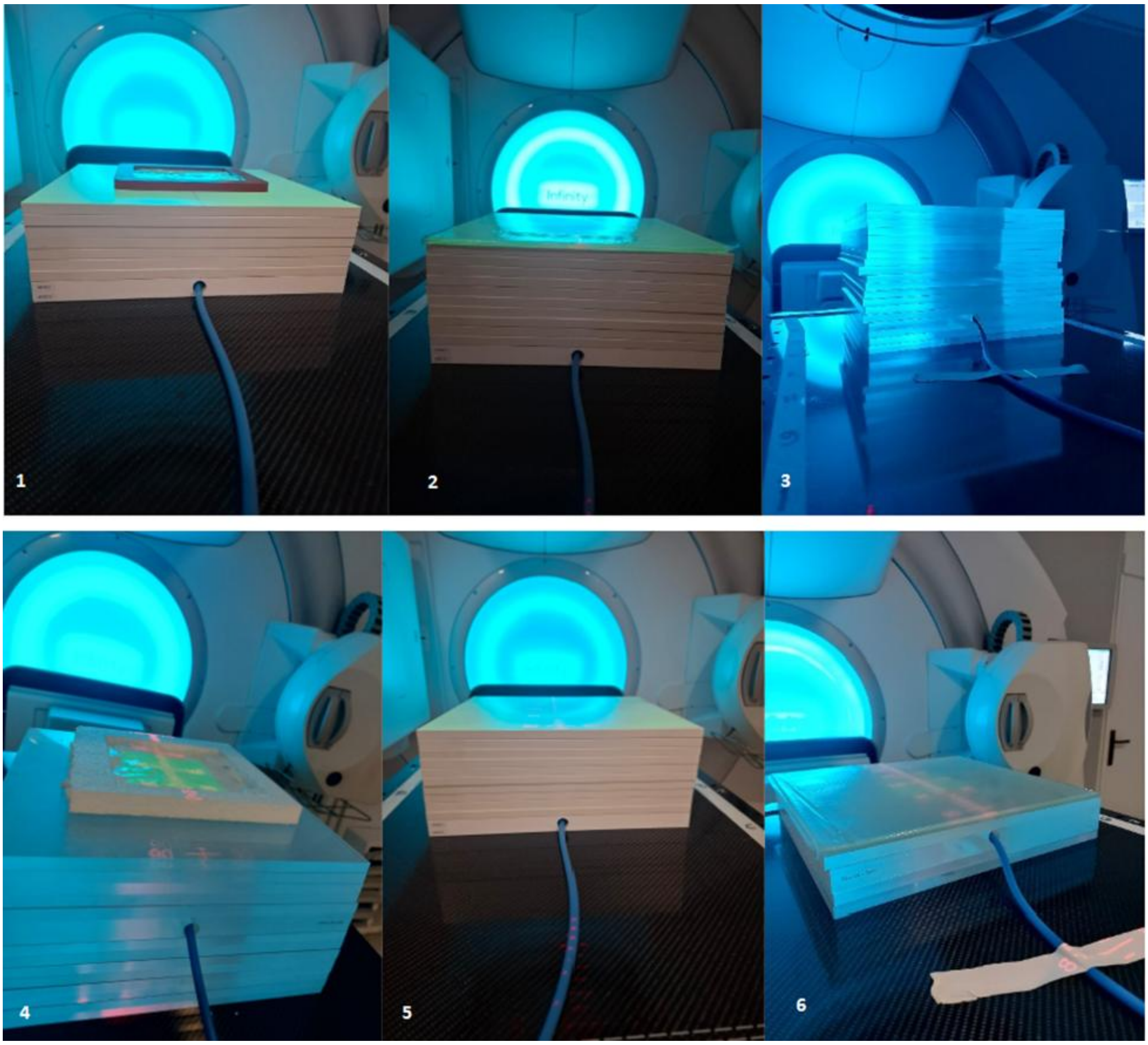


Figure IV-1The measurement setup for determining the attenuation factor of various bolus materials

IV.3Percent Depth Dose (PDD) Measurements

The PDD measurements are summarized below. Key observations include:

- Without bolus, D_{max} occurred at approximately 1.5 cm for the 6 MV photon beam.
- With both bolus materials, the D_{max} shifted closer to the surface, as expected.

- The glycerin–PVA bolus yielded a surface dose of ~91%, compared to ~92% with Superflab and ~48% without any bolus.
- The PDD curve for the novel bolus closely followed that of Superflab throughout the build-up and fall-off regions, with differences remaining within ±1.5%.

These results confirm that the proposed bolus effectively eliminates the build-up region and delivers appropriate surface dosing.

To characterize the depth-dose profile of photon beams in the presence of the new bolus material and validate the position of D_{max}.

PDD measurements were executed in a water-equivalent RW3 slab phantom using a Semiflex 3D ionization chamber (PTW 31021).

Measurements were taken with:

- No bolus (open beam),
- 1 cm commercial Superflab bolus,
- 1 cm developed (PVA-glycerin) bolus.

Depth steps ranged from 0 mm to 50 mm, with denser sampling (1 mm) near the surface to capture the build-up region. All tests were performed with SSD = 100 cm, field size 10 × 10 cm^2, and 6 MV photon beam. PDD curves were normalized to the maximum dose reading (D_{max}) for each setup to facilitate comparison.

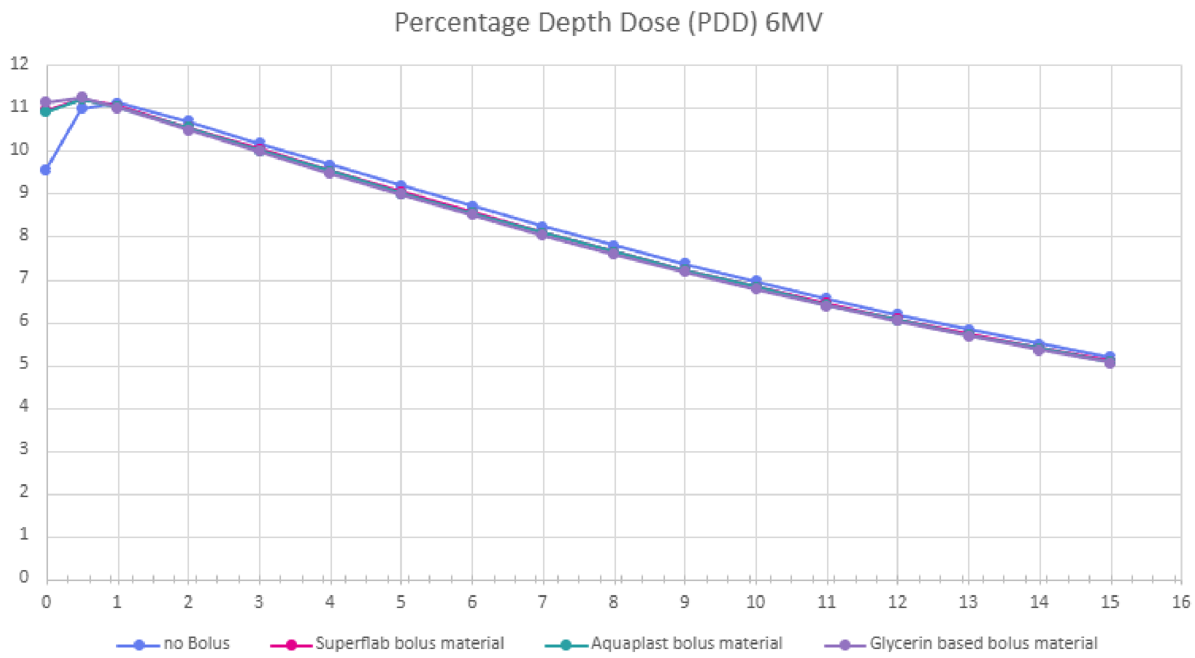


Figure IV-2Measured PDD Profiles for 6 MV Photons With and Without Bolus Materials

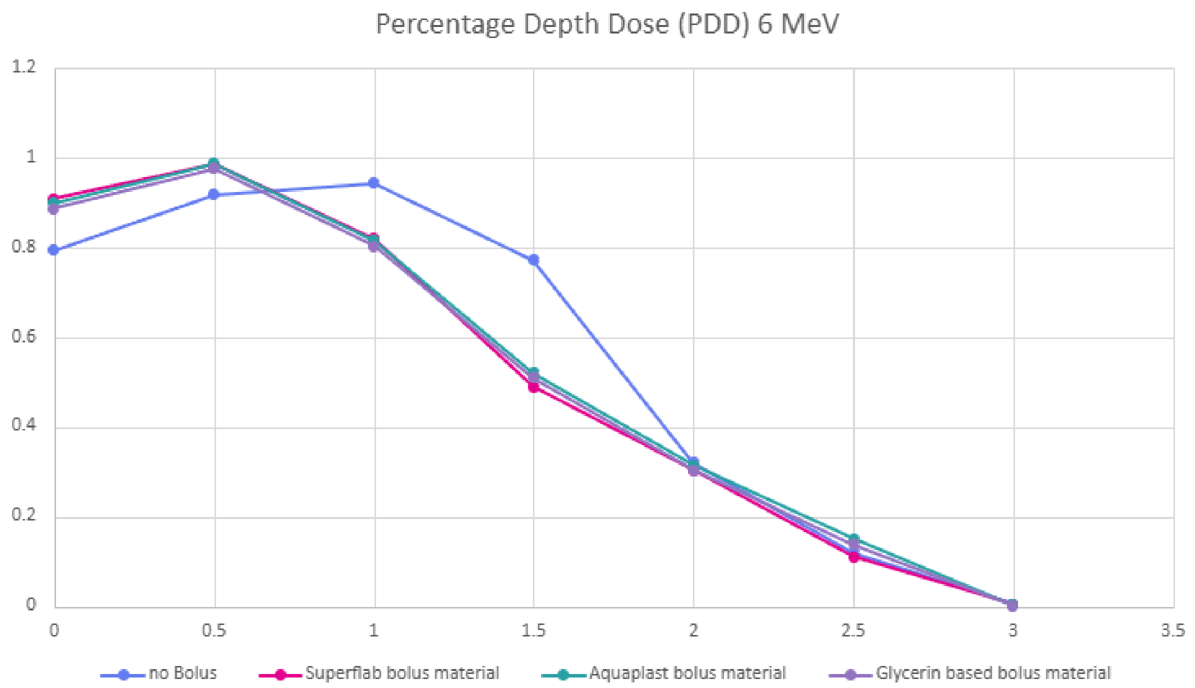


Figure IV-3Measured PDD Profiles for 6 MeV Electrons With and Without Bolus Materials

This subchapter details a rigorous experimental protocol for the measurement of PDD curves for a range of clinically relevant megavoltage photon and electron energies using an Elekta Infinity linear accelerator. These data are subsequently leveraged to quantify and compare the effects of three distinct bolus materials on central axis depth-dose distributions, thereby providing an evidence-based foundation for clinical application and further research.

Experiments were conducted with an Elekta Infinity clinical linear accelerator, providing photon beams at 6 MV and 10 MV, and electron beams at 6, 9, and 12 MeV. These energies were chosen to encompass most treatment scenarios encountered in clinical radiotherapy departments.

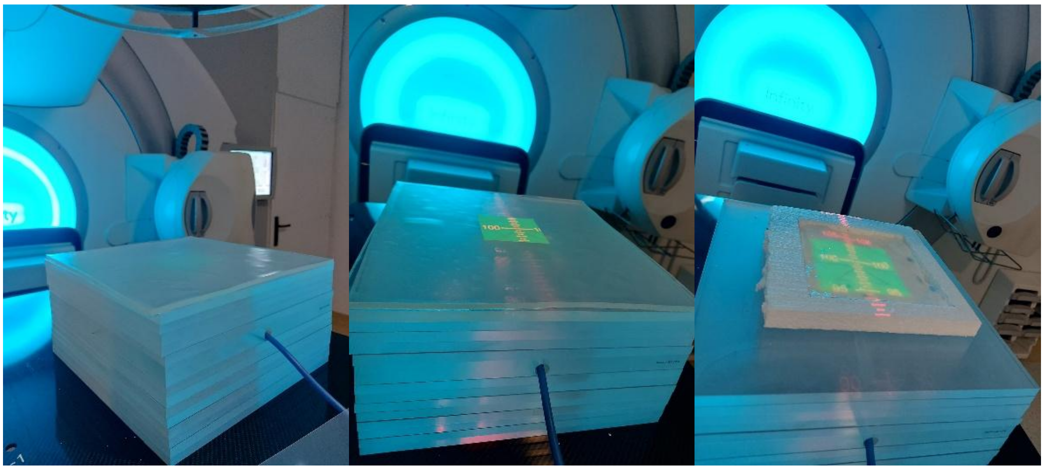


Figure IV-4Photographic illustration of the experimental setup used for bolus material analysis and consistency assessment.

IV.3.1 Significance of Percent Depth Dose in Radiotherapy and Its Clinical Implications

In radiotherapy, exact radiation delivery to the target volume while minimizing exposure to healthy surrounding tissues is of utmost importance. One of the fundamental tools used to characterize and optimize the radiation dose distribution is the percentage depth dose (PDD) curve. PDD curves provide valuable information about the behavior of the radiation beam as it penetrates through the patient's body, allowing healthcare professionals to make informed decisions regarding treatment planning and delivery.

The PDD curve represents the relative radiation dose as a function of the depth within a medium, typically water or a water-equivalent material. The depth is measured from the surface of the medium, and the dose is expressed as a percentage of the maximum dose (dmax) observed within the medium.

Table IV.2Measured Percentage Depth Dose (PDD) Values for Three Bolus Materials at 6 MV Photon Energy

Depth (cm)	no Bolus	Superflab bolus material	Aquaplast bolus material	Glycerin based bolus material
0	**9.571**	**10.96**	**10.92**	**11.14**
0.5	**10.99**	**11.22**	**11.21**	**11.24**
1	**11.12**	**11.05**	**11.03**	**11**
2	**10.7**	**10.55**	**10.55**	**10.49**
3	**10.18**	**10.04**	**10**	**9.981**
4	**9.682**	**9.535**	**9.534**	**9.476**
5	**9.19**	**9.041**	**9.004**	**8.981**
6	**8.708**	**8.559**	**8.543**	**8.5**
7	**8.239**	**8.082**	**8.076**	**8.034**
8	**7.787**	**7.641**	**7.631**	**7.592**
9	**7.355**	**7.218**	**7.214**	**7.171**
10	**6.947**	**6.816**	**6.816**	**6.776**
11	**6.555**	**6.427**	**6.398**	**6.382**
12	**6.178**	**6.063**	**6.045**	**6.019**
13	**5.826**	**5.715**	**5.7**	**5.67**
14	**5.493**	**5.382**	**5.384**	**5.346**

15	**5.172**	**5.076**	**5.067**	**5.041**

Table IV.3Measured Percentage Depth Dose (PDD) Values for Three Bolus Materials at 6 MeV Electron Energy

Depth (cm)	no Bolus	Superflab bolus material	Aquaplast bolus material	Glycerin based bolus material
0	**0.794**	**0.909**	**0.9**	**0.888**
0.5	**0.918**	**0.985**	**0.988**	**0.976**
1	**0.944**	**0.819**	**0.816**	**0.804**
1.5	**0.772**	**0.489**	**0.521**	**0.509**
2	**0.321**	**0.304**	**0.315**	**0.303**
2.5	**0.12**	**0.11**	**0.15**	**0.138**
3	**0.004**	**0.004**	**0.003**	**0.001**

Figure IV-5Photographic documentation of the bolus preparation and experimental setup used for HU evaluation

IV.3 Hounsfield Unit (HU) Analysis

To determine the radiological equivalence of the bolus material in terms of CT number, which is critical for treatment planning system (TPS) dose calculations.
To assess the radiotransparency of the novel bolus material, a comparative analysis was performed using computed tomography (CT) imaging. Specifically, the Hounsfield Unit (HU) values of our experimental bolus materials were measured and compared to those of commercially available counterparts. The results indicate that the glycerin concentration within the formulation significantly influences the radiovisibility of the material; higher or lower glycerin content resulted in proportional changes in HU values, thereby modulating the degree of similarity to tissue-equivalent materials.
The bolus was scanned using a Siemens Somatom CT simulator using standard clinical imaging protocols (120 kVp, 1 mm slice thickness).
Region-of-interest (ROI) measurements were performed on axial slices containing:

- Air
- Water-equivalent phantom material
- Commercial bolus material
- Glycerin–PVA bolus sample

The average CT number (in Hounsfield Units) was calculated for each material from a ROI of 1 cm².
The absolute dosimetry results showed that the novel bolus introduced dose attenuation characteristics like commercial bolus. Specifically:
Table IV.4 Dose Attenuation Differences in Moldable Bolus Materials as Determined by Absolute Dosimetry

Material	Measured Dose at 2 cm Depth (cGy)	% Difference from No Bolus
No Bolus	100.0	0.000 %
Superflab Bolus (1 cm)	99.37	0.006 %

Thermoplastic bolus 1 cm	99.19	0.008 %
Glycerin–PVA Bolus (1 cm)	98.92	0.010 %

These findings suggest near-equivalent attenuation characteristics, demonstrating the feasibility of the material to replicate standard tissue-equivalent properties.

The Hounsfield Unit values for each material are presented in the table below:

Table IV.5Hounsfield Unit Values for different materials

Material	Average HU Value	Standard Deviation
Air	-998	±3
Water-equivalent phantom	0	±5
Commercial Superflab Bolus	84	±12
Glycerin–PVA Bolus	91	±6
Thermoplastic Bolus	104	±7

The HU value of the glycerin–PVA bolus was found to be within an acceptable range of 91±6 indicating its radiodensity is comparable to soft tissue and existing bolus materials. The small discrepancy is well within the CT calibration tolerance used by most TPS software, suggesting no adverse effect on dose calculation accuracy.

The results of the dosimetric tests indicate that the newly formulated glycerin–PVA bolus material exhibits dose attenuation, surface enhancement, and radiological properties that are consistent with clinical requirements for tissue-equivalent bolus materials. The PDD and absolute dosimetry results affirm its ability to reproduce the build-up shift effect, matching the performance of the commercial Superflab material. Moreover, the CT-based HU values confirm the material's compatibility with treatment planning systems that use HU-to-density calibration curves.

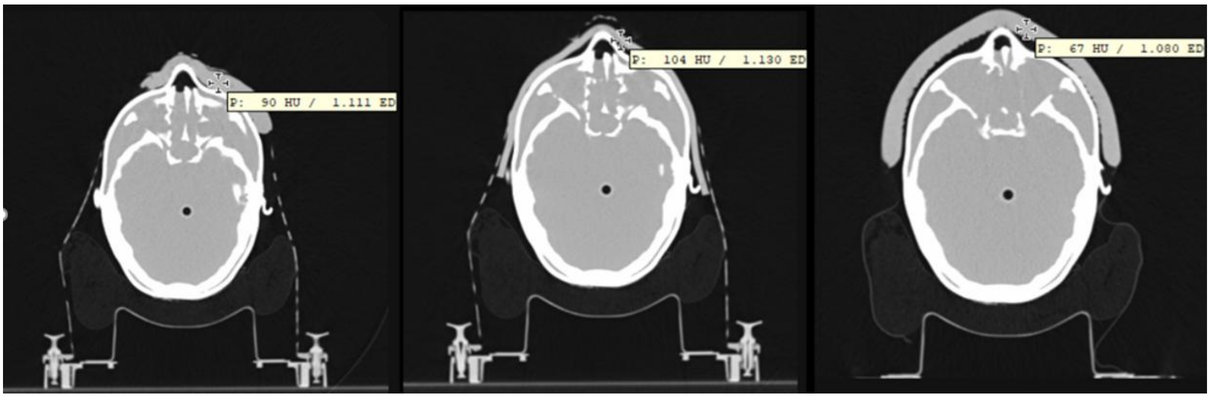
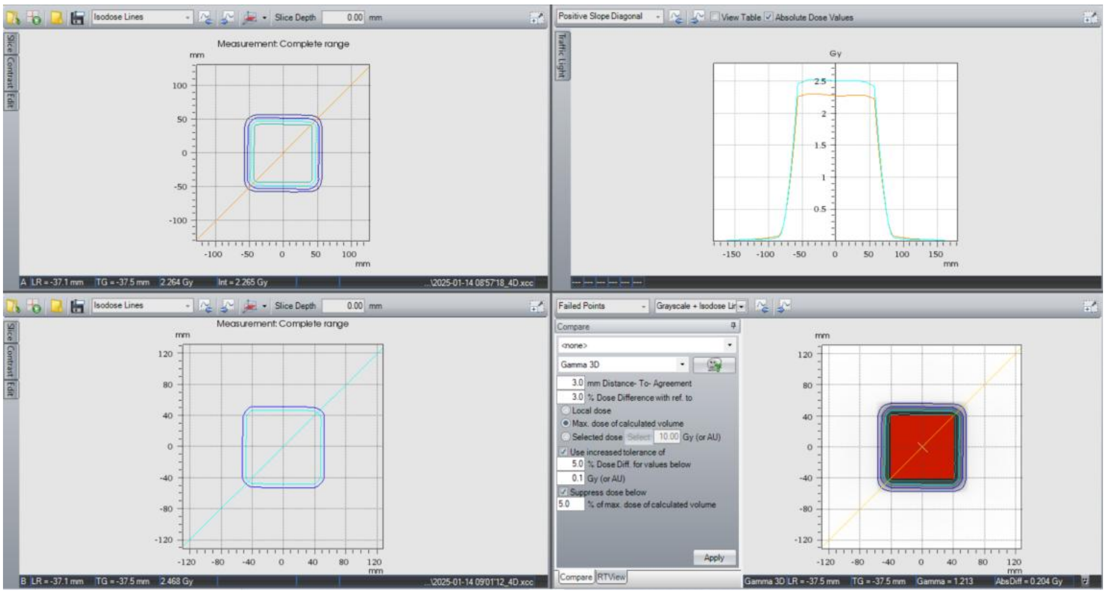


Figure IV-6CT image of the PRIME phantom comparing Hounsfield Units (HU) for one custom moldable bolus and two commercial bolus materials

The dosimetric testing of the glycerin–PVA bolus has demonstrated its clinical viability as an alternative to conventional bolus systems in radiation therapy. It meets the essential physical and radiological criteria for use in photon beam therapy, particularly in scenarios requiring enhanced surface dose. These results validate the bolus for further study in patient-specific applications and clinical workflow integration.



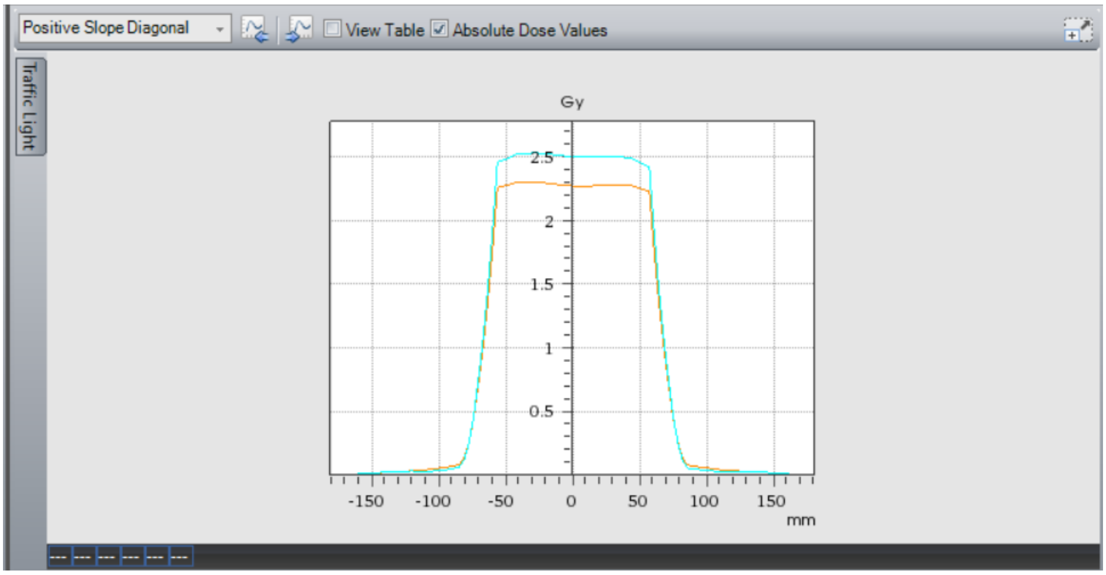


Figure IV-7Assessment of Thickness Uniformity in Moldable Bolus Materials and Verification of Attenuation Characteristics Using a 2D Array Detector

To evaluate the uniformity of the material in terms of both thickness and attenuation properties, additional measurements were conducted using a two-dimensional (2D) array detector. The bolus material does not influence the beam profile shape, as the symmetry and flatness remain unchanged.

The results of this chapter are under evaluation as a submitted paper (Manuscript Number: EJMP-D-25-00314 Manuscript Title: Development and characterization of a novel material based on glycerine as clinical bolus in radiation therapy, Journal: Physica Medica under review IF 2.7) and they were presented at national and international conferences.

V. Chapter Discussion

Radiotherapy remains one of the cornerstone modalities in the treatment of skin cancers and breast cancer with tegumentary infiltration, offering curative or palliative intent depending on disease stage and patient-specific factors. In such cases, the superficial nature of the lesions imposes specific challenges regarding the optimal dose deposition within the target volume and at the skin surface.

The use of a bolus material represents an established method to enhance surface dose by effectively shifting the build-up region closer to the skin. By placing a tissue-equivalent material on the patient's surface, photon beams deposit dose at shallower depths, ensuring that the prescribed dose adequately encompasses the superficial component of the target volume. Without the use of bolus, a significant underdosage of the tegumentary or skin-infiltrated regions may occur, ultimately compromising local control rates. Therefore, in cases of breast cancer with chest wall or skin infiltration and in primary cutaneous malignancies, the proper use of bolus material is not optional but rather an integral part of the treatment strategy.

One of the practical limitations of standard bolus sheets is the occurrence of air gaps between the patient's irregular surface anatomy and the flat bolus material. Such air gaps can significantly alter the dose distribution, reducing the intended dose at the skin and creating hotspots in adjacent regions. Moldable bolus materials have the advantage of conforming closely to the patient's anatomy, thereby minimizing irregularities and eliminating interposed air spaces.

Although the application of bolus is a well-recognized practice, variability in its daily positioning can represent a source of uncertainty in radiotherapy. Our study, "Can the daily position of bolus material influence radiotherapy treatment?", has provided evidence that inconsistencies in bolus placement can have a direct impact on the delivered dose to both the planned target volume (PTV) and organs at risk (OARs). The reproducibility of bolus positioning is therefore critical, since shifts or misplacements from day to day may result in underdosage of superficial tumor areas or unintended irradiation of adjacent normal tissues.

The first step in addressing these clinical inconsistencies was the convening of a joint committee composed of physicians, physicists, and radiation therapists. This multidisciplinary approach enabled the identification of failure points and facilitated the development of a framework to reduce uncertainties arising from bolus use. The committee emphasized the need for patient-specific classification, where individuals are systematically evaluated and identified according to their requirement for bolus. Such structured assessment ensures that the indication for bolus is clear and its use is justified, aligning the technical procedures with individualized patient needs.

Given these findings, it is evident that standardization in bolus application is warranted. Developing clear and evidence-based guidelines for bolus positioning would mitigate technical variability and foster consistency across treatment centers

VI. Conclusion

Cancer incidence rates continue to show dynamic fluctuations globally, influenced by factors such as environmental exposures, genetic predispositions, lifestyle changes, and healthcare accessibility. This variability underscores the critical and growing need for continuous improvement in cancer diagnosis, treatment, and patient management. Among the various types of cancers, skin cancer and breast cancer with tegumentary (cutaneous) invasion represent significant clinical challenges due to their anatomical location and the involvement of the skin surface in the disease process.

In the context of my thesis, I have focused on two primary objectives. First, I have investigated the influence of bolus positioning on treatment outcomes, as presented in the article entitled "Can the Daily Position of Bolus Material Influence Radiotherapy Treatment?" This study, conducted in collaboration with my mentors and colleagues, emphasized the critical importance of consistency in the daily placement of bolus materials throughout the course of radiotherapy. Although the statistical data did not demonstrate a highly significant variance in outcomes based solely on bolus displacement, the clinical implications remain non-trivial. We must remember that we are treating human beings and even minor inconsistencies can influence therapeutic efficacy and patient quality of life. Therefore, variability in bolus positioning should not be overlooked or deemed acceptable purely based on statistical insignificance. This study also contributed to outlining the radiotherapy treatment workflow, highlighting both the continuous evolution of imaging modalities from CT to MRI and synthetic CT (sCT), as well as the persistent absence of standardized operating procedures (SOPs)

The major focus of my thesis involved the development and characterization of a novel bolus material. Recognizing the limitations of currently available commercial boluses, including cost, rigidity, and adaptability to patient anatomy, I proposed and tested a homemade bolus composed primarily of glycerin. This material was designed to be inexpensive, easily moldable, and practical for use in clinical departments with limited resources. Throughout practical testing, it was observed that the glycerin-based bolus retained its physical properties over time when stored in a closed environment. Moreover, comparative dosimetric analyses between the homemade glycerin bolus and standard commercial bolus materials revealed no statistically significant differences in performance. These findings support the potential clinical viability of this alternative material, especially in low- and middle-income settings where access to commercial products may be limited. Despite the encouraging results, the research also highlighted a broader issue: the absence of standardized protocols for bolus application and positioning during radiotherapy. There is a pressing need to develop and implement both national and international guidelines that provide clear instructions on the selection, preparation, and placement of bolus materials. Such standardization is essential to minimize inter-operator variability, ensure treatment reproducibility, and optimize therapeutic outcomes.

In conclusion, this thesis highlights the multifaceted role of bolus materials in the effective delivery of radiotherapy for skin and breast cancers with tegumentary involvement. It underscores the importance of consistency in bolus positioning and presents a viable, low-cost alternative to commercial boluses. However, technological innovation alone is insufficient. Systematic implementation of best practices, standardized protocols, and global cooperation is essential if we are to translate these advancements into meaningful improvements in cancer care.

List of Publications

1.A Villegas F, Dal Bello R, Alvarez-Andres E, Dhont J, Janssen T, Milan L, Robert C, **Salagean GA**, Tejedor N, Trnková P, Fusella M, Placidi L, Cusumano D. Challenges and opportunities in the development and clinical implementation of artificial intelligence based synthetic computed tomography for magnetic resonance only radiotherapy. Radiother Oncol. 2024 Sep;198:110387. doi:10.1016/j.radonc.2024.110387. Epub 2024 Jun 15. PMID: 38885905. **IF 5.3, AIS 1.559**

2.A **Salagean GA**, Bálint Z, Poortmans P, Portik D. Can the daily position of bolus material influence radiotherapy treatment? Rep Pract Oncol Radiother. 2025 Feb 19;29(6):732-739. doi:10.5603/rpor.104013. PMID: 40104657; PMCID: PMC11912895. **IF 2.0 AIS 0.32**

3.A **Ghizela Ana Maria Salagean**, Krisztina Varga, Zoltan Balint, Daniel Portik. In Vivo Lens Dosimetry in a Case of En Face Electron Adjuvant Radiotherapy for Cutaneous Nasal Bridge Basal Cell Carcinoma – a Case Report.JMRO. 1 October 2023. IiI. 2. 71 - 77. DOI:10.53011/JMRO.2023.02.09

4.AManuscript Number: EJMP-D-25-00314 Manuscript Title: Development and characterization of a novel material based on glycerine as clinical bolus in radiation therapy, Journal: Physica Medica *under review* **IF 2.7, AIS 0.714**

Presentations at international and national conferences

1) 03/06/2022 – 04/06/2022 Cluj-Napoca **Oral presentation** Lector at " Modern radiotherapy techniques" Postgraduate course for RTTs, XV edition Presentation "Internal Audit -Bolus Positioning " SRROM
2) 13/10/2022 – 15/10/2022 Cluj-Napoca **Oral presentation** Lector at National Congress of the Romanian Society of Radiotherapy and Medical Oncology 2022, Presentation: Dosimetric Results Of Electron Radiotherapy For Nasal Bridge Basal Cell Carcinoma SRROM
3) 27/03/2023 – 28/03/2023 London, UK (Hybrid event) **Oral presentation** Speaker at "Scholars International Conference on Physics and Quantum Physics" Presentation :"Comparison of Treatment Planning Techniques for a Synchronous Bilateral Breast Cancer Patient in the Setting of a Hypo fractionated Approach"

   Physics Conference | Physics Meet | Atomic Physics Conferences | Physics Conference 2023| UK | London | Asiapacific | Italy | UK | USA | Europe | Middle East | 2023 | Scholars Conferences
4) 11/07/2023 – 12/07/2023 Paris, France **Oral presentation** Speaker - Global Summit on Breast and Women's Cancer Presentation : Comparison Of Volumetric Modulated Arc Therapy Vs. Helical Tomotherapy Treatment Planning In A Case Of Implanted Breast Tissue Expander Speaker Guidelines | Breast and Women's Cancer 2023 | Breast Cancer Conferences | Women Cancer Conferences | Scholars Conferences

5) 04/11/2022 – 05/11/2022 Oradea **Poster** National Congress of Medical Physicist Poster: Comparison of Volumetric Modulated Arc Therapy Vs. Helical TomoTherapy Treatment Planning in a Case of Implanted Breast Tissue Expander XX-a Conferinta Nationala de Fizica Medicala 2022

6) 2023- **Digital Poster** at European Society for Radiotherapy and Oncology Congress- Daily Bolus Position Variability with Dosimetric Implications in Adjuvant Breast Cancer Radiotherapy ESTRO2023 - Ghizela Ana Maria Salagean, *Romania* Presentation Number: PO-2306 Abstract book (ESTRO - Session Item)
7) 2025 - **Digital Poster** at European Society for Radiotherapy and Oncology Congress- Characterization of a homemade moldable material to be used as bolus in radiotherapy Presenter: Ghizela Ana Maria Salagean, *Romania* Presentation Number: E25-183 ESTRO - Programme

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