Kaunas University of Technology

Faculty of Mathematics and Natural Sciences

Re-calculation and Evaluation of Compensative Biological Effective Dose for Unscheduled Interruption in Head and Neck Cancer Radiotherapy

Master's Final Degree Project

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Summary

Head and neck cancers are the seventh type of cancer by mortality globally. These tumours progress at a rapid pace, affecting the upper respiratory and digestive tracts, as well as organs located in close proximity. One of the primary options for treatment is radiotherapy. Timing of treatment sessions is a highly influential factor which must be accounted for in using this treatment approach. Even a one week pause in treatment results may decrease control of the localised tumour by 10-20%. The reasons behind a pause in delivering a planned fraction may vary from technical issues, cybernetic attacks, periods of vacation, natural catastrophes, to public health emergencies, such as the COVID-19 pandemic.

With the goal of compensating for missed treatment sessions, an algorithm for recalculating radiation fractions was implemented as a tool based on “Microsoft Excel”. Following this algorithm, personnel, namely radiation-oncologists and medical physicists, may save time and more easily make decisions in correcting radiation treatment plans. Based on the linear quadratic model and treatment guidelines, the theoretical biological effective dose was calculated for rapidly proliferating cancer cells, as well as for critical organs. The newly calculated/ re-calculated dose (Gy) was compared to the allowed tolerance limits from radiotherapy treatment plans. Obtained results showed that this methodology, replanning treatment may be useful for clinical applications, guaranteeing the quality of the radiation treatment from a radiobiological point of view.

Ieva Jogaitė. Biologiškai efektyvios dozės perskaičiavimas ir įvertinimas esant neplanuotai pertraukai galvos ir kaklo vėžio gydyme. Magistro baigiamasis projektas / vadovas doc. dr. Jurgita Laurikaitienė; Kauno technologijos universitetas, Matematikos ir gamtos mokslų fakultetas, konsultantas lekt. dr. Reda Čerapaitė-Trušinskienė; Lietuvos sveikatos mokslų universitetas, Medicinos fakultetas.

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Santrauka

Visame pasaulyje, galvos ir kaklo navikai užima septintą vietą pagal mirtingumą nuo vėžio. Ši liga greitai progresuoja ir paveikia viršutinius kvėpavimo bei virškinimo takus bei šalia esančius organus. Vienas iš pagrindinių gydymo metodų yra radioterapijos taikymas, kurio metu ypač svarbus faktorius yra laikas. Netgi vienos savaitės pertrauka gydymo metu lemia vietinės naviko kontrolės sumažėjimą 10 – 12 %. Priežastys lemiančios tarpą tarp suplanuotų frakcijų gali būti įvairios: technikinės kliūtys, kibernetinės atakos, atostogos, gamtos katastrofos ir pandemijos (pvz., Covid-19).

Siekiant kompensuoti prarastus gydymo kursus buvo sukurtas skaičiavimo „algoritmas“ naudojantis programa Excel. Naudojantis šiuo skaičiavimo „algoritmu“ gydytojai onkologai radioterapeutai ir medicinos fizikai galėtų lengviau priimti sprendimus, dėl spindulinio gydymo plano koregavimo. Remiantis linijiniu kvadratiniu modeliu ir gydymo rekomendacijomis buvo apskaičiuota teorinė biologinė efektyvi dozė greitai proliferuojančioms vėžinėms ląstelėms ir kritiniams audiniams bei organams. Perskaičiuota dozė (Gy) naudota apšvitos apribojimo vertinimui, panaudojant spindulinio gydymo planus. Gauti rezultatai parodė, jog gydymo perplanavimo metodika gali būti naudojama klinikiniais tikslais, taip užtikrinant paciento spindulinio gydymo kokybę radiobiologiniu požiūriu.

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Abbreviations:

BED – Biological effective dose;

DNA - Deoxyribonucleic acid;

DVH – Dose volume histogram;

Gy – Gray;

HPV - Human papillomavirus;

IMRT - Intensity modulated radiotherapy;

LET – Linear energy transfer;

LQ – Linear quadratic;

SCC – Squamous cell carcinoma;

VMAT – Volumetric modulated arc therapy.

Terms:

BED – defines the biological effect that can be expressed as a logarithmic function of ionizing radiation-induced cell killing. *BED* values diverge depending on the α/β ratio: higher α/β corresponds to the tumour or early proliferating healthy cells, while lower α/β ratio represent late tissue and organ complications. According to the LQ model it can be calculated using the given formula: BED = total dose * $(1 + d / \alpha/\beta)$.

Gy – an International standard unit of measurement for the amount of ionizing radiation that can be absorbed by one kilogram of material. It is commonly used in radiation therapy and radiobiology measurements.

LQ – linear quadratic model, in this study based on the biological and physical interaction between ionizing radiation in terms of cell survival regulation. It involves the α and β parameters.

Introduction

According to the Lithuanian Institute of Hygiene, 16 326 people in 2021 contracted respiratory tract cancer due to smoking [1]. This number represents only a fraction of all head and neck malignancies and continues to increase year by year. Radiation therapy is one of the most effective and commonly used cancer treatments, including for head and neck cancers [2].

The biological effects of radiation therapy have been extensively studied over the past three decades. The development of the linear quadratic (LQ) model has provided the most medical insights into cell survival and radiobiological effects of ionizing radiation. This model incorporates the α/β ratio, based on two parameters which are adjusted to represent individual biological characteristics, and therefore contributes to the establishment of personalized radiation therapy. In the near future, radiobiology will become an inseparable part of medical physics [3].

Head and neck cancer is in most cases a highly proliferative neoplasm. Therefore, a one-day gap in treatment delivery can reduce local control by 1.4%, while a week-long break results in 10-12% deterioration. It is known that within four weeks, the cancer can grow significantly and invade nearby tissues[4]. For this reason, any interruptions in radiation therapy are undesirable and should be prevented. In 2019, during the global pandemic caused by the COVID-19, many patients experienced disruptions that lasted from several days to weeks. The Royal College of Radiologists (RCR, UK) has established instructions for medical personnel after investigating the growing challenges of unplanned treatment gaps [5]. Delays in radiation therapy affect the entire health care system due to the supplementary expenses and resources required to implement another strategy. In addition, it affects patient health by reducing overall survival and locoregional control. However, the primary problem is that most hospitals do not have appropriate and uniform guidance for compensative strategies.

The aim of this work was to implement a compensability "model" simulating interruption to head and neck cancer radiotherapy.

The main task:

1. To simulate various interruption cases for head and neck cancer patients.
2. To analyse and compare the main dosimetry data of planned treatment plans for simulated interrupted radiotherapy of head and neck cancer case.
3. To prepare a compensative "model" and provide recommendations to medical personnel.

1. Literature review

Cancer is an omnipresent life-threatening condition whose number of cases continue to grow globally every year. In wealthy countries, the chance of developing cancer is closer to one in two, which is higher than the global average of one in five, due to sedentary lifestyles, higher consumption of highly processed foods and environmental pollution. The prevalence of cancer cases worldwide is predicted to increase by a factor of two by 2040 because of changes in expected lifespan and daily habits, which are the main causes of the rise in incidents of the illness [6].

W. Roentgen's discovery of X-rays eventually led to the use of ionising radiation for cancer treatment [7]. For the treatment of malignant cells in the human body, radiotherapy continues to be the most effective option. For this reason, numerous researchers have studied the biology of cancerous and healthy tissues to enhance the effectiveness of ionizing radiation therapy and shield patients from its side effects. Radiation therapy can provide long-term tumour control over an extended period or, if necessary, for an entire lifetime. However, as with other available treatment options, there is a chance that the cancer will recur after the bout of radiation. Combinations of tumour cell radiobiology with different therapies should be studied and considered to achieve the best and desired response [4].

1.1. Ionizing radiation interaction with cell

1.1.1. Cells damage pathway

Cells go through three basic phases after irradiation: physical, chemical, and biological. Each of these phases is comprised of distinct reactions that take place gradually over time (Fig. 1). The physical phase, which occurs when ionizing radiation interacts with the target volume's atoms, is the fastest (lasting from 10^{-18} to 10^{-12} s). In this stage, excitation (raising of electrons to a higher quantum level) and ionization (ejection of atoms' electrons) are the dominant processes. Following the disruption of molecular bonds, the chemical phase causes the production of free radicals. Cells experience major changes during the biological stage, which either results in repair of the damage or cell death. However, based on the cell cycle and associated tissue proliferation features, healthy tissue's DNR alterations may not emerge for months or even years [2]. The therapeutic goal is to eliminate all malignant cells using ionizing radiation-induced apoptosis.

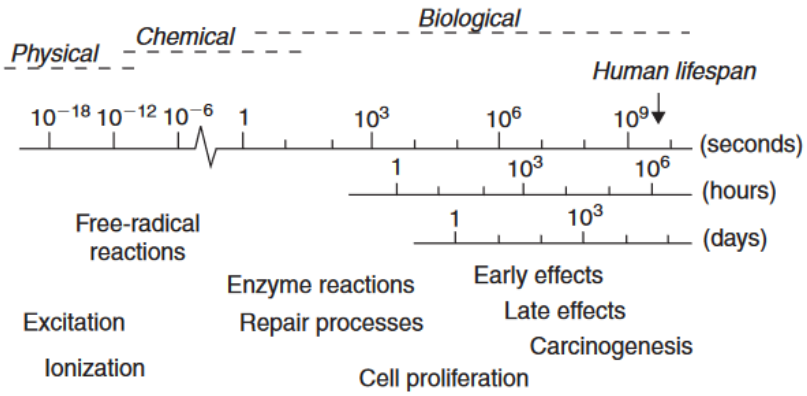


Fig. 1. An effect on cells following exposure to radiation throughout time [2]

Ionizing radiation can also eventually cause cancer, a process known as radiation carcinogenesis. The isoeffect, or fraction number and total doses which correspond to the same radiobiological effect, are used to define the upper limit for healthy tissue to be used in a particular treatment plan. Developing an individualized clinical plan for each patient is one of the highest radiotherapeutic priorities.

1.1.2. DNA – central target

The polymer deoxyribonucleic acid (DNA) is made up of two polynucleotide helixes which contain a cell's genetic code. The existence of life forms and pathogens depends on DNA, which regulates their reproduction, evolution, and other essential processes. Cytosine, quinine, adenine and thymine are the nitrogen bases that stabilize the sugar-phosphate polymer and whose specifically ordered sequence allows the storage of information. The molecule is held together by two types of bonds: hydrogen and covalent [8]. Chemical changes occur when a cell's genetic material is exposed to radiation: molecular hydrogen bonds are then ruptured and the information stored by the sequence of base pairs may be changed (Fig. 2).

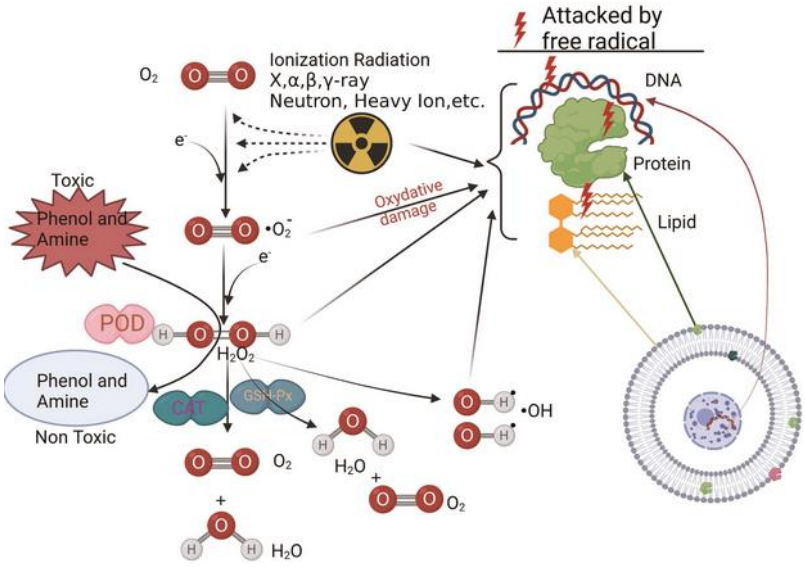


Fig. 2. DNA destruction pathway induced by the cell irradiation [9]

The breakage of DNA strands may ultimately terminate in the death of the cell. Proteins, which help to repair the genetic information contained in DNA, such as ATR and ATM, are involved in repairing damaged DNA and consequently, regulating the gene expression pathway of the cell. Therefore, radio-sensitization processes can be developed by stimulating certain proteins; specific inhibitors as well as other substances have been developed to alter how cancer cells react to the ionizing radiation. Unfortunately, the efficiency of these inhibitors is not sufficiently supported by studies. Another component that affects cancer's susceptibility to radiation is related to the metabolic activities and molecules of the cell. The attachment of sugar molecules to the DNA strand can be another source of damage to the genetic information. This mechanism is called glycation [4]. DNA structure damage can be evaluated using specific computational and quantitative methods. As a result, a corresponding connection between even a low radiation dose and double strand ruptures was established. In their analysis, researchers measured that 1 Gy of radiation can destroy 30 - 60 of these bonds [10].

1.1.3. DNA damage and repair mechanism

The pathway of ionizing radiation penetration into a material can be described by the Poisson distribution. Low energy gamma ray or x-ray particles disseminate within the cell randomly and interact with the nucleus, normally causing limited damage to the DNA sequence. An increase in radiation energy accordingly causes numerous nucleotide chain breaks [10].

In response to predisposing conditions, such as ionizing radiation, the DNA cell repair mechanism may be called into action. Double helix breaks are repaired much more slowly than single breaks of the DNA strand [11]. Cancerous cells have a unique means for keeping DNA multiplication at a more rapid pace than in healthy cells [4]. Depending on the half-time required for tissue recovery, the lengths of time for cell DNA repair may vary from a rapid damage reconstruction, taken to mean a few minutes to half an hour, to a slower one, which can be from an hour to 12 hours in duration [11]. The cell repair pathway controls DNA molecule replacement and regeneration in healthy tissues. For this reason, cells can regain their function following the majority of sub-lethal destructive events, such as following exposure to therapeutic radiation, if it is delivered using fractionated treatment. In contrast, a significant percentage of cancerous cells have vulnerabilities in their recovery processes, making them less capable to fix genetic disruption [7].

1.1.4. 6R - radiobiology

The principle of 6R: radio-susceptibility, repopulation, redistribution, reoxygenation, repair and reactivation of immune response is the cornerstone of the whole central concept of radiobiology (Fig. 3) [11,12]. Cellular repair is mainly represented by the linear quadratic model and varies depending on the radiation dose per single irradiation, while cell redistribution and repopulation are managed by changing duration of time. Oxygen regulation in cells induces sensitivity to radiation and thus improves treatment outcomes [13].

At the beginning of treatment, the stem cell killing effect is expected to rise exponentially. However, this phenomenon changes together with external conditions like vascularisation and oxygenation, leading to the resistant status of the tumour. Other, differentiated cancerous cells have an ability to divide even though they are already sterilized [13]. Cell multiplication levels for the most severe forms of cancer can be unexpectedly low - less than 7 days and contribute to quick repopulation ratios [3].

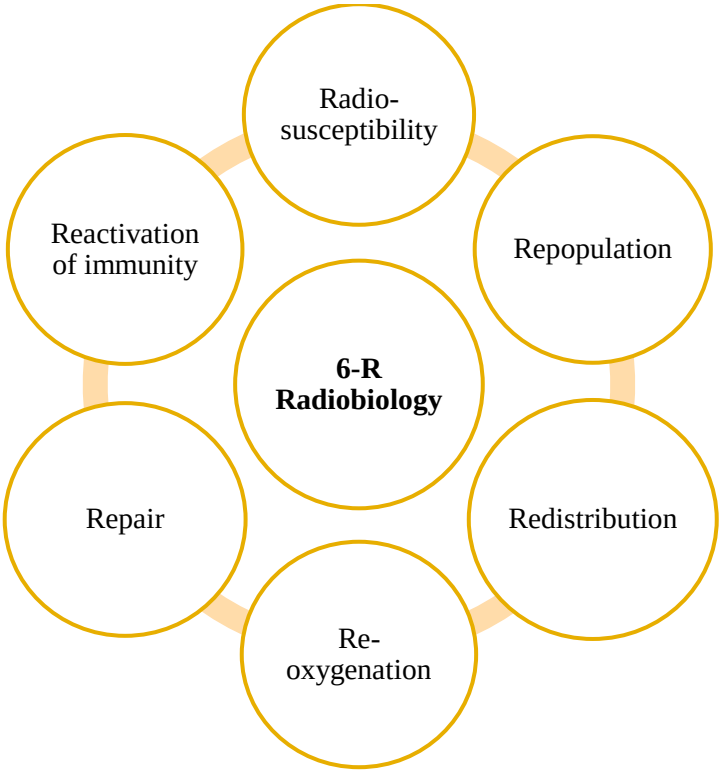


Fig. 3. Components of radiobiology

The term "re-oxygenation" applies to the oxidative stress in radiotherapy-damaged tumour tissue. It consists of the formation of free radicals, which later contribute to the process of cell death. However, malignant cells tend to survive due to hypoxic conditions. Furthermore, oxygen deficiency causes significant physiological mechanisms in tumour cells that trigger them to become more angiogenic and to spread throughout the body (Fig. 4). The hypoxia inducible factor (HIF1), encoded by a correspondingly named gene, has earlier been recognised as the key protein which coordinates expression of the response to hypoxic stress in cells [7]. Alongside HIF1, the cell loss factor (CLF) is typically significantly present at the beginning of a radiotherapy session, particularly in carcinomas of large volume [3]. Cycles of the cellular alterations resulting from exposure to ionising radiation are referred to as redistribution [7].

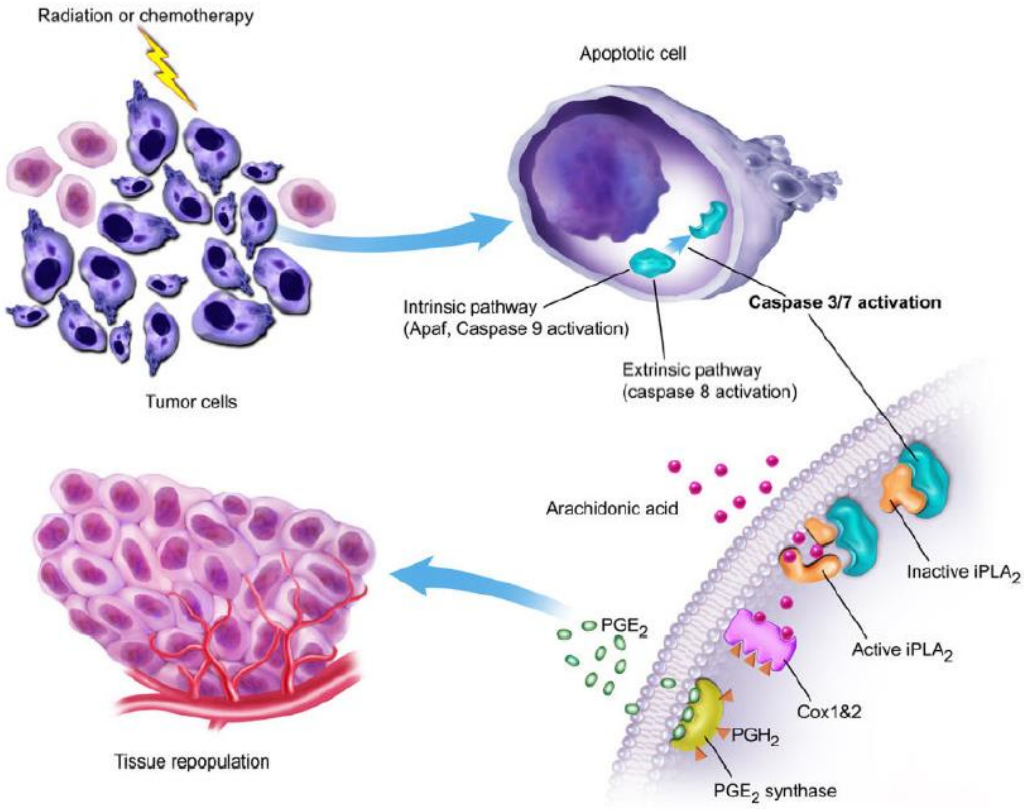


Fig. 4. The emergence of the repopulation process after radiotherapy treatment [7]

The tumour microenvironment needs to be evaluated together with the properties of the particular cancer, which can help to influence the radiotherapy results. Cancer consists of different types of cells surrounded by the stroma [14]. The potential to stop the expansion of the entire tumour by targeting cancerous stem cells is now possible by choosing the right therapeutic parameters.

1.2. Radiobiological model

The biological effects and dose fractionation of radiation therapy have been extensively studied over the past three decades. Clinical optimization of the radiotherapy program is mainly influenced by the relationship between the whole irradiation dose and the individual tissue reaction to the therapy [10]. The radiobiological consideration of the delivered dose over a period of time was first demonstrated and implemented by Dr. Barendsen from the Netherlands. He is credited with developing the LQ algorithm by observing the multiplication of cells in vitro after exposure to radiation [15].

The effect of the total radiation dose on cancerous and healthy tissue differs. For this reason, any changes to radiation dose delivery may enhance the desired effect of killing the malignant cells but concomitantly cause higher rates of complications for at-risk organs, and vice versa. Even small variations during radiation treatment are considered significant according to the radiobiological model. The fundamental purpose of the LQ model used in this study was to characterize biological effects following radiation exposure. In mathematical clinical radiobiology, the linear quadratic model is predominantly used [16].

Before selecting the LQ prototype, another survival model, called the "multiple target - single hit" model was investigated [10]. In this model, an increase in radiation dose was associated with an exponential increase in cell death, distributed according to the Poisson distribution. According to a biological interpretation of this concept, anaplastic cells of the tumour have a heterogeneous structure and must all be targeted to be fully destroyed. The LQ model introduces α and β parameters and thus accounts for cells having different sensitivity for radiation effect. Although some tumours have identical genetic information, their response to ionizing radiation varies, according to oxygen and nutrient supply [10].

1.2.1. Derivation of the linear-quadratic model

To explain the LQ model, we must first define the α and β parameters. The parameter α represents the inherent sensitivity of the tumour cells to radiation defined as the logarithm of destroyed/sterilized cells per unit of radiation, gray (*Gy*). In contrast, β is specified as the natural logarithm of the quantity of regenerated cells, which begin to appear after approximately six hours, in units of squared radiation. The sum of the logarithms of both repaired and not repaired cells (E) can be described by a single formula which integrates the α and β constants:

$$E = n(\alpha * d + \beta * d^2), \tag{1}$$

where *n* is the number of fractions prescribed in the radiation therapy plan, *d* is the dose per fraction.

$$E = n * d(\alpha + \beta * d), \tag{2}$$

$$\frac{E}{\alpha} = nd\ (1\ + \frac{\beta * d}{\alpha}), \tag{3}$$

In order to extract the α/β ratio:

$$\frac{E}{\alpha} = n * d\left(1 + \frac{d}{\alpha/\beta}\right) E = n * d(1 + d), \tag{4}$$

$$BED_3 = \frac{E}{\alpha} = total\ dose * RE, \tag{5}$$

where *RE* means relative efficiency, BED_3 is used for late treatment complications.

$$RE = (1 + \frac{d}{\alpha/\beta}), \tag{6}$$

For an early responding tissue and tumour, BED_{10} is calculated by subtracting the logarithm of potentially repopulated cells from the sum of cells explored above. A detailed explanation requires several steps:

$$E = n * d(\alpha + \beta * d) - (T - T_k) * repopulation\ recovery\ rate\ per\ day, \tag{7}$$

$$E = n * d(\alpha + \beta * d) - log_e 2 * (\frac{T - T_k}{T_p}), \tag{8}$$

where $log_e 2$ is equal to 0.693. *T* is the entire duration of the treatment. *Tp* is the average time in days for cells to replicate twice [17].

1.2.2. Application of the linear-quadratic model

The death of cells in either tissue does not appear immediately following application of radiation therapy. Cells stop functioning after a certain number of divisions. This phenomenon explains why side effects may appear after months or even years. The turnover index defines the rate of repopulation, or cell recovery, in different organs and tissues. Therefore, knowledge about cell repair can be used for radiotherapy planning to reach maximal eradication of cancerous cells. Acknowledging which values should be used for an individual patient is the fundamental challenge of implementing the LQ prototype into practice [18].

The sensitivity of cells to the effects of ionizing radiation can be represented visually using the LQ model (Fig. 5). A cell survival graph is usually plotted on a logarithmic scale. This model is only valid for the evaluation of fractionated radiotherapy treatment doses [19].

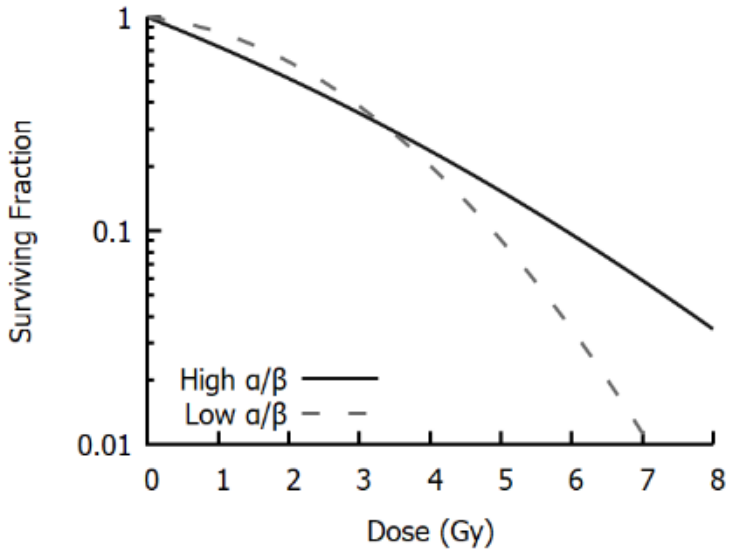


Fig. 5. Linear-quadratic equation representing the fraction of cell survival after increasing the dose (Gy) [19]

The lower dose area has a visible “shoulder”. The α constant accounts for this region, while the effect of the β parameter manifests and predominates in higher doses. As the linear (α) and quadratic (β) parameters are used together to define the curve, the α/β ratio is expressed in Gy. Normally, early responding tissues and tumours have a higher α/β ratio, with an increase in dose inducing greater cell killing. Cells with lower α/β ratios exhibit more pronounced bending of the curve. However, the α/β value is not constant and may shift to one side or another depending on the cell cycle and irradiation circumstances [8,19,20].

Destruction of a chain of the cell’s DNA depends on the dose of radiation and distribution of the particle track around the nucleus (Fig. 6). Single particle hits predominate in lower doses and, therefore, induce fewer lethal breaks in the genetic fragment, while increases in the dose lead to multiple hits of the cell and cause more serious damage. The “breaking point” is where the effect aligns equally to the α/β ratio of 5 Gy. Nevertheless, some of the damage is repaired by the cell itself. The dose accumulated along the path as the radiation travels is defined as the linear energy transfer

(LET). Electromagnetic radiation such as X-rays and gamma rays are classified as low LET and therefore mainly cause single strand breaks inside the genetic material [19].

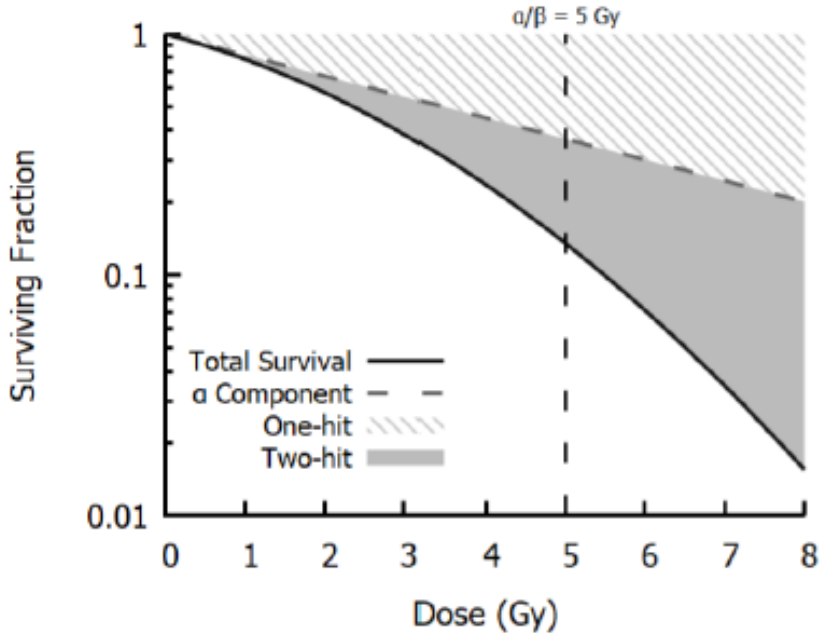


Fig. 6. Differentiation of the radiation-induced DNA strand damages [19]

In the time interval between 6 and 24 hours between fractions, there is evidence of ongoing cell repopulation. Therefore, when treating patients with bi-fractionation it is important to evaluate the DNA repair mechanism pathway [10]. This phenomenon, known as the "shouldering effect," enables disrupted tumour cells to repair and continue to multiply. Nevertheless, the inter-fraction gap should not be less than 6 – 8 hours.

Although the indicated mathematical LQ model is comprehensive, it may be challenging to provide enough re-compensation for interruptions that are exceptionally extended or that occur in the final stages of the planned therapy [16].

The radiobiological effect is best introduced by the application of the linear quadratic model. This includes both healthy tissues and organs as well as tumour complications using different α/β parameters. This model is also useful for assessing cell repopulation factors and thus providing insight into potential compensation for missed radiotherapy treatments.

1.3. Head and neck cancer

1.3.1. Epidemiology

According to the Royal College of Radiologists in UK, head and neck cancer is classified as a rapidly proliferating tumour [21]. In 2018, 835,000 new cases were registered, making head and neck carcinogenesis the 8th most common and deadliest disease in men [22]. With numbers growing every year, this disease has taken the 7th place among fatal cancers by frequency [23].

Worldwide, head and neck cancer is a major health problem. For instance, in the United States of America, 3% of all cancer cases were found to be head and neck-specific, while in European countries, morbidity from this malignancy accounts for 4% of total causes of death. Furthermore, the number of cancer cases fluctuates depending on gender: men have two to four times higher rates of incidence compared with women. Also, different types of head and neck tumours are distributed diversely globally: nasopharyngeal cancer is more prevalent in the Asian region [24], mouth cancer in India, etc. Another aspect is race: African Americans are more often diagnosed with pharynx cancer and have higher mortality rates [21,25,26].

Different conditions including tobacco use and drinking, as well as pathogens such as Epstein-Barr virus and high-risk Human papillomavirus (HPV), are all predisposing factors for head and neck cancer.

1.3.2. Anatomy

The head (Latin *caput*) is flexibly attached to the neck (Latin *collum*), which enables functions such as focusing the head's sensory systems on external signals without moving the entire body towards the object. The cerebrospinal nervous system is protected by the bones of the skeleton that make up the skull and cervical vertebra (the part of the spine in the neck). There are four processing sensory centres in the head: vision, auditory perception and coordination of movements, smell and taste. Moreover, the head is an important component of the digestive and respiratory systems. Altogether, blood supply, nervous control, muscles and bones comprise other important structures of the human body as a unit (Fig. 7).

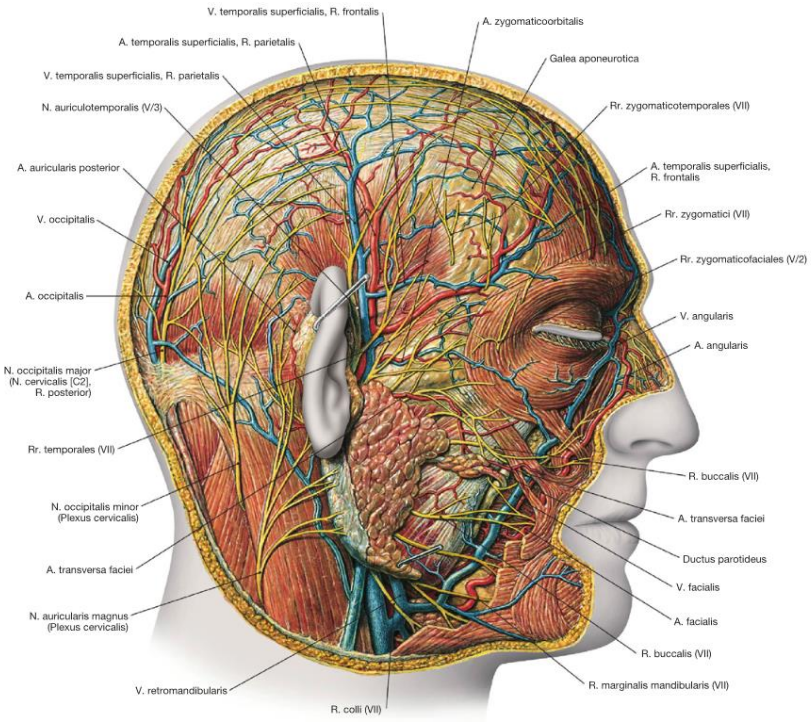


Fig. 7. Anatomical structures of the head [27]

The external occipital protuberance separates the head and neck regions [27]. The base of the neck consists of seven cervical vertebrae connected by a single line (Fig. 8). Inside the spine, cerebrospinal fluid flows up to the lumbar region (backbone). Despite its function in transmitting nervous signals, the neck is highly mobile and can be rotated over a close to 180-degree range. The spinal column also contains specific organs, such as the parathyroid and thyroid gland, and submandibular salivary glands. Due to its many essential components, neck injuries have a higher mortality and morbidity, accounting for 5 to 10% of all significant serious injuries.

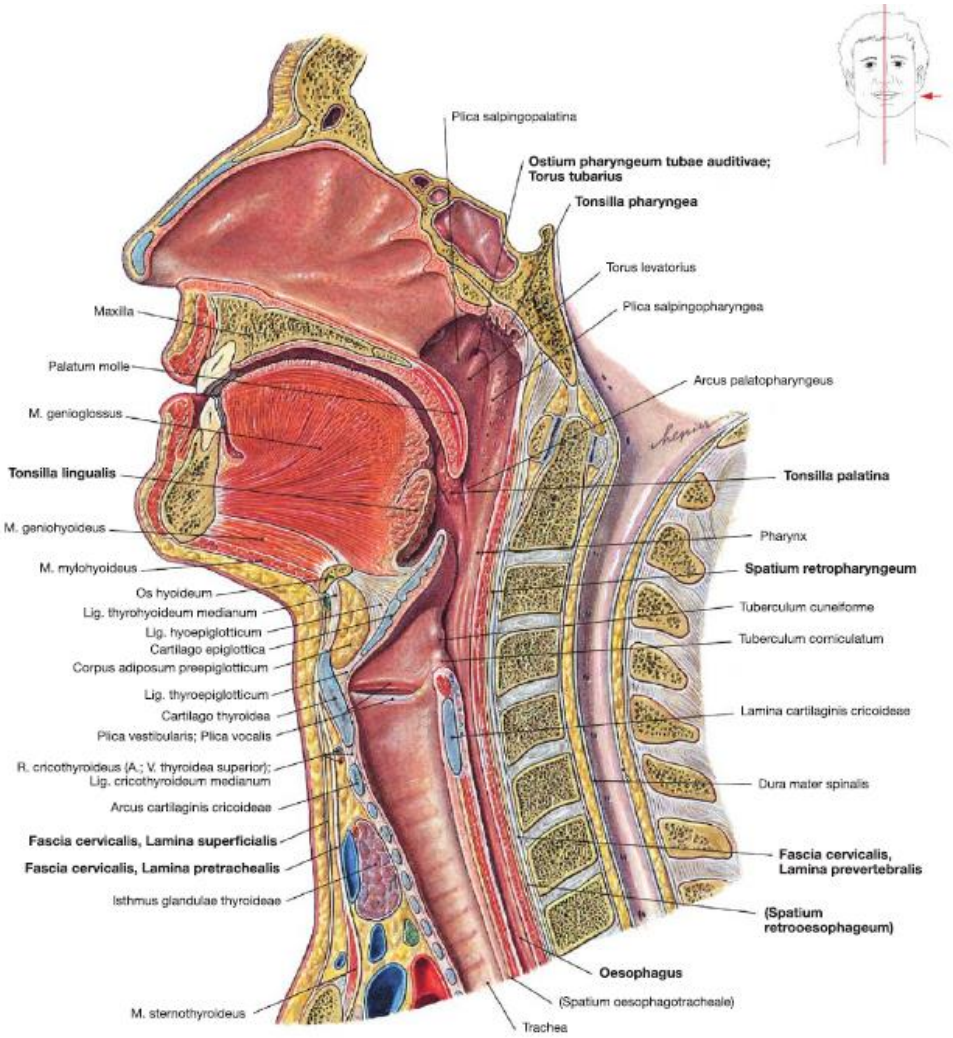


Fig. 8. Midsagittal section of the neck topography [27]

There are three main anatomic classifications of tumours affecting the head and neck: squamous cell carcinoma (SCC) of the larynx, oral cavity, and pharynx. (Fig. 9) [25,28]. SCC accounts for the majority of all the cases [29].

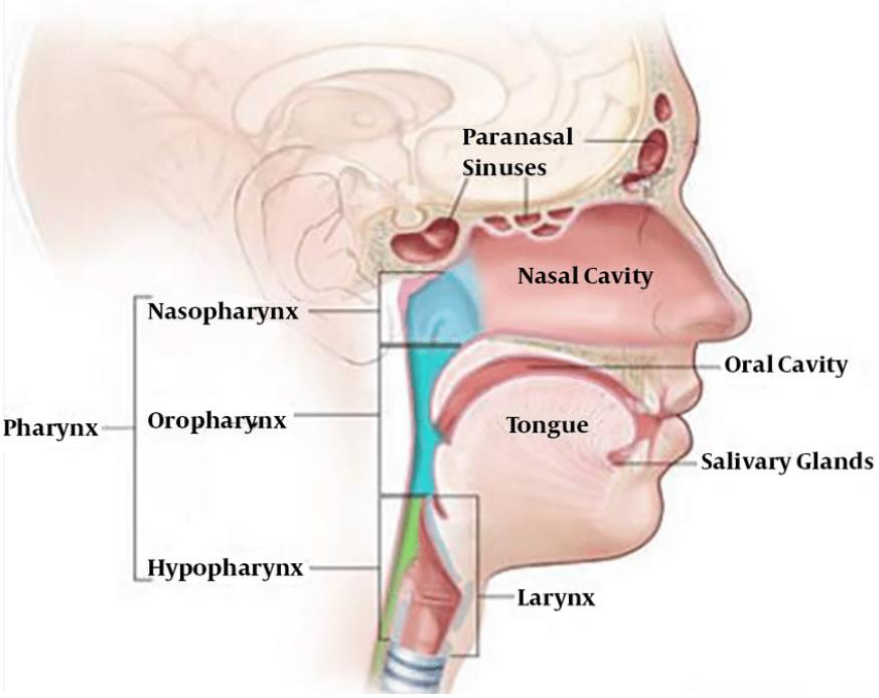


Fig. 9. Anatomical site classification of head and neck cancer [30]

Given the complex anatomy and heterogeneous arrangement of the skull, head and neck cancer appears to be very difficult to manage. Nevertheless, irradiation of the nasopharyngeal region responds well to radiotherapy.

1.3.3. Treatment

Treatment options for the head and neck cancer vary depending on the level of invasion of neighbouring tissues and organs, type, and stage of the cancer. Radiotherapy is the first-line option accounting for the treatment used in 40% of cancer cases [29]. It can be used as a single modality or along with chemotherapy, biological target therapy or surgery. Based on clinical experiments, conformal-intensity modulated radiotherapy (IMRT) proved to be an effective method for malignant cell annihilation [21,31]. The digital data acquired during imaging is displayed in three dimensions. For this reason, using IMRT is much more convenient for detecting the tumour, as well as for protecting healthy cells from excess radiation. As a result, this radiation delivery technique improves the survival probability up to 90% [32,33].

The conventional radiotherapy dose per fraction ranges from 1.5 to 2.5 Gy [13]. Fractionation is designated to spare normal tissues in the exposed volume which receives radiation. The predefined individual and cumulative dose amounts are set by the medical professional and selected in accordance with the type of cancer and therapeutic goal [34]. The proportion of cells that survive after being exposed to radiation for healthy and tumour tissue determines the clinical outcome [10]. Physicians take on liability to manage the compensation method, estimating optimal results as well as the personal criteria. The law of justification must also be applied in the planning process of a radiotherapy procedure. For this reason, treatment relies both on the specialist and on the medical condition in general.

1.3.4. Conventional fractionation and alternatives

Radiotherapy is delivered in a fractionated fashion to lessen both deterministic and stochastic effects on the patient's health [35]. Various studies [4,22,26,35–39] have analysed different dose and fractionation options and their effect on tumour response. The total prescribed dose in radiotherapy (65 – 70 Gy for head and neck tumour) is divided into smaller fractions to achieve the desired result, which is complete destruction of the cancer. An example standard fractionation plan includes 70 Gy over 7 weeks with a course of 35 fractions, which is commonly seen in use across numerous cancer centres. Generally, treatment of cancerous cells of the head and neck is delivered in 2 Gy doses per procedure. This allows for abnormal cell growth to be optimally controlled, as well as for the reduction of potential harm to normal tissue. Many patients' basic radiation fractionation plans had to be revised, beginning with the first peak of COVID-19 pandemic. Due to interruptions and limited time, about half of the patients in the UK received a higher dose than the usual 2 Gy (Fig. 10) [39].

The major factors of radiotherapy are suitable treatment delivery, appropriate dose administration, fractionation, and precise anatomical structure contouring. As a result, radiation therapy should be customised to each patient and focus on the biology of the cancerous cells which can be further specified with additional diagnostic methods, such as genome sequencing.

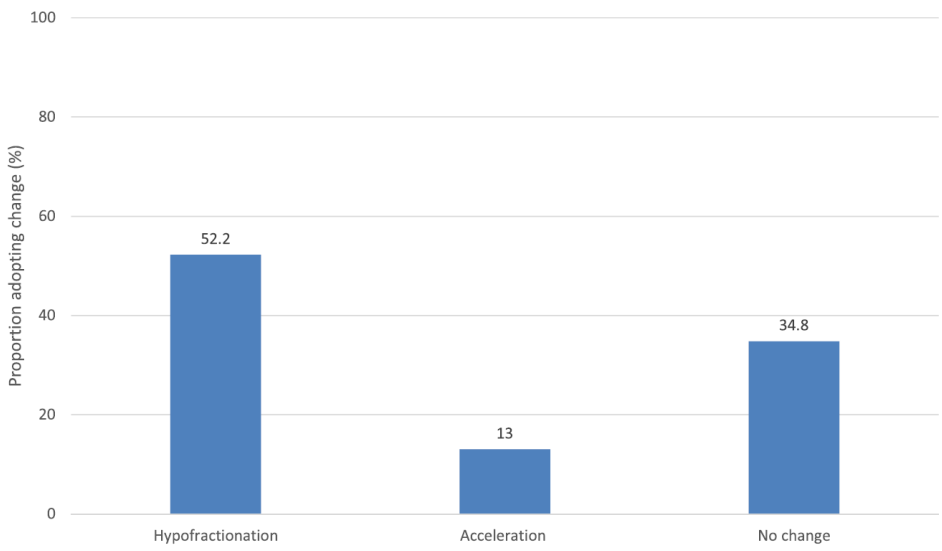


Fig. 10. Radical radiotherapy modification due to the COVID-19 pandemic in the United Kingdom [39]

In additional, the gold standard for head and neck cancer radiotherapy planning was replaced with 65 Gy over 30 fractions.

Some of the principal fractionation techniques are given below:

Accelerated fractions are designed to reduce exposure length, while delivering the conventional amount of radiation. On average, the person receives about 10 Gy on a weekly basis. This fractionation technique controls the repopulation process of cancerous cells.

Hyperfractionation is the practice of performing more fractions on a daily basis than usual, typically 2 to 3, with a dosage which may be above one Gy. As a result, healthy tissue is also protected from increased intoxication.

Hypofractionation refers to fewer radiation sessions with higher dosages per fraction. Patients receive a dose of 30 Gy, which is administered over ten sessions during the entire course of radiotherapy. Typically, palliative care is provided with this technique.

1.3.5. Medical complications

Ionizing radiation is a fundamental component of the treatment options used to battle cancer. The equilibrium between healthy and cancerous tissue may occasionally be disrupted by its effects. When radiation and chemotherapy are combined, the harmful effect can be increased significantly. Unfavourable reactions (Table 1) [40] can be categorized into:

- Acute - deterministic (less than 3 months) tissue effect;
- Long-term - stochastic (up to 3 months) tissue effect.

Table 1. Common complications after radiotherapy procedures in head and neck cancer patients

Onset of adverse effect	**An affected organ or tissue**	**Consequences**
Acute	Mucous membrane	Mucositis
	Skin surface	Dermatitis, erythema
	Upper gastrointestinal tract	Odynophagia, dysphagia
	Vocal bands	Dysphonia
Chronic	Skeleton system	Osteoradionecrosis
	Salivary glands	Xerostomia
	Superficial facia	Fibrosis
	Mandibular muscle	Trismus
	Thyroid gland	Hypothyroidisms
	Acoustic nerve	Ototoxicity
	Musculi pharyngis	Pharyngeal stenosis
	Spinal cord	Myelitis, cerebral radiation necrosis
	Lens	Cataract

The time for an adverse reaction to arise may take minutes or years, depending on the individual case. Some specific anatomical structures, such as part of the gastrointestinal tract from the mouth to the oesophagus, mucosa, and vocal cords have a much greater risk of rapid adverse reactions after prolonged exposure. This variation can be explained by the tissue weighting factor, of which a lower value means a higher susceptibility to ionizing radiation. Although the weighting factors of the salivary and thyroid glands, bone, subcutaneous tissue, jaw muscles, acoustic nerve, and lens vary in some cases, in which they are classified with lower values, these tissues' adverse effects generally belong to the group of stochastic reactions [41].

An additional level of protection of at-risk organs has emerged since IMRT and volumetric modulated arc therapy (VMAT) were introduced into radiotherapy practice. For instance, the preservation of the parotid gland has become more accurate with the transition from conventional to IMRT [31].

Some obstacles are encountered in the assessment of organ toxicity from overexposure:

- accuracy of contours of the structures which need to be preserved;
- dose limits for late tissue complications.

The first challenge depends primarily on the professional performing the anatomical delineation of the organs. Meanwhile, radiation dose limits require an update and more clinical trials with advanced radiotherapy techniques [42].

1.3.6. Acute complications

The basal epithelial damage pathway includes biological and physical aspects, which results in the destruction of the DNA molecule. After the ionizing radiation induces intracellular chemical changes, the free radical transcription element – nuclear factor κB, stimulates the injury of the mucous membrane (Fig. 11).

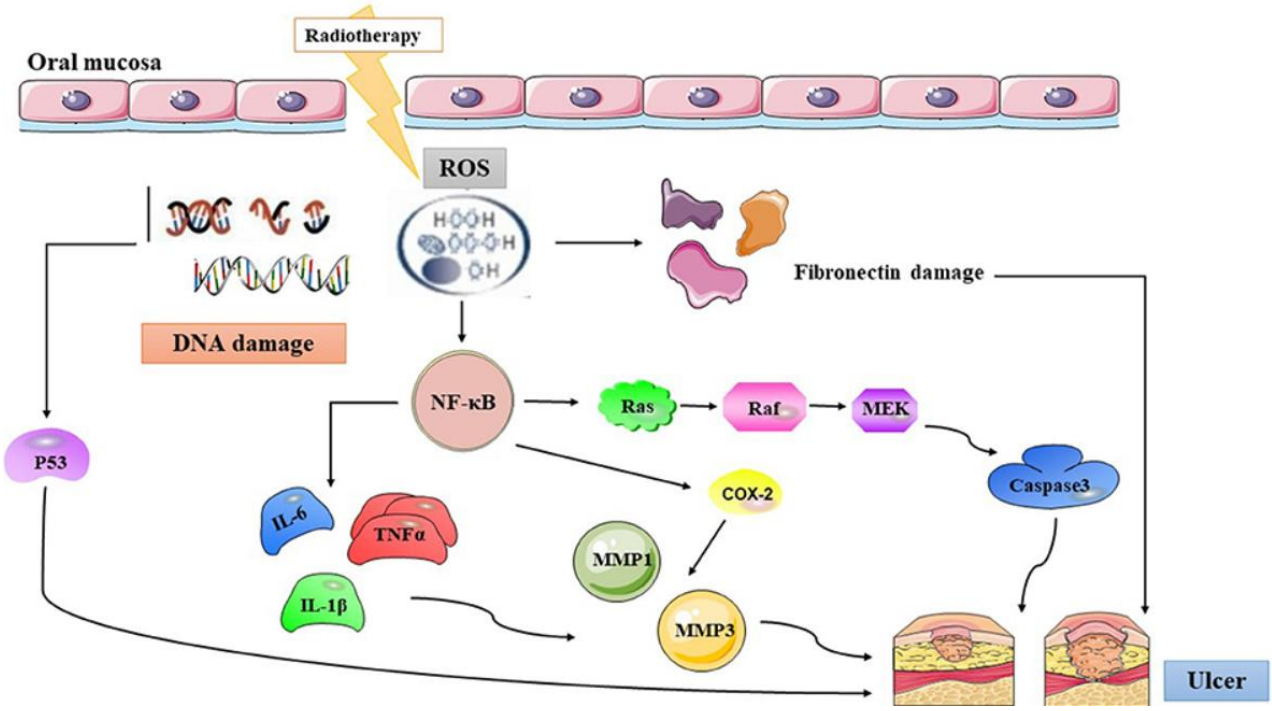


Fig. 11. An overview of the aetiology of ionizing radiation triggered mucositis in the mouth [43]

Mucositis is a major complication of medical cancer treatment and can be characterized as an inflammatory response of the membranes that line the digestive tract. The well-being of patients is strongly affected by mucositis since it is frequently accompanied by mouth and pharynx aching. The level of inflammation and acuteness of mucositis may be impacted by modern radiation treatment delivery technologies [44,45]. The main reasons for mucositis appearance are: radiotherapy regime (dose per fraction, the prescribed whole dose), adjuvant therapy, the size of outlined healthy cells in

the target volume, response of white blood cells (particularly neutrophils), and body weight index below normal [44].

1.3.7. Late complications

A late reaction to irradiation is a type of injury that manifests within months to a few years following the recent completion of a radiation course. For instance, spine injury, brain and bone necrosis, renal disfunction, erythema, skin and subcutaneous fibrosis and pulmonary failure are all considered among possible long-term complications of radiation therapy [10].

Central nervous system (CNS) necrosis is a life-threatening disorder that requires close monitoring. Another frequent stochastic side effect is hearing loss or difficulty and/or maintaining balance. Ototoxicity is associated with excessive irradiation of the inner ear as well as damage of the neighbouring structures (clivus and retropharyngeal lymph nodes) [31]. Difficulty swallowing (dysphagia) is common in patients who undergo radiotherapy procedures, especially those treating head and neck malignancies. Thyroid impairment is another issue which evolves after radiation therapy. Statistically, one to five patients out of ten develop hypothyroidism [31].

1.3.8. Genetic predisposition

As researchers focus on developing novel clinical models, the significance accorded to genetics in determining radiation treatment is expected to rise. A radio sensitivity index has been developed which is calculated according to the presence of a specific reference gene. These reference genes, via gene transcription, determine the cell's susceptibility to irradiation. This method can be applied to head and neck cancer patients in order to prescribe the most suitable treatment method [46,47]. An investigation of genetic predisposition to a specific response to radiation highlighted one gene, DNA-PKcs, which is associated with increased susceptibility to radiation induced damage [7]. In addition, incompletely differentiated tumours demonstrate better treatment outcomes and local control of the delineated target compared with well-differentiated ones [16].

The accuracy of cancer treatment remains a major concern for patients and medical experts. With the development of immune- and biological target therapy in combination with radiotherapy, less toxicity and recurrence of malignant cells can ideally be reached [47]. However, this requires a more detailed study of the human genome and the identification of specific biomarkers that define cancer. Analysis of DNA fragments in tumour cells reveals heterogeneity when comparing different samples. In an effort to learn more about the genome and its relationship to radiotherapy treatments, J.G. Scott et al. published a cohort study and compiled their finding into the GARD (genome adjusted to radiotherapy dose). This model is similarly based on a LQ equation and radio-sensitivity parameter. In the future, GARD may be useful in predicting potential therapy results [48,49].

An intensity ranking formula (from 1 to 10) for ten genes based on their radio-sensitivity properties was derived from the Florida Cancer Dataset. It can be expressed as follow:

$$\mathrm{RSI} = -0.0098009 * AR + 0.0128283 * cJun + 0.0254552 * STAT\,1 - 0 \cdot 0017589 * PKC\text{ - }beta - 0.0038171 * RelA + 0 \cdot 1070213 * cABL - 0 \cdot 0002509 * SUMO1 - 0.0092431 * PAK2 - 0.0204469 * HDAC1 - 0.0441683 * IRF1, \quad (9)$$

GARD is a promising method that can be further developed and applied in daily practice. However, it is only a predictive tool that is not suitable for evaluating treatment outcomes. Another biostatistical model introduced by J. Scott et al. correlated normal tissue and tumour control probabilities together with the highest BED value to optimise radiotherapy dose delivery [50].

The advancement of radiomics and its utilisation will provide significant predictive indicators related to molecular markers. They will hopefully be applied in the near future as supplemental data regarding reaction mechanisms and used to predict tumour physiological behaviour [51].

1.4. An unplanned interruption during radiotherapy

1.4.1. Cancer cell repopulation

Repopulation of cells is considered to be the fast multiplication of either tumour or normal tissue cells after intended eradication using, for example, ionizing radiation [7]. Repopulation is considered to have an onset after 2 – 3 weeks, counting from the first day of treatment [17].

The proliferation of malignant cells depends on the type of cancer [29]. The repopulation mechanism can be explained using a simple image (Fig. 12), where conventional radiotherapy treatment using 2 Gy per fraction is represented. The total dose needed in this area is constant and unaffected by the length of the duration if the therapy is finished just before the start of expected repopulation. T_{delay} denotes the beginning of the ongoing cell division, which can be indicated by the vertical line. For this reason, if the therapy lasts longer than by accounted for T_{delay}, the dose for the isoeffect rises correspondingly. Periods that go beyond the delay will automatically require a higher dose to cope with tumour cell colonization. The figure's distinctive "dog-leg" form demonstrates the presence of a gap for several weeks following the initiation of therapy until quick repopulation begins to occur, after which it advances at a relatively constant pace. Hence, unplanned disruptions that result in intervention sessions extending past this window are especially significant [3].

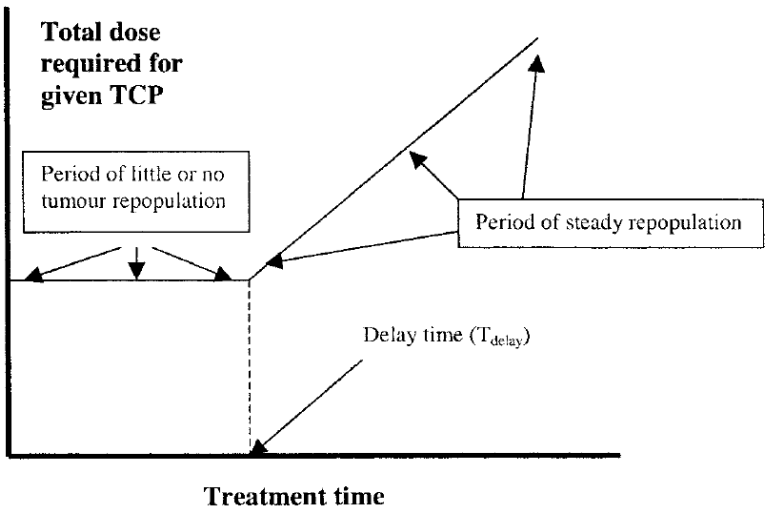


Fig. 12. The treatment dose dependency versus the duration of the radiotherapy and its effect on tumour control [52]

An increase in overall treatment duration may allow malignant cells to divide uncontrollably and thus make it difficult to manage the tumour volume of interest. The reason for the rapid growth of the cancer population depends on the number of cells that become activated due to the effect of a certain biochemical signal, as well as the shorter length of the cell cycle [10]. To achieve the therapeutic goals, the radiation dose must be compensated, avoiding damage to the healthy tissue. All of the tumour stem cells must be damaged in the delineated target volume.

Highly proliferating tissues interfere with more expressed cell division in between radiotherapy procedures [11]. Some of the affected cells are then sterilized and cannot divide any further. However, the surviving cells multiply and can limit the therapeutic progress by increasing up to a third of the total population. As an example, oral mucosa and certain types of cancer (lung, oesophagus, cervix, squamous cell carcinoma (SCC)) of the head and neck and anal region can multiply more rapidly [51]. Stem cells can specialize and perform certain processes, such as rebuilding the tumour. When stem cells can no longer divide, the treatment is expected to be successfully completed. Radiation induced destruction of the nutritional support and apoptosis are the main causes related to cell death. For a more comprehensive analysis of the intervention, survival curves are essential.

Proliferation of malignant cells may begin during radiotherapy and slow down recovery. For this reason, any possible gaps must be avoided during the whole course of the treatment [53]. There is no exact answer, how long it takes for tumour cells to multiply or for the redistribution process to begin. However, if the interruption occurs after approximately 4 weeks, the correlation of reduction in cell death and stimulation of its growth factor in mouth and pharynx cancer is significant [51].

1.4.2. Gap

Radiobiologically, any extension of the radiotherapy course can provoke an abnormal cell division [54]. Clinically, any prolongation of the treatment has a tremendous effect on both rapidly and more "slowly" proliferating tumours. In practice, cancerous cells which multiply in a fast manner are considered a great challenge and any gaps must be avoided in the meantime. Tissues and organs with higher proliferation rate, such as head and neck cancer, are the most affected by occurrence of interruptions between radiotherapy sessions. Even a one-day pause can deteriorate local control by 1.4% [53], while a break of one week can reduce locoregional control by 10-12%. The Ki67 antigen is cell-labelling and is associated with the survival rate. In head and neck cancer, the quantity of this antigen is higher, which significantly increases the recovery rate of the population. Thus, any delay could have tremendous consequences [16,55]. The planning target volume (PTV) prognostic and therapeutic dosage may be decreased as a consequence of the beginning of continuous cell repopulation in tumour tissue between therapeutic absences [56].

1.4.3. Aetiology (reasons)

The major reasons why treatments are interrupted are well acknowledged. An interruption during radiotherapy delivery is not an unusual occurrence [18]. Despite the fact, many of them could be prevented or reduced by setting preventative actions. National holidays and linear accelerator breakdown account for over 70% of disruptions [51]. X. Yang et al. investigated the incidence of

interruptions during a radiotherapy procedure for nasopharyngeal cancer in southern China. Approximately 21% of the population had at least one break during the entire treatment period [24].

The common cause of interruption occurs due to the:

- Technical issues;
- Patient associated problems;
- Holidays;
- Adverse effects;
- Cyberattacks;
- Nature catastrophes (hurricane, tsunami, tornado and etc);
- Covid-19 pandemic.

Gaps in radiation therapy can be related to accidents which occur due to natural causes. As an example, Hurricane Maria caused a three-week countrywide disturbance to health care services in Puerto Rico. In Louisiana, USA, Hurricane Ida lead to the shutdown of some hospital and radiotherapy units [11]. It highlighted the need for updated protocols and estimates for the scale of lengthy treatment interruptions.

Another challenge, which may cause a modification to radiation treatment plans is cyberattacks. In Ireland in 2021, many patients were unable to obtain treatment for up to 12 days due to such an attack. In the future, attacks on information technology (IT) systems might become a critical issue to the health system [56,57].

In China a leading cause (39 – 46%) of radiotherapy gaps were Spring Festival holidays [21]. The treatment of malignancy can be significantly impacted by adverse effects, as an example, ulcers in the mouth or gastrointestinal tract. Moreover, mucositis may contribute to the interruption of radiotherapy delivery and thus reduce expected survival [44].

The evolution of linear accelerators has been dynamic, and their operational accuracy and reliability have significantly increased. Nonetheless, operational malfunction and breakdown do still occur from time to time. The main reasons connected with the machinery break are dysfunctions of the collimator, radiofrequency, “LaserGuard”, potentiometer, blockage of water temperature and amount, and the chamber of the monitor [58].

Severe acute respiratory virus syndrome-CoV-2 (SARS-CoV-2) virus, which was responsible for the COVID-19 pandemic, is extremely contagious and primarily transmitted by airborne droplets [39]. At the time of COVID-19 wave, in the UK a greater awareness of the problems related to the radiotherapy interruption became more relevant [3]. However, the disruption spanned the globe and led to the need for changes in the health care system. Throughout the outbreak, there was a definite tendency for cancer centres to increase single-fraction dose and/or decrease treatment duration [39].

1.4.4. Timing

The timing, when unplanned gap appears, can determine the later consequences for the person being treated with radiotherapy. A previous study [59] represented poorer locoregional control, if the interruption occurred before the nineteenth day from the treatment beginning and the end.

Radiotherapy which is given after surgery is very sensitive to any variation in treatment [16]. However, a two-week interval was proved to exist during which the cell begins to repopulate (lag period). For this reason, early gaps are less relevant in estimating missed days of radiation therapy [16]. Even though, head and neck tumours proliferate in a fast manner, certain types of nasopharyngeal cancer have shown no effect on the timing of the gap [16].

G. Pozo et al. conducted a study, which analysed total duration of missing days within radiotherapy procedure. As a result, most interruptions (~ 77%) lasted from a single day to five consecutive days and only 6% of patients experienced a gap longer than ten days [51]. A study carried out by J. Yao et al. [60] revealed prognostic statistics which state that a gap of more than 7 days results in higher mortality. If the interruption interval exceeds ten days, 5 year survival decreases from 10 to 20% [21]. Therefore, a pause of roughly one week is connected to an apparent decrease in locoregional control from approximately 10 to 14% [16]. Meanwhile, a pause, which lasts 15 days or more caused the radiotherapy results to deteriorate significantly. For SCC, an interruption of even one day can result in a 0.8-1.6% reduction in target control [3]. The most difficult situation occurs, when the gap occurs during the last week of the treatment. Together with a treatment disruption, acute adverse events manifest [18]. Gaps during treatment underline a long-term impact linked to higher mortality rates, depending on when they appeared.

It is extremely difficult to predict the onset of tumour cell repopulation. One of the reasons is that radiotherapy courses can begin on any working day (from Monday to Friday). Therefore, later start of the therapy can negatively affect the overall treatment outcomes. Also, it would be more difficult to implement a compensation scheme. Thus, radiation therapy should not be begun on a Friday. However, precise timing was not marked in any article [53]. From a radiobiological standpoint, interruptions that appears early or later during the therapy are not favourable. However, delay in the beginning of a treatment can be controlled and compensated much more effectively [11,52].

1.4.5. Guidance on missed treatment compensation

A guidance on compensating for missed radiation therapy was first introduced and published in 1996 by the Royal College of Radiologists in the UK. Afterwards, the regulations were corrected in 2002, 2008 and, finally, 2019 [17]. Any interruption of radiation therapy is undesirable and should be avoided if possible. Due to head and neck cancers' relative high propensity for multiplication of clonogenic cells, a one-day break in the treatment schedule could be harmful. Various studies [52,53,61,62] have investigated the potential harm of interrupted radiation treatment delivered alone or together with adjuvant therapy (chemo, biological target, brachytherapy or surgery). When correcting for missed treatment delivery, tolerance boundaries for normal tissue need to be maintained when choosing the compensation strategy.

The initial treatment strategy may be irreversibly altered by the break during radiation course. Following the pause, cancer stem cells have a greater opportunity to proliferate. As a result, clonogenic assays form new colonies in the cancerous tissue, thereby reducing the BED_{10} and leading to worse prognoses [51]. An analysis of cell regeneration and repair is done using the radiobiological concept [46]. The key objective is to get the same result as in the original plan while avoiding unacceptably negative side effects. Nonetheless, the overall radiation dose must never go above the

thresholds for organs at risk. This necessitates to re-evaluate both cancer and healthy tissue plans (Fig. 13) [36].

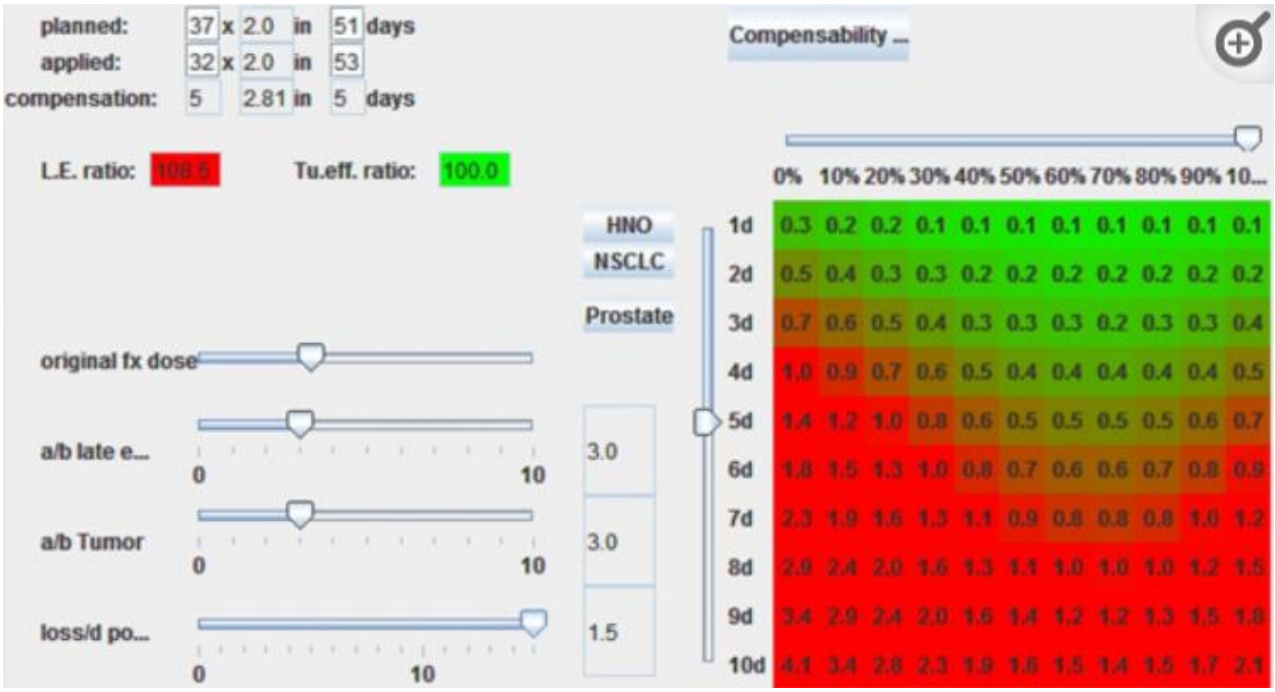


Fig. 13. Visual example of compensation model in 2D matrix [61]

Delays during radiotherapy affect the entire health care system by causing additional expenses and requiring extra resources to implement another treatment strategy. They also affect the patient's health by reducing overall survival and locoregional control.

2. Materials and methods

This scientific project was completed at the Kaunas University of Technology in cooperation with the Lithuanian University of Health Sciences Hospital (LSMUH), Kaunas Clinics, Oncology Hospital as part of a master's thesis. The aim of the research was to develop an acceptable compensative model for unplanned radiotherapy interruptions for head and neck cancer. This was to be done in accordance with the recommendations first proposed by the Royal College of Radiologists in 1996 [62], with the latest guidelines following in 2019 [53]. The mathematical model was implemented using Microsoft Excel. Applying the previously developed LQ model in order to perform BED calculations (for the tumour and organs at risk), new values for dose per fraction were obtained in a set of test cases. The determined values were evaluated using the treatment planning system "Eclipse" and the novel radiotherapy planning technique – volumetric arc therapy (VMAT) (Fig. 14). Its accuracy is ensured by regular testing of the gamma index, which has a clinical reference of 2 mm/ 2% or 3 mm/ 3%.

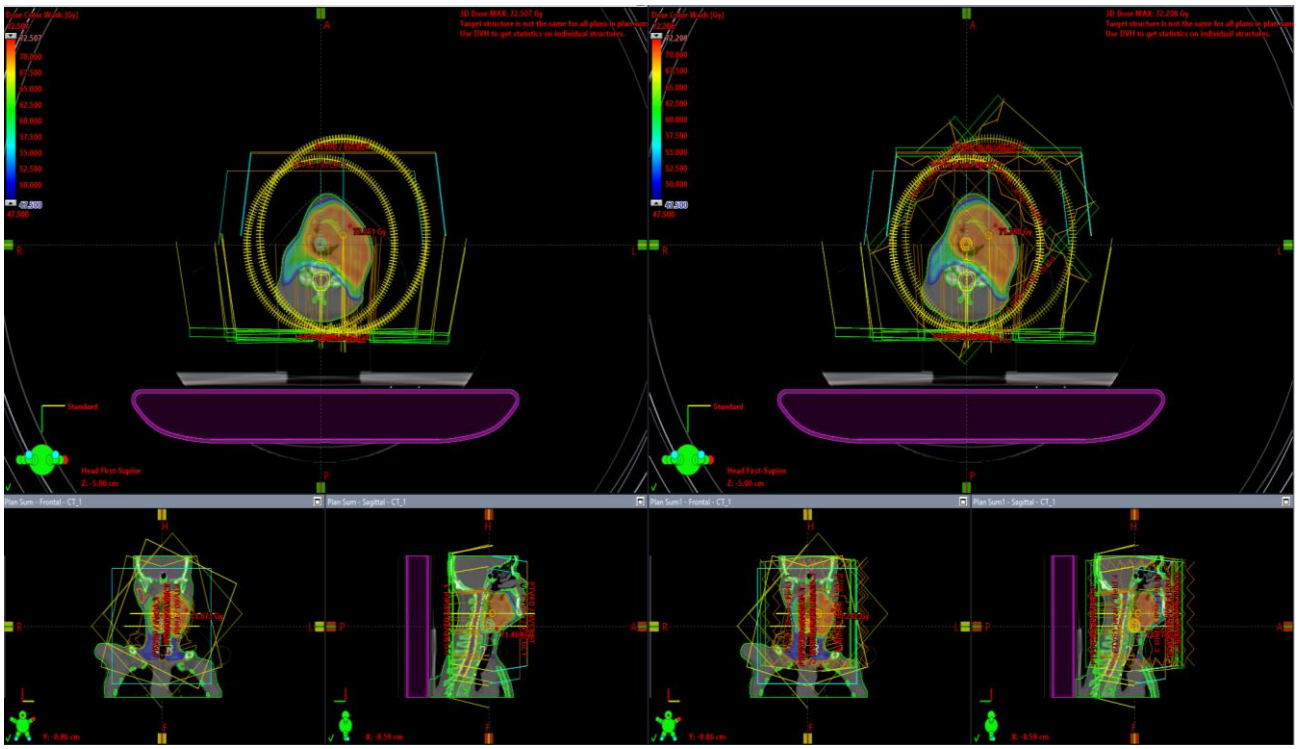


Fig. 14. View of the VMAT radiotherapy re-planning system graphical user interface (GUI)

After re-calculating the modified fractional dose, the amount of irradiation to critical organs also changes. Plans that exceeded the tolerable doses for delineated critical organs were re-planned trying to achieve the tolerable level.

In total 14 patients of the LSMUH - Kaunas Clinics, Oncology Hospital were evaluated. The study group was selected by random sampling. Each patient was estimated in three stages:

- 1 stage: PTV50 – 50 Gy;
- 2 stage: PTV60 – 10 Gy;
- 3 stage: 10 Gy.

These cases were chosen according to the following criteria: gap duration, radiotherapy regime, as well as location of the malignancy. This study focused on patients with certain type of tumours who missed part of their treatment and, therefore, required a recalculated treatment plan. Furthermore, the analysis only assessed depersonalized information, such as cancer site and gap length. For this reason, ethics board approval was not required.

2.1. Categorization of patients

With the aim of decreasing decision-making time and improving treatment outcomes, it is recommended to triage patients into different categories. The concerned physician must follow the classification procedure of various clinical cases proposed by the "Commission on Radiological Protection" [34]:

Category 1: Rapidly proliferating tumours. Head and neck, rectal, vaginal, oesophageal, lung, cervix carcinoma and squamous cell carcinomas (SCC) in other sites.

Category 2: Slower proliferation than the first category, but also requires break compensation. Examples are prostate, brain, and breast cancer, as well as sarcomas.

Category 3: Palliative patients and those with non-malignant cancer.

When individuals are assigned to a specific category, their respective treatment plan must be evaluated in more detail. In analysing similar articles [5,51] a consensus was reached.

Important patient-related clinical parameters include the following:

- Medical records;
- Age;
- The type of the treatment (palliative, radical, with or without operative intervention);
- Histopathology, anatomy, physiology, biochemistry of the cancer cells;
- With or without adjuvant therapy;
- What caused the interruption;
- The need to reassess radiotherapy;
- Protection of healthy tissue.

2.2. The research study process

The development of the compensation model was implemented based on calculations of cell survival and the actual dose that falls within the planning target. With regard to the linear quadratic (LQ) model and biological effective dose (BED), the equations were combined to measure the consequences of missed treatment courses, and to simultaneously recover the assigned dose to the tumour while avoiding excess radiation to healthy tissues. While the derivations of LQ are explained in the literature review (see subsection 1.2.1.), the methodological part focuses on the calculation of the BED.

The arrangement of the present study is divided into three main segments (Fig. 15):

1. Primary calculations, that include BED assessment for early complications and tumours;

– Data on missed treatment duration;
– Designation of a potential compensation plan;
– Re-calculation of BED_{10} for a specific tumour;

2. Application of quadratic equation which incorporates the initial and past courses of radiation therapy in order to obtain a new dose per fraction;

   – Verification of the new fractional dose for critical organs using the radiotherapy planning system;

3. Realization of a compensation plan into the clinical practice if dose limits are not exceeded.

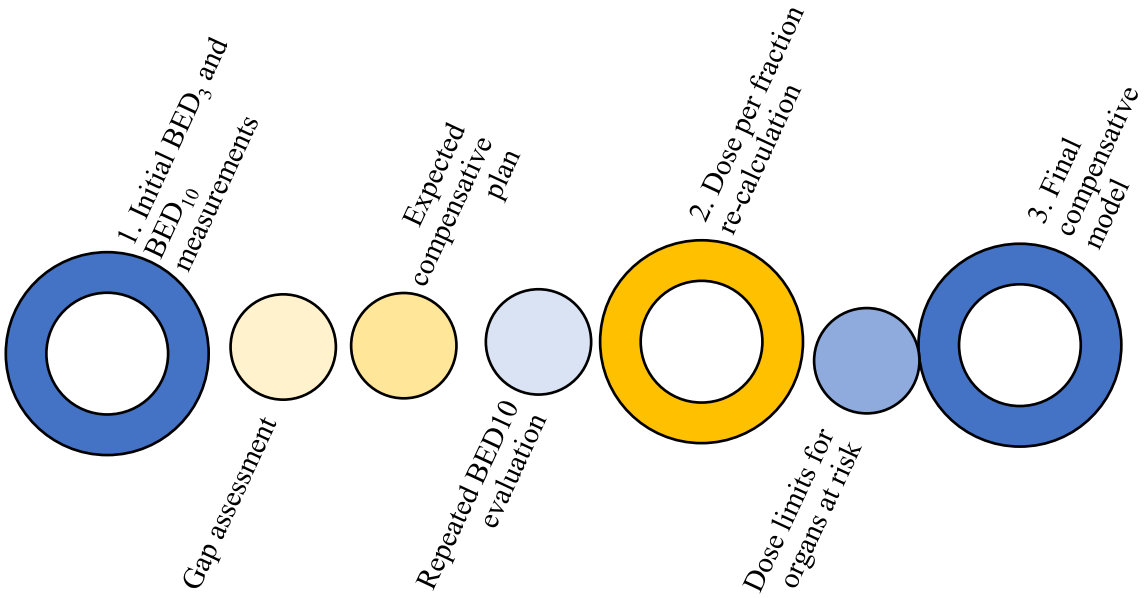


Fig. 15. Development of the compensative model in a time scale

This scheme does not account for cases where lost treatment can be recovered though weekends or bi-fractionation.

2.2.1. Biological effective dose calculation

BED defines the biological effect that can be expressed as a logarithmic function of ionizing radiation-induced cell killing. *BED* values diverge depending on the *α/β* ratio: higher *α/β* corresponds to the tumour or early proliferating healthy cells, while lower *α/β* ratio represent late tissue and organ complications.

First, the initial BED is calculated according to the given formula [63]:

$$BED_3 = \frac{E}{\alpha} = total\ dose * RE = total\ dose * (1 + \frac{d}{\alpha/\beta}), \quad (10)$$

However, this formula can only be applied for measuring late complications, because it does not include a population recovery probability.

For an early responding tissues and tumours, BED_{10} is calculated by subtracting the logarithm of potentially repopulated cells. Therefore, final calculation of the BED_{10} [63]:

$$BED_{10} = n * d\left(1 + \frac{d}{\alpha/\beta}\right) - ((T - T_k) * \left(\frac{0.693}{\alpha * T_p}\right)), \quad (11)$$

The *Tp* for the head and neck tumour is acknowledged to be three days, while for other carcinomas this number is approximately five days. The *Tk* is estimated as the start ("kick off") of a cell proliferation in days. For rapidly multiplying (especially lung, head and neck) cancer, *Tk* varies from 21 – 32 days [17].

A part of the BED_{10} formula - $(\log_e 2 * (\frac{\mathrm{T-Tk}}{\mathrm{Tp}}))$ can be expressed as the *K* coefficient, which describes the amount of radiation necessary to sterilise repopulated cells. Its unit is Gy/day [3]. In some studies, the *K* value may vary from 0.8 to 2.2 Gy/day according to the individual case. However, most of the clinical calculations were performed using an average value of 0.9 for the *K* factor [17,52,54].

The *BED* describes the effective dose, while the equivalent dose measurements using a fraction of 2 Gy (EQD_2) represents the actual dose delivered to the target. The EQD_2 formula [17,63] is expressed as follow:

$$EQD_2 = n * d(\frac{d+\alpha/\beta}{2+\alpha/\beta}), \quad (12)$$

2.2.2. Compensative plan evaluation based on the gap

Discontinuation of radiation therapy should be considered before any compensative strategy is initiated. In this study, the duration of missed treatment was divided into three main periods (Fig. 16):

- Early, which takes place from the beginning to 14 days;
- Medium, from 15 days to 21 days;
- Late, 22 days to completion.

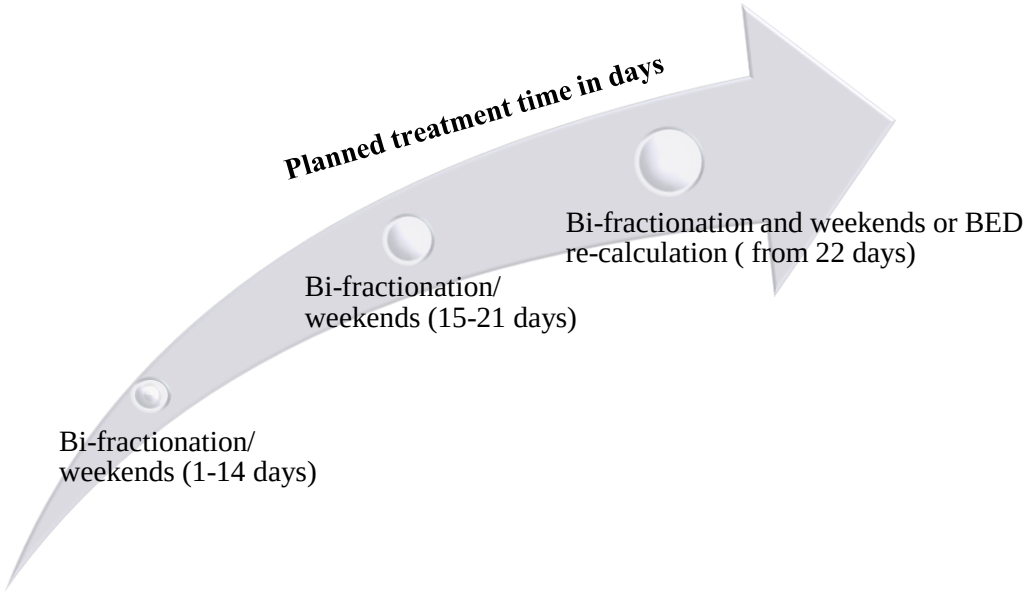


Fig. 16. Simplified layout of the compensation plan for a certain period (days) when a gap occurs

Lost courses at the beginning and in the middle of treatment were usually compensated by a regime of two fractions per day or weekend radiotherapy sessions. However, longer breaks (10 days or more) that occurred at the end required more consideration (Table 2). In addition, the length of the gap also affected the overall evaluation process.

Table 2. The example of lost treatment estimation

Nr. of the situation	Gap length (days)	Applied fractions	Decision
1.	14	20	The interruption occurred after 28 days. The BED_{10} calculated. To avoid a long extension, only 10 factions applied after the break. The amount of radiation for certain organs estimated, based on the results.
2.	10	20	The interruption occurred after 28 days. The BED_{10} calculated. To avoid a long extension, only 12 factions applied after the break. The amount of radiation for certain organs estimated, based on the results.

When deciding the total duration of the treatment, it is noted that the first day of radiotherapy is counted as the zeroth. For this reason, if the initial number of fractions is 35, assuming radiotherapy starts on Monday, treatment would continue for a total of 46 days.

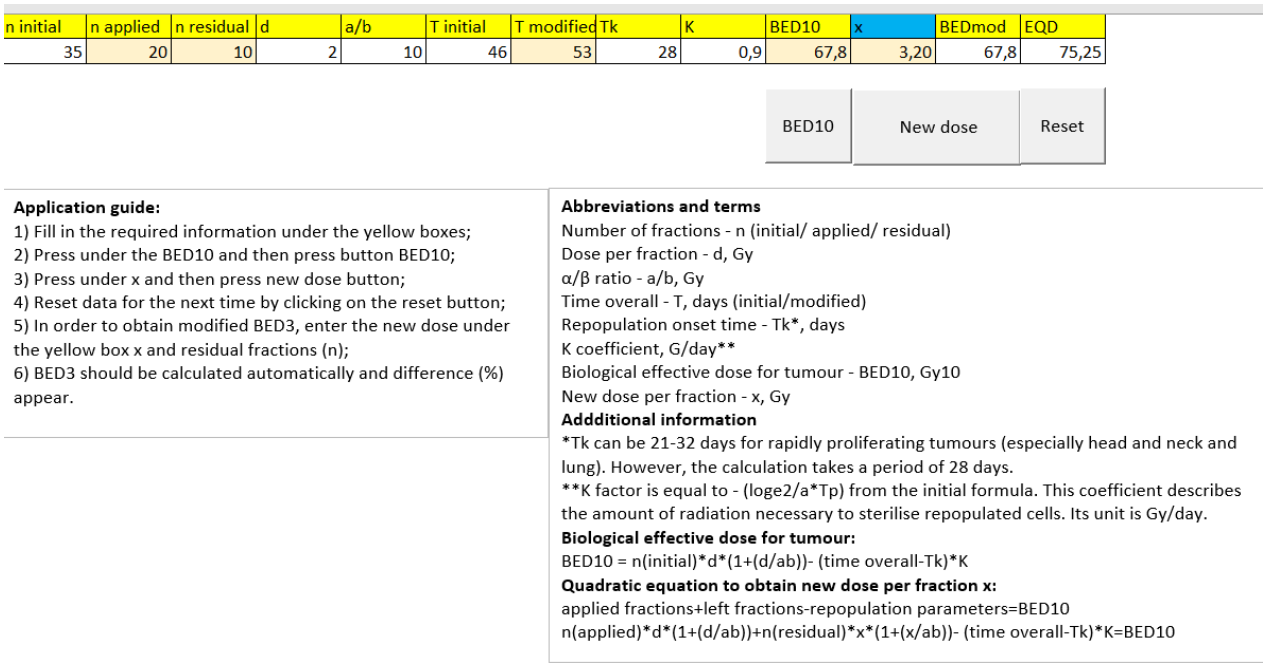
This assessment has some uncertainty and can only be used as an emphasis in recalculating treatment plans in certain situations. For this reason, the responsible personnel (radiologist or medical physicist) must make a decision and evaluate each case individually.

2.2.3. Re-evaluation of biological effective dose

Once the recalculation of the radiobiological model was chosen, the next step was to find a new dose for the fraction. Therefore, the applied and predicted BED_{10} were multiplied by the repopulation recovery factor. The designated formula [63] is given below:

$$BED_{10} = n(applied) * d * \left(1 + \frac{d}{\alpha/\beta}\right) + n(residual) * x * \left(1 + \frac{x}{\alpha/\beta}\right) - (T - T_k) * K, \qquad (13)$$

where *n (applied)* is the number of completed fractions, *n (residual)* the number of planned fractions, and *x* the new dose per fraction in Gy. A quadratic equation was solved to obtain the new experimental dose. An Excel button has been developed to make calculation process simpler (Fig. 17).



n initial	n applied	n residual	d	a/b	T initial	T modified	Tk	K	BED10	x	BEDmod	EQD
35	20	10	2	10	46	53	28	0,9	67,8	3,20	67,8	75,25

BED10 | New dose | Reset

Application guide:
1) Fill in the required information under the yellow boxes;
2) Press under the BED10 and then press button BED10;
3) Press under x and then press new dose button;
4) Reset data for the next time by clicking on the reset button;
5) In order to obtain modified BED3, enter the new dose under the yellow box x and residual fractions (n);
6) BED3 should be calculated automatically and difference (%) appear.

Abbreviations and terms
Number of fractions - n (initial/ applied/ residual)
Dose per fraction - d, Gy
α/β ratio - a/b, Gy
Time overall - T, days (initial/modified)
Repopulation onset time - Tk*, days
K coefficient, G/day**
Biological effective dose for tumour - BED10, Gy10
New dose per fraction - x, Gy
Addditional information
*Tk can be 21-32 days for rapidly proliferating tumours (especially head and neck and lung). However, the calculation takes a period of 28 days.
**K factor is equal to - (loge2/a*Tp) from the initial formula. This coefficient describes the amount of radiation necessary to sterilise repopulated cells. Its unit is Gy/day.
Biological effective dose for tumour:
BED10 = n(initial)*d*(1+(d/ab))- (time overall-Tk)*K
Quadratic equation to obtain new dose per fraction x:
applied fractions+left fractions-repopulation parameters=BED10
n(applied)*d*(1+(d/ab))+n(residual)*x*(1+(x/ab))- (time overall-Tk)*K=BED10

Fig. 17. Microsoft Excel page designed to calculate BED_{10}

2.3. Assessment of complications

Dose limit recommendations for protected tissues and organs were first introduced in the period between 1950 and 1970. The guidelines included restrictions on at-risk organs for physicians and medical physicists to consider (Table 3). In 2010, the "Quantitative Analyses of Normal Tissue Effect in the Clinic" (QUANTEC) protocol was released with new dose constrains, which were approved for conventional radiotherapy techniques, such as 3D technology. These guidelines were ascertained after clinical experiments on healthy tissues. Nevertheless, as radiation delivery methods improve, organ and tissue toxicity limits must continue to be updated [31,42,64,65].

For our studied set of cases, organs such as the spinal cord and parotid glands on both sides were selected. The modified dose was subsequently tested using the computerized radiotherapy planning program "Eclipse". The main criterion was compliance with the limits of organs at risk. Restrictions were designed following the QUANTEC protocol [31,42].

Table 3. Guidelines for limiting radiotherapy dose (Gy) to organs in the head and neck region [31,42,64,65]

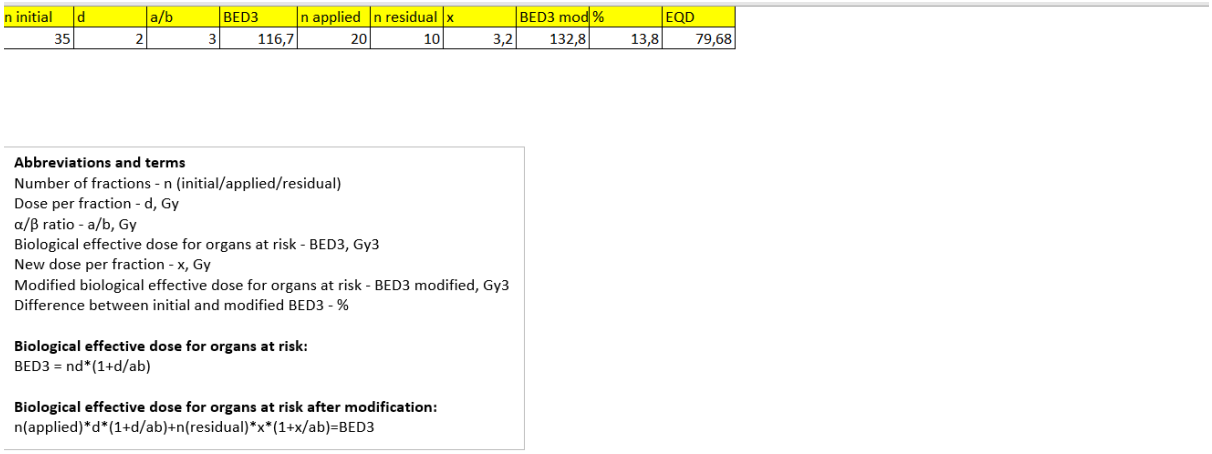
Exposed body structures	**Dose restriction in conventional radiotherapy (Gy)**	**Tolerable dose (Gy)**
Mandible bone	Dmax < 70 – 73.5	Dmax < 65 Dmean < 60
Eye (retina)	Dmax < 40	Dmax < 45
Larynx	Dmax < 50 – 66 Dmean < 40 - 48	Dmean < 50
Lens	Dmax < 4 Dmean < 6	Dmean < 10
Optic nerve and chiasm	Dmax < 50	Dmax < 54 - 55
Parotid gland	Dmean < 25 - 26 (for both glands)	Dmean < 30 (for single gland)
Pharyngeal muscles	Dmean < 50 - 54	Dmean < 60
Spinal cord	Dmax < 45 - 50	Dmax < 54
Thyroid	Dmax < 45 Dmean < 30	

*Dmax – maximal dose for the specific organ. Dmean – the average radiation dose, which can be delivered during the procedure.

Assessment of effects on healthy tissues included theoretical knowledge and practical examination. Therefore, the evaluation process included not only consideration of dose volume histograms (DVH), which define the exposure of surrounding healthy organs, but also spatial properties of radiation allocation, and other comorbidities related to the patient. As new radiation therapy methods are introduced into cancer treatment, limiting doses should be recalculated.

2.3.1. Evaluation of organs at risk

The difference in radiation doses after applying the compensative plan can be compared side by side using Microsoft Excel package (Fig. 18).



n initial	d	a/b	BED3	n applied	n residual	x	BED3 mod	%	EQD
35	2	3	116,7	20	10	3,2	132,8	13,8	79,68

Abbreviations and terms
Number of fractions - n (initial/applied/residual)
Dose per fraction - d, Gy
α/β ratio - a/b, Gy
Biological effective dose for organs at risk - BED3, Gy3
New dose per fraction - x, Gy
Modified biological effective dose for organs at risk - BED3 modified, Gy3
Difference between initial and modified BED3 - %

Biological effective dose for organs at risk:
BED3 = nd*(1+d/ab)

Biological effective dose for organs at risk after modification:
n(applied)*d*(1+d/ab)+n(residual)*x*(1+x/ab)=BED3

Fig. 18. Microsoft Excel page assigned to measure late complications

The formula for late complications was derived from the sum of applied BED_3 and residual BED_3 [63]:

$$BED_{3(modified)} = n(applied) * d * \left(1 + \frac{d}{\alpha/\beta}\right) + n(residual) * x * (1 + \frac{x}{\alpha/\beta}), \qquad (14)$$

Afterwards, the difference (%) was calculated by the given formula:

$$BED_3(\%) = \left(\frac{BED_{3(modified)}*100}{BED_{3(initial)}}\right) - 100, \qquad (15)$$

2.3.2. Completion of compensation strategy

Treatment modification due to a gap in delivery should be done to maintain similarity to the initial plan. In addition, dose limits are recommended to be as low as possible. To develop a suitable plan for the replacement of missed treatment days, it is necessary to evaluate various clinical aspects:

- Number of fractions,
- Dose per fraction,
- Duration of the treatment,
- Duration of the break,
- K factor for repopulation (Table 4),
- α/β value for tumour and normal tissue (Table 4).

Table 4. K factor (Gy/day), which defines the rate of tumour regeneration in specific organs and their α/β (Gy) values

Organ	**K factor value (Gy/day)**	**α/β meaning (Gy)** [20]
Cervix	0.5 – 0.8 [66]	10
Head and neck	0.9 [53,67]	10
Breast	0.3 [68]	4
Prostate	0.1 – 0.3 [69]	4

3. Results and discussion

3.1. Interruption simulation in clinical practice

An analysis of different interruption scenarios presented mixed results (Table 5). The radiobiological data calculations were chosen instead of those from other compensatory methods (bi-fractionation or application of radiotherapy on weekends and public holidays). This method was selected expressly to estimate the average dose and overall duration, when other strategies cannot ensure adequate recovery of lost radiation courses. The main variable was the interruption interval, which ranged from 7 to 14 days. An additional factor, late tissue and organ complications, was evaluated after the introduction of the new fractional dose.

Table 5. Results of the different interruption scenarios and BED_3 for late normal tissue complications following the compensative strategy

Situations	Gap (days)	T modified	n applied	n residual	x (Gy)	BED3 modified (Gy)	Difference in BED_3 (%)
1.	14	53	20	10	3.2	132.8	13.8
2.	14	60	20	15	2.6	139.5	19.5
3.	12	53	20	10	3.2	132.8	13.8
4.	10	53	20	12	2.8	131.6	12.8
5.	10	58	20	15	2.5	135.4	16.1
6.	8	53	20	14	2.43	128.2	9.9
7.	8	56	20	15	2.42	132.2	13.4
8.	7	53	20	15	2.29	127.2	9.1

In the first situation, the duration of the break was chosen to be 14 days. Discontinuation occurred at the end of the course of the radiotherapy. The final plan exceeded only one week (from 46 to 53 days). However, there was not enough time to complete the entire course. Therefore, five fractions were lost and compensated with an increased dose of 3.2 Gy. However, missing fractions should not have a great impact on the overall treatment. This can be considered to have been validated by Vasiliadou's et al. [39] study performed during the COVID-19 pandemic, when malignant tumours were completely cured using a total dose of 65 Gy. It should be considered that the dose for late complications exceeds the initial value by 13.8%, as any increase in dose are unfavourable. Nevertheless, an actual impact on critical organs can be seen applying the new dose in the radiotherapy re-planning program.

A significantly lower dose of 2.6 Gy was registered in the second situation by increasing total treatment time by an additional two weeks and completing a full plan of 15 fractions. Unfortunately, healthy tissue exposure grew from 13.8 to 19.5%. Furthermore, according to the most recent recommendations, extending treatment duration by two weeks would be considered unacceptable.

Results were similar when 12-day and 10-day gaps were evaluated for a total treatment duration of 53 days. Only the number of accomplished fractions varied from 10 to 12. In contrast, the ten-day interruption compared by choosing different timing. In order to complete all 35 fractions, the

treatment period was extended by 5 days. This reduced the new dose from 2.8 to 2.5 Gy, but increased the irradiation effect for healthy organs by 3.3%.

The eight-day break proved easier to compensate and delivery period extended by a week or week and three days to complete initial treatment. Accordingly, there was a 3.5 percent difference in critical organ exposure, even though the received dose diverged by only one hundredth of a decimal point. The seven-day break was the easiest from a compensation point of view and gave satisfactory results: 2.29 Gy dose per fraction and 9.1% increase in dose for organs at risk. This compensation required only a one-week extension.

A similar study was conducted by Putora et al. [61]. A tool was created in Java that simulated a missed treatment compensation calculator (subsection 1.4.5., Fig. 13). The new modified dose per fraction was represented in a 2D matrix. One axis showed the days required for compensation, the other illustrated the intensity of the shift from offensive to defensive treatment. This model, however, is not convenient for rapid assessment of disruption during rescheduling of radiation therapy. Also, this study did not examine adjuvant therapy, different fractionation arrangements, or possible adverse effects.

To conclude the radiobiological assessment, the BED for early and late complications as well as for the tumour were calculated with the program created in "Excel", as a test of its functions. The Methods and Materials chapter provides detailed instructions on how the facilitated calculations were achieved.

3.1.1. Measurements of late complications using a radiotherapy planning system

The evaluation of late-responding organ exposure after radiotherapy re-planning was done for 14 patients (Fig. 19 – 21 and Table 6 - 8).

In this particular situation, cancer of the root of the tongue was chosen. Kilo-voltage cone beam computed tomography (kV-CBCT) imaging was performed during the planning process. Different variables were extracted from the presented results: target structure, number of fractions, dose per fraction and total dose, field number, monitor units (MU) and field weight (Table 6, 7).

Table 6. The sum of the original radiotherapy plan for root of tongue and lymph nodes

Target Structure	Plan weight	Number of Fractions	Dose per Fraction (Gy)	Total Dose (Gy)	Field ID kV-CBCT	MU	Field Weight
PTV50	1.00	25	2.00	50.00	Field 1	161.4	0.807
					Field 2	183.4	0.917
					Field 3	182.8	0.914
PTV60 (boost)	1.00	5	2.00	10.00	Field 1	245.6	1.228
					Field 2	240.7	1.204
PTV70 (boost)	1.00	5	2.00	10.00	Field 1	447.5	2.238

Table 7. The sum of the modified radiotherapy plan for root of tongue and lymph nodes

Target Structure	Plan weight	Number of Fractions	Dose per Fraction (Gy)	Total Dose (Gy)	Field ID kV-CBCT	MU	Field Weight
PTV 70 (boost)	1.00	5	2.00	10.00	Field 1	4.475	2.238
PTV50	1.00	3	3.20	10.02	Field 1	3.323	0.972
					Field 2	306.7	0.897
					Field 3	317.0	0.927
PTV60 (boost)	1.00	3	3.20	10.02	Field 1	3.839	1.000
					Field 2	318.0	1.000
					Field 3	322.9	1.000
					Field 4	219.5	1.000
PTV50	1.00	20	2.00	40.00	Field 1	161.4	0.807
					Field 2	183.4	0.917
					Field 3	182.8	0.914

The two plans were visualized and compared based on their geometry and maximal doses to the target (Fig. 19 and 20). In the original plan, the maximum dose was 75.51 Gy, while in the compensated plan it attained only 72.21 Gy.

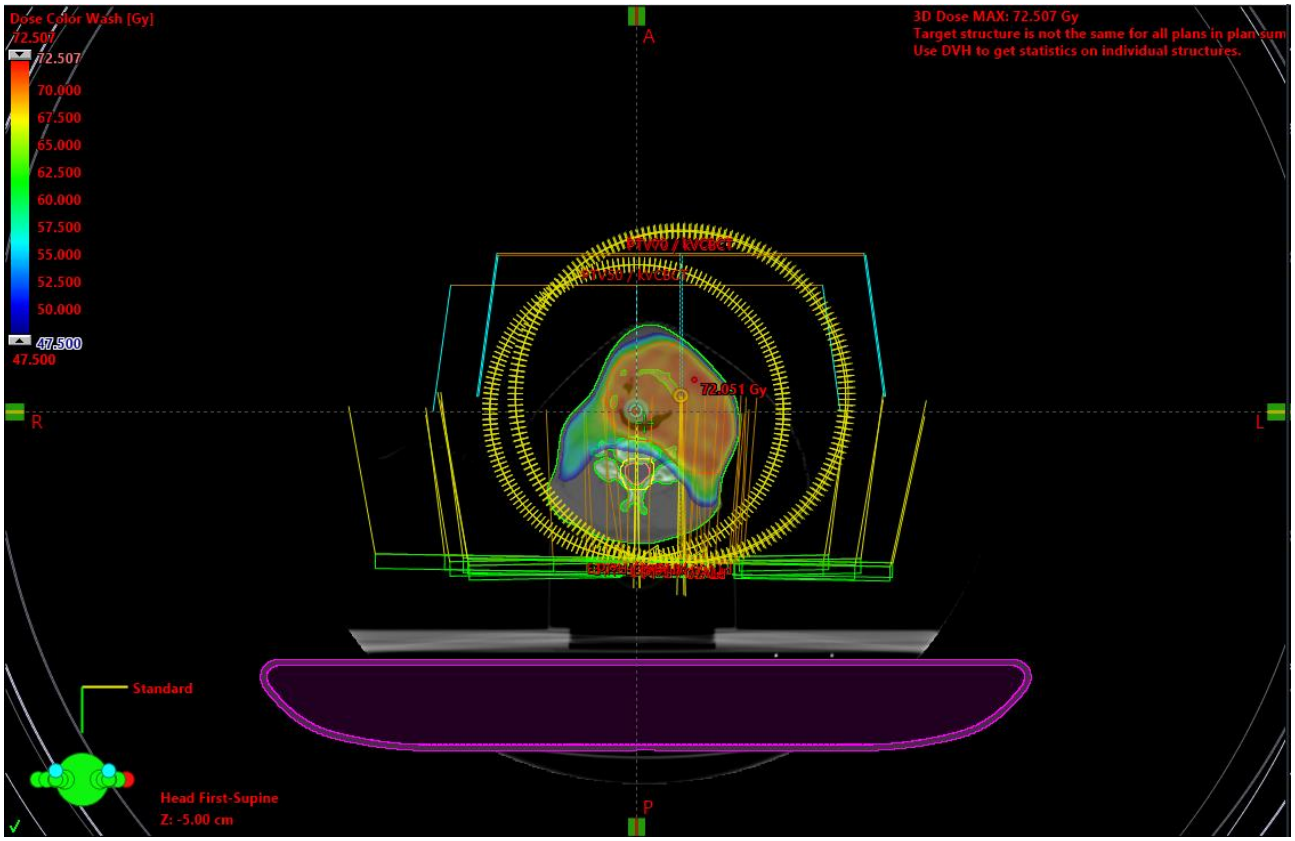


Fig. 19. An original three-dimensional plan for radiotherapy treatment for the root of the tongue

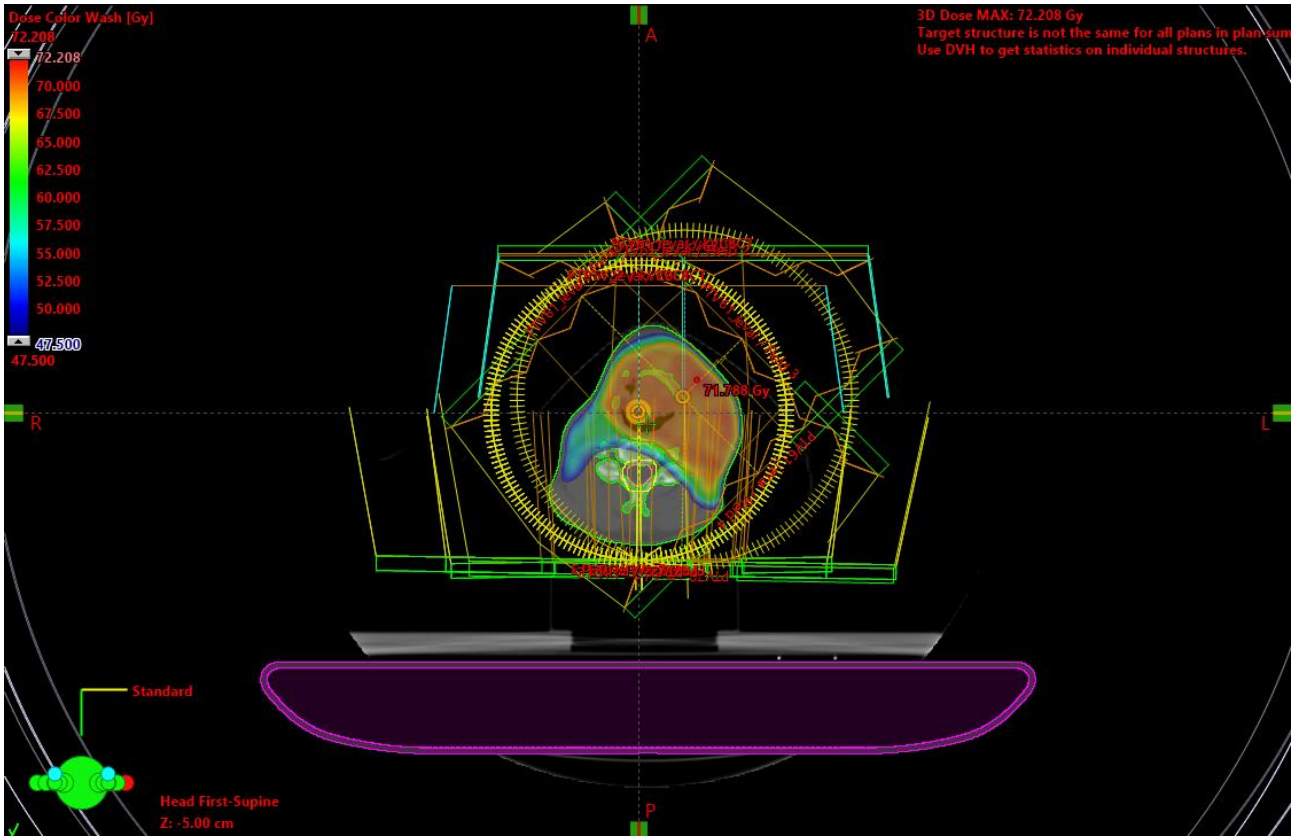
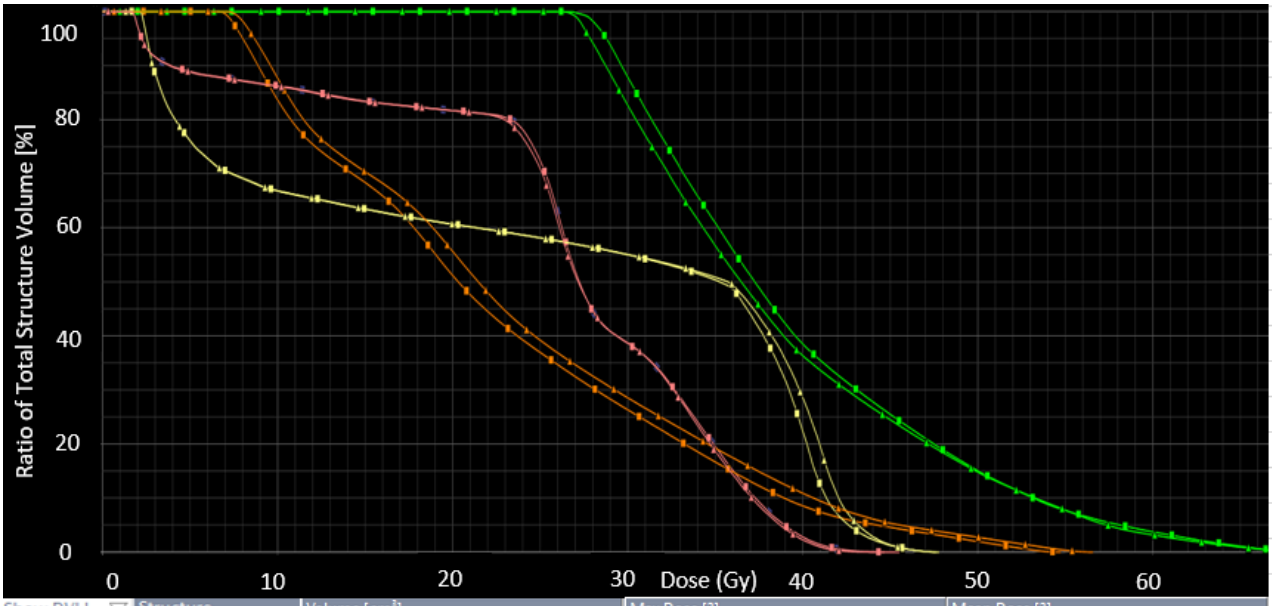


Fig. 20. A modified three-dimensional plan for radiotherapy treatment for the root of the tongue

In total, DVH and volume (cm^3), maximal and mean doses (Gy) data were compared (Fig. 21). In order to avoid late complications, the dose to the spinal cord should not exceed 50 Gy. When the dose to the spine reaches 59 Gy, the probability of developing myelopathy (adverse effect) increases from 0.2 to 5%. Another common late complication of head and neck cancer due to excessive irradiation of the parotid glands is xerostomia. For this reason, less than 25 Gy should be applied to both parotids [70].



Show DVH	Structure	Volume [cm³]	Max Dose [?]	Mean Dose [?]
	SpinalCord	35.4	45.559	26.066
	SpinalCord	35.4	44.697	25.932
	Parotid_R	11.1	56.609	23.554
	Parotid_R	11.1	54.738	22.487
	Larynx	35.2	69.091	39.575
	Larynx	35.2	69.134	38.906
	Esophagus	10.8	47.642	25.574
	Esophagus	10.8	47.797	25.291

Fig. 21. Comparison of original and modified radiation therapy plan using dose volume histogram (DVH) with additional explanation of variables: structure, volume (cm3), max and mean doses (Gy)

Results for critical organs, the spine and both parotid glands, were presented in the Table 8 below. A fifth (3 patients from 14) of participants were beyond the permitted boundary. Patient 1 exceeded the value of 25 Gy in the right parotid gland by 0.1 Gy. The fourth patient's radiation dose to the left parotid (26 Gy) was outside the limits even before the break. After implementing the compensatory "model", the dose reached 27.87 Gy, and the organ was 0.35 Gy above the limit. The seventh and eighth patients exceeded the radiation dose to the right parotid gland, with 0.61 and 1.27 Gy respectively. Since any increase in dose to critical organs is unfavourable, certain cases were rescheduled with a lower dose per fraction. After the re-planning, none of the critical organs exceeded the permissible limits. As a result, the compensative plan proved to be safe and could plausibly be used in clinical settings.

Table 8. Radiation dose (Gy) for the spine and both parotid glands calculated before and after compensation plan (values prior to dose optimisation)

Patient code	Spinal cord (Gy)		Parotid Left (Gy)		Parotid Right (Gy)	
	Without break	With break	Without break (before optimisation)	With break (before optimisation)	Without break	With break (before optimisation)
1	44.7	48.69			23.55	23.81 (25.1)
2	43.16	46.82	21.23	22.48	20.32	21.57
3	41.49	49.63	20.92	21.75	21.90	22.89
4	43.93	45.68	26.00	24.09 (27.87)	23.71	21.86 (25.35)
5	26.73	30.57			6.77	7.18
6	44.17	47.08	18.72	19.48	21.24	22.31
7	44.99	48.01			24.06	23.93 (25.61)
8	40.13	46.45	21.94	21.72	24.59	24.97 (26.27)
9	43.35	48.33	20.37	21.68	18.88	20.14
10	34.31	36.28	20.06	20.98	22.48	23.48
11	44.23	46.74	18.87	20.28		
12	36.59	40.28	19.05	19.95	19.66	20.65
13	41.94	48.01	23.60	24.96	23.90	21.26
14	33.81	41.59	23.76	24.89 (25.31)	20.16	21.26

Based on the collected values from the radiotherapy planning system, the doses to the spinal cord (Fig. 22) ranged from 30.56 to 49.63 Gy after the initial treatment modification. In comparison, the original plans without any alteration in radiation doses and fractionation, received consistently lower irradiation than compensated plans after the break. For this reason, unintended interruption cases in radiotherapy should be minimised as much as possible.

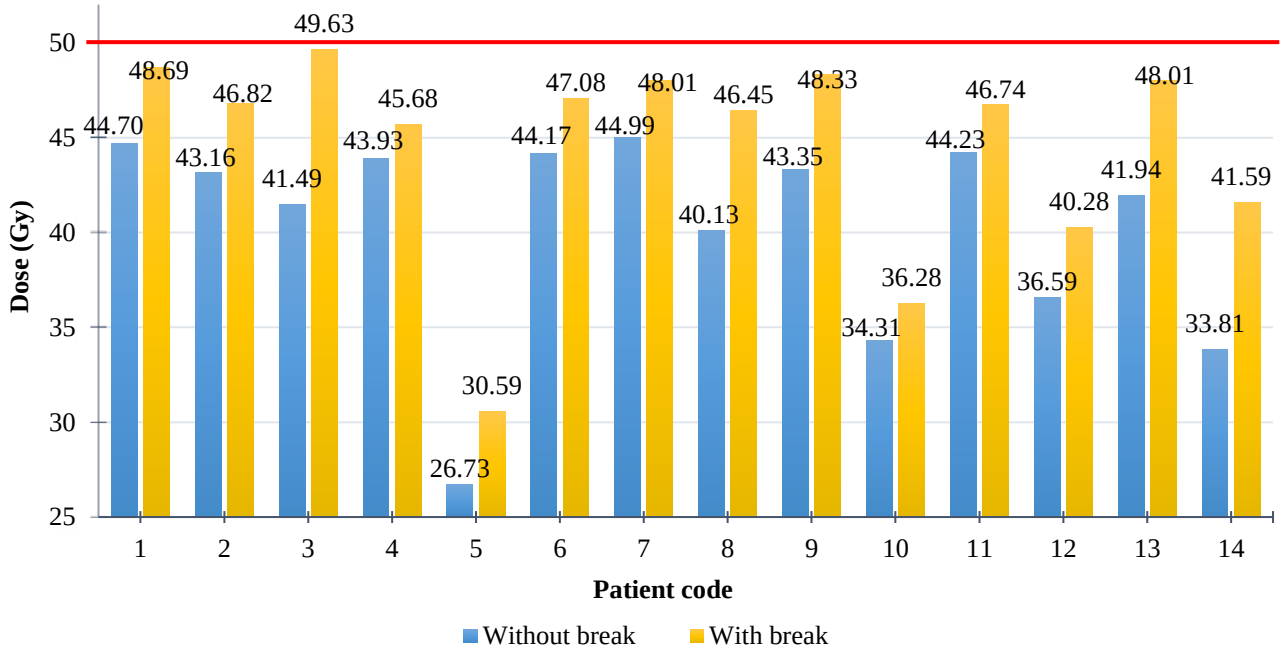


Fig. 22. Comparison of dose (Gy) to the spinal cord before and after compensation

The results for the left parotid gland are presented in two figures (Fig. 23 and 24). The first figure showed the enhanced dose of the 4th patient. Despite the fact than an elevated dose was found even in the original plan, optimization was still applied.

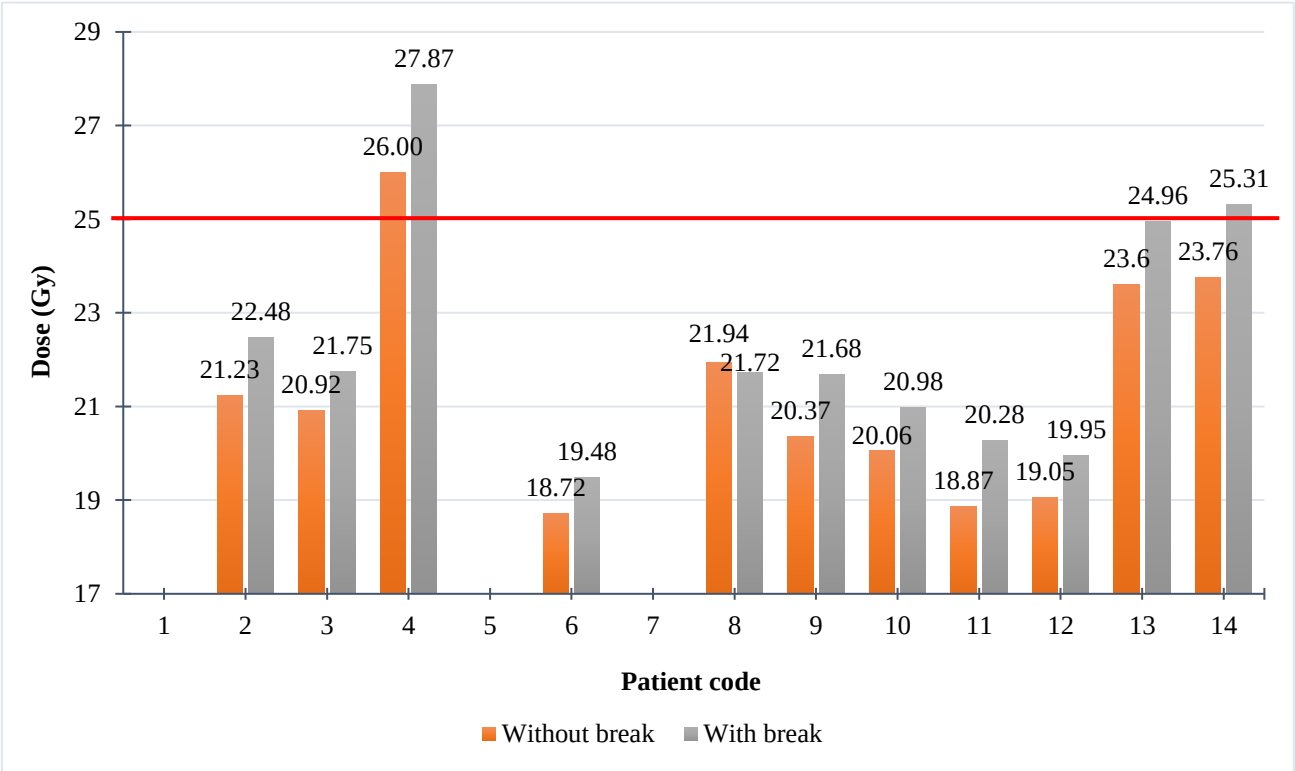


Fig. 23. Comparison of dose (Gy) to the left parotid gland before and after compensation (before optimisation)

After the optimization process, doses to the left parotid gland was reduced from 27.87 to 24.90 Gy of the 4th and from 25.31 to 24.89 Gy of the 14th patient (Fig. 24).

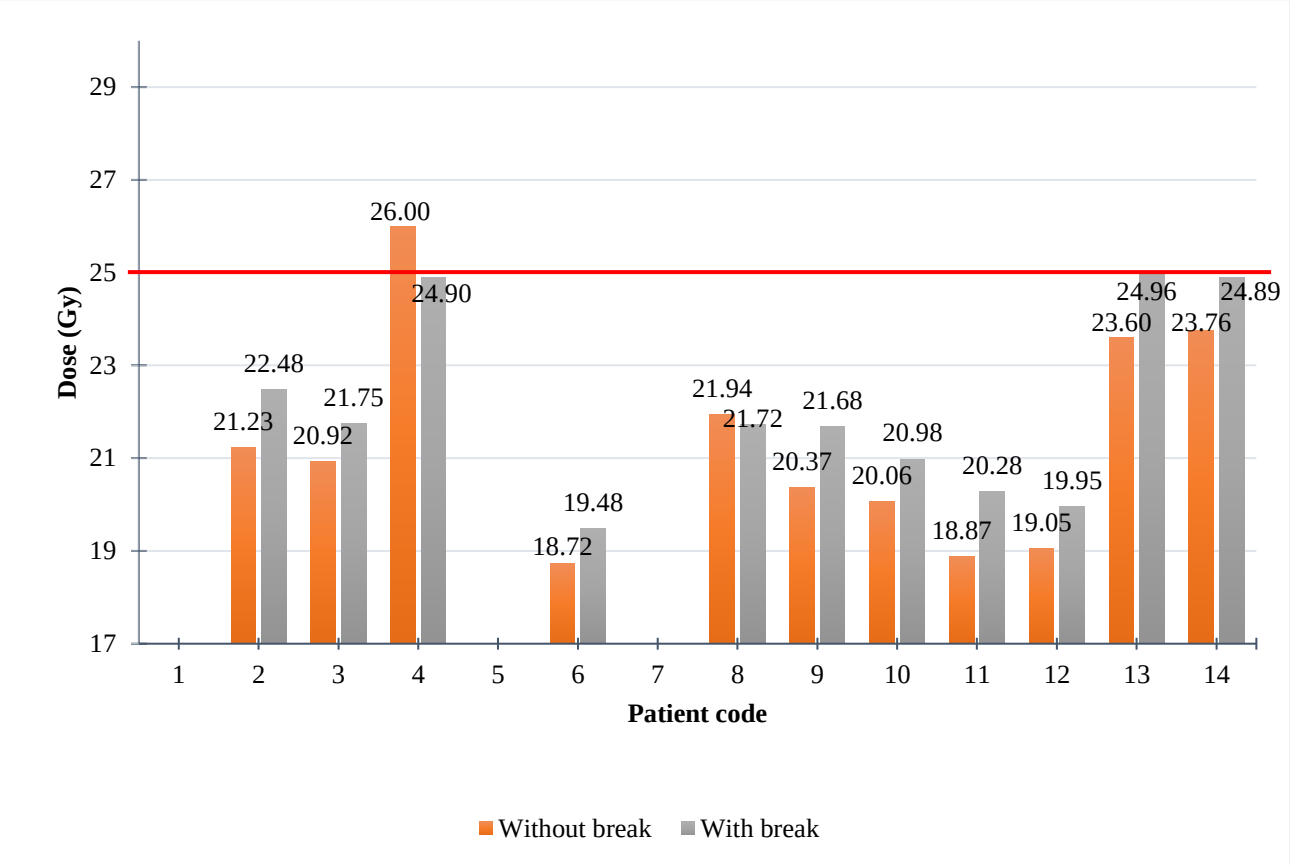


Fig. 24. Comparison of dose (Gy) to the left parotid gland before and after compensation (after optimisation)

A similar method was used to adjust for the right parotid gland. In this scenario four participants, 1, 4, 7 and 8, exceeded the dose constrains (Fig. 25).

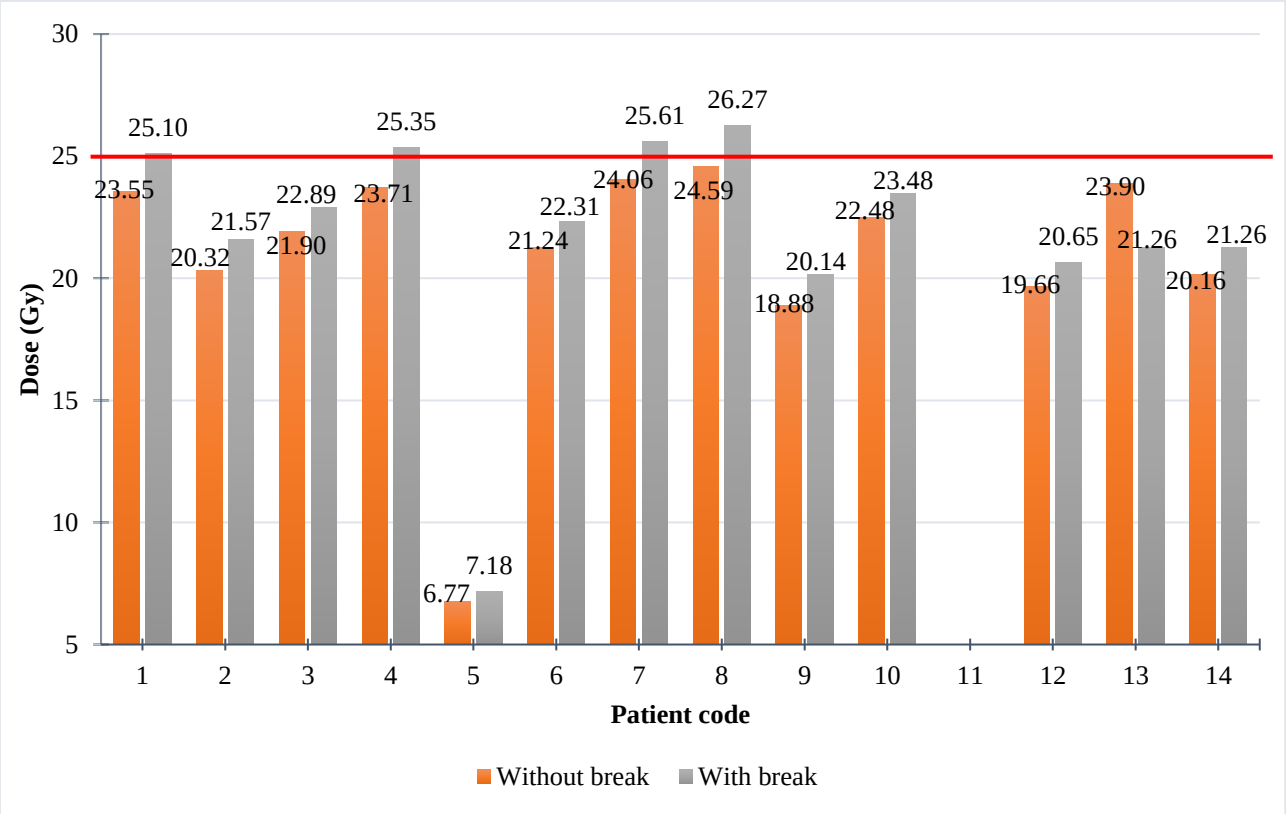


Fig. 25. Comparison of dose (Gy) to the right parotid gland before and after compensation (before optimisation)

However, suitable doses to the right parotid were only achieved when a lower fractional dose than 3.2 Gy was operated on the selected cases (Fig. 26). Therefore, the dose was reduced from 25.10 to 23.81 Gy for the first, from 25.35 to 21.86 Gy for the fourth, from 25.61 to 23.93 Gy for the seventh, and finally from 26.27 to 24.97 Gy for the eighth patient.

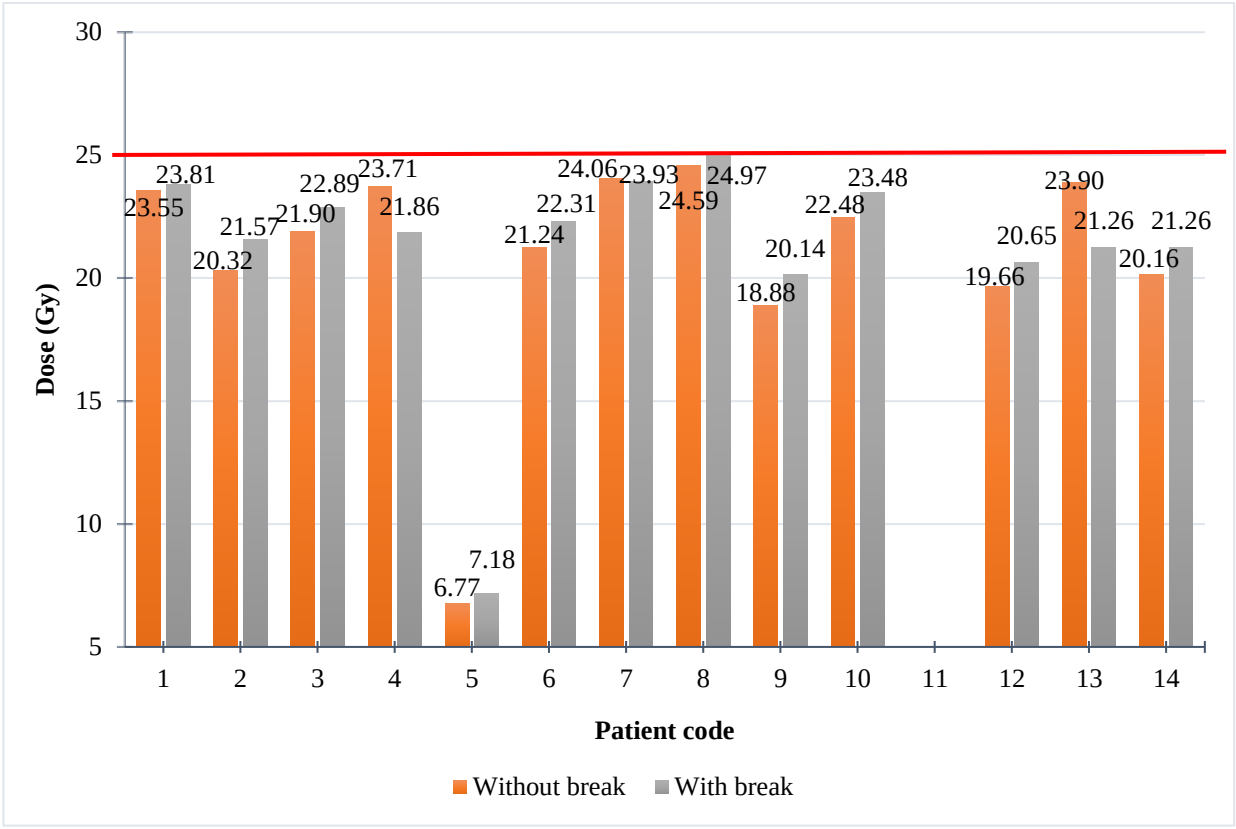


Fig. 26. Results. Comparison of dose (Gy) to the right parotid gland before and after compensation (after optimisations)

Some medical cases were re-evaluated due to dose escalation after a break. As a result, after the optimisation none of the 14 patients evaluated in the first situation exceeded the spinal cord and parotid gland dose limits. Nevertheless, calculation of the biological dose for the missed treatment should not be considered beneficial in every clinical situation and only a qualified specialist can give a final decision on the treatment modification. Late tissue complications remain the most significant detail from the recalculation results [18].

3.2. Compensative radiotherapy implementation

Interruption of radiation therapy is common in everyday practice. According to the national audit performed in Great Britain: 63% of the population has missed a part of treatment at least once [71]. Thus, an additional approach is needed to assess follow up. For this reason, the responsible professionals should track the guidelines already prepared according to the international standards, as an example, recommendations adjusted by the Royal College of Radiologist [53]. However, national hospitals do not have such regulations. The Lithuanian medical standard MN 99:2017 only determines the obligations of the radiologist-oncologist [72]. Unfortunately, this standard does not include an exact plan in the case of unplanned interruption. Adopting a structured plan into the treatment process is a necessary next step.

Later in this section, the importance of timing, when the gap occurred, how long it lasted as well as advantages and disadvantages of twice daily fractionation versus increased fractional dose will be discussed.

3.2.1. Timing

Depending on the number of days required to return to the already assigned treatment plan, further modifications can be implemented. If there is a gap in the first part of radiotherapy (subsection 2.2.2.) the optimal results can be maintained by applying irradiation twice a day with a 6 hour gap (if dose per fraction does not exceed 2 Gy) and thus compensating for lost courses.

A gap at the end of the radiation course (subsection 2.2.2.) requires a more complex approach. The therapeutic goal is to maintain the same duration. However, when it is not possible, greater breaks can be managed by adapting the recalculation method using the radiobiological formulas of the LQ model [3]. This includes BED_{10} re-calculation, which estimates the dose before and after modified treatment. Additional assessment should be given for the BED_3 evaluation, assuming that healthy tissue could exceed the boundaries. In this case, the dose per fraction should be lowered, despite the slight loss of tumour effect.

3.2.2. The consequences bi-daily fractionation

Such a compensation strategy is effective at making up for doses that were missed to PTV. A comprehensive framework for maintaining the treatment duration after re-planning was suggested by the Ravichandran et al. [54]. The recommendation was to apply two fractions per day with no more than 1.6 Gy per fraction and a minimum pause of six hours between procedures. Bi-fractionation on Fridays demonstrated significantly enhanced regional control for advanced stages of head and neck malignancies. It also could reduce overall treatment time by one week [16]. However, the effect for the normal tissues is not fully understood. Due to the inadequate regeneration of healthy tissue within fractions, bi-daily radiation sessions could contribute to a rise in sub-lethal harm to the surrounding organs. Therefore, the likelihood of complications involving normal tissue control probability (NTCP) increases [56].

3.2.3. Increased dose

The acceleration of radiation dose is unavoidable in some situations. One of them is gap occurrence towards the end of the treatment. However, it may be related with higher complication probability [54]. Accumulated radiotherapy toxicity is a term that refers to the effects of the dose escalation with early or late damage to healthy tissue [24]. According to the study by Ravichandran et al. [54], dose increase in normal tissue resulted in first- and second-degree skin reactions, mucositis (8.5%) and pneumonia (19%). N. Slevina et al. published an article [73], where the higher radiation dose after an unplanned interruption for laryngeal cancer was examined. The authors suggested to add approximately 0.5 - 0.7 Gy to the initial treatment to compensate for lost courses and to protect nearby tissues and organs. Besides, additional doses administered by the extra daily fractions results in a prolonged radiotherapy duration and thus further increases the BED for normal tissue. For this reason, Dale et al. [52] recommended to divide the obtained new dose into two fractions per day if it exceeds the limits after compensatory assessment.

3.2.4. Overall treatment time

Timing is considered as an essential part of radiotherapy. A break in the first portion of the therapy can result in smaller dose escalation than interruption near the end of the treatment [54]. Clinical worsening of missed treatment outcomes was investigated by the Radiation Therapy and Oncology Group (RTOG). In total, 291 patients with an anal neoplasm were included in the study. Consequently, it was discovered that prolonged duration of radiotherapy reduced locoregional control [74]. Therefore, the timing of treatment is essential, and tumour recurrence must be taken into account. Prior to performing the appropriate measurements for the compensation scheme, it is important to cautiously analyse medical data. Any dose elevation is most probably associated with a higher likelihood of adverse effects for healthy cells [5]. A medical trial by R. Dale and B. Jones [3] showed that loosened radiation procedures, which lengthen the duration of prescribed treatment, increase the likelihood of regional recurrence in most quickly growing malignancies. Therefore, the compensation of missed treatment should not exceed one week [34].

3.2.5. Treatment plan

Implementation of the compensation strategy for missed radiotherapy courses is a complex mechanism and requires a multidisciplinary team. As suggested by G. Pozo et al. [51], there are well-defined steps in the direction of safer radiation therapy re-planning (Fig. 27):

1. First of all, an appropriate study of any available literature related to the compensative methods for the unplanned gap;
2. Introduction to the medical personnel about the obtained information from the research justifying advantages and disadvantages in any treatment alterations;
3. Finally, designation of the health care specialist committee for the final evaluation and protocol establishment.

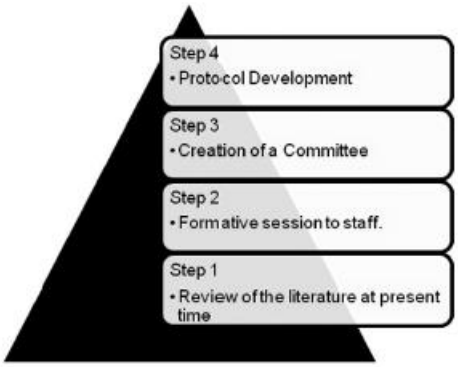


Fig. 27. The interruption management strategy [51]

The clinical team should consist of oncologists-radiologists, medical physicists. and radiological technologists. More systematic preparation of radiobiological elements and BED calculation need to be included into the healthcare trainings [3].

Radiotherapy modification, when part of the treatment has been missed can be differentiated depending on the individual situation. The strategy of unscheduled therapy compensation consists of

changing the initial treatment plan (fractionation twice a day, including weekends and public holidays, recalculation of BED) together with well-developed communication between hospitals and also importantly, increase in investment to allow for additional treatment delivery windows.

3.2.6. Recommendations for medical personnel

Over the last thirty years, therapeutic tactics have changed from surgical intervention or radiotherapy as the single modality to more combined treatment techniques [29]. However, implementation of the individualized therapeutic strategy requires taking into account not just clinical features, but also sociopsychological functions altogether [21]. For this reason, more attention needs to be paid to avoid any deviation from the original plan when involving patients in the treatment process.

The strategy of missed treatment correction includes the selection of the appropriate compensative method, such as fractional dose escalation, irradiation twice a day, adding weekends to the altered plan, etc (Fig. 28). It may contain one or more of the previously mentioned options. The ASARA ("As short as reasonably achievable") principle should be applied to minimise any interference where possible [75]. Although some components of radiotherapy compensation are unquestionably better than others, practical considerations (the available equipment and hospital funding) seem to have an impact on the choice of missed treatment control strategy. In order to find a consensus plan that assists the patient and the medical staff, it is important to consider more than one of the potential solutions.

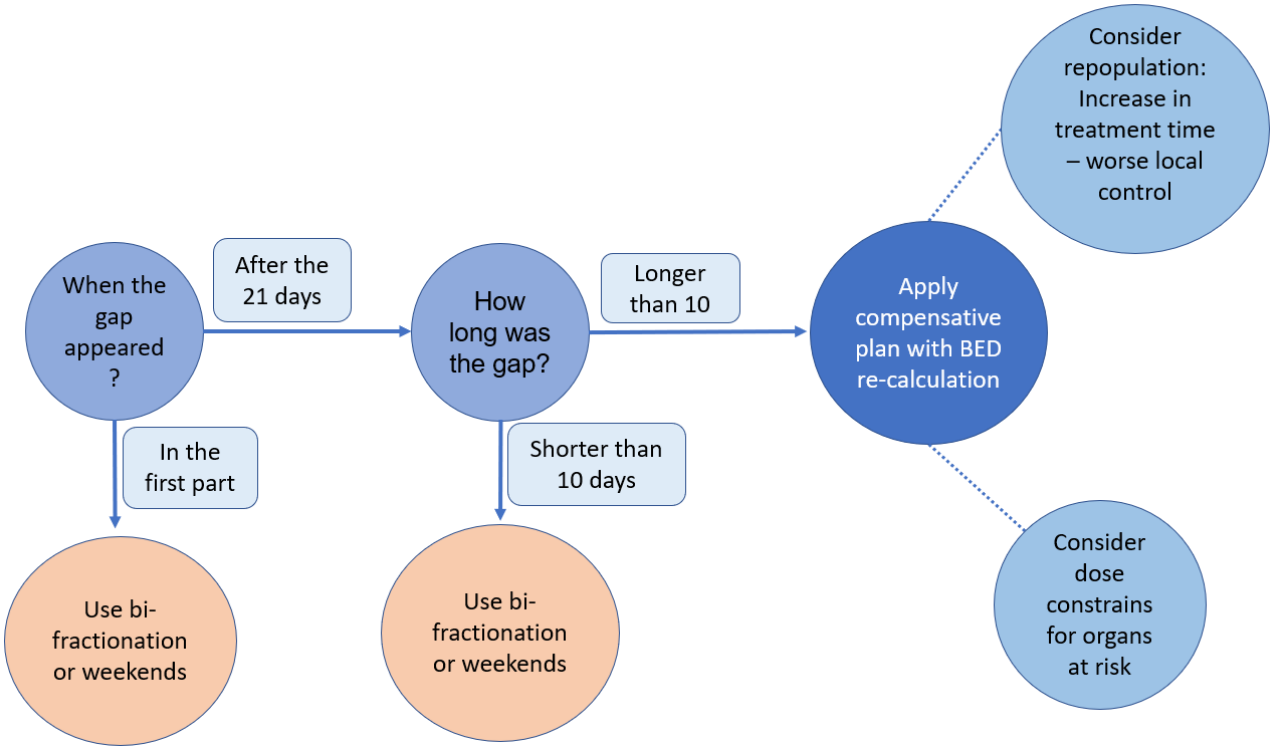


Fig. 28. An algorithm designed for undesirable interruptions in radiation therapy management

The physician must accept the final decision, regarding what kind of alteration in treatment will be adopted (fractionation, timing, dose). Changes in radiation dose in order to control tumour growth should not exceed the normal tissue control. Depending on the circumstances, a radiologist might

keep the same treatment plan [61]. In order to obtain the actual situation of a tumour when the gap has passed, physiological parameters need to be evaluated alongside with the radiobiological data. This includes a reconsideration of the radiotherapy course and estimation of the residual target volume (expansion or shrinkage), which might vary during the treatment [52].

Another recommendation is for oncology hospitals in Lithuania to establish a unified electronic system (database), where physicians and medical physicists could maintain information about unplanned radiotherapy gaps, any alteration of the treatment and its outcomes. This data would be convenient for specific cancer cases observance and statistical analysis in the future.

3.2.7. How to avoid the interruption

In most cases, delays in radiotherapy can be avoided by paying more attention to the patient and their own convenience, or by increasing the resources of medical equipment and recruiting more personnel. However, alternative methods for how to adjust the plan exist and can be classified into 3 important steps:

1. Immediate relocation of the patient into the next radiology department;
2. Acceleration of the radiotherapy, which includes exploitation of the weekends and public holidays and radiation delivery twice a day with a 6-hour gap between courses;
3. Radiobiological compensation of the gap that appears in the later radiotherapy course by increasing the dose per fraction.

Even though the weekend radiotherapy strategy might offer an optimal solution, it cannot be a financially viable option in most institutions because of the budget constraints [51]. Machine-related causes can be fixed by using additional linear accelerators. If compatible radiotherapy devices are not available in the same hospital unit, patients should be transferred to another neighbouring clinic. Accommodation for cancer patients who live further away from the medical facility should be provided by health insurance funds. Patients must be involved in decision making processes regarding any changes to their treatment and give their consent to such decisions.

Furthermore, hospitals should have at least one professional radiobiologist in their medical team who would be familiar with radiobiological measurements in case of unscheduled interruptions. Reports on compensation mechanisms of missed treatments should be easily accessible in the hospital at any time. These guidelines would allow the institutions to justify and optimise the best solution. However, many hospitals do not have on internal procedures regarding radiotherapy delay management and potential compensation methods.

The United Kingdom has integrated the uniform missed treatment management protocol into 55 national oncology departments to address the growing incidence of unintended interruptions, particularly due to rapidly proliferating SCC [62,76]. Nevertheless, this did not prevent further confusion among registered medical practitioners in the country. To date, the UK's National Health Service has declared that there is still a lack of uniformity and guidance on adequate compensatory strategies in the country [5]. Establishing an interruption management protocol is highly recommended as clinical situations diverge and must be fully evaluated.

Conclusions

1. Simulating different interruption cases for head and neck patients showed that 14 days interruption still can be compensated using radiobiological model and it can be considered as a possible alternative after a missed radiotherapy treatment.

2. The most extreme of the simulated cases was analysed based on 3D treatment planning system. Results of analysis showed that the re-calculated dose per fraction increased from 2 Gy/fr. to 3.2 Gy/fr. applied for 14 head and neck cancer patients exceeded the radiation dose limit (> 25 Gy) to the left and right parotid gland only five of them. However, satisfactory results were obtained after reducing the dose to remaining fractions of the specific plans.

3. The compensation "model" was implemented according to the international guidelines. In the first part of radiotherapy, the gap can be managed by using the bi-fractionation method and including weekends in the therapy. However, after approximately 21 days of treatment, the radiobiological effect should be recalculated according to the biologically effective dose. Concordantly, we recommend that healthcare centres should maintain databases in which patient treatment is tracked and implement protocols for missed radiotherapy courses.

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Šį darbą skiriu savo tėčio atminimui, žinau, kad jis manimi labai didžiuotųsi kaip ir visados.

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