Инженерная школа ядерных технологий
Направление подготовки; 14.04.02 Ядерные физика и технологии
Отделение ядерно-топливного цикла

МАГИСТЕРСКАЯ ДИССЕРТАЦИЯ

Тема работы
Определение ожидаемой эффективности лучевого лечения злокачественных новообразований области головы и шеи на основе эквивалентной однородной дозы

УДК 615.849:616.006.04

Студент

Группа	ФИО	Подпись	Дата
0АМ9М	Клиновицкая Марина Игоревна		

Руководитель ВКР

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ИШФВП	Сухих Леонид Григорьевич	д. ф.-м. н.		

КОНСУЛЬТАНТЫ ПО РАЗДЕЛАМ:

По разделу «Финансовый менеджмент, ресурсоэффективность и ресурсосбережение»

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ОСГН ШИП	Спицына Л.Ю.	к.ф.н.		

По разделу «Социальная ответственность»

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ОЯТЦ ИЯТШ	Веригин Д.А.	к.ф-м.н		

ДОПУСТИТЬ К ЗАЩИТЕ:

Руководитель ООП	ФИО	Ученая степень, звание	Подпись	Дата
Nuclear medicine / Ядерная медицина	Верхотурова В.В.	к.и.н.		

Томск – 2021 г.

School of Nuclear Science & Engineering
Field of training (specialty): 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine
Nuclear Fuel Cycle Division

MASTER THESIS

Topic of research work
Estimation of expected radiation treatment effectiveness of head-and-neck cancer based on the equivalent uniform dose concept

UDC 615.849:616.006.04

Student

Group	Full name	Signature	Date
0AM9M	Marina I. Klinovitskaia		

Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Date
Associated Professor Research School of Physics	Leonid G. Sukhikh	Dr. Sc. (Phys.-Math.)		

ADVISERS:

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor Division for Social Sciences and Humanities School of Core Engineering Education	Luibov Y. Spicyna	Ph.D. in Economics		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor Division for Nuclear-Fuel Cycle School of Nuclear Science & Engineering	Dan A. Verigin	Ph.D. in Phys. and Math.		

ADMITTED TO DEFENSE:

Programme Director	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Vera V. Verkhoturova	Ph.D. in Historical Sciences		

Tomsk – 2021

LEARNING OUTCOMES

Competence code	Competence name
Universal competences	
UC(U)-1	Ability to make critical analysis of problem-based situations using the systems analysis approach, and generate decisions and action plans.
UC(U)-2	Ability to run a project at all life-cycle stages.
UC(U)-3	Ability to organize and lead the teamwork and generate a team strategy to achieve the target goal.
UC(U)-4	Ability to use modern communication technologies to realize academic and professional interaction.
UC(U)-5	Ability to analyze and account for cultural diversity in the process of intercultural interaction.
UC(U)-6	Ability to set and pursue individual and professional activity priorities and ways to modify professional activity based on the self-esteem.
General professional competences	
GPC(U)-1	Ability to formulate goals and objectives of the research study, select assessment criteria, identify priorities for solving problems.
GPC(U)-2	Ability to apply modern research methods, evaluate and present the results of the performed research.
GPC(U)-3	Ability to present research outcomes in the form of articles, reports, scientific reports and presentations using computer layout systems and office software packages.
Professional competences	
PC(U)-1	Ability to maintain medical and technical documentation related to medico-physical aspects of radiation therapy, interventional radiology and radionuclide diagnostics and therapy.
PC(U)-2	Ability to ensure radiation safety of personnel, public, and the environment, to carry out monitoring of radiation exposure levels of patients, personnel, public, and the environment.
PC(U)-3	Ability to operate and maintain equipment and tools applied for the medical use of radiation.
PC(U)-4	Ability to manage the quality of physical and technical aspects within radiation therapy, diagnostics, interventional radiology and radionuclide diagnostics and therapy departments in accordance with the specific equipment requirements, regulatory requirements and staffing of a medical organization.
PC(U)-5	Ability to conduct and organize dosimetry planning, clinical dosimetry, quality assurance procedures for radiotherapy, interventional radiology, and radionuclide diagnostics and therapy.
PC(U)-6	Ability to apply knowledge of natural sciences, fundamental laws in the field of nuclear physics and technology, clinical and radiation standards, hygienic measures in nuclear medicine, which is sufficient to study issues associated with medical physics using modern equipment and information technology relying on the latest Russian and international experience.
PC(U)-7	Ability to develop reference books, tables and software containing data for clinical use in dosimetric planning of radiation therapy, radionuclide diagnostics and therapy.

Competence code	Competence name
Professional competences	
PC(U)-8	Ability to take part in the design and physical and technical equipment development for radiation therapy, diagnostics, interventional radiology and radionuclide diagnostics and therapy, and radiation safety divisions.
PC(U)-9	Ability to conduct training sessions and develop instructional materials for the training courses within the cycle of professional training programs (bachelor degree programs).

TOMSK
POLYTECHNIC
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университет

School of Nuclear Science & Engineering
Field of training (specialty): 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine
Nuclear Fuel Cycle Division

APPROVED BY:
Program Director
_____ Verkhoturova V.V.
«____» _____ 2021

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Master Thesis

For a student:

Group	Full name
0AM9M	Marina I. Klinovitskaia

Topic of research work:

Estimation of expected radiation treatment effectiveness of head-and-neck cancer based on the equivalent uniform dose concept	
Approved by the order of the Director of School of Nuclear Science & Engineering (date, number):	№ 29-49/c dated January 29, 2021

Deadline for completion of Master Thesis:	18.06.2021

TERMS OF REFERENCE:

Initial date for research work: *(the name of the object of research or design; performance or load; mode of operation (continuous, periodic, cyclic, etc.); type of raw material or material of the product; requirements for the product, product or process; special requirements to the features of the operation of the object or product in terms of operational safety, environmental impact, energy costs; economic analysis, etc.)*	- 16 patients with malignant neoplasms in head-and-neck area; - Data of dose-volume histogram from radiation therapy planning software for 16 patients.
List of the issues to be investigated, designed and developed *(analytical review of literary sources with the purpose to study global scientific and technological achievements in the target field, formulation of the research purpose, design, construction, determination of the procedure for research,*	- Literature review of the different radiation therapy treatment regimens in head-and-neck region tumors. - Estimation of head-and-neck tumor radiological parameters such as TD50 and γ50 based on literature

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	review. - Development of software for calculation of equivalent uniform dose (EUD), tumor control probability (TCP), normal tissue complication probability (NTCP), plotting mentioned parameters and dose-volume histogram (DVH). - Work with patient's data: prediction of treatment results based on TCP and NTCP approach.
design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).	
List of graphic material *(with an exact indication of mandatory drawings)*	Presentation

Advisors to the sections of the Master Thesis
(with indication of sections)

Section	Advisor
Social responsibility	Dan A. Verigin
Financial Management, Resource Efficiency and Resource Saving	Luibov Y. Spicyna

Date of issuance of the assignment for Master Thesis completion according to the schedule	15.03.2021

Assignment issued by a scientific supervisor / advisor (if any):

Position	Full name	Academic degree, academic status	Signature	Date
Associated Professor Research School of Physics	Leonid G. Sukhukh	Dr. Sc. (Phys.-Math.)		15.03.2021

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM9M	Marina I. Klinovitskaia		15.03.2021

ASSIGNMENT FOR THE DIPLOMA PROJECT SECTION
«FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING»

Student:

Group	Name
0AM9M	Marina I. Klinovitskaia

School	School of Nuclear Science & Engineering	**Department**	Division for Nuclear-Fuel Cycle
Educational level	Master	**Specialization**	14.04.02 Nuclear Science and Technology

Initial data for the section "Financial Management, Resource Efficiency and Resource Saving":	
Initial data for the section "Financial Management, Resource Efficiency and Resource Saving":	
1 *The cost of scientific research resources: material, technical, energy, financial, informational and human*	*Budget of research is 239080.1 rub.*
2 *Norms and standards for spending resources*	*Supervisor' salary – 72698.7 rub, student'(researcher') salary – 112009.7 rub*
3 *The system of taxation used, tax rates, volumes of payments, discounts and loans*	
Problems to research, calculate and describe:	***Problems to research, calculate and describe:***
* *Assessment of the commercial potential of engineering solutions*	*Analysis of alternative ways of conducting research*
* *Planning of research and constructing process and making schedule for all periods of the project*	*The work consist of:* *- Map of segmentation;* *- SWOT – analysis;* *- determination of the complexity of work.*
* *Budgeting an engineering project*	*Scientific and technical research budget consist of:* *- calculation of material costs;* *- calculation of costs for purchasing equipment;* *- calculation of the basic and additional salary of the performers;* *- social contributions;* *- overhead costs;* *- formation of the budget of costs.*

Graphic materials
1 «Portrait» of the consumer *2 Competitive power of the project* *3 SWOT matrix* *4 Plan of investments. The budget for scientific and technical research* *5 Project Efficiency indicators*

Assignment date	15.03.2021

Consultant:

Position	Name	Academic degree	Signature	Date
Associate Professor Division for Social Sciences and Humanities School of Core Engineering Education	Luibov Yu. Spicyna	Ph.D. in Economics		15.03.2021

Student:

Group	Name	Signature	Date
0AM9M	Marina I. Klinovitskaia		15.03.2021

ASSIGNMENT FOR THE DIPLOMA PROJECT SECTION
«SOCIAL RESPONSIBILITY»

Student:

Group	Name
0AM9M	Marina I. Klinovitskaia

School	School of Nuclear Science & Engineering	**Department**	Division for Nuclear-Fuel Cycle
Educational level	Master	**Specialization**	14.04.02 Nuclear Science and Technology

Title of graduation thesis:

Estimation of expected radiation treatment effectiveness of head-and-neck cancer based on the equivalent uniform dose concept

Initial data for section «Social Responsibility»:	
1. Information about object of investigation (matter, material, device, algorithm, procedure, workplace) and area of its application	Object: radiation treatment, evaluation of effectivity of implemented treatment of malignant neoplasms in head-and-neck region with radiation therapy and prediction possible treatment results based on the equivalent uniform dose concept. Application area: radiation therapy.

List of items to be investigated and to be developed:	
1. Legal and organizational issues to provide safety: - Special (specific for operation of objects of investigation, designed workplace) legal rules of labor legislation; - Organizational activities for layout of workplace.	- GOST 12.2.032-78 Occupational safety standards system. Operator's location in a sitting position. General ergonomic requirements. - SR 2.4.3648-20 "Sanitary and Epidemiological Requirements for Organizations of Education and Training, Recreation and Recreation of Children and Youth". - GOST 12.1.038-82 Occupational safety standards system. Electric safety. - Radiation safety standards. NRB-99/2009. Sanitary rules and regulations 2.6.1.2523-09. - GOST R12.1.004-91 Occupational safety standards system. Fire safety.
2. Work Safety: 2.1. Analysis of identified harmful and dangerous factors 2.2. Justification of measures to reduce probability of harmful and dangerous factors	- Enhanced electromagnetic radiation level; - Insufficient illumination of workplace; - Excessive noise; - Deviation of microclimate indicators; - Abnormally high voltage value in the circuit; - Increased level of ionizing radiation.
3. Ecological safety:	- Indicated impact of linear accelerator operation on hydrosphere, atmosphere and lithosphere.
4. Safety in emergency situations:	- Fire safety.

Assignment date	15.03.2021

Consultant:

Position	Name	Academic degree	Signature	Date
Associate Professor Division for Nuclear-Fuel Cycle School of Nuclear Science & Engineering	Dan A. Verigin	Ph.D. in Phys. and Math.		15.03.2021

Student:

Group	Name	Signature	Date
0AM9M	Marina I. Klinovitskaia		15.03.2021

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School of Nuclear Science & Engineering
Field of training (specialty): 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine

Level of education: Master degree program
Nuclear Fuel Cycle Division
Period of completion: spring semester 2020/2021 academic year

Form of presenting the work:

Master Thesis

SCHEDULED ASSESSMENT CALENDAR
for the Master Thesis completion

Deadline for completion of Master's Graduation Thesis:	18.06.2021

Assessment date	Title of section (module) / type of work (research)	Maximum score for the section (module)
15.03.2021	*Drawing up the technical assignment*	
20.03.2021	*Calendar planning*	
30.03.2021	*Literature review*	
29.04.2021	*Selecting a radiological model*	
3.05.2021	*Mathematical analysis of data*	
4.05.2021	*Development of a program for working with data*	
5.05.2021	*Calculation equivalent uniform dose, tumor control probability*	
6.05.2021	*Predicting treatment outcomes based on literature review*	
10.05.2021	*Summarizing*	
14.05.2021	*Drawing up a final report*	
18.06.2021	*Masters's Thesis defense*	

COMPILED BY:
Scientific supervisor:

Position	Full name	Academic degree, academic status	Signature	Date
Associated Professor Research School of Physics	Leonid G. Sukhikh	Dr. Sc. (Phys.-Math.)		

APPROVED BY:

Program Director	Full name	Academic degree, academic status	Signature	Date
Nuclear medicine	Vera V. Verkhoturova	Ph.D. in Historical Sciences		

ABSTRACT

The final master's work consists of 100 pages, 19 figures, 22 tables, 26 equations, 46 sources, 3 appendixes.

Key words: radiation therapy, tumors head-and-neck region, tumor control probability (TCP), normal tissue complication probability (NTCP), equivalent uniform dose (EUD).

Object of study: radiation therapy.

Goal of work: evaluation of effectivity of implemented treatment of malignant neoplasms in head-and-neck region with radiation therapy and prediction possible treatment results.

In the work a literature review was made of the treatment of advanced stages of head-and-neck tumors with radiation therapy. Parameters such as TCP (tumor control probability), NTCP (normal tissue complication probability), EUD (equivalent uniform dose) and DVH (dose-volume histogram) were used for assessment and comparison. Based on the data obtained, the prediction of treatment results was carried out in 16 patients. Suggestions were made for improving the quality of treatment: decreasing treatment time by using hupo- or hyperfractionation and/or simultaneous integrated boost more likely leads to better tumor control.

Scope of application: radiation therapy.

Abbreviations

3D CRT – 3-dimensional Conformal Radiation Therapy;

CT – Computed Tomography;

DNA – Deoxyribonucleic Acid;

DVH – Dose-Volume Histogram;

DVHc – Differential Dose-Volume Histogram;

DVHd – cumulative Dose-Volume Histogram;

EQD_2 – Equivalent Dose in 2 Gy fractions;

EUD – Equivalent Uniform Dose;

IMRT – Intensity-Modulated Radiation Therapy;

LQ-model – Linear-Quadratic model;

MLC – Multileaf Collimator;

NTCP – Normal Tissue Complication Probability;

OAR – Organ At Risk;

SEQ – Sequential Boost;

SIB – Simultaneously Integrated Boost;

TCP – Tumor Control Probability;

VMAT – Volumetric Modulated Arc Therapy.

Content

Introduction

Tumors are one of the most common reasons of morbidity and mortality.

In Russian Federation were registered 640391[1] incidence of malignant neoplasms in 2019, that bigger on 2.5 % than in 2018 and 30.4 % than in 2009.

Some of reasons of tumor appearance are well studied, that allow to prevent not less that 1/3 of all incidence of disease. On other hand, medicine has big amount treatment ways of cancer patients. One of them is radiation therapy based on treatment of malignant neoplasm with ionizing radiation.

Tumor of head-and-neck region are not the most common, however treatment of neoplasm in such localization with radiation therapy is complicated by some parameters:

‐ Side effects: early reactions to radiation occur in the first weeks and continue for some time after the course of radiation therapy. Side effects always causes at least discomfort, but given that some of them are visually noticeable (including erythema), because they are in a visible place, some patients are not ready to finish such a course of therapy.

‐ Rate of cell division and growth: head-and-neck tumors are mainly rapidly growing. Thereby any delays or interruptions in treatment have especially negative effect on the result of treatment.

‐ Localization: head-and-neck region is the most important area of the human body, containing a complex of organs that perform a wide range of functions, which requires careful planning in order to exclude organs from the radiation area or reduce the dose to adjacent tissues.

‐ Tumor control: 90 % of all head and neck tumors are radiosensitive squamous cell carcinoma, that is a type of tumor that responds well to radiation treatment. However, despite the fact that the size of such tumors changes rapidly with a change in the dose (total and/or dose per fraction), the dependence of the tumor response on the dose is ambiguous.

Therefore drawing up a treatment plan for radiation therapy means the development of more than one irradiation method for further analysis of the choice of a more optimal solution. One of the factors in evaluating a treatment plan are the tumor control probability (TCP), normal tissue complications probability(NTCP) and their combination, determining probability of damaging tumor by irradiation without harm to healthy tissue. Both mentioned parameters depends on equivalent uniform dose (EUD), the absorbed dose if it homogeneously distributed in the tumor, which defined through the dose distribution, volume received specific dose and parameter describing tissue behavior on irradiation. Evaluation of the plan implies the prediction of expected outcomes, and since dose value is directly correlated with results of treatment, the EUD concept can be used to analyze treatment plans.

The relevance of the work is the need to improve the quality of treatment for patients with advanced stages of head-and-neck tumors receiving radiation therapy.

Goal of work: evaluation of effectivity of implemented treatment of malignant neoplasms in head-and-neck region with radiation therapy and prediction possible treatment results.

Tasks:

- Literature review of the different radiation therapy treatment regimens in head-and-neck region tumors.

- Estimation of head-and-neck tumor radiological parameters such as TD_{50} and γ_{50} based on literature review.

- Development of software for calculation of equivalent uniform dose (EUD), tumor control probability (TCP), normal tissue complication probability (NTCP), plotting mentioned parameters and dose-volume histogram (DVH).

- Work with patient's data: prediction of treatment results based on TCP and NTCP approach.

1 Radiation therapy

1.1 Radiobiological basis of radiation therapy

Radiation therapy (radiotherapy) is a cancer treatment that uses high doses of ionizing radiation to kill cancer cells and shrink tumors.

Action of ionizing radiation on biological object can be separated on 3 temporary stages: physical, chemical and biological (figure 1).
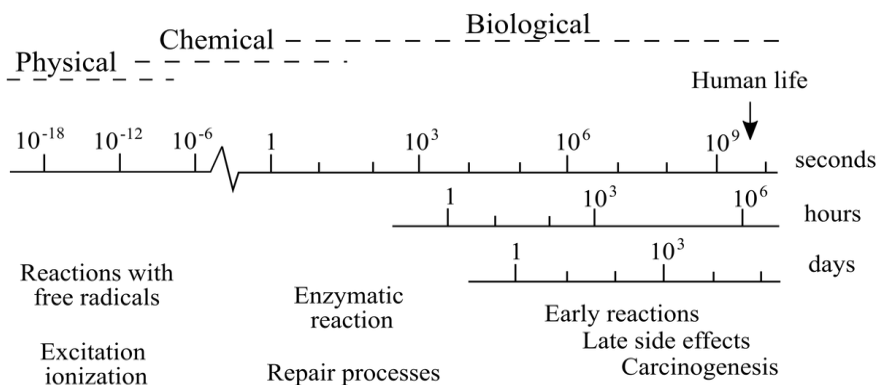
Figure 1 – Time scale of processes, induced in biological systems after irradiation of IR [2]

Physical stage includes interaction of radiation with atoms of tissue. Moving in medium, photon mostly transmits energy to orbital electrons. In result, electrons or fly out from atom, either move on higher level inside of atom (excitation of molecules). If electrons have enough energy, they start to ionize other atoms [2].

Chemical stage include process, in which excited and ionized atoms react with other components of cell in fast chemical reactions. It leads to breaking down chemical links and formation of non-stable molecules, free radicals [3], which react with neighboring molecules due to which the composition of medium changes.

Biological stage starts from enzymatic reactions which influence on saved chemical damages. The most part of damages successfully repairs. Some reparation are not successful enough that leads to cell death [2].

The main types of structural radiation damages (figure 2):

1. single DNA breaks, breaking one DNA strand;

2. double-stranded DNA breaks, the coincidence of breaks at opposite DNA

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strands;

3. violation of the DNA-protein bond;

4. damage to the structure of the DNA membrane complex;

5. destruction of nuclear membranes;

6. damage to the mitochondrial membrane;

7. damage to the cytoplasmic membrane [2].
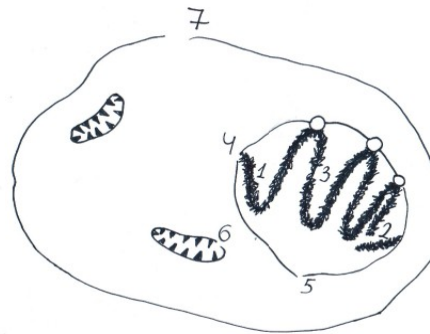
Figure 2 – The main type of structural radiation damages:
1 –single DNA breaks, 2 – double-stranded breaks of DNA, 3 – violation of the DNA-protein bond,
4 – damage to the structure of the DNA membrane complex, 5 – destruction of nuclear membranes,
6 – damage to the mitochondrial membrane, 7 – damage to the cytoplasmic membrane

According to this, the most vulnerable cell part to radiation damaging is DNA.

1.2 Linear-quadratic model (LQ-model)

After irradiation the cells do not perish immediately, but after reaching a sufficient number of non-fatal injuries that accumulate with each subsequent division, the cells lose their ability to divide and perish. For experiments *in vitro* If a cell creates less than 50 of its own during division, it is considered that the cell has died. In a living organism, there is no way to count the exact number of cells and their descendants. The proportion of surviving cells after irradiation is called clonal survival.

For quantitative description of cell death, the most common model is linear-quadratic model (LQ-model)[2] shown on Figure 3:

$$SF = \exp\left(-\alpha \cdot D - \beta \cdot D^2\right), \tag{1}$$

where SF is surviving fraction, i.e. number of survival cells;

D is the radiation dose, Gy;

α,β is empirical coefficients specific for each organ or tissue, Gy^{-1} and Gy^{-2} respectively.
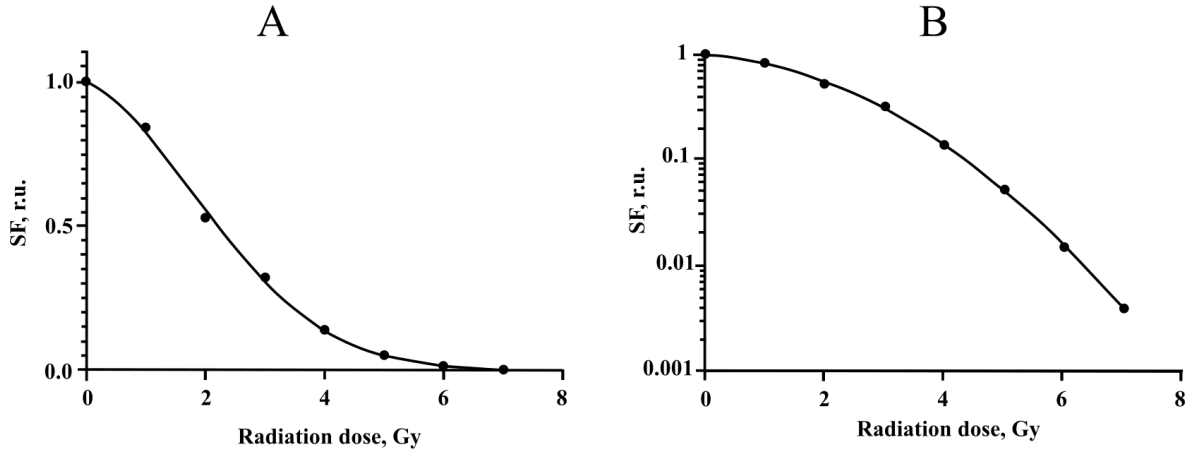
Figure 3– Typical view of the survival curve: A – linear scale, B – semi logarithmic scale [2]

Equation for LQ-model taking into account fractionation in radiation therapy[4]:

$$SF(D)=e^{-n(\alpha d+\beta d^2)},$$ (2)

where n is a number of fractions;

d is fraction dose (single dose of radiation), Gy.

For taking into account treatment time which directly correlate with cell repopulation, additional exponential factor was introduced [4]:

$$SF(D)=e^{-n(\alpha d+\beta d^2)}\cdot e^{\lambda(t-t_0)},$$
$$SF(D)=e^{-n(\alpha d+\beta d^2)+\lambda(t-t_0)},$$ (3)

Where λ is proportionality factor determined experimentally;

t_0 is time delay (if tumor repopulation begins after some time delay);

t is time since therapy started ($t \geq t_0$).

1.3 Fractionation in radiation therapy

Treatment of radiation therapy consists of high total dose which delivered by portion spread during all treatment time (except stereotactic radiosurgery (SRS). Such

single dose called fraction.

The reason for using this method is the different radiosensitivity of the irradiated cells, as well as the repair of normal cells, which takes time. Radiosensitivity can change during few hours that connects with stage of cell cycle: whole cycle of cell division takes about 10 – 24 hours, cell has the highest sensitivity in last stage due to DNA vulnerabilities. Moreover cell has mechanism for reparation that stop cell cycle if specific enzymes notice some violations. Thereby normal cells should have some time to repair induced damages and become normal functional cell again.

The initial radiation therapy was based on low energy with a significantly low penetrating power. Until 1950, remote radiation therapy was performed mainly using X-rays generated by a maximum of 300 kV. In the 1950s and 1960s, existing kV machines were gradually replaced by high-energy machines, as the development of high-energy photon-emitting accelerators and Co-60 therapy machines became very popular[5]. For Co-60 therapy machine with square irradiation field dose delivery limit is 2 Gy per fraction, therefore, 1.8 – 2 Gy was taken as the classical (conventional) fractionation mode. The duration of treatment for the classic fractionation mode usually ranges from 4 to 7 weeks.

Also there are treatment methods that short treatment time with increasing total dose per day. Some of them call hyperfractionated. In this case, radiation can be delivered more than one time per day with dose 1 – 1.5 Gy. The radiobiological basis of its application is that most tumors are rapidly proliferating tissue, and summing up several small fractions per day allows healthy tissues to recover while maintaining a highly effective effect on the tumor [6]. Dose per fraction can be increased to 2 Gy if patient irradiates no more than 2 times a day, this fractionation method calls accelerated radiation therapy.

On the other hand, there are irradiation mode which also leads to decreasing treatment time but consisting in increasing dose per fraction. In hypofractionated radiation therapy dose 3 Gy or more can be delivered to patients 3 – 4 times per

week. Radiobiological prerequisites for the use of this method are the prevention of accelerated depopulation during treatment by reducing the duration of exposure.

In additional, for all methods of radiation therapy boost, i.e. local irradiation of tumor, can be used. Given to the area at highest risk for cancer recurrence doost increases the amount of radiation. There are two types of boost which used:

- sequential boost (SEQ), this type of boost delivery consists of sequential irradiation two and more volumes. For examples, lymph nodes should have smaller dose than primary part of target (tumor) and, in this case, after all fractions of lymph nodes irradiation an additional fractions will deliver prescribed dose to the tumor;

- simultaneous integrated boost (SIB), modern type of dose delivery which consists of dose escalation in area of interest simultaneously with irradiation of other volume. It means that while one session lymph nodes should get one fractionated dose, tumor will receive another.

According to researches noticed in article [7], SIB has advantages over SEQ especially for fast-growth tumors due to decreasing duration of whole treatment course.

1.4 Radiation therapy techniques

Before irradiation, the contour of the tumor and surrounding tissues, called critical organs or organs at risk (OARs), must be determined. For this purpose diagnostic scans are usually used. It can be data from computed tomography, magnetic-resonance imaging or positron-emission tomography.

Special treatment system planning is used in radiotherapy for delineation and planning. Companies that produce their own equipment provide a planning system for it. The most common companies producing radiation therapy equipment and software for them are Elekta and Varian. Now Elekta support only Monaco system, which mostly suitable for IMRT and VMAT, for Varian it is Eclipse system. Figure 4 shows example of head-and-neck region delineation in Monaco system.
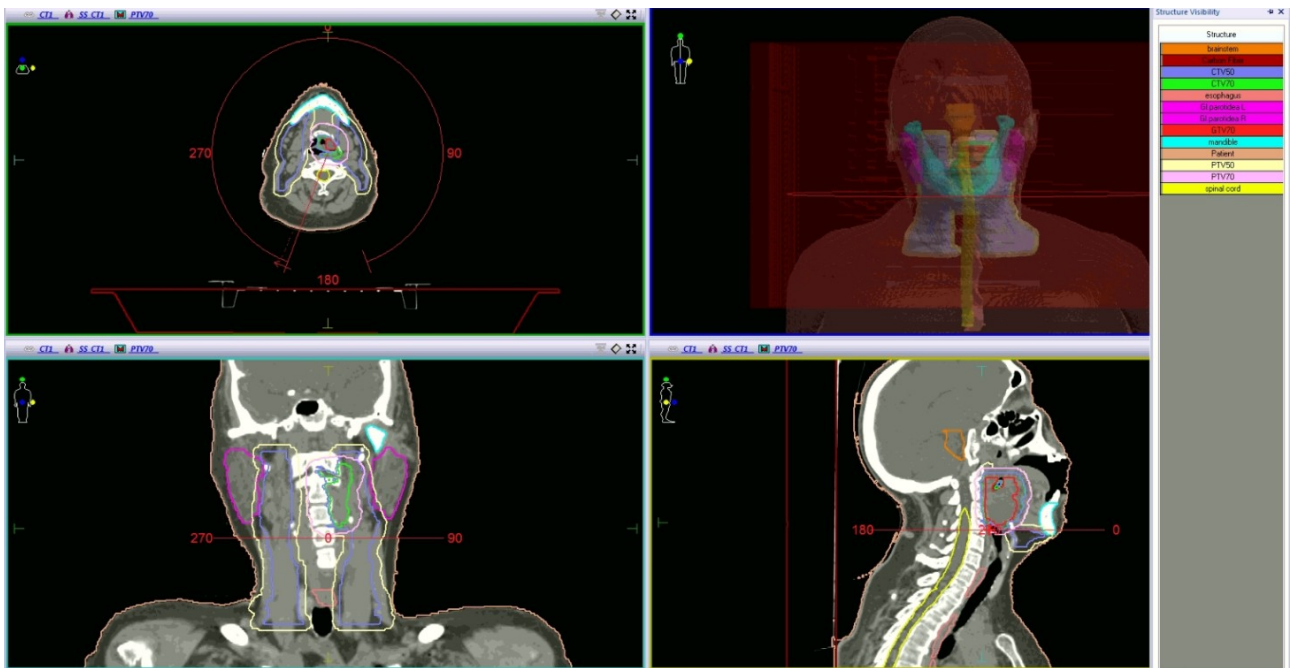
Figure 4– Example of head-and-neck region delineation.

After delineation patient should be positioned on the couch in the same position as in CT scans for further dose delivery.

Four types of radiation therapy techniques here are considered:

- conventional radiotherapy;
- conformal radiotherapy;
- intensity-modulated radiation therapy;
- volumetric modulated arc therapy.

Conventional radiotherapy is the oldest techniques for dose delivery, which implies using only of jaws of gantry for shaping where jaws are simply represented as two metal blocks. It means that irradiation field can be only either square or rectangle form that leads to big dose load on OARs. For delineation in this case planar radiograph or limited CT data were used.

With advances of opportunities in software and radiation therapy equipment, it became possible to treat the tumor more precisely while preventing of irradiation of healthy surrounding tissue. In conformal radiation therapy (3D CRT) the shape of each beam, field, determines using an multileaf collimator (MLC) which allow to match the shape of the target. When the treatment volume corresponds to the shape of

the tumor, the relative radiation toxicity to surrounding normal tissues is reduced because the largest share of dose is located in tumor area, that allows to deliver a higher dose of radiation to target. Figure 5 shows example of MLC.

<div align="center">A   B</div>
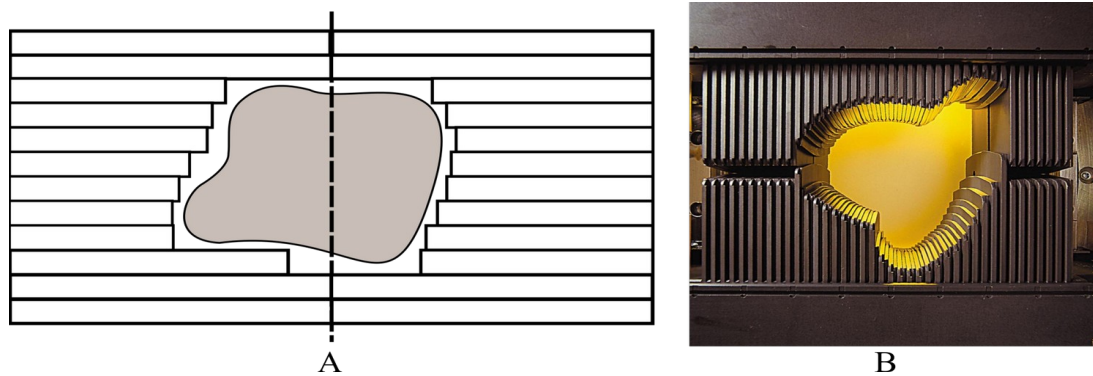
Figure 5 – Example of MLC: A – schematic representation, B – real view

Moreover, it became possible to use non - coplanar beams and 3D planning (volumetric calculations) with 3D visualization due to ability to reconstruct model of interest.

The next stage of progress is intensity-modulated radiation therapy (IMRT) which allows to work with the irregular shape of the tumor and change intensity of beam when volume is irradiated while reducing the burden on healthy tissues and delivering radiation to the tumor with greater accuracy. Figure 6 represents comparative analyzes for three mentioned radiation techniques.
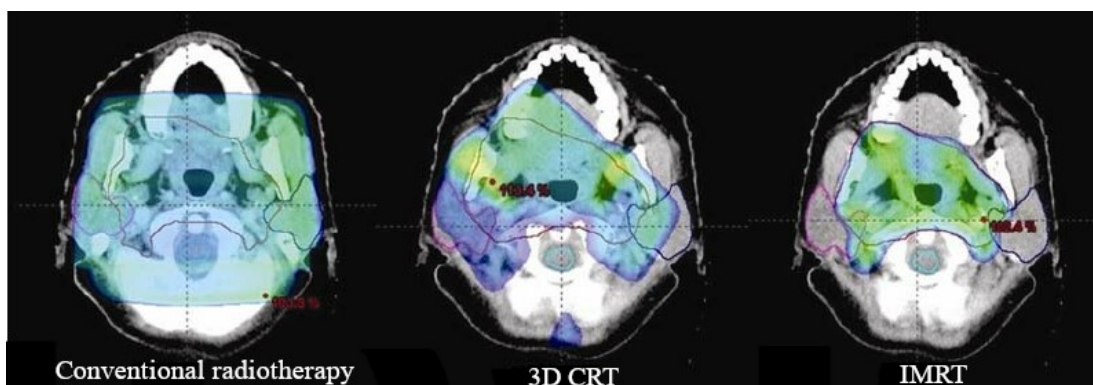
Figure 6 – Dose distribution for three types of radiation techniques [8]: value of dose increase from blue to yellow color

Volumetric modulated arc therapy (VMAT) implies continuously rotation around the patient during irradiation. It also uses MLC as 3D CRT and IMRT, VMAT can change dose rate while irradiated as IMRT but, in this case, every second

while rotates and can optimize speed of each beam rotation. The radiation is delivered to the intended area, allowing to spare more surrounding healthy tissue. Treatment time for VMAT is significantly shorter, thus benefits patients who require longer (30 minutes or more) treatment time.

Using VMAT implies creating arcs, i.e. designation of the trajectory of movement of the gantry around the isocenter. The number of arcs and their length is determined by the area of irradiation, the stage of the disease, as well as the desired dose distribution.

For 3D CRT, IMRT and VMAT immobilization devices are of great importance due to precise dose delivery (increased precise of delivery requires more accuracy in positioning): it is necessary to minimizing positioning errors and do not over-irradiate normal tissues. The main task of positioning is the alignment of the isocenter of the patient during the current position and during the acquisition of CT scans. For immobilization, thermoplastic masks and holders (figure 7) are specially made for different parts of the body in compliance with individual anatomy, special mattresses that remember the previous position of the patient, and additional blocks and clamps can also be used.

Figure 7 – Example of immobilization device: A – SBRT base plate with rolls ans wedges; B – invasive head frame; C – individual thermoplastic mask; D – vacuum mattress; E – thermoplastic holder for pelvis region

Irradiation and non irradiation systems of image-guided radiation therapy (IGRT) are used to check the position of the isocentre, as well as to account for

breath and other movements that affect the position of the isocentre. Figure 8 shows typical assembly of a modern linear accelerator with cone beam CT which used x-ray for CT image acquisition during treatment.
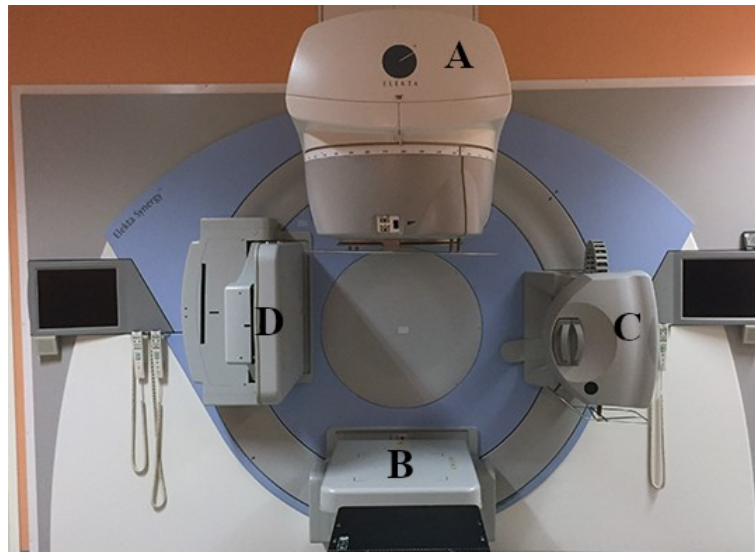
Figure 8 – Typical assembly of a modern linear accelerator with cone beam CT: A – MV-irradiation source, b- – digital MV-image converter to check patient position with the treatment beam, C – kV-x-ray generator, D – kV-image converter to acquire CT-data.

For 3D CRT and conventional radiotherapy medical physicist set beams, dose value and size of field by himself. For IMRT and VMAT inverse planning is used. In this case, for each given angle (beam or arc) dose will be calculated with treatment planning systems based on such set parameters as cost functions. Cost functions impose certain restrictions or set goals that must be achieved in the course of treatment. for example, 95% of the planned irradiated volume should be covered by 95% of the prescribed dose, but no more than 2% exceeding 107% of the prescribed dose. For organs at risk, restrictions are imposed on the size of the dose and/or the volume of the structure.

3D CRT is obviously inferior in quality of treatment to IMRT and VMAT, but which of the two is the most preferred method is still a matter of debate. Figure 9 shows example of both techniques.
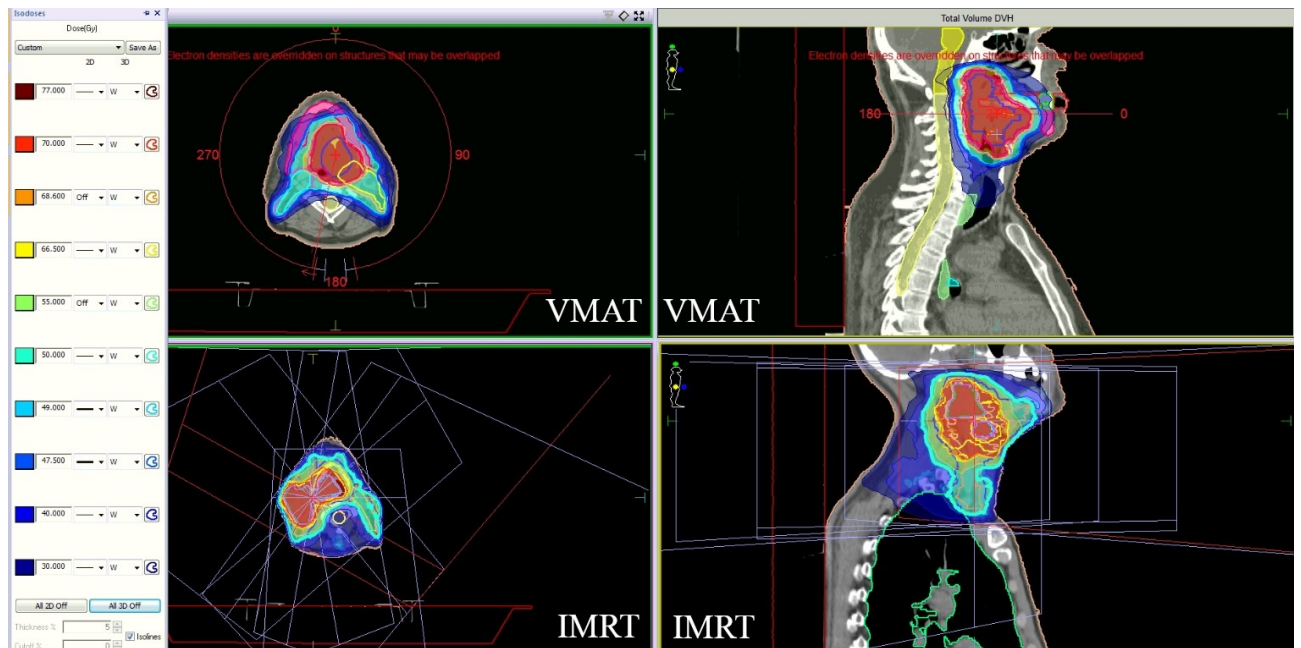
Figure 9 – Example of IMRT and VMAT for head-and-neck region

When choosing between irradiation methods, it is necessary to take into account the great capabilities of VMAT in setting cost functions and their parameters. In VMAT a lot is determined by the selected set of parameter in cost fucntions, while IMRT depends more on the choice of the direction of the gantry. It is worth emphasizing that VMAT implies continuous irradiation, i.e. when moving along a trajectory, the gantry irradiates not only the tumor, but also the adjacent tissues along the arc, while IMRT irradiates only in specific fixed positions. The most important criterion for choosing a particular method is the irradiation area: localization, size, inclusion of adjacent structures in tumor growth [9, 10, 11, 12].

At the end of planning software calculates dose values for each volume point, voxel, and represents results not only in way of dose distribution on delineated CT slices, but also as dependence volume on dose, that is called dose-volume histogram.

2 Dose-volume histogram (DVH)

In three-dimensional planning the exposure plan represent three-dimensional massive of dose values in voxels, distributing in planing target volume of patient. To analyze this number of points (the number of which can reach several thousand), dose-volume histograms (DVH) are widely used. This plot allows to summarize information consisting of three-dimensional distributions, and serves as a powerful resource for quantifying the treatment plan[2].

In simplest form DVH is frequency distribution of doses values inside the volume. Instead of frequency the "percentage of total volume" usually uses. This value is the ordinate axis, and the dose is the abscissa axis. On practice two types of DVH usually use(figure 10):

- differential DVH;
- cumulative DVH.

Disadvantage of DVH is loss of spatial information about dose distribution.

DVH calculate for target volume (tumor) and for OARs (figure 10).
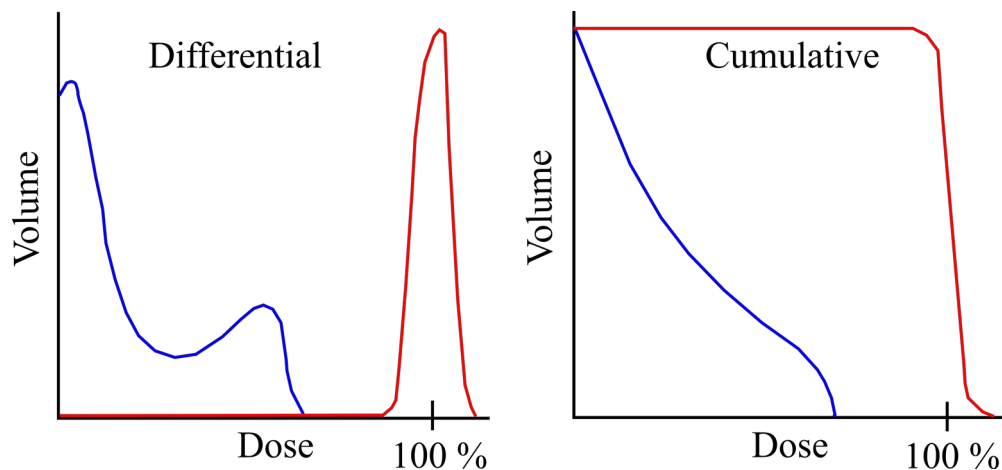
Figure 10 – Differential and cumulative histogram dose-volume: red line – target volume, blue line – OAR

While creating differential DVH (DVHd) the numbers of voxels with average dose inside choosing range are summarized. DVHd shows the dependence of volume percent of the total body dose. DVHd for target volume look like column showing that almost all volume of target received a dose in the range of which is prescribed.

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For critical structure DVH can have several peaks, indicating that part of organs received different doses. In ideal case it should be narrow peak for target and 0 Gy for critical organ.

Cumulative DVH (DVHc) uses often than differential, because it allows to determine to dose, which receive the biggest part (95%) of volume.

While creating cumulative DVH the program calculate the value of target volume, which received dose less or equal to set value. Ideal cumulative DVH for target volume has Heaviside function form (step), for critical organ is the straight line equal to 0% volume on all range of dose.

3 Equivalent uniform dose (EUD) concept

3.1 Normal tissue structural organization

In radiotherapy concept of serial and parallel architecture of organs is used. The architecture has a strong impact on the tolerance to radiotherapy. Figure 11 shows simplest representation of structure organization for this concept.
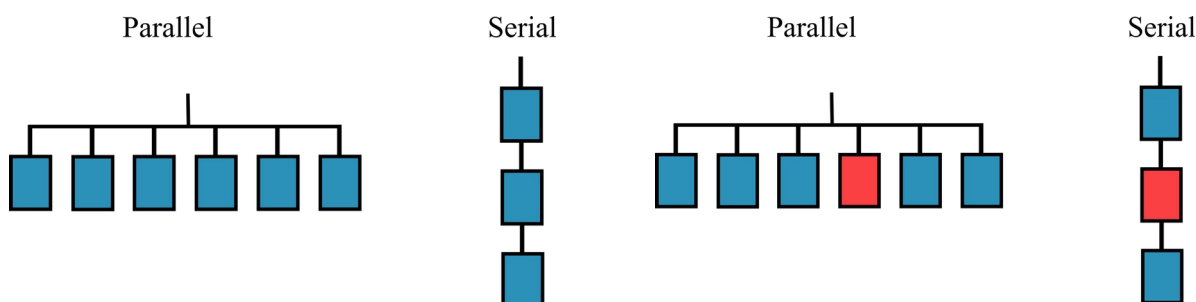
Figure 11 – Normal tissue structural organization:
a – normal structure organization, b – damaging of sub-unit in structure

According to this it can be assumed that for organs with parallel organization sub-units work independently from each other. It means that damage of one sub-unit do not leads to failure of a whole organ but damaging of some numbers sub-units can. For such organs it is necessary to set limits for "number" of such sub-units which can create severe side effects and thereby protocol QUANTEC (Quantitative Analyses of Normal Tissue Effects) [13] recommends to restrict a value of irradiated organ volume.

On other hand, when one sub-unit of organ with serial organization had damage whole organ will failure. Such organs work as conveyor where dysfunction of previous step causes the current step to fail. For such organs QUANTEC set others recommendations not to exceed the dose.

Both architectures, serial and parallel, are sometimes combined in the same organ, because different tissues cooperate to a common function. The lung, for example, has a parallel architecture at the level of parenchyma where gas exchanges take place. On the other hand, airways carrying air in and out of the alveoli have a serial arrangement.

3.2 Side effects of radiation therapy

Induced in biological phase depending on time of appearance radiation effects can be divide on early (damaging of hematopoetic organs, suppuration of skin) and late side effects (cancerogenesis, fibrosis). Time scale of observing effects spreads on many years.

The reason of such side effects is irradiation not only area of tumor, but normal organs situated near. Based on this, a treatment plan should be drawn up in such a way as to cause the greatest harm to the tumor while minimizing complications for normal organs.

3.3 Volume effect

It is a common radiotherapeutic perception that the severity of acute and chronic side effects increases as the volume of normal tissue irradiated is increased. In radiobiological studies, the volume effect is defined by the relationship between the radiation doses that cause the same probability of a certain acute or late normal tissue damage and the irradiated proportion or the irradiated volume of the investigated tissue or organ.

The situation is complicated when several different organs are located in the area of radiation (for example, the area near the renal pelvis). Then the volume effect depends on the probability of complications, which, in turn, depends on the proportion of each organ in the high dose area The serial type of tissues will show a significantly steeper dependence than the parallel type. In addition, it is noted that the concept of complications is determined not only by measurable biological factors, but also by the migration of cells to replace cells damaged by radiation, as well as the patient's perception. However, authors of the article [14] notice that the according to their research the major part of volume effect is contained in organ's architecture and way of functionality.

The main difficulty is related to the fact that laboratory tests are carried out mainly with small animals (rats and mice). The specific amount of the reaction

volume of the organ exposed to radiation may be critical, but it is difficult to scale over a wide range of body sizes.

3.4 Equivalent uniform dose (EUD)

Equivalent uniform dose (EUD) is the absorbed dose if it homogeneously distributed in the tumor:

$$EUD = \left(\sum_{i=1} \left(v_i D_i^{\alpha} \right) \right)^{\frac{1}{\alpha}}, \tag{4}$$

where v_i is volume, received dose D_i;

α is tissue-specific parameter that describes the volume effect: for tumors is negative value, for organ at risk (OAR) is positive.

The cell survival-based EUD concept assumes that the dose distributions are biologically equivalent if the number of killed cells are identical, when α is equal to 1 EUD is equal to mean dose.

The α is a large negative value for tumor as the tumor control depends on the minimum dose received by the tumor. In case of normal tissues such as serial and parallel architectures, the values of α are large positive and small positive values depending on small and large volume effects respectively.

Except EUD, EQD_2 can be a value for comparison of different fractionation modes, where EQD_2 is the dose delivered in 2 Gy fractions that is biologically equivalent to a total dose which is delivered with d fraction dose[2]:

$$EQD_2 = D \frac{d + \alpha/\beta}{2 + \alpha/\beta}. \tag{5}$$

Typically α/β = 10 Gy for early-responding tissues and tumors and 3 Gy for late-responding tissues (normal tissue).

It is important to note that value of EQD_2 can be numerical sum of separate parts of irradiation mode, implemented with different single dose.

3.5 The model of Niemierko for the tumor control probability (TCP) and the normal tissue complication probability (NTCP)

Mathematical expression of tumor control probability (TCP) determine

probability of absent viable colony forming cells in tumor after irradiation, using binomial (in limit Poison) probability distribution:

$$TCP(N_0, D) = \prod_{i=1}^{N_0} (1 - SF(D)) = (1 - SF(D))^{N_0} \approx \exp(-N_0 SF(D)) = \exp(-V_0 \cdot \rho_0 SF(D)), \quad (6)$$

where N_0 is number of colony forming cells in tumor,

V_0 is volume of tumor, cm³;

ρ_0 is density of malignant cells, cm⁻³;

SF(D) is a function of surviving malignant cells irradiating in dose D.

The transition to the Poisson distribution does not allow the fulfillment of the limit relation: when $D = 0$, SF(D) $= 1$, than TCP is not equal to zero. But it is neglected on practice.

The model of Niemerko for the tumor control probability (TCP) is defined as follows[15,16]:

$$TCP = \frac{1}{1 + \left(\dfrac{TD_{50}}{EUD}\right)^{4 \cdot \gamma_{50}}}, \quad (7)$$

where TD_{50} is control of 50% of the tumor with a dose of a uniformly irradiated tumor,Gy;

γ_{50} is coefficient of LQ-model, specific for tumor and determine slop of curve in LQ-model;

EUD is a equivalent uniform dose, calculated by formula (4).

The model of Niemierko for the normal tissue complication probability (NTCP) is define by the same expression as TCP:

$$NTCP = \frac{1}{1 + \left(\dfrac{TCD_{50}}{EUD}\right)^{4 \cdot \gamma_{50}}}, \quad (8)$$

where TCD_{50} is tolerant dose for 50% of the complication rate for a certain period of time when the whole organ is irradiated uniformly, Gy;

γ_{50} is coefficient of LQ-model, specific for normal tissue and determine slop of curve in LQ-model;

EUD is a equivalent uniform dose, calculated by formula (4).

Figure 12 shows example of NTCP and TCP curves.
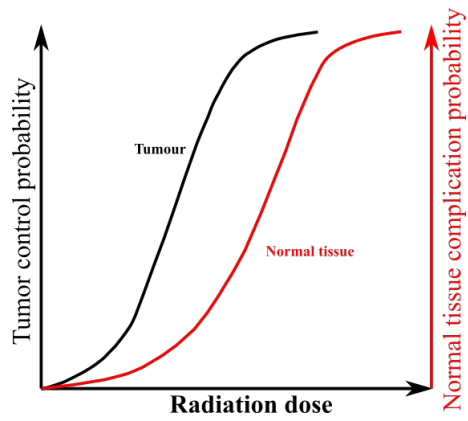
Figure 12 – Example of NTCP and TCP curves

4 Practical part

4.1 Literature review

In literature review researches which match to follow parameters was considered:

- publication years: 1989 – 2021;
- type of treatment: radiation therapy with combination of chemotherapy, immunotherapy;
- localization: head-and-neck region, mainly pharynx, oropharynx, hypopharynx;
- stages of disease: mainly T3,4 (incl. III, IV) stages, according to TNM classification [17];
- type of radiation: photons;
- primary tumor;
- mainly without surgical interruption.

Table A.1 summarizes the studies reviewed, all dose for tumor were recalculated according to equation (5) in EQD_2 with $\alpha/\beta = 10$ Gy. Local or locoregional controls in researches were calculated according to the Kaplan-Meier survival function:

$$S(t) = \prod_{i=1}^{t} \left(1 - \frac{d_i}{n_i}\right), \tag{9}$$

where d is number of adverse outcomes (deaths) at time i;

n is number of patients who are observed at time i.

Treatment of head-and-neck tumors with chemoradiation therapy is considered in studies [18 – 25]. Generally, according to results, 3-year locoregional control with dose bigger than 69 Gy reaches at least 70 %. High but acceptable toxicity is noted for conventional and accelerated [18, 19, 22, 24] fractionation modes. However Huang S. et al. [24] conclude that hypo fractionation mode can be used as alternative treatment of chemoradiation therapy for some stage of cancer.

In work of Katsoulakis E. at al [26] IMRT and 3D CRT dose delivery

methods analyze. According to authors opinion, there was no increased local failure with IMRT and IMRT has better 3-year locoregional control (for IMRT 85 %, for 3D CRT 76 %).

Comparing radiation and chemoradiation treatment, Calais G. et al. [27], Denis F. et al. [28] and Regine W. F. et al. [29] conclude that the most favorable prognosis will be in the case of concomitant chemotherapy: 5-year locoregional control is 56 % [27], 47 % [28] for chemoradiation therapy while 32 % [27], 24.7 [28] for radiotherapy.

Influence of immunotherapy is described in researches of Habl G. et al. [30] and Ho C. et al. [31]. Ho C. et al. [31] note that immunotherapy with radiation therapy reach worse 3-year tumor control (43 %) comparing with chemoradiation therapy(88 %), high side effects of both treatment methods belong to different toxicity profiles. In work [30] higher side effects is observed for patients with immunotherapy.

Schüttrumpf L. et al. [32] write that it is important to stratify and optimize procedure of radical chemotherapy and note that patients with human papillomavirus-associated oropharynx cancer (HPVOPC) has better tumor control parameters for conventional mode (3-year locoregional control 70 %). Low level of hemoglobin and lymph nodes involvement, according to the authors, leads to failure in long-term perspective.

In studies of Horiot J. C. et al. [33] and Poulsen M. G. et al. [34] two fractionation modes, accelerated and conventional, is compared. Better tumor control is reached for accelerated mode, according to authors [33], however in research [34] there was no significant difference between the modes. Both studies note about high toxicity of normal tissue.

For plotting TCP function, in first way, value of TD_{50} was averaged for all the indicated tumors [4], according to stages III, IV [17] (i. e. either T3 − 4, or T2 with N1 − 3) with irradiation time of 49 days, recalculated by equation (5). Than TD_{50} is equals to (70.6 ± 2.6) Gy. Slope of curve, γ_{50}, was determined through TD_{50} and

$TD_{90} = (73.7 \pm 2.6)$ Gy, which was calculated with the same way as TD_{50}. Figure 13 shows obtained result: for $TD_{50} = 73.2$ Gy, $TD_{90} = 71.6$ Gy γ_{50} is negative value, for $TD_{50} = 70.6$ Gy, $TD_{90} = 71.6$ Gy and $TD_{50} = 73.2$ Gy, $TD_{90} = 73.7$ Gy γ_{50} is very large, 77.8 and 80.7 respectively, that does not make sense.
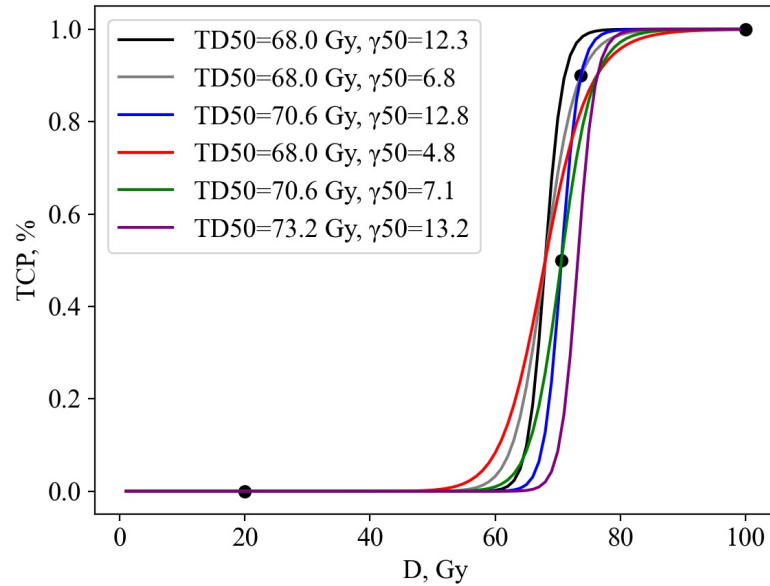
Figure 13 – γ_{50} for different TD_{50} and TD_{90}, points on plot: TCP(20 Gy) = 0 %, TCP(TD$_{50}$) = 50 %, TCP(TD$_{90}$) = 90 %, TCP(100 Gy) = 100 %

From other hand, in study of Okunieff M. D. et al. [35] values of TD_{50} and γ_{50} study are different from study [4] mentioned above. Here some of them are considered:

- Supraglottic, stage I, II, IIIa, $TD_{50} = 63.43$ Gy, $\gamma_{50} = 2.66$;
- Pharyngeal wall, stage T1–4, $TD_{50} = 63.66$ Gy, $\gamma_{50} = 4.01$;
- Pharyngeal wall, stage T3+T4, $TD_{50} = 72.19$ Gy, $\gamma_{50} = 0.8$;
- Supraglottic, stage IIIb, IV, $TD_{50} = 83.35$ Gy, $\gamma_{50} = 0.97$.

Figure 14, 15 show TCP curve for head-and-neck tumors, the points on the curve correspond to the results (tumor control) of the studies indicated in Table A.1 according to their serial number. TCP curve is plotted only for $TD_{50} = 70.6$ Gy because deviation for this value was calculated.
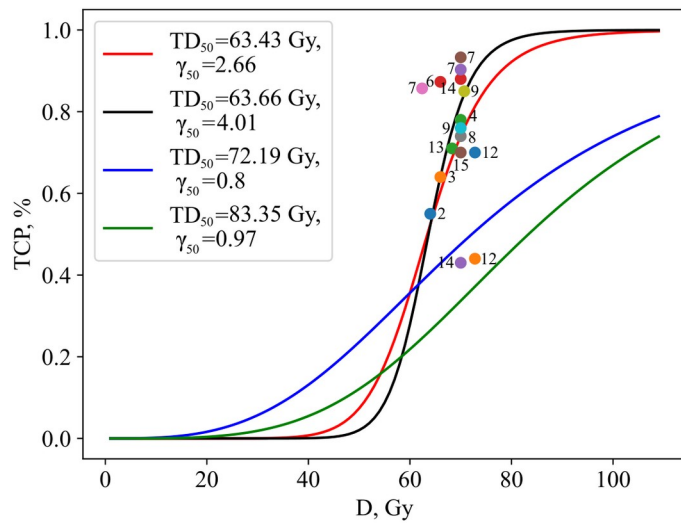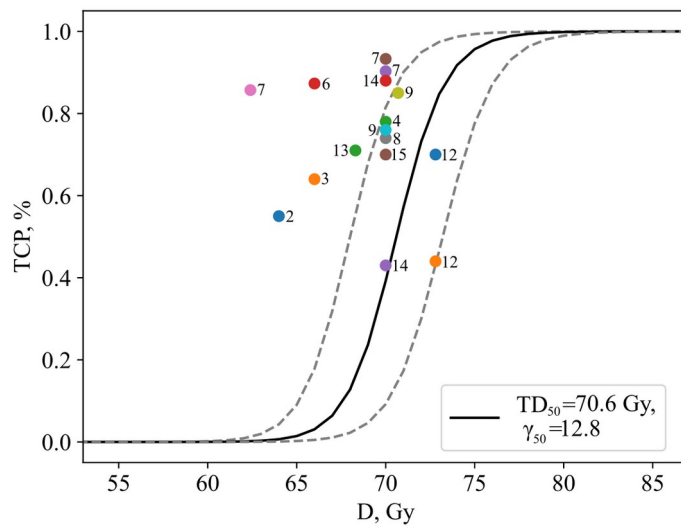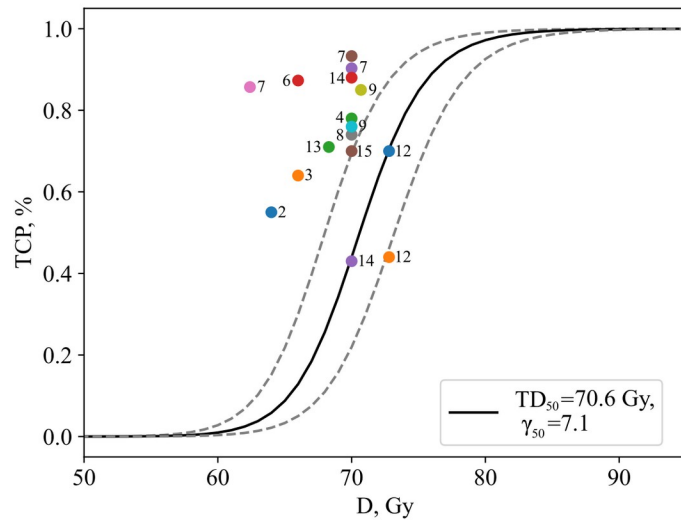
Figure 14 – TCP for 3 years, dashed lines represent error limits for mean, where
$TD_{50} = (70.6 \pm 2.6)$ Gy
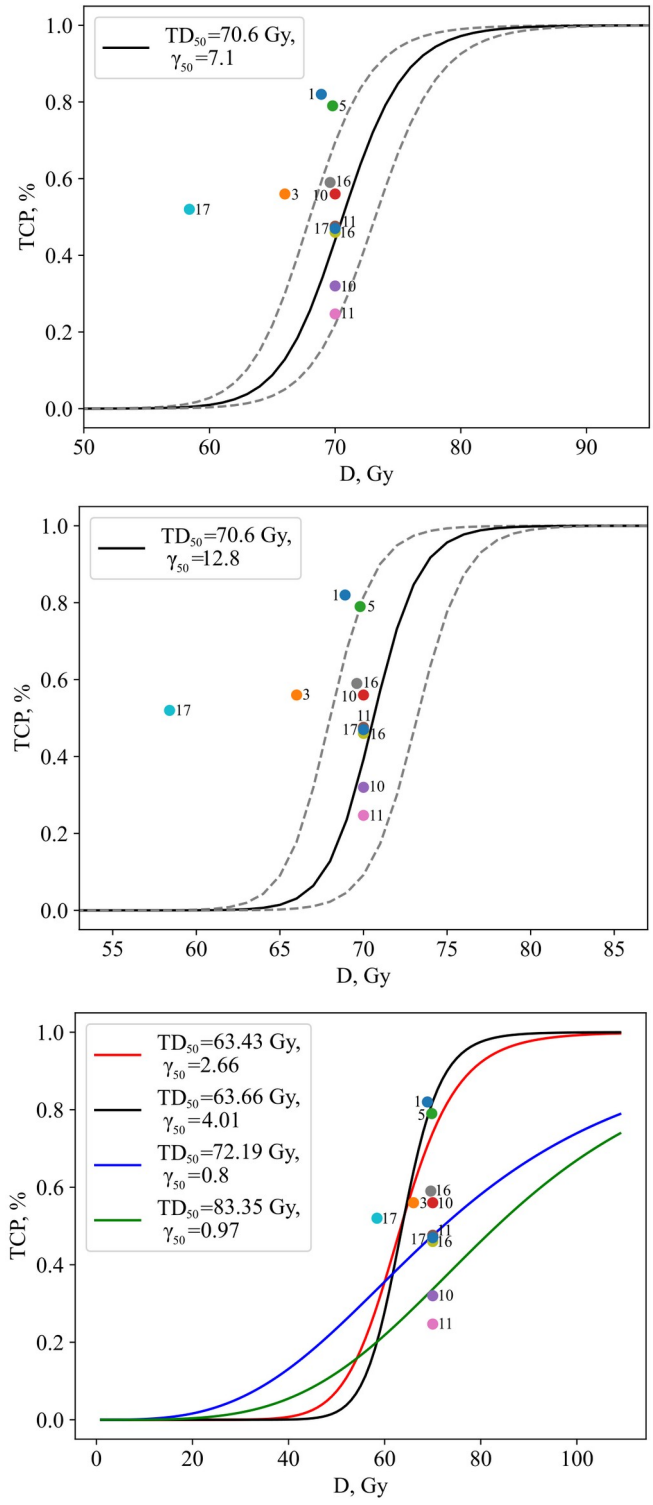
Figure 15 – TCP for 5 years, dashed lines represent error limits for mean, where
$$TD_{50} = (70.6 \pm 2.6) \text{ Gy}$$

According to obtained plots, it can be seen that generally calculated TD_{50} and γ_{50} are in good agreement with the data from the literature review for conventional mode, while the data obtained by [35] are applicable more or less only for 3-year

locoregional control. For 3-year locoregional control, a high γ_{50} (7.1 and 12.8) would probably be better combined with a TD_{50} of slightly less than 70.6 Gy. However, for 5-year locoregional control the current calculated parameters fall within the error limits of the mean.

Points 1, 2, 5, 6, 13, some of 7 and 17 for the 3-year and 5-year locoregional did not fall within the error limits, possibly due to the use of hypo- or hyperfractionation. According to plot, it can be seen that this values located to the left in area with lower total dose, but bigger part of this points are not inferior to locoregional control for conventional mode.

Figure 16 show TCP for 35 and 42 days of treatment (overall treatment time) for all tumor sites [4].
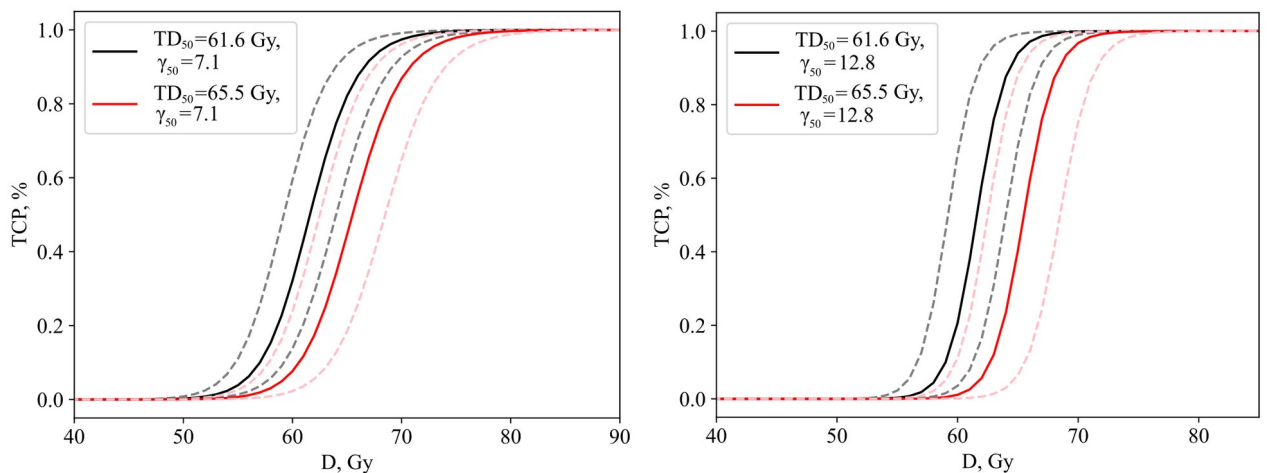
Figure 16 – TCP for two treatment duration,dashed lines represent error limits for mean, where TD_{50} (35 days)$= (61.6 \pm 2.4)$ Gy

TD_{50} (42 days)$= (65.5 \pm 3.0)$ Gy

Head-and-neck tumors are fast-growth malignancies and thereby duration of the course has a very large impact, including on the final total dose. With an increase in the duration of the course, the dose of TD_{50} increases noteworthily (Figure 13, 16), the proliferative ability of tumor cells significantly reduces the effect of radiation, which should be compensated by an increase in the total dose, or reduction in the duration of the course.

Figure 17 shows points of locoregional control for hypo- or hyperfractionation modes according to Table A.1.

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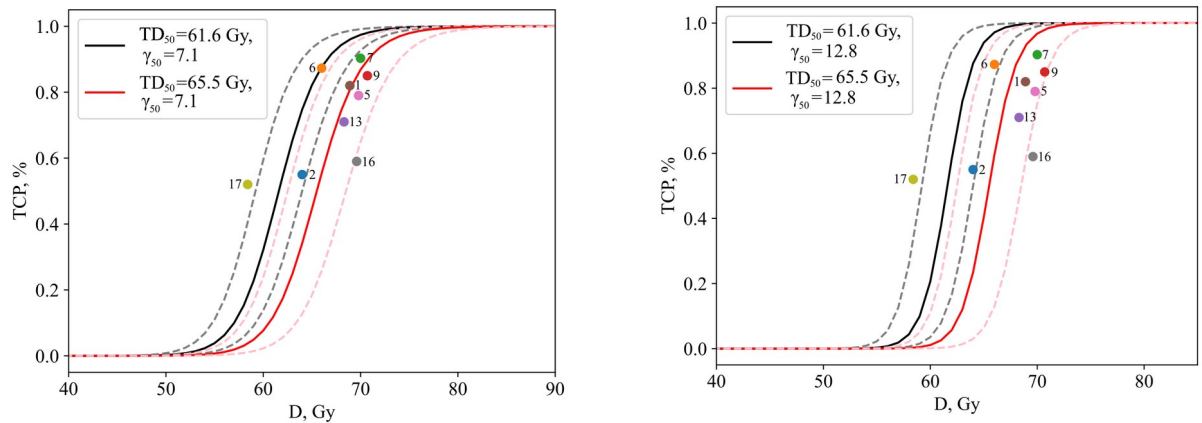
Figure 17 – TCP for 3-year (points 2, 6, 7, 9, 13,) and 5-year (points 1, 5, 16, 17) locoregional control for two treatment duration,dashed lines represent error limits for mean, where TD_{50} (35 days)= (61.6 ± 2.4) Gy, TD_{50} (42 days)= (65.5 ± 3.0) Gy

Points 12 did not considered because, despite on hypofractionation mode, total duration of treatment is almost the same as for conventional mode due to total dose escalation. According to Figure 17, control for hypo- and hyperfractionation modes fits well to data for 35 and 42 days of treatment duration.

In studies corresponding to points 12, 14 for 3-year locoregional control and 10, 11 for 5-year locoregional, oropharynx is predominant as a site of tumor, but in most of the studies shown on the plot, the oropharynx is also one of the most common sites.

According to literature review the following statement can be concluded:

‑ conventional mode (70 Gy, 35 fractions) leads to wide range of results and all of them do not fall lower 70% for 3 years control (points 4, 6, 7, 8, 9, 13, 14, 15) but for 5 years locoregional control is located around 50% (points 3, 10, 11, 16, 17);

‑ for 5 years local control for non-conventional(accelerated, hypo- or hyperfractionation) mode bigger than for conventional but for 3 years this difference do not significant (points 1, 5, 16, 17);

‑ decreasing of dose lower than 66 Gy do not leads to sufficient tumor control already after three years of observation (points 2, 3);

‑ obtained in study of Maciejewski B. et. al. [4] values of TD_{50} and calculated values of γ_{50} correlate well with experimental data almost of all mentioned studies, therefore, they will be used for further TCP calculation of real patients.

4.2 Patient treatment analysis

The data in this section was obtained from two different cities and different therapeutic devices:

- Tomsk, Tomsk Regional Oncology Center, Elekta Synergy;

- Tyumen, Tyumen Regional Oncological Dispensary, Varian TrueBeam STx, Varian Clinac, Elekta Synergy.

Table 1 contains brief description of studying patients.

Table 1 – Brief Description of patients

№	Diagnosis	Treatment	Location
Patient 1	T2N0M0 II, oropharyngeal cancer	IMRT, 70 Gy, 2Gy – tumor, 50 Gy, 2 Gy – lymph nodes	Tomsk
Patient 2*	T2N0M0 II, oropharyngeal cancer	VMAT-SIB, 70 Gy, 2Gy	Tomsk
Patient 3	T4N1M0 IVa, oropharyngeal cancer	IMRT, 70 Gy, 2 Gy – tumor, 60 Gy, 2 Gy – lymph nodes	Tomsk
Patient 4	T4N2M0 IV, oropharyngeal cancer	VMAT, 70 Gy, 2 Gy – tumor, 50 Gy, 2 Gy – right lymph nodes	Tyumen, TrueBeam
Patient 5	T2N3M0 IVb, oropharyngeal cancer	VMAT-SIB, 70 Gy, 2.5 Gy – tumor**, 50 Gy, 2 Gy – lymph nodes	Tomsk
Patient 6	T4N2M0 IV, oropharyngeal cancer	IMRT-SIB, 70 Gy, 2.5 Gy – tumor**, 60 Gy, 2 Gy, 50 Gy, 2 Gy– lymph nodes	Tomsk
Patient 7	T3N0M0 III, tongue cancer	3D CRT, 70 Gy, 2 Gy– tumor, 54 Gy, 2 Gy– lymph nodes	Tomsk
Patient 8*	T3N0M0 III, base of tongue cancer	VMAT-SIB,70 Gy, 2.5 Gy – tumor**, 50 Gy, 2 Gy– lymph nodes	Tomsk
Patient 9	T2N1M0 III, cancer of the lateral surface of the tongue	VMAT, 70 Gy, 2.12 Gy – tumor**, affected right lymph node, 60 Gy, 1.8 Gy – right lymph nodes, 54 Gy, 1.64 Gy – left lymph nodes	Tyumen, TrueBeam
Patient 10	T1N2M0 III, oropharyngeal cancer	VMAT, 70 Gy, 2 Gy– tumor, 50 Gy, 2 Gy – lymph nodes	Tyumen, TrueBeam
Patient 11	T3N2M0 IV, laryngeal cancer	VMAT, 70 Gy, 2 Gy – tumor, 50 Gy, 2 Gy – lymph nodes	Tyumen, Clinac
Patient 12	T4N1M0 IV, laryngeal cancer	VMAT, 70 Gy, 2 Gy – tumor, 50 Gy, 2 Gy – lymph nodes	Tyumen, TrueBeam
Patient 13	T3N0M0 III, laryngeal cancer	VMAT, 70 Gy, 2 Gy – tumor, 50 Gy, 2 Gy – lymph nodes	Tyumen, Elekta Synergy

Continuation of Table 1

№	Diagnosis	Treatment	Location
Patient 14	T2N1M0 III, laryngeal cancer	IMRT-SIB, 70 Gy, 2.5 Gy – tumor**, 50 Gy, 2 Gy – lymph nodes	Tomsk
Patient 15	T2N0M0 II, laryngeal cancer	VMAT, 66 Gy, 2 Gy – tumor, 50 Gy, 2 Gy – lymph nodes	Tyumen, Clinac
Patient 16	T1N0M0 I, laryngeal cancer	VMAT, 60 Gy, 2 Gy – tumor, 44 Gy, 2 Gy – lymph nodes	Tyumen, TrueBeam
*patients without chemotherapy ** dose for tumor according to equation (5) with α/β = 10 Gy: EQD$_2$ (70 Gy, 2.5 Gy) = 72.9 Gy, EQD2 (70 Gy, 2.12 Gy) = 70.7 Gy			

In the process of work, a program has been developed for conversion of the integral DVH into a differential one for subsequent calculations of EUD, TCP and NTCP. Appendix B consists of two DVH examples from different software (for Elekta – Monaco, for Varian – Eclipse).

Figure 18 and 19 shows two examples of differential and integral DVH for tumor and OARs of patients.
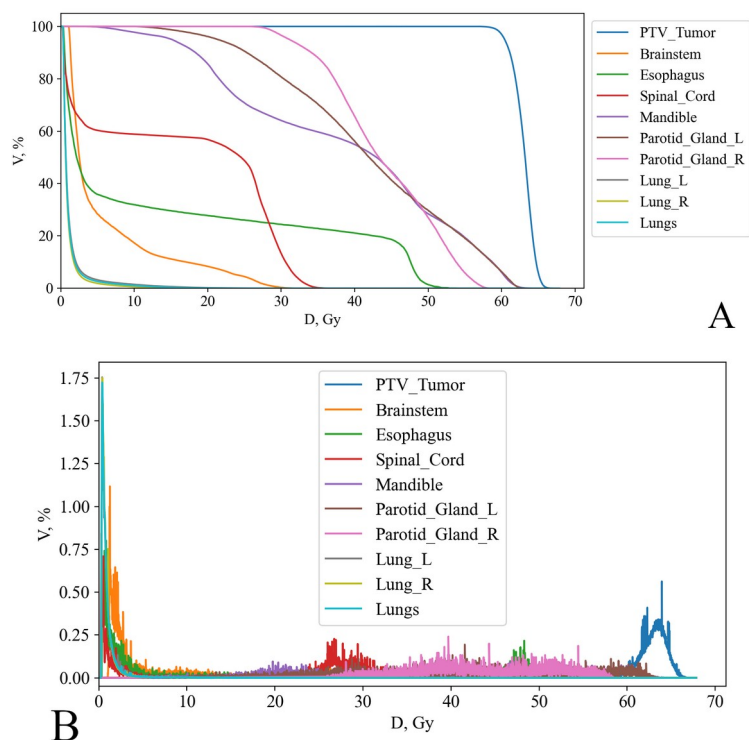
Figure 18 – DVH for tumor and OARs for patient 3, where PTV_Tumor is planning target volume for tumor: A – integral DVH, B – differential DVH
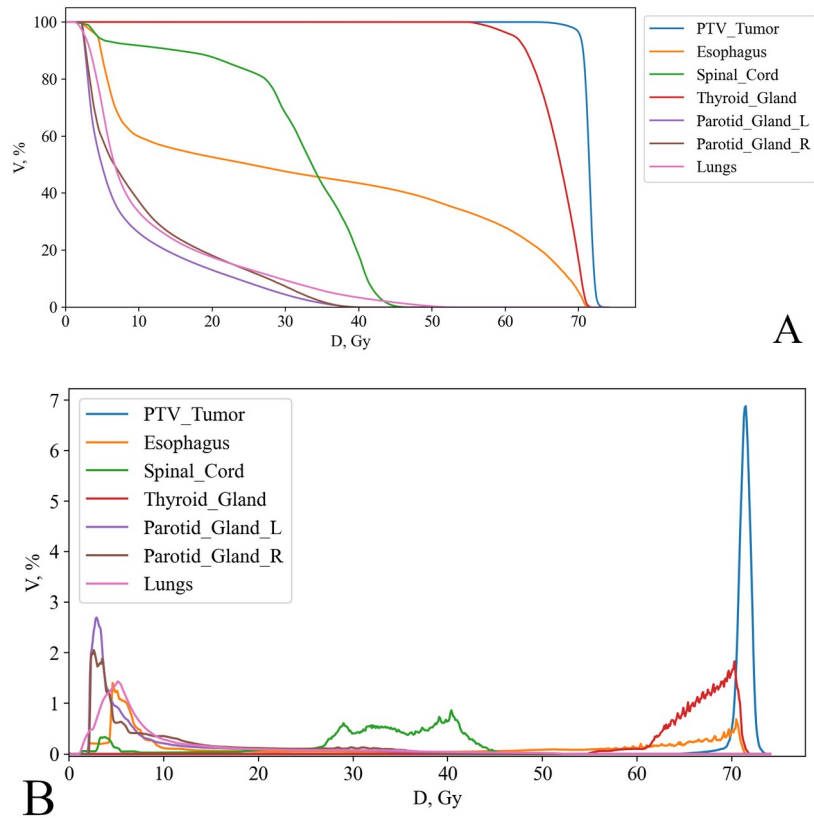
Figure 19 – DVH for tumor and OARs for patient 12, where PTV_Tumor is planning target volume for tumor: A – integral DVH, B – differential DVH

Calculated by equations 4, 7, 8 EUD, TCP, NTCP, respectively, are listed in Table 2 (TCP) and Table C.2 (NTCP), Table C.1 consists of parameters for EUD and NTCP calculations. TCP was calculated based on TD_{50} value according to tumor site and stage of disease [4, 35] with using equation (5) if necessary, for EUD $\alpha = -8$ [36].

Table 2 – Obtained EUD ans TCP for all patients

№	EUD, Gy	TD_{50}, γ_{50}	TCP	№	EUD, Gy	TD_{50}, γ_{50}	TCP
Patient 1* (96.3 %)	62.22	$TD_{50} = 66.3$ Gy $\gamma_{50} = 11.3$	5.4 %	Patient 9	70.34	$TD_{50} = 69.8$ Gy $\gamma_{50} = 9.4$	57.1 %
Patient 2	72.08		97.8 %	Patient 10	66.31	$TD_{50} = 63.66$ Gy $\gamma_{50} = 1.67$	56.8 %
Patient 3* (98.1 %)	62.87	$TD_{50} = 71.3$ Gy $\gamma_{50} = 12.1$	0.02 %	Patient 11	64.56	$TD_{50} = 70.6**$ Gy $\gamma_{50} = 12.8**$	1.0 %
Patient 4	71.36		51.1 %	Patient 12	71.28		71.3 %
Patient 5	71.38	$TD_{50} = 65.8$ Gy $\gamma_{50} = 12.3$	98.2 %	Patient 13	69.73	$TD_{50} = 63.4$ Gy $\gamma_{50} = 2.7$	73.6 %

Continuation of Table 2

№	EUD, Gy	TD_{50}, γ_{50}	TCP	№	EUD, Gy	TD_{50}, γ_{50}	TCP
Patient 6	71.53	TD_{50} = 66.8 Gy γ_{50} = 12.1	96.5 %	Patient 14	71.70	TD_{50} = 63.4 Gy γ_{50} = 2.7	79.0 %
Patient 7* (96.3 %)	71.21	TD_{50} = 69.8 Gy γ_{50} = 9.4	68.0 %	Patient 15	67.47	TD_{50} = 61.97 Gy γ_{50} = 2.69	71.4 %
Patient 8	72.47	TD_{50} = 65.6 Gy γ_{50} = 9.5	97.8 %	Patient 16	67.31		70.9 %

*gamma analysis (% Passed) values obtained when checking the plan with Sun Nuclear ArcCHECK are shown in brackets
** for laryngeal cancer with IV stage and hypopharynx cancer with III stage the obtaining values of TD_{50} and γ_{50} calculated early was taken

Taking into account fractionation mode and treatment duration, it can be concluded that locoregional control for patient in Table 2 will, in general, correspond to the locoregional control for the classic regime indicated in the literature review:

- 3-year locoregional control is about 65 – 75 %;

- 5-year locoregional control is about 40 – 50 %.

For patients 1, 3 and 11 who has 70 Gy as total dose this prediction is not an exception because described irradiation methods in literature review with total dose 70 Gy do not mean that EUD also will be equal to 70 Gy.

It is worth noticing that following differences in control calculation methods has important and affect on final result:

- The difference in the calculation method: the results obtained in Chapter 4.1 are calculated using equation 9, while those obtained in the study are calculated using equations 4, 7, 8.

- Statistical data processing: the studies considered in Chapter 4.1 are obtained for a group of people and, therefore, are averaged.

- The parameters used for TCP calculation may not be true values.

Also almost all mentioned studies in literature review has total dose around or equal 70 Gy but EUD value is unknown. For example, prescribed dose for patient 2 is 70 Gy but EUD is 72 Gy. This value indicates uniform coverage that leads to better treatment results (including tumor control) than prescribed dose. The opposite effect

can be observed for patient 1. A similar prescribed dose results in an EUD of less than the TD_{50} due to insufficient or uneven coverage, which results in less than 10% tumor control. For patient 16, the prescribed dose is 60 Gy, however the EUD is 67 Gy. This value represents the threshold for 70% dose control. Consequently, the control value depends not only on the delivered dose, but also on the dose distribution, coverage, inside volume of interest.

The next point is that not for all tumor sites 70 Gy is enough to reach 70 % of locoregional control, according to TD_{50}, γ_{50} values, which used. Particularly, advanced stage of oropharyngeal cancer require at least 72.6 Gy of EUD for 70 % of control. But this problem can be solve if decrease treatment time.

It can be seemed that difference in TD_{50} is 9 Gy between averaged values for 49 and 35 days (Figure 13, 16). In theory, for patient 4 with the same dose but decreased treatment duration, local control can be 100 % for 35 days and 96 % for 42 days.

Also patients 5, 6 and 8 irradiated with SIB where fraction dose for tumor is 2.5 Gy. Treatment duration for this patients was equalized to 42 days (real duration a little bit less but the exact duration is unknown), for patient 10 with 2.12 Gy per fraction for tumor treatment duration was taken as 49 day because real duration is between 42 days and 49 days and also is unknown. It can be noticed that control for patient 6 is much more than for patient 4 who has the same stage and site of disease. Moreover, EUD of patient 4 is not enough for 70 % of TCP while TCP of patient 6 is very large with almost the same dose. Similar conclusion can be made for patient 7 and 8, but, in this case, great importance is method of dose delivery: dose distribution of VMAT is better than 3D CRT.

According to literature review, 3-year locoregional control for hypo- or hyperfraction therapy is about the same but hypofractionation for 5-year gives better results than conventional mode.

For normal tissues, according to the results of Table C.2, the doctor's examinations and the studied sources in Chapter 4.1 (Table 1, Figures 14, 15), acute

radiation reactions develop approximately the same, and late ones, as a rule, are absent provided that the tolerance of the organ is observed:

- at 3 – 8 weeks epitheliitis of a different sites appears;

- xerostomia, esophagitis, candidiasis, mucositis, dermatitis, stomatitis (if the mandible falls into the irradiation area of the tumor or lymph nodes) with 3 – 4 grade of severity.

Early radiation reactions, excluding epithelitis, have a different duration, in particular, on average, xerostomia lasts at least a year.

5 Financial management, resource efficiency and resource saving

5.1 Project initiation

Initiation processes define initial goals and content and fix initial financial resources. The internal and external stakeholders of the project are determined, which will interact and influence the overall result of the scientific project.

5.1.1 Project goals and results

Information about the hierarchy of project goals and criteria for achieving goals is given in the Table 3.

Table 3 – Project goals and results

Project goals	Estimation of expected radiation treatment effectiveness of head-and-neck cancer, predicting treatment results based on the research performed, statistical evaluation of data.
Expected results of the project	The classical regime of treatment does not lead to the satisfactory control of tumor, i.e. to the desired treatment outcomes.
Acceptance criteria of the project result	Proposal and justification for choosing an alternative solution
Requirements to the project results	Project completion on time
	Alternative treatment offer

5.1.2 Organization structure of the project

The organizational structure of the project is presented in the Table 4.

Table 4 – Project Working Group

№	Name	Position	Functions	Hours spent
1	Klinovitskaia M.I.	Student	Work on project implementation	416
2	Sukhikh L.G.	Superviser	Coordination of work activities and assistance in project implementation	120
Total:				536

As a result of the initialization of the project, the goals and expected results were formulated, the stakeholders of the project and the financial framework were identified, which is very important for the successful completion of the project and its

implementation.

5.1.3 Deadlines for the project stages

Deadlines for the project stages are listed in Table 5. In addition, Table 6 visualized project schedule in form of bar chart also called Gantt chart.

Table 5 – Project timeline

Job title	Duration, working days	Start date	Date of completion	Participants
Drawing up the technical assignment	5	15.03.2021	19.03.2021	Supervisor
Calendar planning	6	20.03.2021	29.03.2021	Supervisor, Student
Literature review	22	30.03.2021	28.04.2021	Student
Selecting a radiological model	3	29.04.2021	3.05.2021	Student
Mathematical analysis of data	2	3.05.2021	4.05.2021	Student
Development of a program for working with data	1	4.05.2021	4.05.2021	Student
Calculation equivalent uniform dose, tumor control probability	1	5.05.2021	5.05.2021	Student
Predicting treatment outcomes based on literature review	3	6.05.2021	10.05.2021	Student 4
Summarizing	4	10.05.2021	13.05.2021	Supervisor, Student
Drawing up a final report	10	14.05.2021	27.04.2021	Student

Table 6 – Schedule of the project design

№	Activities	Participants	T_c, days	March 3	March 4	April 1	April 2	April 3	April 4	May 1	May 2	May 3	May 4
1	Drawing up the technical assignment	Supervisor	5	■									
2	Calendar planning	Supervisor, Student	6		■▨								
3	Literature review	Student	22			▨	▨	▨	▨				
4	Selecting a radiological model	Student	3							▨			
5	Mathematical analysis of data	Student	2							▨			
6	Development of a program for working with data	Student	1							▨			
7	Calculation equivalent uniform dose, tumor control probability	Student	1								▨		
8	Predicting treatment outcomes based on literature review	Student	3								▨		
9	Summarizing	Supervisor, Student	4								■▨		
10	Drawing up a final report	Student	10									▨	▨

* T_c – calendar days

■	Supervisor	▨	Student

Total duration: Klinovitskaia M.I. (Student) – 52 days, Sukhikh L.G. (Supervisor) – 15 days

5.1.4 Project budgeting

The project budget must display reliable values for all types of costs associated with its implementation. The costs of this project include:

- Costs of purchasing equipment;
- Costs for materials and other products;
- Expenses for the main and additional salaries of the theme performers;
- Costs for special equipment;
- Costs of social security contributions;
- Overhead costs.

5.1.4.1 Costs of purchasing equipment

Table 7 shows needful basic equipment and accessories, and also its cost for scientific work.

Table 7 – Cost of equipment and accessories for project

Name of equipment	Quantity, units	Price per unit, rub	Total cost for position, rub
Monitor	1	10000	10000
Hard Disk Drive (HDD)	1	5000	5000
Computer mouse	1	300	300
Keyboard	1	700	700
Central Processing Unit (CPU)	1	10000	10000
Power Supply	1	3000	3000
Random Access Memory (RAM)	1	11000	11000
Motherboard	1	7000	7000
Total:			47000

All equipment (but not accessory) indicated in the table is in stock and does not require purchase, therefore, the price of equipment is determined by amortization costs. depreciation charges.

Depreciation is the gradual transfer of costs incurred to purchase or build

property, plant and equipment to the cost of the finished product. With its help, money spent on the construction or purchase of property is compensated. Depreciation deductions are paid during the entire period of property exploitation.

Deprecation were calculated in linear way, annual (N_D) and academic year (D) deprecations were calculated according following equations:

$$N_D = \frac{1}{t} \cdot 100 [\%], \qquad (10)$$

$$D = \frac{S \cdot N_D}{100} \cdot \frac{T}{365} [rub], \qquad (11)$$

Where t – operating life, years;

S – price of one unit, rub;

T – number of working days.

Table 8 shows obtained results.

Table 8 – Depreciation of equipment for project

Position	t, years	T, days	N_D, %	D, rub
Monitor	10		10.00	140
Hard Disk Drive (HDD)	7		14.30	50
Computer mouse	1		100	43
Keyboard	10		10.00	10
Central Processing Unit (CPU)	20	52	5.00	71
Power Supply	10		10.00	43
Random Access Memory (RAM)	15		6.70	104
Motherboard	15		6.70	66
Total:				527

5.1.4.2 Costs of additional materials

Table 9 shows needful other materials for scientific work. These costs include office supplies, printing costs and various equipment required for research except specialized equipment.

Table 9 – Cost of additional materials for project

Name of equipment	Quantity, units	Price per unit, rub	Total cost for position, rub
Pen	2	10	20
Paper	2 packs (200 units)	60	120
Folder	1	5	5
Stapler	1	150	150
Staples	1 pack (48 units)	40	40
Hole puncher	1	250	250
Total:			585

5.1.4.3 Salary

The amount of expenses for wages of employees is determined based on the labor intensity of the work performed and the current system of salaries and tariff rates.

The calculation of the basic salary of the head of a scientific project is based on the sectoral wage system. The branch system of remuneration at TPU assumes the following composition of wages:

- Salary – determined by the enterprise. In TPU, salaries are distributed in accordance with the positions held, for example, assistant, art. lecturer, associate professor, professor.

- Incentive payments – set by the head of departments for effective work, performance of additional duties, etc.

- Other payments, district coefficient.

Since incentive bonuses, other payments and incentives depend on the activities of the manager in particular, we will take the coefficient of incentive bonuses (k_b) equal to 30%, and the coefficient of incentives for the manager for conscientious work (k_{pr}) activity is 25%, regional coefficient (k_r) – 1.3.

Average daily salary S_d for a 5-day working week:

$$S_d = \frac{S_M}{F_d},$$ (12)

where S_M – monthly salary, rub;

F_d – average number of working days in a month, days.

Monthly salary S_M can be determined according next equation:

$$S_M = S_r \cdot (1 + k_{pr} + k_b) \cdot k_r [rub].$$
(13)

where S_r – average daily salary, rub;

Additional salary:

$$S_{add} = k_{extra} \cdot S_M [rub].$$
(14)

where k_{extra} – additional salary coefficient (10-15%). For calculation values 10% is used.

Average number of working days in a month F_d was determined as:

$$F_d = 247 / 12 = 20.58,$$
(15)

where 247 – number of working days in year.

The basic salary S_b is determined by next equation:

$$S_b = S_d \cdot T [rub],$$
(16)

where S_d – average daily salary, rub;

T – duration of work, days.

Daily additional salaries S_D:

$$S_D = \frac{S_{add}}{F_d} [rub].$$
(17)

Additional salary for the entire project period:

$$S_{ADD} = S_D \cdot T [rub].$$
(18)

Full salary for the period of the project:

$$S = S_b + S_{ADD} [rub].$$
(19)

Table 10 shows obtained values for salary, S_r is average value for Tomsk. Student was equalized to engineer-researcher.

Table 10 – Salaries of participants in the project

Participants	S_r, rub	S_M, rub	S_{add}, rub	S_d, rub	T, days	S_b, rub	S_D, rub	S_{ADD}, rub	S, rub
Sukhikh L.G.	45000	90675	9067.5	4406	15	66089.7	440.6	6609	72698
Klinovitskaia M.I.	20000	40300	4030	1958.2	52	101827	195.8	10182.7	112009
Total:									184707

5.1.4.4 Contributions to social funds

Here I will consider the obligatory contributions according to the norms established by the legislation of the Russian Federation to the state social insurance bodies (FSS), the pension fund (PF) and medical insurance (FFOMS) from the costs of wages of employees. The amount of contributions to extra-budgetary funds S_{exb} is determined by the formula:

$$S_{exb} = k_{exb}(S_b + S_{ADD})[rub], \qquad (20)$$

where k_{exb} – contribution rate to extrabudgetary funds.

In accordance with Federal Law No. 212-FZ of 24.07.2009, the amount of insurance premiums is set at 30 %. On the basis of paragraph 6 of Part 1 of Article 58 of Law No. 212-FZ for institutions engaged in educational and scientific activities in 2019. there is a reduced rate of 28 %.

Table 11 shows contributions to social funds.

Table 11 – Contributions to social funds

Participants	S, rub	k_{exb}	S_{exb}, rub
Sukhikh L.G.	72698.7	28%	20356
Klinovitskaia M.I.	112009.7		31362
Total:			51718

5.1.4.4 Overhead costs

Average operating time for Researcher 1 – 320 hours , rate – 2,97 rub/kWh, for Researcher 2 – 320 hours , rate – 2,56 rub/kWh, for Student (laptop) – 416 hours , rate – 2,56 rub/kWh.

Electricity costs are calculated using the formula:

$$C = R_{el} \cdot P \cdot t, [rub], \qquad (21)$$

where R_{el} – industrial electricity tariff rate, rub/kWh;

P – equipment power, kW;

t – time of equipment use, h.

Equipment power was taken as 0.065 kW.

Table 12 shows overhead cost.

Table 12 – Overhead costs

Service		Rate,units	*n*	Cost
Electricity	Computer	2.56 rub/kWh	416	192
Internet		350 rub/month	3	1050
Printing		2 rub/pages	150	300
Total:				1542
n – amount of service using according to units in rate (for electricity – hours, for internet – month)				

5.1.4.5 Formation of the budget of the costs of a research project

The total budget of research costs shown in the Table 13.

Table 13 – The total budget of research

Name	Cost, rub	Cost, %
Costs of purchasing equipment	527	0.02 %
Costs of additional materials	585	0.02 %
Supervisor salary costs	72698	30.4 %
Student (Researcher) salary costs	112009	47.5 %
Contributions to social funds	51718	22 %
Overheads	1542	0.06 %
Research budget	239079	100

5.2 Economic model development

5.1.2.1 Potential consumers of the research results

In order to find out in which direction to conduct research, a consumer analysis was made. The Table 14 shows a map of the segmentation of the market for patients with malignant neoplasms in the head-and-neck region, depending on age.

Table 14 – Segmentation of patients with cancers in head-and-neck region [1]

		Age of patients, years			
		0 – 19	20 – 44	45 – 64	65 and older
Localization	Tonque	2	303	1888	1278

Continuation of Table 14

		Age of patients, years			
		0 – 19	20 – 44	45 – 64	65 and older
	Oropharynx	1	197	1775	898
	Laryngopharynx	1	143	1437	886

According to data it can be concluded that the biggest number of cases occur in middle age. People in this age group, in contrast to the elderly population, do not have enough palliative treatment, they need full therapy, which will provide them with the opportunity to live to old age in a satisfactory condition.

It is difficult to draw conclusions about old age, as the share of the population that has overcome the threshold of 75-80 years is small.

5.1.2.2 Analysis of alternative technical solutions

Analysis of competitive technical solutions in terms of resource efficiency and resource saving allows to evaluate the comparative effectiveness of scientific development. For this purposes evaluation card is used.

As an alternative solution, 3 methods of increasing tumor control by changing the total dose and fractionation were considered:

- Conventional fractionation mode with chemotherapy;
- Hypo- or hyperfractionated mode with chemotherapy;
- radiation therapy alone with conventional fractionation.

The position of the development and competitors is assessed for each indicator by an expert method on a five-point scale: 1 - the weakest position, 5 - the strongest. The weights of the indicators, determined by expert judgment, should add up to one.

The analysis of competitive technical solutions is determined by the equation:

$$C = \sum_i P_i \cdot W_i, \tag{22}$$

where C – the competitiveness of research or a competitor;

W_i – criterion weight;

P_i – point of i-th criteria.

The Table 15 shows comparison of three solutions: index *f* means conventional mode with chemotherapy, *i1* – hypo- or hyperfractionated mode with chemotherapy, *i2* – radiation therapy with conventional fractionation.

Table 15 – Evaluation card for comparison of competitive technical solutions

Evaluation criteria	Criterion weight	Points			Competitiveness		
		P_f	P_{i1}	P_{i2}	C_f	C_{i1}	C_{i2}
1	2	3	4	5	6	7	8
Technical criteria for evaluating resource efficiency							
1.Critical organ sparing	0.2	4	4	4	0.8	0.8	0.8
2.Tumor control	0.2	4	5	3	0.8	1	0.6
3.Cell proliferation	0.08	4	5	3	0.32	0.4	0.24
4.Acute toxicity	0.08	4	3	5	0.32	0.24	0.4
5.Late toxicity	0.04	4	4	4	0.16	0.16	0.16
6.Radiosensitivity	0.08	4	4	3	0.32	0.32	0.24
Economic criteria for performance evaluation							
1.Price	0.13	4	4	5	0.52	0.52	0.65
2.Time expenditures	0.05	3	4	3	0.15	0.2	0.15
3.Market penetration	0.07	5	4	3	0.35	0.28	0.21
4.Method competitiveness	0.07	4	5	3	0.28	0.35	0.21
Total	1	40	41	32	4.02	4.27	3.66

According to comparison the most technically and economically profitable is implementation chemotherapy with hypo- or hyperfractionation mode of radiation therapy. Radiation therapy alone now is not used method of treatment for head-and-neck tumors, due to low effectivity. Conventional fractionation with chemotherapy is the most common way to treat, but now this method should be revised.

5.1.2.3 SWOT-analysis

Complex analysis solution with the greatest competitiveness is carried out with the method of the SWOT analysis: Strengths, Weaknesses, Opportunities and Threats.

Strengths are factors that characterize the competitive side of a research project. Strengths indicate that a project has a distinctive advantage or special

resources that are special in terms of competition. In other words, strengths are the resources or capabilities that project management has and that can be effectively used to achieve the goals set.

Research strengths include:

- Analysis of therapies for head-and-neck radiotherapy over the past 30 years.
- Application of the most modern method of treatment – VMAT.
- High-tech equipment and accessories.

Weaknesses are a flaw, omission or limitation of a research project that hinders the achievement of its objectives. This is something that does not work well within a project or where it lacks the capacity or resources compared to its competitors.

Weaknesses of research work:

- A large number of patients are needed to obtain meaningful values.
- Patients are randomized, it is impossible to check the influence of age, gender and other factors on treatment.
- Failure to account for the effect of chemotherapy on treatment.

Opportunities include any preferable present or future situation that arises in the project's environment, such as a trend, change, or perceived need, that sustains demand for project outcomes and allows the project management to improve its competitive position.

Opportunities include:

- Improving the quality of treatment.
- Review and analysis of a large number of patients.

A threat is any undesirable situation, trend, or change in the environmental conditions of a project that is destructive or threatening to its current or future competitiveness. A threat can be a barrier, restriction, or anything else that can cause problems, destruction, harm or damage to the project.

Threats include:

- Equipment breakdown during treatment.

- Refusal of the patient to continue treatment.

- Failure to comply with positioning requirements.

Table 16 presents the final SWOT-analysis matrix.

Table 16 – SWOT-analysis

	Strengths: S1. Analysis of therapies for head-and-neck radiotherapy over the past 30 years. S2. Application of the most modern method of treatment – VMAT. S3. High-tech equipment and accessories.	Weaknesses: W1. A large number of patients are needed to obtain meaningful values. W2. Patients are randomized, it is impossible to check the influence of age, gender and other factors on treatment. W3. Failure to account for the effect of chemotherapy on treatment.
Oportunities: O1. Improving the quality of treatment. O2. Review and analysis of a large number of patients.	S1O1. The work is aimed at analyzing existing and accepted methods of treatment, as well as finding new and alternative ones that will improve the quality of treatment. S2O1. VMAT, in comparison with other methods, allows to increase control on the tumor and reduce the dose to neighboring organs.	W1O1. The project involves two localities, which allows to increase the sample if it need to create a larger study. W1O2. With a large sample, it is possible to analyze the influence of some factors on the course and outcome of treatment.
Threats: T1. Equipment breakdown during treatment. T2. Refusal of the patient to continue treatment. T3. Failure to comply with positioning requirements.	T2S2. Patient refusal from treatment is associated with early radiation effects, which can be minimized by using more accurate dose delivery using VMAT. T3S3. Use of modern equipment and accessories minimizes positioning errors.	W1T2. Refusal of a patient to continue treatment complicate preparation of large samples. W1T3. In the presence of a large number of patients, the likelihood of a positioning error due to the human factor increases, including a shortage of immobilization equipment.

5.1.2.4 Methods of commercialization of the results of scientific and technical research

Transfer of know-how was chosen as a suitable method of commercialization. In general, the aim of the current work is to analyze the effectiveness of treatment with the classical method and assess the need to find an alternative solution. Proceeding from this, the obtained results of the work can be used by any

organizations involved in the field of radiotherapy for further own research or application.

Basically, oncological dispensaries ("representatives" of radiation therapy) are municipal institutions, therefore financing of such institutions providing by city, however, it is possible that outside interested investors will be attracted.

Improving the quality of treatment, in financial terms, entails an increase in the number of potential customers, i.e. patients who will go to a specific hospital, which will increase the flow of profits either to the city budget or to the budget of a private entrepreneur.

There is an ambiguous situation in the identification of potential competitors. In terms of service delivery, competitors are any center that provides radiation therapy on more modern equipment. From a research point of view, as such, competitors are also focused on finding the optimal treatment, and as soon as the necessary amount of data (reliable statistics) is available, the new treatment method will be recognized and legalized. But, according to the method of commercialization that was indicated, the technology will be located in the public domain, which will allow it to be used regardless of the location of the study. Also, it is worth pointing out that when conducting such studies, in order to obtain reliable results, a large amount of data is needed, which, as a rule, are collected in more than one place (not in one hospital or city), which leads to the "implementation" of the study in several places at the same time, which reduces the number of potential competitors in such studies.

Foreign research can be an exception, because the introduction of a new solution method abroad does not mean legalizing it in any other country. In this case, there may be an outflow of potential clients (patients) to countries with better treatment.

Also it should be emphasized that the implementation of the classical solution method and the alternative is carried out on the same equipment and does not require additional financial costs.

5.3 Evaluation of the comparative efficiency of the scientific research project

Determination of efficiency is based on the calculation of the integral indicator of the effectiveness of scientific research. Its finding is associated with the determination of two weighted averages: financial efficiency and resource efficiency.

Integral financial indicator I_f^p of a scientific research is obtained in the course of assessing the budget of the costs of three (or more) variants of the implementation of a scientific research. For this, the largest integral indicator of the implementation of a technical problem is taken as the calculation base (as the denominator), with which the financial values for all execution options are correlated.

Integral financial indicator I_f^p of current project is determined in the equation:

$$I_f^P = \frac{F_{pi}}{F_{max}},$$ (23)

where F_{pi} – price for i-th variant of execution;

F_{max} – maximum cost of execution of a research project (including analogs).

The resulting value of the integral financial indicator of development reflects the corresponding numerical increase in the budget of development costs in times (a value greater than one), or the corresponding numerical reduction in the cost of development in times (a value less than one, but higher than zero).

The integral indicator of the resource efficiency I_m^p, I_m^a of the variants of the object of research can be defined as follows:

$$I_m^a = \sum_{i=1}^{n} a_i b_i^a,$$
$$I_m^p = \sum_{i=1}^{n} a_i b_i^p,$$ (24)

Where a_i – the weight coefficient of the i-th parameter;

b_i^a, b_i^p – the score of the i-th parameter for the analog and development, set by an expert method on the selected rating scale, index a means alternative, p – project;

n – the number of comparison parameters.

The implementation of all three alternatives is economically equal, since the analysis is carried out without equipment. However, even with the application of the research results, any therapeutic radiation therapy equipment will be able to implement the indicated fractionation modes.

Table 17 shows comparison for way which is used and two alternative.

Table 17 – Comparative evaluation of the characteristics of the project

Criteria	Weighting factor	Scientific research project (ChemoCRT*)	Alternative 1 (ChemoHypRT*)	Alternative 2 (RT*)
1. Critical organ sparing	0.2	4	4	4
2. Tumor control	0.3	4	5	3
3.Novelty	0.1	4	5	3
4.Scope of application	0.2	4	5	3
5. Price	0.2	4	4	5
Total:	1	20	23	18
*ChemoCRT – chemotherapy with conventional mode; ChemoHypRt – chemotherapy with hypo- or hyperfractionation mode; RT – radiation therapy alone with conventional fractionation.				

An integral efficiency indicator of the scientific research project I^p_{fin} and of the analog I^a_{fin} are determined according to the formula of the integral basis of the financial integral resource efficiency:

$$I^a_{fin} = \frac{I^a_m}{I^a_f},,$$

$$I^a_{fin} = \frac{I^p_m}{I^p_f}. \tag{25}$$

Comparison of the integral indicator of the efficiency of the current project and analogs will determine the comparative efficiency the project. Comparative project efficiency E_{av}:

$$E_{av} = \frac{I^p_{fin}}{I^a_{fin}}. \tag{26}$$

All calculated indicators are listed in Table 18.

Table 18 – Comparative project efficiency

№	Indicator	Project	Alternative 1	Alternative 2
	Final cost, rub	239079	239079	239079
1	Integral financial indicator I_f^p	1	1	1
2	Integral resource efficiency indicator I_m^p, I_m^a	4	4.6	3.6
3	Integral efficiency indicator I_{fin}^a, I_{fin}^p	4	4.6	3.6
4	Comparative evaluation of the project execution variants	Alternative 1: 0.87 Alternative 2: 1.11	Alternative 2: 1.15	Alternative 1: 0.09

Comparison of the integral indicator allows to understand and choose a cheaper option for solving the technical problem in terms of financial and resource efficiency. As a result, it can be concluded that alternative 1, chemotherapy with hypo- or hyperfractionation mode, is best option along presented: all realization is equal from economical view but from technical view alternative 1 is better.

5.4 Conclusions

In this chapter, an analysis of the competitive technical solutions of scientific research is carried out, in which it was found that the methodology chosen in the study is the most preferable due to its availability and ease of use. The conducted SWOT-analysis showed that the advantages of the developed methodology prevail over its disadvantages, and the identified threats are removable.

For better planning of the work and the implementation of the work of the performers, a Gantt chart was built, which clearly illustrates how much time it takes to carry out a scientific research. The total number of calendar days during which the student worked was 52, supervisor – 15.

Also, the estimate of the scientific research was determined, the main items of expenditure were identified. The budget for this research work amounted to 239079 rubles.

Evaluation of the effectiveness of research work was carried out by

determining the integral efficiency indicator of the research. Its value is 4.00 compared to 4.6 and 3.6 for alternatives. It means that scientific development is in second place in terms of efficiency.

6 Social responsibility

6.1 Introduction

Research topic is estimation of expected radiation treatment effectiveness of head-and-neck cancer based on the equivalent uniform dose concept. Application area of research is radiation therapy, i.e. data can be used by a radiologist-oncologist and a medical physicist for patients receiving radiation therapy. Radiation therapy is carried out in special centers, which have rooms that provide for compliance with radiation safety standards.

The work is aimed at revising the already used treatment method to assess the need to introduce an alternative quality-enhancing one.

6.2 Legal and organizational items in providing safety

Nowadays one of the main ways to radical improvement of all prophylactic work referred to reduce Total Incidents Rate and occupational morbidity is the widespread implementation of an integrated Occupational Safety and Health management system. That means combining isolated activities into a single system of targeted actions at all levels and stages of the production process.

Occupational safety is a system of legislative, socio-economic, organizational, technological, hygienic and therapeutic and prophylactic measures and tools that ensure the safety, preservation of health and human performance in the work process.

According to the Labor Code of the Russian Federation, every employee has the right[42]:

‑ to have a workplace that meets Occupational safety requirements;

‑ to have a compulsory social insurance against accidents at manufacturing and occupational diseases;

‑ to receive reliable information from the employer, relevant government bodies and public organizations on conditions and Occupational safety at the workplace, about the existing risk of damage to health, as well as measures to protect

against harmful and (or) hazardous factors;

- to refuse carrying out work in case of danger to his life and health due to violation of Occupational safety requirements;

- be provided with personal and collective protective equipment in compliance with Occupational safety requirements at the expense of the employer;

- for training in safe work methods and techniques at the expense of the employer;

- for personal participation or participation through their representatives in consideration of issues related to ensuring safe working conditions in his workplace, and in the investigation of the accident with him at work or occupational disease;

- for extraordinary medical examination in accordance with medical recommendations with preservation of his place of work (position) and secondary earnings during the passage of the specified medical examination;

- for warranties and compensation established in accordance with this Code, collective agreement, agreement, local regulatory an act, an employment contract, if he is engaged in work with harmful and (or) hazardous working conditions.

The labor code of the Russian Federation states that normal working hours may not exceed 40 hours per week, The employer must keep track of the time worked by each employee.

Rules for labor protection and safety measures are introduced in order to prevent accidents, ensure safe working conditions for workers and are mandatory for workers, managers, engineers and technicians.

6.3 Basic ergonomic requirements for the correct location and arrangement of researcher's workplace

The workplace when working with a personal computer (PC) should be at least 6 square meters. The legroom should correspond to the following parameters: the legroom height is at least 600 mm, the seat distance to the lower edge of the working surface is at least 150 mm, and the seat height is 420 mm. It is worth noting

that the height of the table should depend on the growth of the operator.

The following requirements are also provided for the organization of the workplace of the PC user: the design of the working chair should ensure the maintenance of a rational working posture while working on the PC and allow the posture to be changed in order to reduce the static tension of the neck and shoulder muscles and back to prevent the development of fatigue.

The type of working chair should be selected taking into account the growth of the user, the nature and duration of work with the PC. The working chair should be lifting and swivel, adjustable in height and angle of inclination of the seat and back, as well as the distance of the back from the front edge of the seat, while the adjustment of each parameter should be independent, easy to carry out and have a secure fit.

6.4 Occupational safety

6.4.1 Analysis of harmful and dangerous factors that can create object of investigation

The object of investigation is radiation therapy. Object of investigation itself can be source of harmful and (or)dangerous factor such as increased levels of ionizing radiation and excessive noise.

6.4.2 Analysis of harmful and dangerous factors that can arise at workplace during investigation

The working conditions in the workplace are characterized by the presence of dangerous and harmful factors:

- a dangerous factor or industrial hazard is a factor whose impact under certain conditions leads to trauma or other sudden, severe deterioration of health of the worker.

- a harmful factor or industrial health hazard is a factor, the effect of which on a worker under certain conditions leads to a disease or a decrease in working

capacity.

Based on the nature of the impact of these factors on the body, there are 4 categories:

‐ physical factors (increased levels of noise and vibration, electromagnetic and ionizing radiation, insufficient illumination, etc.);

‐ chemical factors (toxic, irritant, mutagenic effects of substances and compounds);

‐ biological factors (pathogenic microorganisms also animals and plants)

‐ psychophysiological factors (factors of the labor process: mental stress, monotony of work, emotional overload)

The main elements of the production process that form dangerous and harmful factors are presented in Table 19.

Table 19 – Possible dangerous and harmful factors

Factors of GOST 12.012.0.003-74	Work type		Regulatory documentation
	Medical accelerators operation	Work with a PC, data processing	
Deviation of microclimate indicators		+	Sanitary rules 2.4.3648-20 Sanitary and Epidemiological Requirements for Organizations of Education and Training, Recreation and Recreation of Children and Youth, GOST 12.2.032-78 Occupational safety standards system. Operator's location in a sitting position. General ergonomic requirements
Excessive noise	+	+	
Increased level of electromagnetic radiation		+	
Insufficient illumination of the working area		+	
Abnormally high voltage value in the circuit, the closure which may occur through the human body	+	+	Sanitary rules GOST 12.1.038-82 Occupational safety standards system. Electrical safety
Increased levels of ionizing radiation	+		Radiation safety standards. NRB- 99/2009. Sanitary rules and regulations 2.6.1.2523-09

The following factors effect on person working on a computer:

- physical: temperature and humidity, noise, static electricity, electromagnetic field of low purity, illumination;

- psychophysiological: psychophysiological dangerous and harmful factors are divided into: physical overload (static, dynamic) and mental stress (mental overstrain, monotony of work, emotional overload).

6.4.2.1 Deviation of microclimate indicators

The air of the working area (microclimate) is determined by the following parameters: temperature, relative humidity, air speed. The optimum and permissible values of the microclimate characteristics are established in accordance with [43] and are given in Table 20.

Table 20 - Optimal and permissible parameters of the microclimate

Period of the year	Temperature,°C	Relative humidity,%	Speed of air movement, m/s
Cold and changing of seasons	23 – 25	40 – 60	0.1
Warm	23 – 25	40	0.1

6.4.2.2 Excessive noise

Noise and vibration worsen working conditions, have a harmful effect on the human body, namely, the organs of hearing and the whole body through the central nervous system. It result in weakened attention, deteriorated memory, decreased response, and increased number of errors in work. Noise can be generated by operating equipment, air conditioning units, daylight illuminating devices, as well as spread from the outside. When working on a PC, the noise level in the workplace should not exceed 50 dB.

6.4.2.3 Increased level of electromagnetic radiation

The screen and system blocks produce electromagnetic radiation. Its main part comes from the system unit and the video cable. According to [43], the intensity of the electromagnetic field at a distance of 50 cm around the screen along the electrical component should be no more than:

- in the frequency range 5 Hz – 2 kHz – 25 V/m;

- in the frequency range 2 kHz – 400 kHz – 2.5 V/m.

The magnetic flux density should be no more than:

- in the frequency range 5 Hz – 2 kHz – 250 nT;

- in the frequency range 2 kHz – 400 kHz – 25 nT.

6.4.2.4 Abnormally high voltage value in the circuit

Depending on the conditions in the room, the risk of electric shock to a person increases or decreases. Do not operate the electronic device in conditions of high humidity (relative air humidity exceeds 75% for a long time), high temperature (more than 35 °C), the presence of conductive dust, conductive floors and the possibility of simultaneous contact with metal components connected to the ground and the metal casing of electrical equipment. The operator works with electrical devices: a computer (display, system unit, etc.) and peripheral devices. There is a risk of electric shock in the following cases:

- with direct contact with current-carrying parts during computer repair;

- when touched by non-live parts that are under voltage (in case of violation of insulation of current-carrying parts of the computer);

- when touched with the floor, walls that are under voltage;

- short-circuited in high-voltage units: power supply and display unit.

Table 21 presents upper limits for values of contact current and voltage.

Table 21– Upper limits for values of contact current and voltage

	Voltage, V	Current, mA
Alternate, 50 Hz	2	0.3
Alternate, 400 Hz	3	0.4
Direct	8	1.0

6.4.2.5 Insufficient illumination of the working area

According to the standard, the illumination on the table surface in the area of the working document should be 300-500 lux. Lighting should not create glare on the surface of the monitor. Illumination of the monitor surface should not be more than

300 lux.

The brightness of the lamps of common light in the area with radiation angles from 50 to 90° should be no more than 200 cd/m, the protective angle of the lamps should be at least 40°. The safety factor for lamps of common light should be assumed to be 1.4. The ripple coefficient should not exceed 5%.

6.4.2.6 Increased levels of ionizing radiation

Ionizing radiation is radiation that could ionize molecules and atoms. This effect is widely used in energetics and industry. However, there is health hazard. In living tissue, this radiation could damage cells that result in two types of effects. Deterministic effects (harmful tissue reactions) due to exposure with high doses and stochastic effects due to DNA destruction and mutations (for example, induction of cancer).

To provide radiation safety with using sources of ionizing radiation one must use next principles:

- keep individual radiation doses from all radiation sources not higher than permissible exposure;

- forbid all activity with using radiation sources if profit is low than risk of possible hazard;

- keep individual radiation doses from all radiation sources as low as possible.

According to NRB-99/2009[44], there are three groups of people related to work with radiation:

- Personnel A – personnel who work directly with radiation sources.

- Personnel B – personnel who do not directly work with radiation sources, but are exposed to them.

- Population.

Table 71 shows dose limits for all three groups of people.

Table 22– Basic dose limits

Quantity		Dose limits	
		Personnel* A	Population
Effective dose		20 mSv per year in average during 5 years, but not higher than 50 mSv per year	1 mSv per year in average during 5 years, but not higher than 5 mSv per year
Equivalent dose per year	Eye's lens	150 mSv	15 mSv
	Skin	500 mSv	50 mSv
	Hands and feet	500 mSv	50 mSv
* Dose limits for personnel B are quarter part of dose limits of stuff A.			

In addition, for women from personnel of age below 45 years there is limit of 1 mSv per month of equivalent dose on lower abdomen. During gestation and breast feeding women must not work with radiation sources.

6.4.3 Justification of measures to reduce the levels of exposure to hazardous and harmful factors on the researcher

6.4.3.1 Deviation of microclimate indicators

The measures for improving the air environment in the production room include: the correct organization of ventilation and air conditioning, heating of room. Ventilation can be realized naturally and mechanically. In the room, the following volumes of outside air must be delivered:

- at least 30 m³ per hour per person for the volume of the room up to 20 m³ per person;

- natural ventilation is allowed for the volume of the room more than 40 m³ per person and if there is no emission of harmful substances.

The heating system must provide sufficient, constant and uniform heating of the air. Water heating should be used in rooms with increased requirements for clean air.

The parameters of the microclimate in the laboratory regulated by the central

heating system, have the following values: humidity 40%, air speed 0.1 m/s, summer temperature 20-25 °C, in winter 13-15 °C. Natural ventilation is provided in the laboratory. Air enters and leaves through the cracks, windows, doors. The main disadvantage of such ventilation is that the fresh air enters the room without preliminary cleaning and heating.

6.4.3.2 Excessive noise

In this paper, the source of the noise can be either radiation therapy equipment or computers. If the maximum permissible conditions are exceeded, it is sufficient to use sound-absorbing materials in the room (sound-absorbing wall and ceiling cladding, window curtains). To reduce the noise penetrating outside the premises, install seals around the perimeter of the doors and windows.

6.4.3.3 Increased level of electromagnetic radiation

There are the following ways to protect against electromagnetic radiation:

- increase the distance from the source (the screen should be at least 50 cm from the user);

- the use of pre-screen filters, special screens and other personal protective equipment.

Fatigue of the organs of vision can be associated with both insufficient illumination and excessive illumination, as well as with the wrong direction of light.

6.4.3.4 Abnormally high voltage value in the circuit

To ensure the safety of work in electrical installations, next steps should be performed [45]:

- disconnecting the installation (part of the installation) from the power source;

- checking the absence of voltage;

- mechanical locking of the drives of switching devices, removal of fuses, disconnection of the ends of supply lines and other measures that exclude the possibility of erroneous supply of voltage to the place of work;

- grounding of disconnected live parts (application of portable earthing

switches, switching on of grounding knives);

- fencing of the workplace or live parts that remain under voltage, which can be touched or approached to an unacceptable distance during operation.

6.4.3.5 Insufficient illumination of the working area

Light sources can be both natural and artificial. The natural source of the light in the room is the sun, artificial light are lamps. With long work in low illumination conditions and in violation of other parameters of the illumination, visual perception decreases, myopia, eye disease develops, and headaches appear.

Desktops should be placed in such a way that the monitors are oriented sideways to the light openings, so that natural light falls mainly on the left.

Also, as a means of protection to minimize the impact of the factor, local lighting should be installed due to insufficient lighting, window openings should be equipped with adjustable devices such as blinds, curtains, external visors, etc.

6.4.2.6 Increased levels of ionizing radiation

In case of radiation accident, responsible personnel must take all measures to restore control of radiation sources and reduce to minimum radiation doses, number of irradiated persons, radioactive pollution of the environment, economic and social losses caused with radioactive pollution.

Radiation control is a main part of radiation safety and radiation protection. It is aimed at not exceeding the established basic dose limits and permissible levels of radiation, obtaining the necessary information to optimize protection and making decisions about interference in the case of radiation accidents, contamination of the environment and buildings with radionuclides.

The radiation control is control of:

- radiation characteristics of radiation sources, pollution in air, liquid and solid wastes;

- radiation factors developed with technological processes in working places and environment;

- radiation factors of contaminated environment;

- irradiation dose levels of personnel and population.

The main controlled parameters are:

- annual effective and equivalent doses;

- intake and body content of radionuclides;

- volume or specific activity of radionuclides in air, water, food products, building materials and etc;

- radioactive contamination of skin, clothes, footwear, working places and etc;

- dose and power of external irradiation;

- particles and photons flux density.

Radiation protection office establish control levels of all controlled parameters in according to not exceed dose limits and keep dose levels as low as possible. In case of exceeding control levels radiation protection officers start investigation of exceed causes and take actions to eliminate this exceeding.

During planning and implementation of radiation safety precautions, taking any actions about radiation safety and analysis of effectiveness of mentioned action and precautions one must value radiation safety with next factors:

- characteristics of radioactive contamination of the environment;

- probability of radiation accidents and scale of accidents;

- degree of readiness to effective elimination of radiation accidents and its aftermathches;

- number of persons irradiated with doses higher than controlled limits of doses;

- analysis of actions for providing radiation safety, meeting requirements, rules, standards of radiation safety;

- analysis of irradiation doses obtained by groups of population from all ionizing radiation sources.

6.5 Ecological safety

Sources of ionizing radiation used in medicine could be divided into two groups: radioactive substances and radiation generators. The difference is that radiation generators like accelerators and x-ray tubes emit ionizing radiation only when they are turned on.

In ordinary work with necessary safety precautions, there are insignificant impact of using sources of ionizing radiation on environment. The immediate effect of ionizing radiation is ionization of air in room, but after a specified time the ionization disappears.

For the implementation of the work, special therapeutic installations of radiation therapy are required. Two types of equipment can be used, the first of which is an electron accelerator. Electron accelerators represent radiation generators which can be turn off and turn on of necessity. The danger of such in devices is minimized and work on such equipment does not have a significant impact on the environment.

The second type of equipment, it is device with a radioactive source. In case of using radioactive materials, the danger could occur only in accidents with stealing and loosing such materials due to high radioactivity.

6.6 Safety in emergency

6.6.1 Analysis of probable emergencies that may occur at the workplace during research

6.6.1.1 Fire safety

According to the explosion and fire hazard, the premises are divided into groups A, B, C,G, D (from A to D to reduce the hazard). A room with a personal computer belongs to category B. This group includes [46] flammable and hardly combustible liquids, solid combustible and hardly combustible substances and materials (including dust and fibers), substances and materials capable of interacting with water, air oxygen or only burn with each other.

Possible causes of fire include:

- short circuit in the power supply unit;

- work with uncovered electrical equipment or with equipment that does not have adequate insulation;

- malfunction of live parts of the electrical installation;

- non-observance of the rules for the safe operation of equipment;

- presence of flammable or combustible substances in the immediate vicinity of the electrical installation (paper, cables, etc.).

In connection with the possibility of fire hazardous situations, it is necessary to carry out preventive measures aimed at fire safety: organizational, technical, regime and operational.

To prevent fire from short circuits, overloads, etc., the following fire safety rules must be observed:

- elimination of the formation of a flammable environment (sealing equipment, control of the air, working and emergency ventilation);

- use in the construction and decoration of buildings of non-combustible or difficultly combustible materials;

- the correct operation of the equipment (proper inclusion of equipment in the electrical supply network, monitoring of heating equipment);

- correct maintenance of buildings and territories (exclusion of the source of ignition - prevention of spontaneous combustion of substances, restriction of fire works);

- training of production personnel in fire safety rules;

- the publication of instructions, posters, the existence of an evacuation plan;

- compliance with fire regulations, norms in the design of buildings, in the organization of electrical wires and equipment, heating, ventilation, lighting;

- the correct placement of equipment;

- well-time preventive inspection, repair and testing of equipment.

In the case of an emergency, it is necessary to:

- inform the management (duty officer, if it is not an apartment or a private

house);

- call the Emergency Service or the Ministry of Emergency Situations - tel.112;

- take measures to eliminate the accident in accordance with the instructions.

6.7 Conclusions

In this section about social responsibility the hazardous and harmful factors were revealed. All necessary safety measures and precaution to minimize probability of accidents and traumas during investigation are given.

The possible negative impact on the environment due to the study has been considered and is not significant.

It could be stated that with respect to all regulations and standards, investigation itself and object of investigation do not pose special risks to stuff,equipments and environment.

Conclusion

In this work the effectiveness of radiation therapy for head-and-neck tumors was analyzed. According to the literature review, the implemented conventional mode leads to good control of the tumor in a relatively short period of time (3-year locoregional control is about 70 %), while not conventional fractionation of radiation therapy leads to better control results in the long term: 5-year locoregional control for conventional mode is around 50 %, for accelerated, hypo- and hyperfractionation is more than 60 %.

Also the study presents predictions of the treatment results of 16 patients who received treatment in Tomsk, in the Tomsk Regional Oncology Center, and Tyumen, in the Tyumen Regional Oncological Dispensary, based on the resources analyzed in the literature review. In both cases, the data from the cumulative DVH were transformed into differential, with subsequent calculation of EUD, TCP and NTCP.

Since the method of calculating control in the literature review sources and for current patients is not the same, there is a difference in control. Patients who were analyzed, mainly, were treated with conventional fractionation mode, i.e. 2 Gy per fraction up to 70 Gy to tumor. And also most of the researches in literature review describe results of the same fractionation mode. It allows to suppose that, in generally, 3-year locoregional control and 5-year locoregional control are in range of 65 – 75 % and 40 – 50 % respectively for conventional mode.

Patients with SIB (simultaneously integrated boost) has bigger TCP values control with the same EUD as patient who treated with conventional radiation mode. However, based on literature review it is difficult to draw conclusion because of lack on studies and different values of total dose.

For critical organs, late complications are not observed, however, early complications, depending on the area of irradiation, have 3 – 4 grade of severity.

Based on the results obtained, it can be saying that there is a need to revise the treatment of head-and-neck tumors, at least for the later stages of tumor development.

For control at least 70 %, 70 – 71 Gy of EUD is minimum dose which should

be delivered to patient with stages III and IV when conventional mode is used. On the other hand, for some sites such as oropharynx, oral cavity, including tongue, this dose will not lead to satisfied results. Escalation of total dose causes increasing of normal tissue irradiation, therefore, this treatment option should be considered in the absence of other options. Alternatively, to improve tumor control, hypo- or hyperfractionation can be used, which implies a decrease in the duration of treatment and an increase in tumor control by decreasing the TD_{50}. With the same total dose as in the classic fractionation mode, according to calculations, it is possible to achieve a better control.

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Appendix A

Table A.1 – Brief Description of the Studies Reviewed

№	Authors	Diagnosis	Chemo-therapy	Treatment	EQD$_2$, Gy	Locoregional control (LRC)
1	Montejo, M. E., Shrieve, D. C. et al.[18]	III, IV, squamous cell carcinoma	+	IMRT-SIB 67.5 Gy, 60.0 Gy (30 fractions)	EQD$_2$(67.5 Gy, 2.25 Gy) = 68.9 Gy	LRC 5 years – 82%
2	Widder, J., Dobrowsky, W. et al. [19]	IV, squamous cell carcinoma	+	Accelerated mode, 64 – 66 Gy (4 weeks)	EQD$_2$(36 Gy, 1.8 Gy) = 35.4 Gy, EQD$_2$(30 Gy, 1.45 Gy) =28.6 Gy, EQD$_2$ = 64 Gy	LRC 3 years – 55%
3	Numico, G., Russi, E. G. et al.[20]	IV, squamous cell carcinoma	+	66 Gy (33 fractions)	-	LRC 3 years – 64 %, 5 years – 56 %
4	Rabbani, A., Hinerman, R. W. et al. [21]	III, IV, squamous cell carcinoma	+	70 Gy (35 fractions)	-	LRC 3 years– 78 %
5	Newlin, H. E., Amdur, R. J. et al.[22]	III, IV, squamous cell carcinoma	+	IMRT, hyperfractionted mode – 72 Gy (42 fractions), 74.4 Gy (62 fractions)	EQD$_2$(72 Gy, 1.7 Gy) = 70.2 Gy, EQD$_2$(74.4 Gy, 1.2 Gy) = 69.4 Gy	LRC 5 years – 79%
6	Rumley, C. N., Nedev, N. et al.[23]	III, IV, squamous cell carcinoma	+	IMRT, 66 Gy (30 fractions)	EQD$_2$(66 Gy, 2.2 Gy) = 67.1 Gy	LRC 3 years – 87.3 %
7	Huang, S. H., O'Sullivan, B. et al. [24]	III, IV, squamous cell carcinoma	+	Chemoradiotherapy, classic mode 70 Gy (35 fractions) , hypofractionted mode 60 Gy (25 fractions)	EQD$_2$(60 Gy, 2.4 Gy) = 62 Gy	LRC 3 years – 93.3 % (Chemoradiotherapy), 85.7 % (hypofractioned mode), 90.3 % (conventional mode)
8	Haehl, E., Rühle, A. et al.[25]	III, IV, squamous cell carcinoma	+	3D CRT, IMRT – 70 Gy (35 fractions)	-	LRC 3 years – 74%
9	Katsoulakis, E., Riaz, N. et al.[26]	II, III, IV, squamous cell carcinoma	+	3D CRT 70 Gy (35 fractions), IMRT 70 Gy (33 fractions)	EQD$_2$(70 Gy, 2.12 Gy) = 70.7 Gy	LRC 3 years – 85% (IMRT), 76 % (3D CRT)
10	Calais, G., Alfonsi, M. et al. [27]	III, IV, squamous cell carcinoma	+	70 Gy (35 fractions)	-	LRC 5 years – 56 % (Chemoradiotherapy), 32 % (radiotherapy)

Continuation of Table A.1

№	Authors	Diagnosis	Chemo-therapy	Treatment	EQD$_2$, Gy	Locoregional control (LRC)
11	Denis, F., Garaud, P. et al.[28]	III, IV, squamous cell carcinoma	+	70 Gy (35 fractions)	-	LRC 5 years – 47.6% (Chemoradiotherapy), 24.7% (radiotherapy)
12	Regine, W. F., Valentino, J. et al.[29]	III, IV, squamous cell carcinoma	+	Accelerated mode, 76.8–79.2 Gy (1.2 Gy, 6 – 7 weeks)	EQD$_2$(76.8 Gy, 1.2 Gy) = 71.7 Gy , EQD$_2$(79.2 Gy, 1.2 Gy) = 73.9 Gy	LRC 4 years – 70 % (Chemoradiotherapy), 44% (radiotherapy)
13	Habl, G., Jensen, A. D. et al.[30]	III, IV, squamous cell carcinoma	+	IMRT 69.9 Gy (6 weeks)	EQD$_2$(50.4 Gy, 1.8 Gy) = 49.6 Gy, EQD$_2$(19.5 Gy, 1.5 Gy) = 18.7 Gy, EQD$_2$ = 68.3 Gy	LRC 3 years – 71%
14	Ho, C., Ye, A. et al. [31]	III, IV, squamous cell carcinoma	+	3D CRT, IMRT 70 Gy (35 fractions)	-	LRC 3 years – 88% (Chemoradiotherapy), 43% (immunotherapy +radiotherapy)
15	Schüttrumpf L., Marschner S. et al.[32]	II, III, IV, squamous cell carcinoma	+	70 Gy (35 fractions)	-	LRC 3 years – 70 %
16	Horiot, J. C., Bontemps, P. et al.[33]	II, III, IV, squamous cell carcinoma	-	Accelerated mode – 72 Gy (45 fractions, 5 weeks), classic mode – 70 Gy (35 fractions, 7 weeks),	EQD$_2$(72 Gy, 1.6 Gy) = 69.6 Gy	LRC 5 year – 59 %(accelerated mode), 46% (conventional mode)
17	Poulsen, M. G., Denham, J. W. et al. [34]	III, IV, squamous cell carcinoma	-	Accelerated mode – 59.4 Gy (33 fractions, 3.5 weeks), classic mode – 70 Gy (35 fractions, 7 weeks),	EQD$_2$(59.4 Gy, 1.8 Gy) = 58.4 Gy	LRC 5 year – 52 %(accelerated mode), 47% (conventional mode)

Appendix B

Example of integral DVH from Eclipse software

Patient Name   :

Patient ID   :

Comment   : DVHs for one plan

Date   :

Exported by   :

Type   : Cumulative Dose Volume Histogram

Description   : The cumulative DVH displays the percentage (relative)

or volume (absolute) of structures that receive a dose

equal to or greater than a given dose.

Plan: Boost

Course: VMAT

Plan Status: Treatment Approved

Total dose [Gy]: 10.000

% for dose (%): 100.0

Structure: Brain

Approval Status: Approved

Plan: Boost

Course: VMAT

Volume [cm³]: 1390.5

Dose Cover.[%]: 100.0

Sampling Cover.[%]: 100.0

Min Dose [Gy]: 0.057

Max Dose [Gy]: 10.632

Mean Dose [Gy]: 1.631

Modal Dose [Gy]: 0.106

Median Dose [Gy]: 0.820

STD [Gy]: 1.906

Equiv. Sphere Diam. [cm]: 13.8

Conformity Index: N/A

Gradient Measure [cm]: N/A

Dose Level [Gy]:

RTOG CI:

Paddick CI:

GI:

ICRU83 HI:

D1.0% [Gy]: 9.325

D2.0% [Gy]: 7.717

D5.0% [Gy]: 5.317

D10.0% [Gy]: 3.944

D20.0% [Gy]: 2.823

D30.0% [Gy]: 2.228

D50.0% [Gy]: 0.820

D95.0% [%]: 1.0

D95.0% [Gy]: 0.096

D98.0% [Gy]: 0.083

:

Dose [Gy]	Relative dose [%]	Ratio of Total Structure Volume [%]
0	0	100
0.1	1	93.8889
0.2	2	72.8406
0.3	3	63.51
0.4	4	58.7395
0.5	5	55.7221
/.../		
10	100	0.526663
10.1	101	0.432565
10.2	102	0.327042
10.3	103	0.198939
10.4	104	0.0795901
10.5	105	0.0157932
10.6	106	9.9537e-005

10.7	107	0
10.8	108	0

Structure: PTV_Boost10

Approval Status: Approved

Plan: Boost

Course: VMAT

Volume [cm³]: 60.1

Dose Cover.[%]: 100.0

Sampling Cover.[%]: 100.0

Min Dose [Gy]: 8.621

Max Dose [Gy]: 10.868

Mean Dose [Gy]: 10.346

Modal Dose [Gy]: 10.400

Median Dose [Gy]: 10.378

STD [Gy]: 0.179

Equiv. Sphere Diam. [cm]: 4.9

Conformity Index: 1.24

Gradient Measure [cm]: 1.28

Dose Level [Gy]:

RTOG CI:

Paddick CI:

GI:

ICRU83 HI:

D1.0% [Gy]: 10.637

D2.0% [Gy]: 10.608

D5.0% [Gy]: 10.562

D10.0% [Gy]: 10.522

D20.0% [Gy]: 10.474

D30.0% [Gy]: 10.439

D50.0% [Gy]: 10.378

D95.0% [%]: 100.0

D95.0% [Gy]: 10.000

D98.0% [Gy]: 9.815

:

Dose [Gy]	Relative dose [%]	Ratio of Total Structure Volume [%]
0	0	100
0.1	1	100
0.2	2	100
0.3	3	100
0.4	4	100
/.../		
8.5	85	100
8.6	86	100
8.7	87	99.9999
8.8	88	99.9993
8.9	89	99.9968
9	90	99.9887
9.1	91	99.9719
/.../		
10.6	106	2.36472
10.7	107	0.200784
10.8	108	0.00780836

Example of differential DVH from Monaco software

Patient ID: 40~TM20208468 | Plan Name: PTV60 | Resolution: 0.10(cm) | Bin Width: 0.010(Gy) | Dose Units: Gy | Volume Units: %

Structure Name		Dose		Volume
Brainstem	0.000	0.000
Brainstem	0.605	0.000
Brainstem	0.615	0.007
Brainstem	0.625	0.007
Brainstem	0.635	0.027
/.../		
Brainstem	15.895	0.000

Brainstem	15.905	0.003
Brainstem	15.915	0.000
Brainstem	66.645	0.000
Brainstem	66.650	0.000
/.../		
PTV60	0.000	0.000
PTV60	52.205	0.000
PTV60	52.215	0.001
PTV60	52.225	0.000
PTV60	52.375	0.000
PTV60	52.385	0.001
PTV60	52.395	0.000
/.../		
PTV60	66.435	0.000
PTV60	66.475	0.000
PTV60	66.485	0.001
PTV60	66.495	0.000
PTV60	66.635	0.000
PTV60	66.645	0.001
PTV60	66.650	0.001
Spinal_Cord	0.000	0.000
Spinal_Cord	0.005	0.000
Spinal_Cord	0.015	0.006
Spinal_Cord	0.025	2.043
Spinal_Cord	0.035	6.515
Spinal_Cord	0.045	7.251
/.../		
Spinal_Cord	7.645	0.000
Spinal_Cord	7.695	0.000
Spinal_Cord	7.705	0.004
Spinal_Cord	7.715	0.000
Spinal_Cord	66.645	0.000
Spinal_Cord	66.650	0.000
Thyroid_Gland	0.000	0.000

Thyroid_Gland	0.225	0.000
Thyroid_Gland	0.235	0.060
Thyroid_Gland	0.245	0.181
Thyroid_Gland	0.255	0.377
Thyroid_Gland	0.265	0.603
/.../		
Thyroid_Gland	0.895	0.000
Thyroid_Gland	0.905	0.015
Thyroid_Gland	0.915	0.000
Thyroid_Gland	66.645	0.000
Thyroid_Gland	66.650	0.000

Appendix C

Table C.1 – Parameters for EUD and NTCP calculations

Structure	α	γ_{50}	TD_{50}, Gy	Structure	α	γ_{50}	TD_{50}, Gy
Brain [37]	5	3	60	Thyroid gland [40]	0.92	1.05	44.3
Brainstem [37]	7	3	65	Parotid gland [39]	0.5	2.2	28.4
Esophagus [37]	19	4	68	Lung [37]	1	2	24.5
Spinal cord[38]	7	4	66.5	Larynx [38]	12.5	4	70
Mandible [39]	14	4	72	Cochlea [41]	1	1.27	46.3

Table C.2 – Obtained EUD and NTCP for all patients

№		Brain	Brainstem	Esophagus	Thyroid gland	Spinal cord	Mandible	Lungs L	Lungs R	Parotid gland L	Parotid gland R	Larynx	Cochlea L	Cochlea R
Patient 1	EUD, Gy	-	9.49	0.43	0.44	4.67	44.53	-	-	-	-	-	-	-
	NTCP	-	$9.38{\cdot}10^{-11}$	$7.47{\cdot}10^{-36}$	$3.83{\cdot}10^{-9}$	$3.51{\cdot}10^{-19}$	$4.59{\cdot}10^{-4}$	-	-	-	-	-	-	-
Patient 2	EUD, Gy	-	19.12	45.54	-	30.73	59.57	2.16	2.16	-	-	-	-	-
	NTCP	-	$4.20{\cdot}10^{-7}$	$1.64{\cdot}10^{-3}$	-	$4.32{\cdot}10^{-6}$	$4.59{\cdot}10^{-2}$	$3.69{\cdot}10^{-9}$	$3.64{\cdot}10^{-9}$	-	-	-	-	-
Patient 3	EUD, Gy	-	18.27	44.24	-	26.53	53.13	1.14		40.94	43.54	-	-	-
	NTCP	-	$2.44{\cdot}10^{-7}$	$1.03{\cdot}10^{-3}$	-	$4.11{\cdot}10^{-7}$	$7.67{\cdot}10^{-3}$	$2.18{\cdot}10^{-11}$		$9.62{\cdot}10^{-1}$	$9.77{\cdot}10^{-1}$	-	-	-
Patient 4	EUD, Gy	12.75	25.53	49.84	58.19	-	65.13	6.49	6.44	22.32	27.77	53.61	4.96	5.28
	NTCP	$8.48{\cdot}10^{-9}$	$1.35{\cdot}10^{-5}$	$6.89{\cdot}10^{-3}$	$7.59{\cdot}10^{-1}$	-	$1.67{\cdot}10^{-1}$	$2.43{\cdot}10^{-5}$	$2.29{\cdot}10^{-5}$	$1.07{\cdot}10^{-1}$	$4.51{\cdot}10^{-1}$	$1.38{\cdot}10^{-2}$	$1.18{\cdot}10^{-5}$	$1.63{\cdot}10^{-5}$

Continuation of Table C.2

№		Brain	Brainstem	Esophagus	Thyroid gland	Spinal cord	Mandible	Lungs L	Lungs R	Parotid gland L	Parotid gland R	Larynx	Cochlea L	Cochlea R
Patient 5	EUD, Gy	-	24.59	27.50	-	20.55	56.59	0.59		-	-	-	-	-
	NTCP	-	$8.61\cdot10^{-6}$	$5.11\cdot10^{-7}$	-	$6.90\cdot10^{-9}$	$2.08\cdot10^{-2}$	$1.11\cdot10^{-13}$		-	-	-	-	-
Patient 6	EUD, Gy	-	-	44.50	-	30.29	50.43	2.59		33.07	21.23	-	-	-
	NTCP	-	-	$1.13\cdot10^{-3}$	-	$3.43\cdot10^{-6}$	$3.35\cdot10^{-3}$	$1.56\cdot10^{-8}$		$7.92\cdot10^{-1}$	$7.17\cdot10^{-2}$	-	-	-
Patient 7	EUD, Gy	-	15.64	39.46	-	26.14	52.83	1.37		30.90	33.64	-	-	-
	NTCP	-	$3.77\cdot10^{-8}$	$1.66\cdot10^{-4}$	-	$3.25\cdot10^{-7}$	$7.01\cdot10^{-3}$	$9.34\cdot10^{-11}$		$6.77\cdot10^{-1}$	$8.16\cdot10^{-1}$	-	-	-
Patient 8	EUD, Gy	-	27.54	44.14	-	33.95	59.18	-	-	34.18	35.43	-	-	-
	NTCP	-	$3.35\cdot10^{-5}$	$9.93\cdot10^{-4}$	-	$2.13\cdot10^{-5}$	$4.15\cdot10^{-2}$	-	-	$8.36\cdot10^{-1}$	$8.75\cdot10^{-1}$	-	-	-
Patient 9	EUD, Gy	-	12.96	34.46	-	-	56.00	-	-	18.03	17.85	44.16	5.53	10.34
	NTCP	-	$3.95\cdot10^{-9}$	$1.89\cdot10^{-5}$	-	-	$1.76\cdot10^{-2}$	-	-	$1.80\cdot10^{-2}$	$1.65\cdot10^{-2}$	$6.29\cdot10^{-4}$	$2.04\cdot10^{-5}$	$4.91\cdot10^{-4}$
Patient 10	EUD, Gy	0.98	-	58.35	58.10	24.99	53.65	4.73	3.90	10.18	9.32	-	-	-
	NTCP	$3.40\cdot10^{-22}$	-	$7.96\cdot10^{-2}$	$7.58\cdot10^{-1}$	$1.59\cdot10^{-7}$	$8.94\cdot10^{-3}$	$1.92\cdot10^{-6}$	$4.14\cdot10^{-7}$	$1.20\cdot10^{-4}$	$5.53\cdot10^{-5}$	-	-	-
Patient 11	EUD, Gy	16.22	-	-	-	-	56.17	10.29	7.92	-	-	-	-	-
	NTCP	$1.52\cdot10^{-7}$	-	-	-	-	$1.85\cdot10^{-2}$	$9.68\cdot10^{-4}$	$1.19\cdot10^{-4}$	-	-	-	-	-

Continuation of Table C.2

№		Structures												
		Brain	Brainstem	Esophagus	Thyroid gland	Spinal cord	Mandible	Lungs		Parotid gland		Larynx	Cochlea	
								L	R	L	R		L	R
Patient 12	EUD, Gy	-	-	63.50	66.90	36.14	-	11.42		7.27	8.99	-	-	-
	NTCP	-	-	$2.50 \cdot 10^{-1}$	$8.50 \cdot 10^{-1}$	$5.79 \cdot 10^{-5}$	-	$2.23 \cdot 10^{-3}$		$6.19 \cdot 10^{-6}$	$4.03 \cdot 10^{-5}$	-	-	-
Patient 13	EUD, Gy	6.51	-	-	45.97	32.39	-	5.59	4.70	-	-	-	-	-
	NTCP	$2.66 \cdot 10^{-12}$	-	-	$5.39 \cdot 10^{-1}$	$1.00 \cdot 10^{-5}$	-	$7.29 \cdot 10^{-6}$	$1.82 \cdot 10^{-6}$	-	-	-	-	-
Patient 14	EUD, Gy	-	14.45	44.65	-	25.03	46.57	2.64	2.31	33.48	39.98	-	-	-
	NTCP	-	$1.46 \cdot 10^{-8}$	$1.19 \cdot 10^{-3}$	-	$1.62 \cdot 10^{-7}$	$9.39 \cdot 10^{-4}$	$1.84 \cdot 10^{-8}$	$6.18 \cdot 10^{-9}$	$8.10 \cdot 10^{-1}$	$9.53 \cdot 10^{-1}$	-	-	-
Patient 15	EUD, Gy	2.56	-	-	-	24.34	-	-	-	19.08	20.96	-	-	-
	NTCP	$3.71 \cdot 10^{-17}$	-	-	-	$1.03 \cdot 10^{-7}$	-	-	-	$2.93 \cdot 10^{-2}$	$6.46 \cdot 10^{-2}$	-	-	-
Patient 16	EUD, Gy	8.50	-	-	-	26.05	-	-	-	19.63	19.68	-	-	-
	NTCP	$6.58 \cdot 10^{-11}$	-	-	-	$3.07 \cdot 10^{-7}$	-	-	-	$3.73 \cdot 10^{-2}$	$3.81 \cdot 10^{-2}$	-	-	-