TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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

School School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 «Nuclear physics and technology»
Division Division for Nuclear fuel cycle

MASTER'S GRADUATION THESIS

Topic of research work
Quantitative evaluation of set-up uncertainties for patients with head and neck cancer using cone beam computed tomography

UDC 615.849-027.236

Student

Group	Full name	Signature	Date
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Associate Professor	E.V. Menshikova	Ph.D.		

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Tomsk – 2020

Expected learning outcomes

Learning outcome (LO)code	Learning outcome (a graduate should be ready)	Requirements of the FSES HE, criteria and / or interested parties
Professional competencies		
LO1	To apply deep mathematical, scientific, socio-economic and professional knowledge for conducting theoretical and experimental research in the field of the use of nuclear science and technology.	FSES HE Requirements (BPC-1,2, PC-3, UC-1,3), Criterion 5 RAEE (p 1.1) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO2	To demonstrate ability to define, formulate, and solve interdisciplinary engineering tasks in the nuclear field using professional knowledge and modern research methods.	FSES HE Requirements (PC-9,10,13,14,15, BPC-1,3), Criterion 5 RAEE (p 1.2) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO3	To plan and conduct analytical, simulation and experimental studies in complex and uncertain conditions using modern technologies, and to evaluate critically research results.	FSES HE Requirements (PC-1,13,22, UC-2, BPC-1), Criterion 5 RAEE (p 1.3) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO4	To use basic and special approaches, skills and methods for identification, analysis, and solution of technical problems in the field of nuclear science and technology.	FSES HE Requirements (PC-2,4,6,8, UC-2, BPC-1), Criterion 5 RAEE (p 1.4) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO5	To operate modern physical equipment and instruments, to master technological processes in the course of preparation for the production of new materials, instruments, installations, and systems.	FSES HE Requirements (PC-5,7,11,12, UC-2, BPC-1), Criterion 5 RAEE (p 1.4) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers,

		specialists and non-manual workers for the position of “medical physicist”
LO6	To demonstrate ability to develop multioption schemes for achieving production goals with the effective use of available technical means and resources.	FSES HE Requirements (PC-16-21,23), Criterion 5 RAEE (p 1.5) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of “medical physicist”
Cultural competencies		
LO7	To demonstrate ability to use a creative approach to develop new ideas and methods for designing nuclear facilities, as well as to modernize and improve the applied technologies of nuclear production.	FSES HE Requirements (BPC-1,3, UC-3), Criterion 5 RAEE (p 2.4,2.5)
Basic professional competencies		
LO8	To demonstrate skills of independent learning and readiness for continuous self-development within the whole period of professional activity.	FSES HE Requirements (UC-3, PC-1, BPC-1), Criterion 5 RAEE (p 2.6) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of “medical physicist”
LO9	To use a foreign language at a level that enables a graduate to function successfully in the international environment, to develop documentation, and to introduce the results of their professional activity.	FSES HE Requirements (PC-11,16,17, BPC-3), Criterion 5 RAEE (p 2.2) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of “medical physicist”
LO10	To demonstrate independent thinking, to function efficiently in command-oriented tasks and to have a high level of productivity in the professional (sectoral), ethical and social environments, to lead professional teams, to set tasks, to assign responsibilities and bear liability for the results of work.	FSES HE Requirements (PC-18,23, UC-2), Criterion 5 RAEE (p 1.6,2.3) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of “medical physicist”

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School School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 «Nuclear physics and technology»
Division Division for Nuclear fuel cycle

APPROVED BY:
Director of the programme
_____ Y.M. Cherepennikov
(Signature) (Date) (Full name)

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Master's thesis

For a student:

Group	**Full name**
0AM8M	Olga Mikhailovna Stakhova

Topic of research work:

Quantitative evaluation of set-up uncertainties for patients with head and neck cancer using cone beam computed tomography	
Approved by the order of the Director of School of Nuclear Science & Engineering (date, number):	

Deadline for completion of Master's Graduation Thesis:	

TERMS OF REFERENCE:

Initial data 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.)*	Investigation of set-up uncertainties measurement has significant applied meaning. The purpose of this research is to quantify systematic and random patient set-up uncertainties in head and neck irradiation when off-line and online correction protocols have been applied and to investigate the influence of chosen correction protocol on size of planning target volume.

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, design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).*	1. To consider clinical experience of using set-up correction protocols for head and neck cancer patients 2. To receive statistical data of patients' set-ups during the course of radiation therapy according to image guided radiation therapy offline and online protocols: • No action level • Extended no action level; • Online protocol. 3. To obtain systematic and random set-up uncertainties. 4. To evaluate the magnitude of uncertainties and its influence to planning target volume.

Advisors to the sections of the Master's Graduation Thesis

(with indication of sections)

Section	Advisor
Financial Management, Resource Efficiency and Resource Saving	E.V. Menshikova
Socoial responcibility	D.A. Verigin

Date of issuance of the assignment for Master's Graduation Thesis completion according to the schedule	

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

Position	Full name	Academic degree, academic status	Signature	Date
Associate Professor	E.S. Sukhikh	Ph.D.		

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM8M	Stakhova Olga Mikhailovna		

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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School School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 «Nuclear physics and technology»
Level of education Master Degree Program
Division Division for Nuclear fuel cycle
Period of completion 2019 /2020 academic years

Form of presenting the work:

Master's Thesis

SCHEDULED ASSESSMENT CALENDAR
for the Master's Graduation Thesis completion

Deadline for completion of Master's Graduation Thesis:	

Assessment date	Title of section (module) / type of work (research)	Maximum score for the section (module)
03.02.2020	Creation and approving of technical specification	5
10.02.2020	Searching and selection of material for research	10
24.02.2020	Selection of study way	5
26.02.2020	Development of general methodology of the research	10
05.03.2020	Calendar planning of research activities	5
09.03.2020	Reviewing of manuals and list of literature	10
23.03.2020	Measurements performing	15
05.05.2020	Processing of measurements results	15
12.05.2020	Analysis and description of the results	20
26.05.2020	Composition of master's thesis	5

COMPILED BY:
Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Date
Assosiate professor	E.S. Sukhikh	Ph.D.		

AGREED BY:
Director of the programme

Position	Full name	Academic degree, academic rank	Signature	Date
Assosiate professor	Y.M. Cherepennikov	Ph.D.		

TASK FOR SECTION
«SOCIAL RESPONSIBILITY»

For a student:

Group	Full name
0AM8M	Olga Mikhailovna Stakhova

School	School of Nuclear Science and Engineering	**Division**	Division for Nuclear-Fuel Cycle
Degree	Master Degree programme	**Field of training/programme**	14.04.02 Nuclear Physics and Technology/Nuclear Medicine

Topic of research work:

Quantitative evaluation of set-up uncertainties for patients with head and neck cancer using cone beam computed tomography	
Initial data for section «Social Responsibility»:	
1. Information about object of investigation (matter, material, device, algorithm, procedure, workplace) and area of its application	Investigation of patient set-up uncertainties has been performed during a course of radiotherapy on linear accelerator. Application area: image-guided 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.	– Labor code of Russian Federation #197 from 30/12/2001 GOST 12.2.032-78 SSBT – Sanitary Rules 2.2.2/2.4.1340-03. Hygienic requirements for PC and work with it
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 – Electric shock – Ionizing radiation
3. Ecological safety:	– Indicate impact of linear accelerator on hydrosphere, atmosphere and lithosphere
4. Safety in emergency situations:	– Fire safety

Date of issuance of the task for the section according to the schedule	

The task was issued by adviser:

Position	Full name	Scientific degree, rank	Signature	date
Associate professor	D.A Verigin.	Ph.D.		

The task was accepted by the student:

Group	Full name	Signature	date
0AM8M	Olga Mikhailovna Stakhova		

TASK FOR SECTION
«FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING»

For a student:

Group	Full name
0AM8M	Olga Mikhailovna Stakhova

School	School of Nuclear Science and Engineering	**Division**	Division for Nuclear-Fuel Cycle
Degree	Master Degree programme	**Field of training/programme**	14.04.02 Nuclear Physics and Technology/Nuclear Medicine

Topic of research work:

Quantitative evaluation of set-up uncertainties for patients with head and neck cancer using cone beam computed tomography	
Initial data for section « Financial management, resource efficiency and resource saving»:	
1. Cost of scientific research resources: material and technical, energy, financial, informational and human	Equipment deprecation 19 104 000 Material costs 30 000 Basic salary 20 0661 Additional salary 20 066 Labor tax 56 899 Overhead 140 463 Other direct cost 5 220
2. Norms and standards for resource expenditure	Power rates 5.8 rubles per 1 kWh Regional rate 1.15
3. The using system of taxation, tax rates, deductions, discounting and crediting	Coefficient of deductions 30% Scientific activities have rate - 27.1%
List of items to be investigated and to be developed:	
1. Assessment of commercial potential, prospects and alternatives for scientific research from the point of view of resource efficiency and resource saving	Competitiveness analysis of technical solutions
2. Research planning and budgeting	Hierarchical structure of work
3. Determination of resource (resource-saving), financial, budgetary, social and economic efficiency of the research	Competitiveness analysis of technical solutions SWOT analysis Calendar schedule of master's thesis performing and budget of scientific research A Gantt chart
List of graphic material:	
1. Evaluation card for comparison of competitive technical solutions *2. SWOT- analysis* *3. Calendar schedule of master's thesis performing* *4. A Gantt chart*	

Date of issuance of the task for the section according to the schedule	

The task was issued by consultant:

Position	Full name	Scientific degree, rank	Signature	date
Assosiate professor	E.V. Menshikova	Ph.D.		

The task was accepted by the student:

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0AM8M	Olga Mikhailovna Stakhova		

Abstract

This master's thesis consists of 86 pages, 17 figures, 24 tables, 30 sources and 4 appendixes.

Key words: IMAGE GUIDED RADIATION THERAPY, INTENSITY-MODULATED RADIATION THERAPY, ONCOLOGY, HEAD AND NECK CANCER, CONE BEAM COMPUTED TOMOGRAPHY, SET-UP UNCERTAINTIES, SET-UP CORRECTION PROTOCOLS, PLANNING TARGET VOLUME.

The objectives of investigation are set-up uncertainties of patients, with head and neck cancer, occurring through a course of radiotherapy on linear accelerator.

The purpose of this research is to quantify systematic and random patient set-up uncertainties in head and neck irradiation when off-line and online correction protocols have been applied and to investigate the influence of chosen correction protocol on size of planning target volume.

During the research process modeling of application recommended by IAEA set-up correction strategies have been performed for a group of patients with head and neck cancer.

In the result of the investigation, values of set-up uncertainties have been measured for each correction protocol. This values have allowed to calculate required magnitude of planning target volume.

List of Notations and Abbreviations

RT – radiation therapy;

EBRT – external beam radiation therapy;

IGRT – image guided radiation therapy;

IMRT – intensity modulated radiation therapy;

DVH – dose-volume histogram;

H&N – head and neck;

3D-CRT – 3-dimension conformal radiation therapy;

CT – computed tomography;

CBCT – cone beam computed tomography;

MRI – magnetic resonance imaging;

PET – positron emission tomography;

VMAT – Volume Modulated Arc Therapy;

MLC – Multileaf Collimator;

TPS – treatment planning system;

SAL – shrinking action level;

NAL – no action level;

e-NAL – extended no action level;

SD – standard deviation;

MC – Monte-Carlo;

PTV – planning target volume;

CTV – clinical target volume;

GTV – gross tumor volume;

OAR – organ at risk.

Table of content

Introduction

Radiotherapy is one of the essentials components in treatment of cancer patients alongside surgery and chemotherapy. Imaging the patient is the important part of safe and effective radiotherapy to get high accuracy in treatment delivery. Recent technology achievements have made this procedure available to perform frequently, in treatment room, in treatment position and at the time of treatment.

Image guided radiation therapy approaches can be broadly divided into two categories off-line and on-line. Off-line protocols are effective to correct systematic uncertainties, which, if uncorrected may be cause of constant shifts of dose distribution. These protocols usually noticeably facilitate the workload and are most suitable when the ratio of random to systematic effects are small. Online imaging protocols correct both systematic and random effects, but increase the workload. The decision what way to use depends on clinical department resources, treatment site, modality and method of immobilization including the needs to balance treatment accuracy with workload and expertise.

The purpose of this research is to quantify systematic and random patient set-up uncertainties in head and neck irradiation when off-line and online correction protocols have been applied and to investigate the influence of chosen correction protocol on size of planning target volume.

The objectives of investigation are set-up uncertainties of patients, with head and neck cancer, occurring through a course of radiotherapy on linear accelerator.

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Chapter 1

In this chapter there are described patient group and set-up method using for research. In other words, it describes issues and risk factors of H&N cancer treatment, some statistical data of morbidity rate and clinical workflow from treatment preparation to treatment execution.

1.1. Statistic data of H&N cancer

According to the statistics malignant tumors of H&N site reach about 5 percent from the all cases of cancer morbidity rates all over the globe [1]. H&N cancer is a broad concept which includes tumors of nasal cavity, paranasal sinus, salivary glands, throat, oral cavity, larynx. These organs consist of followings:

- Paranasal sinuses are air-filled spaces that surround the nasal cavity, which include frontal sinuses, maxillary sinus, sphenoid sinus.
- Throat is a hollow tube about 12 centimeters long that begins behind the nose and leads to the esophagus. Throat includes nasopharynx, oropharynx, hypopharynx.
- Oral cavity is the first part of gastrointestinal tract and consists of tongue, mouth floor, palate mucosa, cheek and lips mucosa.
- Larynx is a voice organ is in the top of the neck involved in breathing, producing sound and protecting the trachea against food aspiration, which consist of cartilages that are attached to one another and to surroundings structures by muscles or by fibrous and elastic tissue components.

Schematic image of these organs is presented in Fig. 1.1.

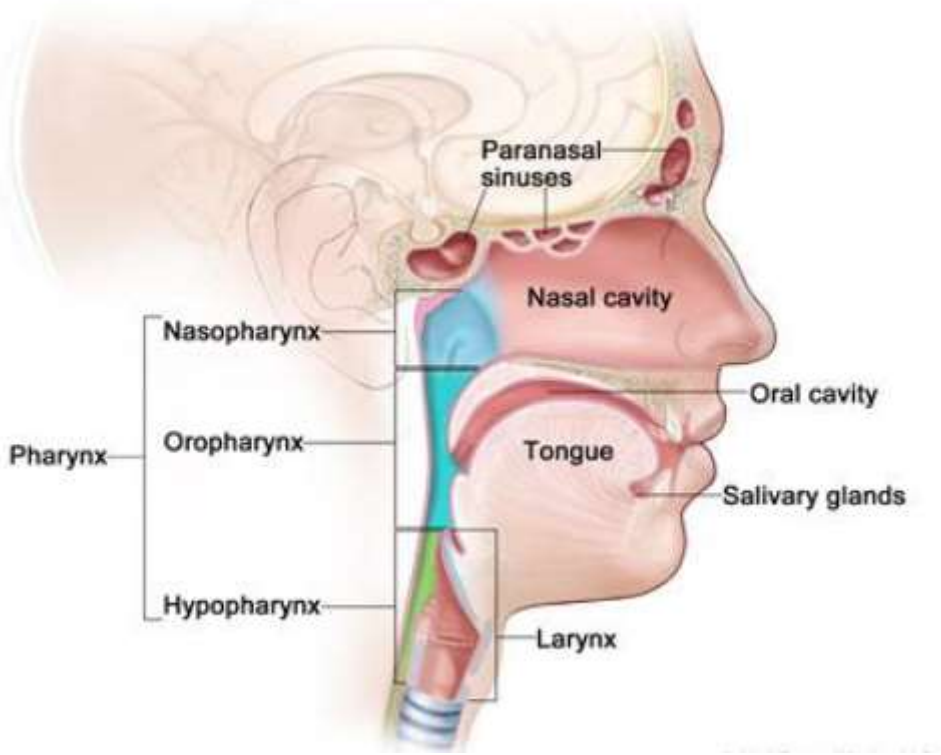


Fig. 1.1. Regions of H&N cancer.

The large majority of patients (60-70%) start their treatment with stage III-IV of the disease. About 90% of patients are people of working age (30-60 years) [2-4]. If it is possible to perform surgical treatment, preference is given to this method. However, if it is impossible to perform surgery, or in addition to this method, patients receive chemoradiotherapy.

Even with successful treatment of head and neck tumors, it is important that the quality of life of these patients is significantly reduced. According to the Rutgers school of medicine (New Jersey), the suicide rate in these patients is 3 times higher than in the General population, and most often they were patients who received radiation treatment.

Over the past 20 years, radiotherapy has undergone significant changes, especially for squamous cell carcinoma of the H&N.

Classically, these patients were treated with three-dimensional conformal radiation therapy (3D-CRT), where the entire volume of the target was sequentially irradiated, and then an additional dose of radiation was delivered to an area with a higher risk of disease. Patients often experienced severe acute and late toxicity, including mucositis, dermatitis, and xerostomia. With the introduction of intensity-

modulated radiation therapy (IMRT), it became possible to improve the conformity of high doses, minimize radiation toxicity while maintaining similar control parameters [5-8].

One of the main etiological causes of H&N cancer is morphological disorders of flat epithelial cells lining the mucous membranes of organs. Alcohol and tobacco use (including smokeless tobacco, sometimes called "chewing tobacco") are the two most important risk factors for head and neck cancer, especially cancer of the mouth, oropharynx, hypopharynx, and larynx. At least 75% of H&N cancers are caused by tobacco and alcohol use. When two bad habits are combined, the risk of disease increases by about 25% compared to the presence of only one of them. More specific factors, such as the presence of human papillomavirus (HPV) in the body, can increase the risk of developing cancer of the throat, tonsils, and root of the tongue. Other risk factors for head and neck cancer include the following:

- The use of leaves of betel (a plant genus of the Pepper);
- Poor oral hygiene’
- The use of mouthwash for the oral cavity with a high percentage of alcohol;
- Exposure to harmful substances;
- Local irradiation;
- Epstein Bar virus infection.

1.2. Workflow

1.2.1. Immobilization of patients

The start of the treatment preparations begins with appropriate immobilization according to treatment anatomical site, purposes and treatment modality. Radiotherapy treatment delivery in H&N tumors requires a highly accurate and reproducible treatment set-up. The devices for immobilization have two main roles:

● To prevent movements of the patient during treatment;

● To make patient position reproducible from CT-scanning to treatment on linac table, and from one fraction to another.

There are three essential components to a H&N system:

- Thermoplastic masks, providing positioning and immobilization from imaging through treatment;
- Headrests, providing enhanced repositioning, accuracy and patient comfort;
- Extensions, Baseplates or Overlays, providing the foundation for the system

The commonly used immobilization staff in radiotherapy is the headrest, shaped to fit comfortably under the patient's H&N site, enabling the patient to lie relaxed on the treatment table. Fig. 1.2 shows usual headrests used for patient during thetreatment. Modern radiotherapy generally requires additional immobilization accessories during the treatment of patients [9].

Fig. 1.2. Common head supports for immobilization of patients.

Patients to be treated in the H&N areas are fixed with a thermoplastic mask that, when heated, can be changed to the patient's contour of H&N area. The mask is attached directly on to the treatment table or to a baseplate that lies under the patient to prevent movements. There are many types of thermoplastic masks, for instance masks, which leaves eyes, nose and mouth exposed. It is the ideal immobilization solution for brain, head and neck patients who suffer from claustrophobia and for treatments with a long duration. An example of immobilization mask is shown in Fig. 1.3.

Fig. 1.3. Perforated and solid thermoplastic mask for immobilization.

Baseplate is used for providing the foundation of the system. An example of such baseplate is shown on Fig. 1.4. Positioning indicators on the base plate help to reduce patient setup time and ensure precise positioning and immobilization during each fraction.

Fig. 1.4. Illustration of the baseplate.

1.2.2. Scanning process

In 1990's CT scanners became widespread. Since that it is applied for oncology patients in diagnostic and treatment purposes. Information from CT scans is presented in form of crosswise slices, containing images of very high resolution and contrast,

based on very important for planning electron density. CT images provide great soft tissue contrast, allowing for improved tumor localization and definition, the contour of patient skin, and any OAR's. Information about electron density from the CT data set is very useful in the calculation of dose distribution due to inhomogeneity of human tissues. Shown in Fig. 1.5 is a CT image is a slice through a patient's neck using conventionally in CT.

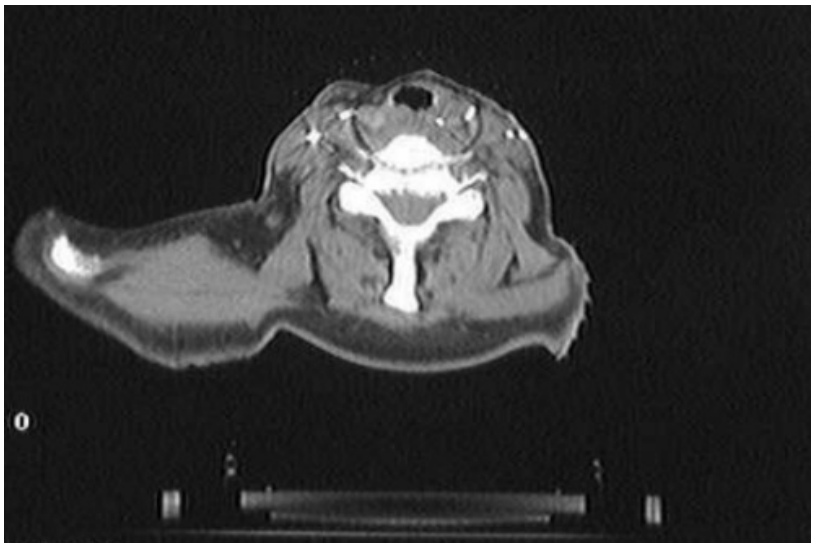


Fig. 1.5. A CT image through a patient's neck.

The patient is scanned in the required treatment position, with a suitable slice spacing.

In addition to CT scanning it is possible to carry out MR or PET scanning to help physician delineate tumor and organs at risk. To ease delineation, these scans usually fused with the patient's CT scans by the help of the software.

1.2.3. Definition of volumes

After scanning process, the physician needs to delineate tumor and healthy tissues, that can be injured by radiation expose. For uniform approach and basis to comparison it is recommended by ICRU Reports No. 50 and 62 to define and describe targets and critical structures in a common way [10-11]. The main volumes for 3D treatment planning have been defined:

- Gross tumor volume is a visible part of a tumor, or a place after surgery, where concentrated tumor cells.
- Clinical target volume is usually placed around GTV or zone of positive lymph nodes that contains with a high probability malignant tumor cells. This volume needs to be treated as well, to avoid progression of tumor growth.
- Internal planning volume includes GTV and CTV, but also it takes into account some CTV motions or shape changes.
- Planning target volume includes ITV and creates to be sure, that CTV or ITV volumes receive treatment dose despite some geometrical uncertainties.
- Organ at risk defines due to sensitivity to radiation healthy structures, that can receive significant dose through a treatment course, comparable to its tolerance level.

Crosswise CT scans contain the information which needed for treatment planning in contemporary radiotherapy treatment.

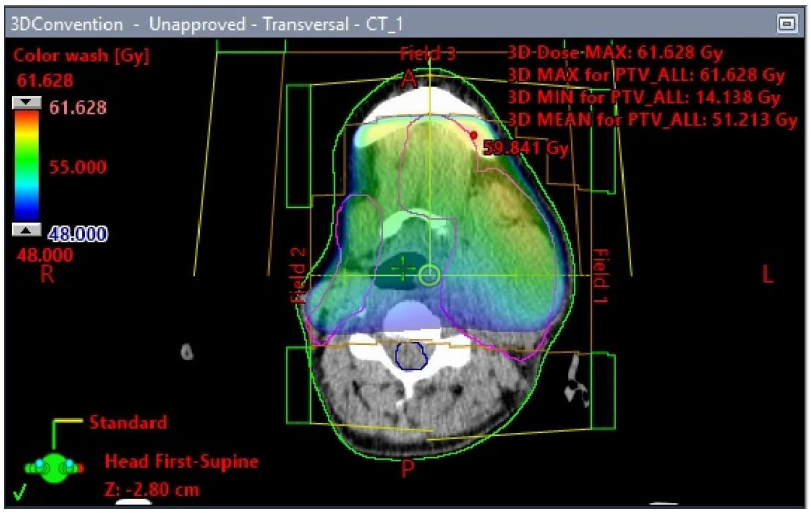
1.2.4. Planning process and treatment modalities

Planning process is one of the most difficult steps during radiation therapy workflow. The main purpose of this stage is treatment dose supplying in PTV with safe influence on OARs within their tolerance limits. Nowadays it is widespread to use special software to import in it CT slices and calculate dose distribution [12]. As soon as CT data set with information about region of interest is imported in treatment planning system physicist starts planning process, as it has been shown at fig. 3 and 4. First of all, external contour of patient needs to be detected and delineated. Then physicist chooses modality of treatment, energy of photon beams, calculates 3D dose distribution and estimates this distribution.

Nowadays there are several types of external beam radiation therapy with photons: conventional, conformal radiotherapy and IMRT.

Two-dimensional (conventional) radiotherapy uses x-rays to determining the target position and beam placement. The bones in this picture serve anatomical reference point. Rays are usually placed from opposite positions, anterior/posterior and lateral (box). Planning process of this type of treatment takes place when one needs to execute fast and urgent procedure. Bringing high doses to the target may be limited by the tolerance of healthy tissues, for example, when irradiating the prostate – rectum is falling into the irradiation zone, limiting the therapeutic dose reducing the probability of control tumors. The illustration of dose distribution is showed on Fig. 1.6.

Fig. 1.6. Conventional radiation therapy dose distribution.



Due to the improved quality and availability of computed tomography, the largest majority of hospitals use CT scans for conformal radiotherapy.

Conformal radiation therapy is rapidly developing and prospective part of modern radiotherapy. A three-dimensional image helps to determine tumor position and organs at risk. Dose distribution fits to target as much as possible, the beams are placed from the optimal positions, so dose exposure of healthy tissues becomes lower than tolerant limits. The target contour fitting is provided using the multi-leaf collimator, consisting of 20-60 pairs of narrow, closely located to each other plates made of tungsten, which can move according to the program. Conformal radiotherapy is illustrated at Fig. 1.7.

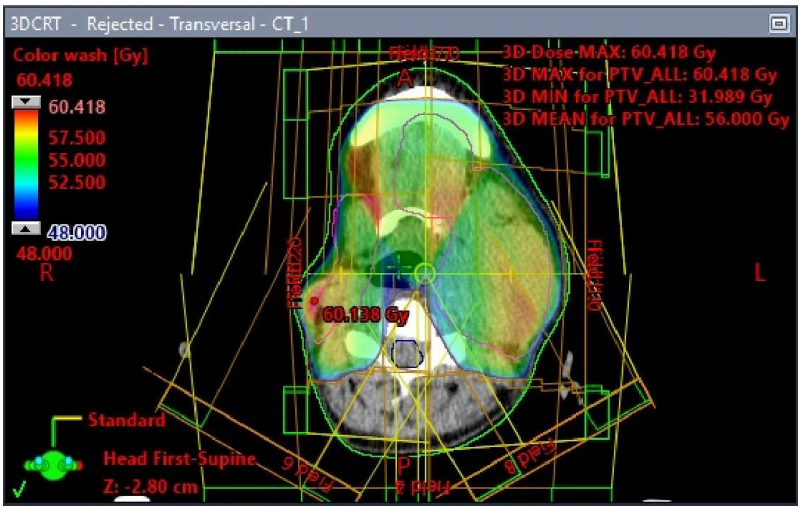


Fig. 1.7. Dose distribution of conformal radiotherapy.

An advanced technology of conformal radiation therapy is irradiation with modulation of the radiation beam intensity (IMRT), which reduces the dose exposure on the organ at risk and ensures optimal target dose distribution. This feature has a particular value in the complex shape of the target and the presence of adjacent radio-sensitive structures. The key difference of IMRT is inverse planning. Fig. 1.8 shows the dose distribution of IMRT modality in H&N case.

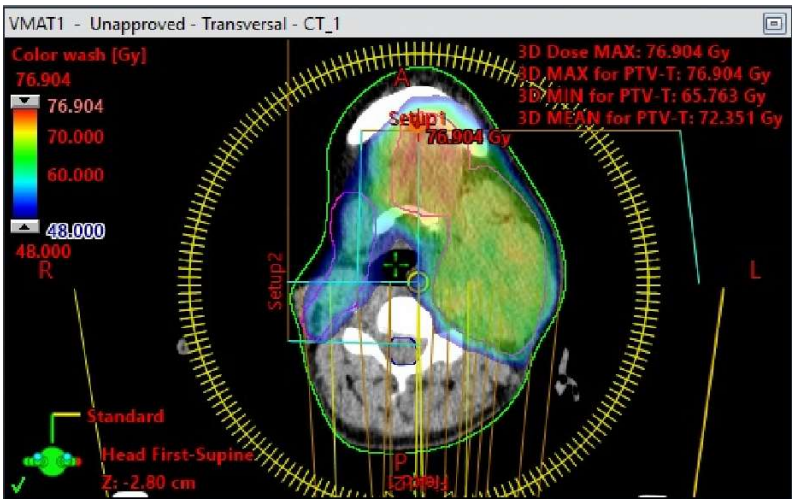


Fig. 1.8. Example of dose distribution for IMRT.

The IMRT planning process similarly to conformal radiotherapy begins with delineation of the target and risk organs, positioning the beams [13]. Then, with the help of treatment planning system each of these beams is divided into many elementary beamlets, that have their own dose contribution, which makes it possible to obtain a very complex dose distribution. The advantages of this type of treatment are:

- improved matching the dose distribution to a complex target contour;
- creating unequal dose distribution to different structures in the target;
- a lower dose exposure on the organs risk;
- the possibility of increasing the dose to the target.

Disadvantages are:

- increased time of treatment preparation;
- necessity of program quality assurance;
- increase in treatment time on the linac;
- increase in the total dose irradiation of the body.

These days IMRT treatment is introduced in many clinical departments. But IMRT without some form of in-room image guidance can lead to compromised treatment. Technological advances have meant that verification of the positioning of the patient has progressed from radiographic film analyzed after treatment to advanced imaging of the patient volume at the time of treatment with immediate corrective strategies as part of IGRT. IMRT treatment modality requires more technology, equipment, staff and training resources. with obligatory IGRT standards

1.2.5. Verification process

To ensure that the correct therapeutic dose has been given to the proper place, two types of measures are required – geometric and dosimetric verification. The purpose of a verification is the objective, systematic monitoring of the quality and expediency of providing medical care to patients. Verification is only one part of the treatment process.

After the planning process has been finished, physicist checks dose of the plan at treatment machine with ionization chamber or matrix of detectors.

The goal of geometric verification is to provide the geometric accuracy of treatment within the threshols set by the uncertainty margin enabled in the treatment

plan. Also planning procedure must be reproducible. Getting good quality reference images are important to good comparing of delivery information against planning [14].

Chapter 2

This chapter includes information about imaging technologies, types of geometrical uncertainties, measurement methods of set-up errors, and main strategies of IGRT protocols.

2.1. Imaging

It has lately become possible to image anatomy of patient just before radiotherapeutic fraction delivery to aim accuracy in dose distribution location and the hole process has become easier for users. This process is known as IGRT. It helps to significantly reduce treatment margins, to escalate treatment dose, to avoid geographical misses.

The ideal system must give good resolution of soft tissues, be fast, simple and accurate to define target volumes. Many IGRT systems are available at the market now. These systems allow to make imaging after patient positioned on treatment table for radiotherapy. Following IGRT systems based on direct integration of:

- Kilovoltage and megavoltage imaging systems having a single isocenter with linac, called to as cone beam computed tomography (CBCT) and offered by two linac producers as build-in imaging options: Varian and Elekta;
- CT scanner integrated with linac by Siemens;
- Megavoltage computed tomography offered by TomoTherapy;
- On-line imaging consisting of two kV X-Ray units installed into the procedure room floor and two flat panel detectors consists of ceiling-mounted amorphous silicon offered by Brainlab. The dual generators allow for great stereoscopic imaging of the target structure.

In this work kV-CBCT system is used for H&N cases. Let’s take a look more closely at this technology.

CBCT system gives visualization of tumor location before the treatment. CT imaging system integrated the linac and made possible to acquire multiple planar images, produced by kilovoltage cone beam rotating a full 360° around the patient in treatment position on the linac table. (see Fig. 2.1).

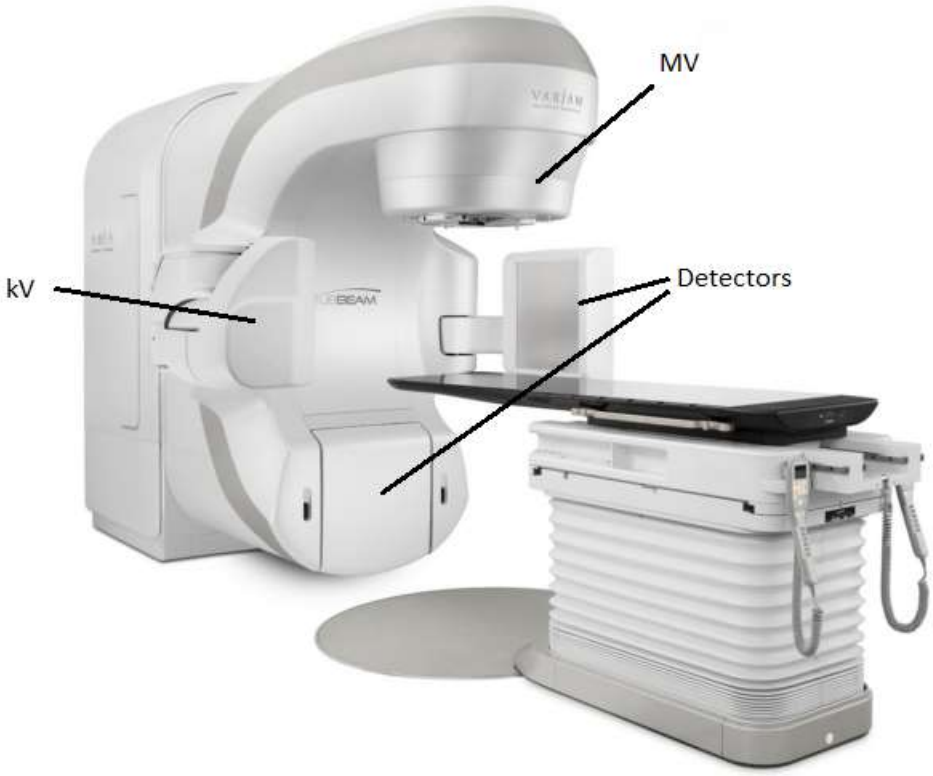


Fig. 2.1. CBCT sources and detectors integrated with linac.

CBCT method similar to CT scanning process is used to reconstruct the volumetric images of the tumor, OAR's and landmarks in the patient. Then the CBCT images are compared with the planning CT data as well as the related dose distribution, and it is need to decide how to change the patient position according to tumor movements or set-up error. The kV system includes a conventional X ray tube fitted on a retractable arm at 90º to the linac gantry and a flat panel X-ray detector fitted on a retractable arm opposite the X ray tube. The X ray system can, besides cone beam images, produce radiographic and fluoroscopic images. Beams based on kV produce good soft tissue contrast [9].

2.2. Uncertainties in radiotherapy

The treatment process of EBRT of solid tumors basically represents geometrical uncertainties or errors. Radiotherapy treatment is required to be precise. However, there are many sources of error that happen during treatment preparation and realization that constrain the precision. As a result, a safety margin is needed to guarantee that the planned dose is really delivered to the PTV for (almost) all patients. Before planning process, a CT scans are made. In particular, motion of skin in relation to the internal anatomy reduce the repeatability of this part of the process, entering a systematic set-up uncertainty. One else important source of uncertainties is organ movement. The target imaging in a random position leads to a systematic organ motion uncertainty. The interference of the scanning process may also distort CT image because of organ motion. A next systematic error occurs during delineation process of GTV. In the course of treatment, one of the most significant errors are setup error and organ motion leading to daily changes. There are many ways to determine appropriate value of margins respectively these errors. Here are given an overview of errors in radiotherapy, based on physical and biological considerations [15].

Set-up error describes the difference between planned and actual treatment position of the patient. It includes a systematic and random element.

It is normally calculated as a shift of patient position when planned images are compared against reference images. This type of error may be defined relatively to the isocentre, the field edges or both and can include translational and rotational information [14].

2.2.1. Gross errors

A gross error is an intolerably large set-up error that could lead to underdose part or hole of the clinical target volume (CTV) and overdose an organ at risk. CTV to PTV margins do not account for errors of such values and therefore gross errors must be corrected before treatment execution.

Mechanisms for detecting gross errors should be in performed before any treatment course begins. The common way to achieve this is to perform visualization before the beginning of treatment.

Causes of gross error includes:

- Incorrect patient, anatomical site, patient position or orientation
- Wrong field size, shape or spatial orientation
- False isocentre shift of unappropriated value.

Clinical departments should make a decision on an acceptable value for gross error, it can be different for various treatment sites. The selected value must exceed any that could happen from expected daily changes in treatment patient position. In practice a gross error action level of 10 mm is suitable for a wide range of anatomical sites and methods.

2.2.2. Systematic errors

The distinctive feature of the systematic component of any uncertainties is a shift that occurs in the same direction and is of near the same value for every fraction of the course.

The term systematic error may be used for individual patient or for patient's group. It is important to distinguish these meanings to avoid confusion.

- Individual systematic error for a patient is the mean value of uncertainties over the course of treatment.
- Population systematic uncertainties are calculated for a group of patients, describe the spread of individual mean uncertainties and calculated as the standard deviation (SD) of the distribution of average uncertainties for individual patient and is usually labeled as the capital sigma symbol Σ_{error} where the subscript 'error' refers to the particular error considered (for example, $\Sigma_{set\text{-}up}$ for the measured systematic set-up error).

Systematic uncertainties appear in a patient's treatment at the delineation, planning or treatment delivery steps. That's why, these types of uncertainties often are called as treatment preparation uncertainties. Once appear in some phase of the process,

systematic uncertainties will occur in every treatment fraction. Treatment preparation uncertainties may be following:

- Target localization (delineation) uncertainty represents the distinction between the defined and real CTV.
- Target position and shape uncertainties occur between delineation and treatment. Possible causes include tumor regression or growth, bladder filling and rectal bloating.
- Phantom transfer uncertainty occurs when transferring image data from CT through TPS to the linac. It can be measured with the help of special test phantom and includes treatment imaging, TPS and linac geometry uncertainties. Possible causes include differences in laser alignment between CT and linear accelerator, CT couch longitudinal position indication, image resolution, margin growing algorithm, field edge and multileaf collimator leaf position, isocentre location, source to surface distance indication, gantry and collimator angle precision.

Most of these parameters are checked during quality assurance program which help to ensure that all deviations lie within allowed limits, for instance 1 mm for a distance and +1° for an angle indication.

- Patient set-up uncertainty describes all possible causes of treatment set-up error, except the phantom transfer error, and includes all the uncertainties of gross errors. Possible causes include changes in the patient's position, shape or size (weight or hair loss). It also includes such effects as the displacement of the tumor relative to skin markers due to the CT scanner and linac have different couches.

Patient set-up uncertainty is only one possible component of the overall measured systematic set-up uncertainty. The treatment verification method identifies how many sources of systematic uncertainties will include into measurements of set-up uncertainty [14].

Individual systematic set-up error is expressed by the formula 2.1:

$$m_{individual} = \frac{\Delta_1 + \Delta_2 + \Delta_3 + \cdots + \Delta_n}{n} \quad (2.1)$$

Where shifts for each imaged fraction ($\Delta_1+\Delta_2+\Delta_3+\cdots+\Delta_n$) are divided by the number of fractions with imaging.

Mean population set-up error is calculated for a group of patients (P). Ideally it should be zero. The calculation is similar to equation 2.1.

$$M_{pop} = \frac{m_1 + m_2 + m_3 + \cdots + m_P}{P} \quad (2.2)$$

Population systematic error ($\sum_{set\text{-}up}$) is calculated as standard deviation (SD) of individual mean set-up errors about overall population mean deviation.

$$\sum\nolimits^2_{set-up=} = \frac{(m_1 - M_{pop})^2 + (m_2 - M_{pop})^2 + \cdots + (m_n - M_{pop})^2}{(P-1)} \quad (2.3)$$

2.2.3. Random errors

The main feature of random uncertainty is that it can be differ in direction and value for every treatment fraction. Fig. 2.2 shoes the influence of systematic and random deviations on cumulative dose.

The term “random error” also can be referred to an individual patient or patient group. The difference should be clear to avoid confusion.

- Individual random uncertainty calculates for individual patient, represent the SD of the measured uncertainties over the course of treatment and evaluate the scatter of errors.

- Population random error calculates for a group of patients like the mean value of the individual random errors and is labeled the lower sigma symbol σ_{error}.

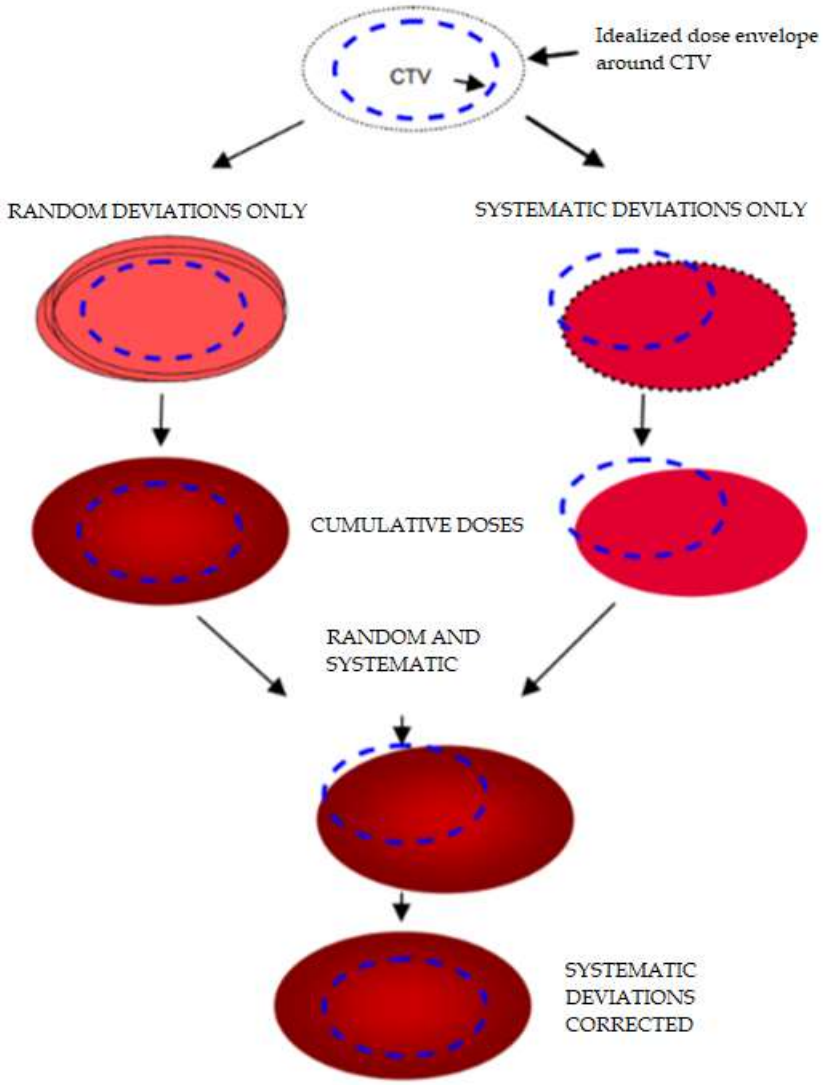


Fig. 2.2. The influence of uncertainties on total dose distribution to CTV.

As opposed to systematic error, random uncertainties occur during treatment delivery process and often named as treatment execution errors. They include following:

- Patient set-up errors are unforeseen changes occurring from change in position of a patient, equipment or set-up methodology between every fraction.
- Target position and shape uncertainty, in contradiction from delineation process in systematic error, accounts for organ motion between treatment fractions.

- Intrafraction errors refer to the patient's and internal anatomy motion during the fraction, for instance, due to breathing.

Random errors are influenced by the immobilisation system, patient compliance and department protocols. An offline correction protocols cannot predict the random error component, so this uncertainty should be included in treatment margin. Online correction protocols allow to control random component.

In approaches when only one first fraction is corrected may lead to overcorrection, because value of that day random error is unknown.

Individual random deviation is a sum of squares of the differences between the mean and set-up deviation for each measurement, it is calculated as following:

$$\sigma^2_{individual} = \frac{(\Delta_1 - m)^2 + (\Delta_2 - m)^2 + \cdots (\Delta_n - m)^2}{(n-1)} \quad (2.4)$$

Random error for population $\sigma_{set\text{-}up}$ is calculated as the mean of individual random deviations:

$$\sigma_{set-up} = \frac{\sigma_1 + \sigma_2 + \cdots + \sigma_P}{P} \quad (2.5)$$

2.2.4. Set-up error and treatment margin

As it mentioned above, information from only one measurement contain systematic component as well as random. The systematic error is constant in magnitude and direction for each fraction, the random error in contrast will differ in an unpredictable way.

More than one measurement must be taken to find the difference between the systematic and random uncertainties and perform a good estimate of corrections. One should make activities based on a single imaging with caution because it can lead to overcorrection. Further images taken and shifted on independently can lead also to the same result performing a series of unnecessary shifts around the mean value position. That is why, most offline imaging correction protocols take images over the first few fractions to guarantee a more precise evaluation of the mean.

Ideally, all clinical departments should calculate their own population systematic and random set-up uncertainty for each patient anatomical site and immobilization method.

PTV margin and patient set-up errors are closely related. Figure 2.3 illustrates the influence of IGRT strategy to size of margin.

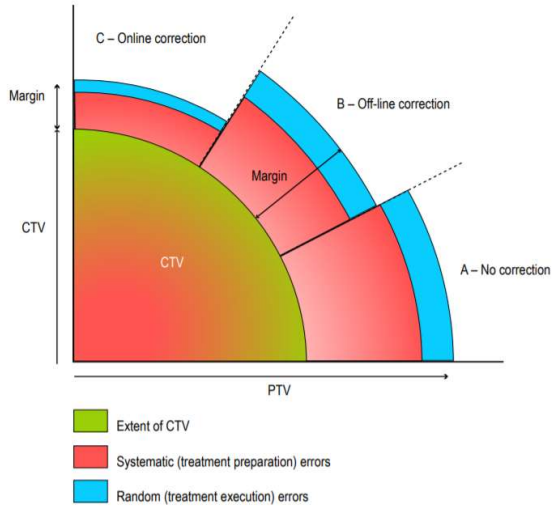


Fig. 2.3. Influence of IGRT strategy to size of PTV.

As it has been demonstrated previously, random uncertainty leads to blurring of total dose, systematic uncertainty introduces a constant shift of total dose. PTV margin should be adequate to guarantee the right coverage of CTV despite the various sources of systematic error. PTV margin may be changed depending on amount of detected and corrected errors and treatment verification method.

The target delineation uncertainty is present for the treatment course and cannot be measured for an individual patient. This and any other uncorrected uncertainties should be summed into the geometric PTV treatment margin.

There are several margin calculation recipes. The combined treatment preparation and treatment execution deviations in different proportion.

In the margin recipe, the impact of treatment preparation (systematic) errors and execution (random) variations is fully separated. It is therefore possible to use separate calculations for the margin, due to preparation (systematic) errors (which is a margin to compensate for an unknown shift of the CTV) and the margin due to

execution variations (which is a margin to compensate for the blurring of the dose distribution due-to-day to day variation).

Based on the dose population histograms of Van Herk et al have derived a margin recipe to guarantee that 90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose. This margin is approximately 2.5 times the total SD of systematic plus 0.7 times the total SD of random errors as it seen in formula 2.6. [15-16].

$$PTV = 2.5\Sigma + 0.7\sigma \qquad (2.6)$$

Where systematic error for the population $\sum$ includes delineation, motion, transfer and patient set-up uncertainties. And population random error σ includes patient set-up and motion errors.

2.3. IGRT strategies

IAEA recommends several protocols of IGRT. They can be broadly divided into the two main categories offline and online. Which way to choose to find the optimal correction strategy depends on clinical department resources, treatment modality, site being treated, and the level of competence [17].

2.3.1. Offline protocols of set-up corrections

In an offline approach the errors of previous fractions are considered and analyzed. The purpose of such protocols to effectively correct systematic deviations with minimum number of patient set-up measurements and corrections [16]. Three types of protocols are generally accepted: Shrinking action level (SAL) protocol [17], no action level (NAL) protocol [18], further developed into the extended no action level (e-NAL) [19].

In 1993 Bel et al has introduced SAL protocol (fig. 2.4). Firstly, for each anatomical site it is needed to define applicable values of the two SAL protocol parameters initial action level α and number of measurements N_{max} were based on typical patient set-up accuracy values found in literature. Patient set-up deviations are measured during a consecutive number of fractions of the treatment. The vector-length d_N is tested against the action level for this measurement, $\alpha_N = \alpha/\sqrt{N}$ where a is the initial action level. If the vector-length exceeds the action level, a set-up correction is performed in all subsequent fractions and the procedure is repeated with N reset to 1. This process continues until $N=N_{max}$ subsequent measurements have been obtained without the need for a correction, after which the 'first stage' of the protocol is finished. The first stage of the SAL protocol intends to correct initial large systematic set-up

errors, and we aimed at finishing this stage no later than the second week of treatment [20].

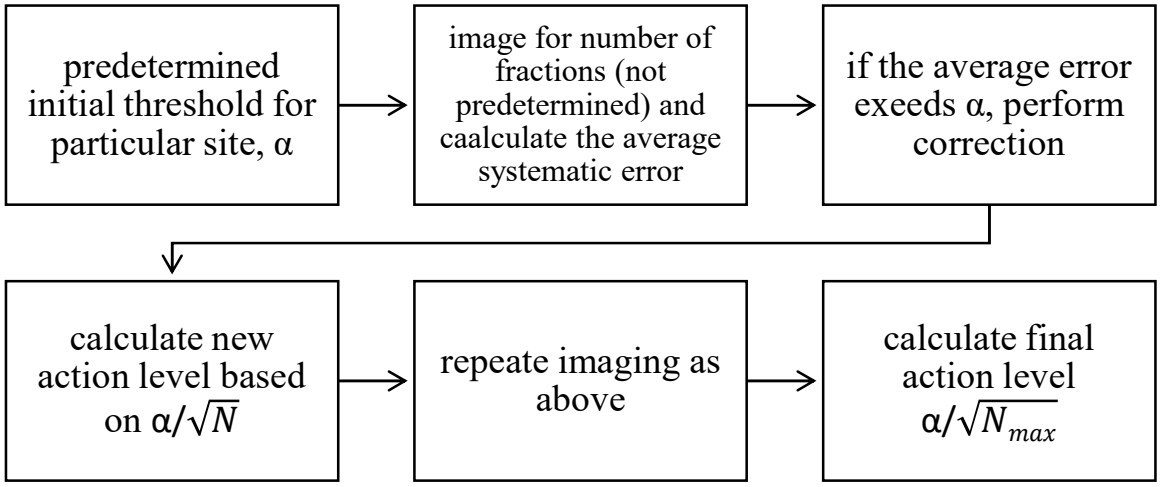


Fig. 2.4. SAL protocol.

The problems with the SAL protocol largely arise from the use of action levels. Such action levels introduce a subpopulation of patients who do not get a correction, i.e., patients for whom the estimate of the systematic error is sufficiently small. In addition, SAL protocol required unknown in advance number of imaged fractions.

Then, in 2001, de Boer et al, in the alternative to SAL protocol, has proposed no action level (NAL), where every patient has one setup correction and for each patient, the same number of images is used to estimate the systematic setup error. The NAL protocol is very simple to conceive (fig. 2.5). It has only one parameter, which is the (fixed) number of fractions to be measured per patient ($N_m << N_f$). The average setup vector over the first N_m fractions (V_{Nm}) is determined, and a setup correction equal to $-V_{Nm}$ is applied in all subsequent fractions, irrespective of its length d_{Nm}. Because the averaged error is the unbiased estimator of the true systematic error with minimal variance, it is the optimal setup correction based on Nm measurements for a single patient [21]. This protocol is very simple to use and show effective results, however it

doesn't take into account some time-trends effects, that could influence on patient set-up accuracy.

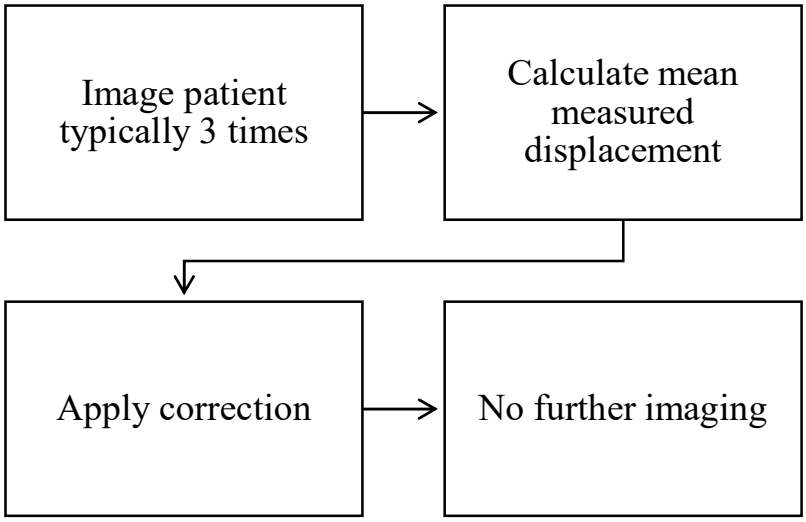


Fig. 2.5. NAL protocol.

So, the authors of NAL protocol have developed extended NAL to cope with time trends or transmissions in the systematic errors of patients (see fig. 2.6).

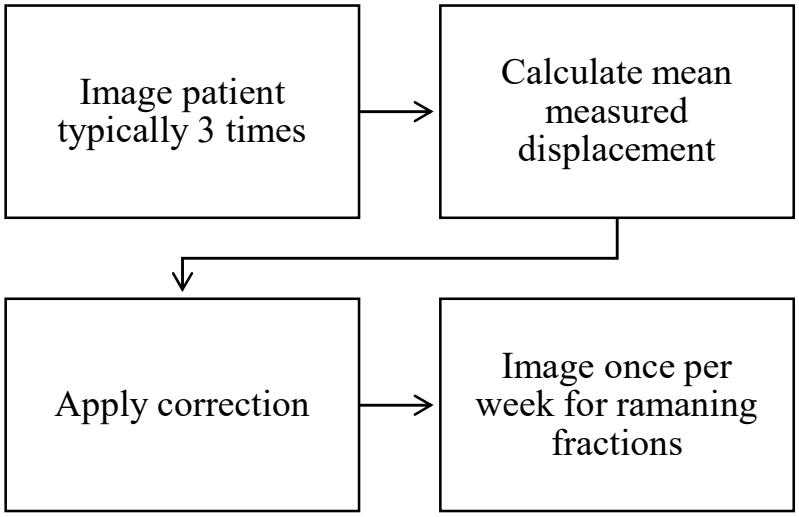


Fig. 2.6. E-NAL protocol.

The first stage of eNAL is the standard NAL protocol. First, measurements are performed in a fixed number of initial treatment fractions (N_m). During these initial fractions, the patient is positioned according to reference marks defined in the treatment preparation phase, without application of a positioning correction. The estimate of the systematic displacement of a patient p is calculated as the mean displacement over these N_m fractions. In the second stage, measurments are separated by the period of $\Delta f_{rep}=5$ fractions, so the k-th measurement is at $f=N_m+k\Delta f_{rep=}f_{rep}(k)$. For weekly measurements and five treatment fractions per week, $\Delta f_{rep}=5$. The fraction

interval is called the (k+1)-th period. The displacement in a particular fraction patient p is denoted by d(p,f) [22]. The displacements that would have been obtained without setup corrections can be calculated as $d_{uncor}(f)=d(p,f)-C(f)$. In the eNAL protocol, the applied corrections C(f) are defined as follows:

1) $f \leq N_m$: apply no correction, i.e., C(f) =0
2) $Nm+1 \leq f \leq f_{rep}(1)$ (first period): $C(f)=C_{NAL}$.
3) $f_{rep}(k)+ 1 \leq f \leq f_{rep}(k+1)$ and $k \geq 1$((k+1)-th period).

$C(f)=(\hat{S}_k+\hat{a}_k(f_{rep}(k)-1))$.

The $\hat{S}_k$ and $\hat{a}_k$ are obtained from the least squares linear fit $d_{uncor}(f)= \hat{S}_k+r(f)+ \hat{a}_k(f-1)$ to the N_m+k measured values of $d_{uncor}(f)$ available at the start of the (k+1)-th period [25].

2.3.2. Online protocols of set-up corrections

In online IGRT protocol, after imaging of the patient the shifts are determined from the reference image. In case of zero action level protocols, the shift is applied anyway, even if that shifts are really small. In case of action level protocols, shifts are applied only if they are larger than a predetermined action level (for instance. 2 mm), if it is not – shifts are recorded electronically and reviewed [24]. The online protocol can be differing in the frequency of imaging, for instance, in some cases the repeat imaging is performed after shifts to confirm their accuracy. Moreover, clinical departments should considerate in the protocol the actions levels when the size of the shift is above a certain threshold, including re-entering the treatment room to check the patient set-up, removing the patient from the treatment couch to correct for patient related factors (e.g. bladder filling) or consulting with a radiation oncologist [23].

Chapter 3

In this chapter the results of IGRT protocols application have been compared between each other for group of 10 patients with head and neck cancer. Then PTV margin has been calculated for each protocol.

3.1. Materials and methods

Practice part has been performed in Tyumen Multidisciplinary Clinical Medical Center “Medical City”. The four correction protocols have been compared to each other: no correction, NAL, e-NAL and online. The alignment data from 10 patients with H&N cancer (oral cavity, nasopharynx, larynx, etc.) from daily CBCT imaging of 25 fractions has been obtained and recorded. For all of these patients has been prepared treatment plan with Varian solution of VMAT calling RapidArc®. “Eclipse: External Beam Planning” version 15.6 has been used as TPS. Then calculation of PTV margins are performed and estimated with respect to IGRT strategy. Dose distribution in VMAT modality is perfectly conforms PTV.

These patients have been immobilized in the same way in supine position, laying on baseplate with headrest fixed with individual thermoplastic mask (QFix®) (see fig. 3.1).

CT imaging for treatment planning has been performed with Siemens Somatom Definition AS CT scanner and 3mm thickness of slices. Radiation oncologist has delineated OARs, CTV and 5 mm of PTV margin.

All patients have been treated on TrueBeam STx by Varian Medical Systems, with On Board Imaging (OBI) capabilities. Daily verification has been performed (Machine Performance Check - MPC) to be sure of accuracy of OBI system and reduce the potential sources of errors.

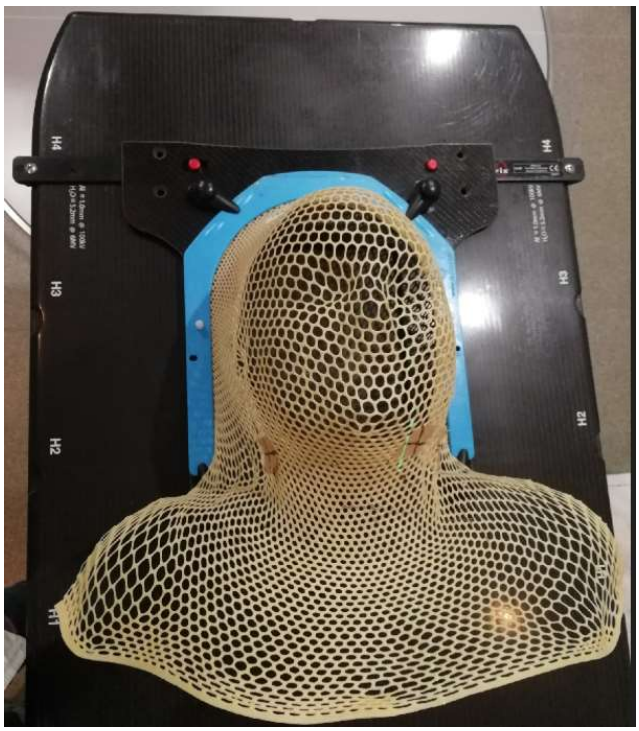


Fig. 3.1. Photo of the mask with baseplate

Before each fraction of radiotherapy course CBCT image has been obtained with the help of OBI device. The comparison between CT and CBCT images has been executed by automatic matching in Portal Vision Advanced Imaging soft by Varian and manually controlled basing on motionless structures.

Shifts in vertical, lateral and longitudinal directions have been recorded from every treatment delivery. All displacements and shifts have been reviewed and exported by and physicist in Varian Offline Review. Also in appendixes there are 4 tables of NAL, e-NAL and online simulations, with prediction meanings, of correction shifts and no correction table (appendixes A-D). All calculations with patient's displacements data have been performed in Microsoft Excel 2016.

3.1.1. Correction protocol simulation

It is compared three protocols of set-up corrections based on 10 patients' data. The uncertainties have been decomposed into longitudinal, lateral and vertical translations. Simulations are performed to determine remainder uncertainties for three protocols: NAL, e-NAL and online and no correction data.

All displacements without corrections for 10 patients are shown in table A in appendix. All next calculations of protocols based on values from this table.

For NAL protocol number of measurements to calculate shift vector is 5 (N_{max}=5). According to the protocol, it is calculated the mean vector value from first five fractions for each direction, then the opposite shift applies to the rest of fractions without any additional correction (see tab. B in appendix).

For e-NAL protocol, after the first stage of NAL protocol, measurements repeat once a week, previous displacement is cancelled and new shift calculated for the next fraction, according to the influence of new sixth measurement on mean vector value. So the whole number of imaging became 9 (see tab.C in appendix).

Online pretreatment correction performs every fraction, and this protocol has fixed threshold for action equal 2 mm. If every error in each direction is low, then 2 mm – no shifts apply that day. If error is bigger than 2 mm, shift is applied, and we consider, that there is no remaining set-up error that day (see tab. D in appendix).

3.1.2. PTV margin simulation

Data of residual shifts is used to determine required PTV margin. This calculation follows the approach of van Hark et al. [20]. Protocol for dose coverage in clinical department requires that 100 percent of the dose covers 95 percent of PTV. So the treatment goal must account for remaindered errors. According to van Herk formula (2.6) 90% of patients will receive 95% of prescribed dose.

3.4. Results

The standard deviations of remaining uncertainties for each protocol are shown in table 3.1. All protocols with correction are able to reduce the systematic component. However only online protocol reduces random component. In fact, the random uncertainties were slightly larger for both off-line protocols than when no correction protocol was used. In appendix tables of calculated displacements for every protocol are shown (appendix B-D).

Table 3.1 – The standard deviations of remaining uncertainties for each protocol.

Protocol	Systematic (mm)			Random (mm)		
	Vrt	Long	Lat	Vrt	Long	Lat
No correction	1.0	3.3	1.1	1.7	2.6	1.8
NAL	1.0	2.1	1.1	1.8	2.7	2.1
e-NAL	0.9	2.0	0.8	1.8	2.8	2.0
Online	0.2	0.2	0.2	0.5	0.4	0.4

The value of population mean set-up error also has a trend to decrease, according to complexity of choosing protocol. The biggest value in no correction protocol, both offline protocols shows similar results, but e-NAL is more effective, and at last online protocol has the smallest mean value of set-up error. The meanings are demonstrated in table 3.2.

	Population mean set-up error, M_{pop}, mm		
	Vrt,	Long	Lat
No correction	-0.6	0.4	-0.7
NAL	-0.2	0.8	-0.4
e-NAL	-0.3	0.5	-0.3
Online	0.0	0.0	0.0

In table 3.3 it is shown the number of required images vary according of using protocol. Noteworthy, that NAL protocol and no correction protocol have quite similar results, but in case of gross errors no correction protocol is very dangerous in practice. E-NAL protocol shows better results. Online protocol takes the most times of imaging, and almost every fraction finished with correction. Offline corrections do not perform on daily basis.

Table 3.3 – The mean number of imaged fractions and performed corrections for each protocol.

Protocol	Imaged Fraction	Corrections calculated
No correction	0	0
NAL	5	1
e-NAL	9	5
Online	25	20.2

When set of displacements for each protocol has been obtained, it is possible to calculate appropriate PTV margin for each direction (see tab. 3.4). The offline protocols reduce margin times comparing to no correction protocol. The online protocol reduces this margin much more, from 4 to 10 of requiring margin in offline protocol.

Table 3.4 – Values of PTV margin according to IGRT protocol.

Protocol	PTV margin (mm)		
	Vrt	Long	Lat
No correction	3.6	10.0	4.1
NAL	3.8	7.1	4.1
e-NAL	3.3	6.8	3.2
Online	0.8	0.7	0.7

Tendency of mismatches when use protocols for one patient are shown in fig. 3.2.

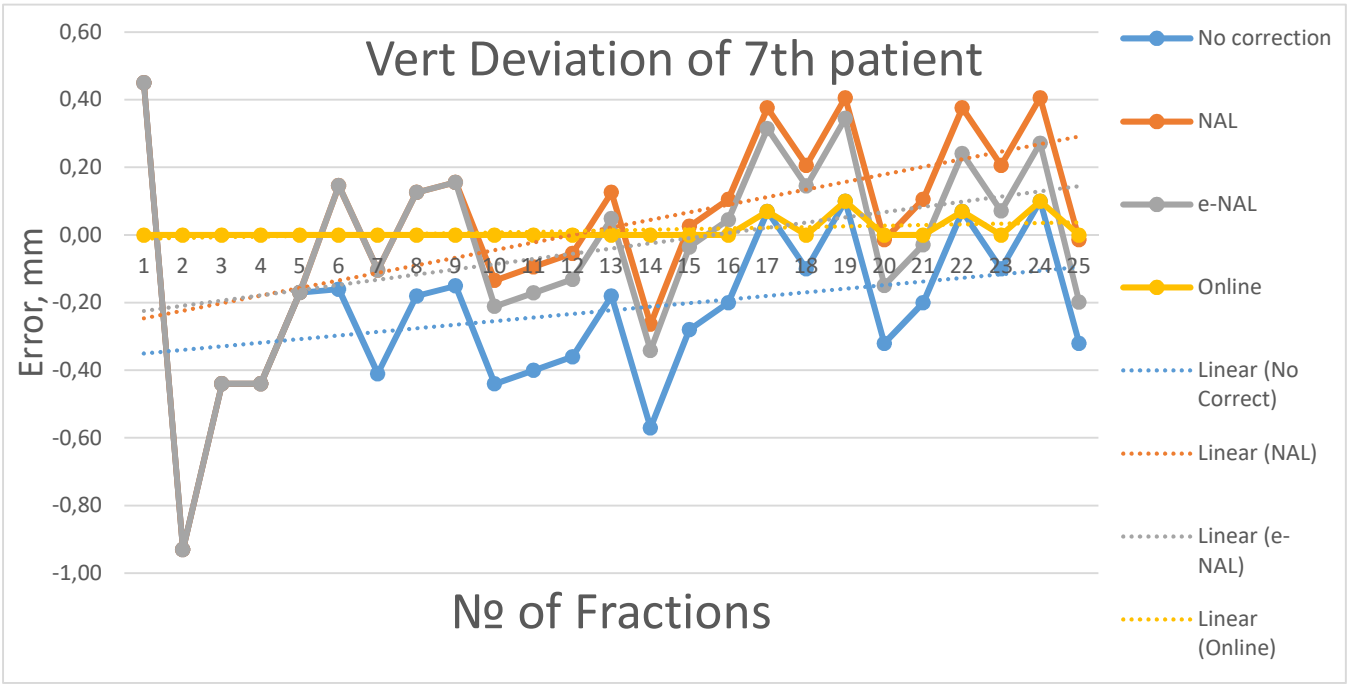


Fig. 3.2. Tendency of mismatches with applied IGRT protocols.

Values of PTV margins significantly influence on treatment volume. To see the difference, four different margins for real CTV (volume of choosing CTV is 438 cm^3) have been created in H&N region (see fig. 3.3).

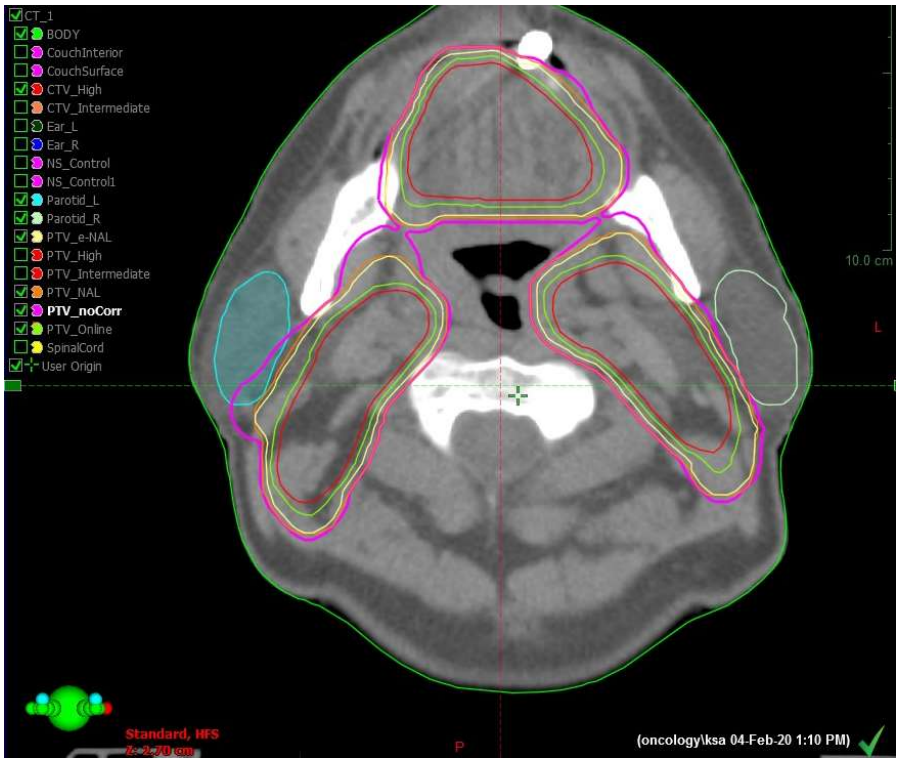


Fig. 3.3. Visible demonstration of differences in sizes of PTV.

After that, four different volumes of PTV have been calculated (see tab. 3.5)

Tab. 3.5 – Influence of IGRT protocols on volume of PTV.

	No correction	NAL	e-NAL	Online
PTV, cm^3	911	837	753	579

Conclusion

In this paper recommended by IAEA set-up correction strategies have been investigates for H&N anatomical site. Issues of geometric accuracy takes an important part in radiation therapy. The use of recommended IGRT strategies to be sure of more precise target position allow for increase tumor control and reduce complications in healthy tissue. The results of this paper research shows the ability of offline protocols reduce required size of PTV margin in almost 1.4 times. Online protocol, compared with offline strategies, helps to reduce PTV in even more significantly, approximately in 5 times.

This research work area includes only set-up uncertainties, and it do not include tumor delineation process errors, phantom transfer or observer uncertainties when CBCT matching.

Which protocol to choose in clinical department depends on the particular interests of each center. No correction approach is undesirable one, it is required big size of PTV, and do not correct gross errors if they are taking a place. If it is needed to reduce systematic uncertainties with maximize patient throughput (minimum acquired imaging), NAL becomes the most desirable one. E-NAL applies in case of some tendency in systematic displacements. H&N patient group usually have that tendency, because during the treatment they may lose weight and size of the target can reduce. However, when time allows to use CBCT frequently, online protocol is more valuable. In Tyumen Oncology Centre online imaging takes approximately 5 minutes. It is acceptable time, when patients traffic is low. In fact, this clinical department data shows good result of uncertainties magnitude, comparing to population published uncertainties of that anatomical site, except for longitudinal direction. The possible way to reduce this error is more careful patient preparation and immobilization.

Chapter 4. Financial management, resource efficiency and resource saving

The purpose of this section discusses the issues of competitiveness, resource efficiency and resource saving, as well as financial costs regarding the object of study of Master's thesis. Competitiveness analysis is carried out for this purpose. SWOT analysis helps to identify strengths, weaknesses, opportunities and threats associated with the project, and give an idea of working with them in each particular case. For the development of the project requires funds that go to the salaries of project participants and the necessary equipment, a complete list is given in the relevant section. The calculation of the resource efficiency indicator helps to make a final assessment of the technical decision on individual criteria and in general.

Estimation of the commercial value of the study is one of the most important stages in the design of the research, it is a necessary condition when searching for sources of funding for study and commercialization of their results. This characterization helps to evaluate the prospects of scientific research, and find a partners for further study.

Nowadays, medicine has a wide range of technologies and sophisticated equipment for diagnosis and treatment of cancer. Radiotherapy is one of the most effective methods, alongside with surgery or chemotherapy. Current progress of radiotherapy allows to escalate the dose in the tumor, without unwanted injury of normal tissue. The realization of such state-of-the-art technologies requires high accuracy in execution. In this study the effectiveness of NAL, e-NAL and online protocols of patient set-up correction and their impact on treatment margins magnitude has been evaluated.

This master’s thesis is performed on clinical base in Tyumen Multidisciplinary Clinical Medical center “Medical city”. This research has been made with the help of special equipment, linear accelerator Varian TrueBeam Stx with implemented cone beam computed tomography system to help correcting patient set-up errors.

4.1. Competitiveness analysis of technical solutions

In order to find sources of financing for the project, it is necessary, first, to determine the commercial value of the work. Analysis of competitive technical solutions in terms of resource efficiency and resource saving allows to evaluate the comparative effectiveness of scientific development. This analysis is advisable to carry out using an evaluation card [26].

First of all, it is necessary to analyze possible technical solutions and choose the best one based on the considered technical and economic criteria.

Evaluation map analysis presented in Table 4.1. As the competitive methods are chosen NAL (C_1), e-NAL (C_2) and online (C_3) protocols of set-up patient correction. These protocols are evaluated with the five-point scale for each chosen criteria, where 1 is the weakest position and 5 is the strongest. The weights of indicators in the amount should be 1. Analysis of competitive technical solutions is determined by the formula 1:

$$C = \sum W_i \cdot P_i, \tag{4.1}$$

C - the competitiveness of research or a competitor;

Wi– criterion weight;

Pi – point of i-th criteria.

Table 4.1 – Evaluation card for comparison of competitive technical solutions

Evaluation criteria	Criterion weight	Points			Competitiveness		
		P1	P2	P3	C_1	C_2	C_3
1	2	3	4	5	6	7	8
Technical criteria for evaluating resource efficiency							
1. Energy efficiency	0.1	5	4	3	0.5	0.4	0.3
2. Reliability of results	0.25	3	4	5	0.75	1	1.25
3. Patient radiation load	0.05	4	3	2	0.2	0.15	0.1

Continuation of table 4.1 – Evaluation card for comparison of competitive technical solutions

4. Functional capacity	0.1	3	4	5	0.3	0.4	0.5
5. Labor intensity	0.2	5	4	3	1	0.8	0.6
6. Ease of use	0.1	5	3	4	0.5	0.3	0.4
Economic criteria for performance evaluation							
1. Competitive ability	0.05	4	4	5	0.2	0.15	0.25
2. Widely accepted method	0.05	2	2	4	0.15	0.15	0.25
3. Expected life cycle	0.1	5	5	5	0.5	0.5	0.5
Total	1				4.1	3.85	4.15

The results of this competitiveness analysis shows all these methods have their peculiar pros and cons, that make all these protocols applicable for specific situations in clinical departments. Online protocol has the best score because of the reliability of results, but this approach increases the workload. NAL protocol is very simple in clinical application and it has lowest labor intensity, however this protocols shows not excellent accuracy in calculations. E-NAL protocol is like a compromise of these two methods in the reliability of results, still it is not popular and has some difficulties in practice.

4.2. SWOT analysis

Complex analysis solution with the greatest competitiveness is carried out with the method of the SWOT analysis: Strengths, Weaknesses, Opportunities and Threats. The analysis has several stages. The first stage consists of describing the strengths and weaknesses of the project, identifying opportunities and threats to the project that have emerged or may appear in its external environment. The second stage consists of identifying the compatibility of the strengths and weaknesses of the project with the external environmental conditions. This compatibility or incompatibility should help to identify what strategic changes are needed. SWOT analysis of this study is shown in the table 4.2.

Table 4.2 – SWOT analysis.

	Strengths: S1. Increasing of dose distribution accuracy S2. Development of single approach based on clinical reality and aims	**Weaknesses:** W1. Lack of equipment W2. Lack of stuff expertise
Opportunities: O1. Reduction of patient set-up error O2. Reduction of tumor PTV margin	Strategy which based on strengths and opportunities: 1) Ability to improve the quality of treatment 2) Reduction of tumor underdose risk	Strategy which based on weaknesses and opportunities: 1) Employee advanced trainings allow to improve the accuracy of treatment and calculating set-up errors 2) Competent approach would allow to use equipment according to aims

Continuation of table 4.2 – SWOT analysis.

Threats: T1. Threat of CBCT injury T2. Lack of commercial interest to these methods	Strategy which based on strengths and threats: 1) Writing science papers which show the benefits of using such methods of geometric verification, that would show the necessity of using this equipment and enough financing 2) High rate of treatment quality would influence on enough financing of overhead expenses	Strategy which based on strengths and threats: 1) Regular courses of medical stuff increase the level of education, which potentially raise interest to new technologies 2) Getting research grants

The results of SWOT analysis are used in science research structure development.

4.3. Project initiation

The initiation process group consists of processes that are performed to define a new project or a new phase of an existing one. In the initiation processes, the initial purpose and content are determined and the initial financial resources are fixed.

The internal and external stakeholders of the project who will interact and influence the overall result of the research project are determined (table 4.3 and 4.4).

Table 4.3 – Stakeholders of the project

Project stakeholders	Stakeholder expectations
Clinical departments	Research of advantages comparison of using IGRT online and offline protocols of patient set-up correction
Research center	

Table 4.4 – Purpose and results of the project

Purpose of project:	• To quantify systematic and random patient set-up uncertainties in head and neck irradiation and to investigate the impact of an off-line correction protocols on the systematic errors and its value on planning target volume.
Expected results of the project:	• Creation of graphical spread of patient set-up errors for each fraction depending on IGRT protocol and time trends. • Calculation of standard deviation of random and systematic set-up error for a group of patients. • Calculation of PTV margin magnitude for each protocol of patient set-up correction
Criteria for acceptance of the project result:	• Increasing of effectiveness of treatment to 90% of patient receiving 95% of prescribed dose in CTV.

Continuation of table 4.4 – Purpose and results of the project.

Requirements for the project result:	• Project should be finished to the 1st of June.
	• The results of the project should meet the criteria for acceptance.
	• The results of this research should be demonstrated at Russian conference.
	• In case of unacceptable results it is necessary to increase the number of patients taking participation in this research.

The organizational structure of the project

It is necessary to solve some questions: who will be part of the working group of this project, determine the role of each participant in this project, and prescribe the functions of the participants and their number of labor hours in the project. This information is collected in table 4.5.

Table 4.5 – The working group of the project

№	Participant	Role in the project	Functions	Labor time, hours.
1	E.S. Sukhikh, PhD, Chief Medical Physicist of Tomsk Regional Oncology Center	Research advisor	Control of the project	150
2	O.M. Stakhova, radiological safety engineer, Tyumen Multidisciplinary Clinical Medical Center “Medical City”	Masters student	Preforming of measurements and calculation of the results	456
Total				606

Project limitations are all factors that can be as a restriction on the degree of freedom of the project team members. Project limitations are illustrated in the table 4.6.

Table 4.6 – Project limitations.

Factors	Limitations / Assumptions
Project's budget	191525049 of rubles
Source of financing	Government budget
Project timeline:	February 2020-June 2020
Date of approval of plan of project	01.02.2020
Completion date	01.06.2020

Project Schedule

As part of planning a science project, it is necessary to build a project timeline and a Gantt Chart (tab. 4.7 and 4.8).

Table 4.7 – Project timeline.

	Job title	Duration, working days	Start date	Date of completion	Participants
1	Creation and approving of technical specification	5	The 3rd of February 2020	The 7th of February 2020	Research advisor
2	Searching and selection of material for research	10	The 10th of February 2020	The 21th of February 2020	Master's student
3	Selection of study way	2	The 24th of February 2020	The 25th of February 2020	Research advisor
4	Development of general methodology of the research	6	The 26th of February 2020	The 4th of March 2020	Research advisor, master's student
5	Calendar planning of research activities	2	The 5th of March 2020	The 6th of March 2020	Research advisor

Continuation of table 4.7 – Project timeline.

6	Reviewing of manuals and list of literature	10	The 9th of March 2020	The 20th of March 2020	Master's student
7	Measurements performing	30	The 23th of March 2020	The 4th of May 2020	Master's student
8	Processing of measurements results	5	The 5th of May 2020	The 11th of May 2020	Master's student
9	Analysis and description of the results	10	The 12th of May 2020	The 25th of May 2020	Research advisor, master's student
10	Composition of master's thesis	5	The 26th of May 2020	The 1st of June 2020	Master's student

A Gantt chart, or harmonogram, is a type of bar chart that illustrates a project schedule (tab. 4.7). This chart lists the tasks to be performed on the vertical axis, and time intervals on the horizontal axis. The width of the horizontal bars in the graph shows the duration of each activity.

Table 4.7 – Calendar schedule of master's thesis performing

№	Activities	Participants	T_c, days	Duration of the project											
				February			March			April			May		
				1	2	3	1	2	3	1	2	3	1	2	3
1	Creation and approving of technical specification	RA	5												
2	Searching and selection of material for research	MS	10												
3	Selection of study way	RA	2												
4	Development of general methodology of the research	RA, MS	6												

Continuation of table 4.7. Calendar schedule of master's thesis performing

5	Calendar planning of research activities	RA	2				▨								
6	Reviewing of manuals and list of literature	MS	10					■							
7	Measurements performing	MS	30						■	■	■	■			
8	Processing of measurements results	MS	5										■		
9	Analysis and description of the results	RA, MS	10											▨■	
10	Composition of master's thesis	MS	5												■

Icons show participations activity, ■ -master's student, ▨ - research advisor.

4.4. Scientific and technical research budget

The amount of costs associated with the implementation of this work is the basis for the formation of the project budget. This budget will be presented as the lower limit of project costs when forming a contract with the customer.

To form the final cost value, all calculated costs for individual items related to the manager and the student are summed.

In the process of budgeting, the following grouping of costs by items is used:

- Material costs of scientific and technical research;
- costs of special equipment for scientific work (Depreciation of equipment used for design);
- basic salary;
- additional salary;
- labor tax;
- overhead.

The budget for scientific and technical research is shown in table 4.8.

Table 4.8 – The budget for scientific and technical research.

Name	Material costs	Costs of special equipment	Basic salary	Addi-tional salary	labor tax	Over-head	Total cost
Cost, rub.	36960	191070000	200661	20066	56899	140463	191525049

Calculation of material costs

The calculation of material costs is carried out according to the formula:

$$C_{mT} = (1 + k_i) \times \sum_{i=1}^{m} P \times N_{const} \qquad (4.2)$$

where m – the number of types of material resources consumed in the performance of scientific research;

N_{consi} – the amount of material resources of the i-th species planned to be used when performing scientific research (units, kg, m, m^2, etc.);

P_i – the acquisition price of a unit of the i-th type of material resources consumed (rub./units, rub./kg, rub./m, rub./m^2, etc.);

k_T – coefficient taking into account transportation costs.

Prices for material resources can be set according to data posted on relevant websites on the Internet by manufacturers (or supplier organizations).

Table4.9 – Material costs.

№	Name	Units	Amount	Price per unit, rub.	Material costs, rub.
1	Thermoplastic mask	Pieces	10	3500	30000
Total					30000

For this kind of work some equipment have been already bought. So we need to calculate deprecation of such equipment per year. It is calculated by the formula:

$$D = \frac{C_{primary} \times N_d}{100} \quad (4.3)$$

, where D – annual deprecation;

$C_{primary}$ – primary cost of equipment;

$N_d=100/T_{life}$ – norms of depreciation deductions, T_{life} – service life of equipment. It is supposed, that service life of all equipment is 10 years.

Table 4.10 – Special equipment.

№	Name	Manufacturer	Amount	Price per unit, thousands rubles.	Material deprecation costs, thousands rubles
1	Linac TrueBeam Stx	Varian	1	190000	19000
2	Aria software	Varian	1	1000	100
3	Headrest	QFix	1	10	1
4	Baseplate	QFix	1	30	3
Total					19104

Basic salary

This point includes the basic salary of participants directly involved in the implementation of work on this research, research advisor am master's student. The value of salary costs is determined based on the labor intensity of the work performed and the current salary system.

The basic salary (S_b) is calculated according to the following formula:

$$S_b = S_a \times T_w \quad (4.4)$$

where S_b – basic salary per participant;

T_w – the duration of the work performed by the scientific and technical worker, working days;

The average daily salary is calculated by the formula:

$$S_d = \frac{S_m \times M}{F_v} \quad (4.5)$$

где S_m – monthly salary of an participant, rub;

M – the number of months of work without leave during the year:

at holiday in 49 days, M = 10.4 months, 5 days per week;

F_v – valid annual fund of working time of scientific and technical personnel (251 days).

Table 4.11 – The valid annual fund of working time

Working time indicators	Participants
Calendar number of days	366
The number of non-working days - weekend - holidays	 104 14
Loss of working time - vacation - sick absence	 49 0
The valid annual fund of working time	248

Monthly salary is calculated by formula:

$$S_{month} = S_{base} \times (k_{premium} + k_{bonus}) \times k_{reg} \quad (4.6)$$

where S_{base} – base salary, rubles;

$k_{premium}$ – premium rate;

k_{bonus} – bonus rate;

k_{reg} – regional rate.

Table 4.12 – Calculation of the base salaries

Performers	S_{base}, rubles	$k_{premium}$	k_{bonus}	k_{reg}	S_{month}, rub.	W_d, rub.	T_w, work days	W_{base}, rub.
Research advisor	35300	1.1	1.1	1.15	56500	2369	25	59225
Masrer's student	27280				44400	1861	76	141436

Additional salary.

This point includes the amount of payments stipulated by the legislation on labor, for example, payment of regular and additional holidays; payment of time associated with state and public duties; payment for work experience, etc.

Additional salaries are calculated on the basis of 10-15% of the base salary of workers:

$$W_{add} = k_{extra} \times W_{base} \quad (4.7)$$

where W_{add} – additional salary, rubles;

k_{extra} – additional salary coefficient (10%);

W_{base} – base salary, rubles.

Labor tax

Tax to extra-budgetary funds are compulsory according to the norms established by the legislation of the Russian Federation to the state social insurance (SIF), pension fund (PF) and medical insurance (FCMIF) from the costs of workers.

Payment to extra-budgetary funds is determined of the formula:

$$P_{social} = k_b(W_{base} + W_{add}) \quad (4.8)$$

where k_b – coefficient of deductions for labor tax.

In accordance with the Federal law of July 24, 2009 No. 212-FL, the amount of insurance contributions is set at 30%. Institutions conducting educational and scientific activities have rate - 27.1%.

Table 4.13 – Labor tax

	Research advisor	**Master's student**
Coefficient of deductions	30%	
Salary, rubles	59225	141436
Labor tax, rubles	17768	42431

Overhead costs.

Overhead costs include other management and maintenance costs that can be allocated directly to the project. In addition, this includes expenses for the maintenance, operation and repair of equipment, production tools and equipment, buildings, structures, etc.

Overhead costs account from 30% to 90% of the amount of base and additional salary of employees.

Overhead is calculated according to the formula:

$$C_{ov} = k_{ov} \times (W_{base} + W_{add}) \quad (4.9)$$

where k_{ov} – overhead rate.

Table 4.14 – Overhead costs

	Research advisor	Master's student
Overhead rate	70%	
Salary, rubles	59225	141436
Overhead, rubles	41458	99005

Other direct cost

PC work duration for this research is about 800 hours, linac measurement duration is 6 hours. Energy costs which include equipment and computer work are calculated by the formula:

$$C = P_{el} \times P \times F_{eq} = 5.8 \times (50\text{kW} \times 6\text{hours} + 0.75\text{kW} \times 800\text{hours}) = 5220 \quad (4.10)$$

where P_{el}– power rates (5.8 rubles per 1 kWh);
P – power of equipment, kW;
F_{eq}– equipment usage time, hours.

Formation of budget costs

The calculated cost of research is the basis for budgeting project costs. Determining the budget for the scientific research is given in the table 4.15.

Table 4.15 – Items expenses grouping

Name	Cost, rubles
1. Equipment deprecation	19 104 000
2. Material costs	30 000
3. Basic salary	20 0661
4. Additional salary	20 066
5. Labor tax	56 899
6. Overhead	140 463
7. Other direct cost	5 220
Total planned cost	19 557309

4.5. Conclusion

The research has been divided in a few stages. In the first stage competitiveness analysis of technical solutions has been performed. The results of this stage shows, that online method has more benefits, than others, because of the reliability of results, nevertheless, this approach increases the workload.

In the second stage SWOT-analysis has been formed on the base of competitive technical solutions. It shows strong and weak fringes of the project.

The third stage highlights project initiation. Primary purposes, content, financial recourses, expected results and stakeholders are noted.

In the fourth stage scientific and technical research budget is calculated. The total budget of the project is 19 557 309 of rubles.

Chapter 5. Social responsibility

5.1. Introduction

In this paper measurement of patient set-up error has been performed during a course of radiotherapy on linear accelerator. Deviations are measured according recommended international offline and protocols to correct patient set-up uncertainties in clinical department. Such procedures help to increase the accuracy of treatment. Experimental calculations have been performed to compare three types of protocols to each other: no action level (NAL) protocol, further developed into the extended no action level (e-NAL) and online protocol. These measurements allow to calculate planning target volume margin. In conclusion there is discussed the effectiveness of each protocol and preferences of using such approaches in clinic. Measurements have been performed on the basis of Tyumen Multidisciplinary Clinical Medical Center "Medical City".

5.2. Legal and organizational items in providing safety

Nowadays one of the main way 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 [27].

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

- 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.

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

The workplace when working with a 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.

5.4. Occupational safety

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 [27].

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.

5.4.1. Analysis of harmful and dangerous factors that can create object of investigation

The object of investigation is “set-up uncertainties and its influence on size of planning target volume”. Therefore, object of investigation itself cannot cause harmful and dangerous factors.

5.4.2. 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 hazardous and harmful factors, which are classified by groups of elements: physical, chemical, biological, psychophysiological. The main elements of the production process that form dangerous and harmful factors are presented in Table 5.1.

Table 5.1 - Possible hazardous and harmful factors

Factors (GOST 12.0.003-2015)	Work stages			Legal documents
	Develop-ment	Manu-facture	Exploi-tation	
1. Deviation of microclimate indicators	+	+	+	Sanitary rules 2.2.2 / 2.4.1340–03. Sanitary and epidemiological rules and regulations "Hygienic requirements for personal electronic computers and work organization." Sanitary rules 2.2.1 / 2.1.1.1278–03. Hygienic requirements for natural, artificial and combined lighting of residential and public buildings. Sanitary rules 2.2.4 / 2.1.8.562–96. Noise at workplaces, in premises of residential, public buildings and in the construction area. Sanitary rules 2.2.4.548–96. Hygienic requirements for the microclimate of industrial premises.
2. Excessive noise		+	+	
3.Increased level of electromagnetic radiation	+	+	+	
4.Insufficient illumination of the working area		+	+	

Continuation of the Table 5.1 – Possible hazardous and harmful factors

5. Abnormally high voltage value in the circuit, the closure which may occur through the human body	+	+	+	Sanitary rules GOST 12.1.038-82 SSBT. Electrical safety. Maximum permissible levels of touch voltages and currents.
6. Increased levels of ionizing radiation	+	+	+	Sanitary Rules 2.6.1. 2523 -0 9. Radiation Safety Standards (NRB-99/2009).

The following factors effect on person working on a computer:

- physical:
  - temperature and humidity;
  - noise;
  - static electricity;
  - electromagnetic field of low purity;
  - illumination;
  - presence of radiation;
- psychophysiological:
  - psychophysiological dangerous and harmful factors are divided into:
    - physical overload (static, dynamic)
    - mental stress (mental overstrain, monotony of work, emotional overload).

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 [28] and are given in Table 5.2.

Table 5.2 - 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

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 results 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.

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 [28], 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.

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.

Upper limits for values of contact current and voltage are represented in Table 5.3.

Table 5.3 – 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

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.

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%.

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:

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

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

c) keep individual radiation doses from all radiation sources as low as possible.

There are two groups of people related to work with radiation: personnel, who works with ionizing radiation, and population (see Table 5.4).

Table5.4 – Dose limits for groups of people related to work with radiation

Quantity	Dose limits	
	personnel	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 in eye's lens	150 mSv	15 mSv
skin	500 mSv	50 mSv
Hands and feet	500 mSv	50 mSv

Effective dose for personnel must not exceed 1000 mSv for 50 years of working activity, and for population must not exceed 70 mSv for 70 years of life.

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.

For students older than 16, who uses radiation sources in study process or who is in rooms with increased level of ionizing radiation, dose limits are quarter part of dose limits of personnel.

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

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 m 3 per hour per person for the volume of the room up to 20 m 3 per person;

- natural ventilation is allowed for the volume of the room more than 40 m 3 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.

Excessive noise

In research audiences, there are various kinds of noises that are generated by both internal and external noise sources. The internal sources of noise are working equipment, personal computer, printer, ventilation system, as well as computer equipment of other engineers in the audience. 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.

Increased level of electromagnetic radiation

There are the following ways to protect against EMF:

- 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.

When working with a computer, the ionizing radiation source is a display. Under the influence of ionizing radiation in the body, there may be a violation of normal blood coagulability, an increase in the fragility of blood vessels, a decrease in

immunity, etc. The dose of irradiation at a distance of 20 cm to the display is 50 μrem / hr. According to the norms [28], the design of the computer should provide the power of the exposure dose of x-rays at any point at a distance of 0.05 m from the screen no more than 100 μR / h.

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.

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.

Abnormally high voltage value in the circuit

Measures to ensure the electrical safety of electrical installations:

- disconnection of voltage from live parts, on which or near to which work will be carried out, and taking measures to ensure the impossibility of applying voltage to the workplace;
- posting of posters indicating the place of work;
- electrical grounding of the housings of all installations through a neutral wire;

- coating of metal surfaces of tools with reliable insulation;
- inaccessibility of current-carrying parts of equipment (the conclusion in the case of electroporating elements, the conclusion in the body of current-carrying parts) [29].

Insufficient illumination of the working area

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.

5.5. Ecological safety

5.5.1. Analysis of the impact of the research object on the environment

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.

The danger of using radioactive materials could occur only in accidents with stealing and loosing these materials due to high toxicity.

5.5.2 Analysis of the environmental impact of the research process

Process of investigation itself in the thesis do not have essential effect on environment. One of hazardous waste is fluorescent lamps. Mercury in fluorescent lamps is a hazardous substance and its improper disposal greatly poisons the environment.

Outdated devices go to an enterprise that has the right to process wastes. It is possible to isolate precious metals with a purity in the range of 99.95–99.99% from computer components. A closed production cycle consists of the following stages: primary sorting of equipment; the allocation of precious, ferrous and non-ferrous metals and other materials; melting; refining and processing of metals. Thus, there is an effective disposal of computer devices.

5.5.3 Justification of environmental protection measures

Pollution reduction is possible due to the improvement of devices that produces electricity, the use of more economical and efficient technologies, the use of new methods for generating electricity and the introduction of modern methods and methods for cleaning and neutralizing industrial waste. In addition, this problem should be solved by efficient and economical use of electricity by consumers themselves. This is the use of more economical devices, as well as efficient regimes of these devices. This also includes compliance with production discipline in the framework of the proper use of electricity [29].

Simple conclusion is that it is necessary to strive to reduce energy consumption, to develop and implement systems with low energy consumption. In modern computers, modes with reduced power consumption during long-term idle are widely used.

5.6 Safety in emergency

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

The fire is the most probable emergency in our life. Possible causes of fire:

- malfunction of current-carrying parts of installations;
- work with open electrical equipment;
- short circuits in the power supply;
- non-compliance with fire safety regulations;
- presence of combustible components: documents, doors, tables, cable insulation, etc.

Activities on fire prevention are divided into: organizational, technical, operational and regime.

5.6.2 Substantiation of measures for the prevention of emergencies and the development of procedures in case of emergencies

Organizational measures provide for correct operation of equipment, proper maintenance of buildings and territories, fire instruction for workers and employees, training of production personnel for fire safety rules, issuing instructions, posters, and the existence of an evacuation plan.

The technical measures include compliance with fire regulations, norms for the design of buildings, the installation of electrical wires and equipment, heating, ventilation, lighting, the correct placement of equipment [30].

The regime measures include the establishment of rules for the organization of work, and compliance with fire-fighting measures. 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 fireworks);
- 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);
- call the Emergency Service or the Ministry of Emergency Situations - tel. 112;
- take measures to eliminate the accident in accordance with the instructions.

5.7 Conclusion

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.

Possible negative effect on environment were given in compact form describing main ecological problem of using nuclear energy.

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

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APPENDIX A

No correction	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7			Patient 8			Patient 9			Patient 10		
Fraction	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat
1	-0,03	0,07	-0,32	-0,18	0,47	0,01	0,02	-0,88	0,19	0,06	-0,20	0,02	0,55	-0,22	-0,48	-0,10	-0,02	0,24	-0,07	0,45	0,05	0,00	0,37	0,00	-0,60	-1,30	-0,71	0,10	0,00	0,09
2	0,08	0,01	-0,13	-0,04	0,35	-0,19	0,11	0,16	-0,36	-0,14	0,48	-0,20	-0,15	0,20	-0,12	0,08	-0,01	0,37	-0,05	-0,93	-0,29	-0,01	-0,08	0,22	-0,63	-1,53	-0,41	0,03	-0,35	-0,11
3	-0,03	0,05	-0,35	-0,02	0,22	-0,05	0,12	-0,37	0,04	-0,18	0,34	0,02	-0,16	0,03	0,11	0,22	0,08	0,01	-0,50	-0,44	0,19	0,10	-0,18	0,00	0,00	0,48	-0,08	-0,02	-0,39	-0,01
4	0,15	0,13	-0,36	0,07	0,59	-0,17	0,11	-0,09	-0,23	-0,09	-0,05	0,05	-0,16	0,04	-0,01	-0,21	0,02	0,64	0,02	-0,44	0,16	0,21	-0,17	0,54	-0,02	0,53	-0,16	0,02	-0,26	0,04
5	0,19	0,03	-0,29	-0,18	0,42	-0,07	-0,39	-0,37	-0,32	-0,23	0,43	-0,08	-0,29	0,07	0,11	-0,16	0,02	0,38	-0,36	-0,17	-0,35	0,01	0,11	0,29	0,03	0,57	-0,12	0,03	-0,35	0,02
6	0,22	-0,19	-0,13	-0,16	0,48	0,19	-0,25	-0,11	-0,10	-0,07	0,37	-0,08	-0,30	0,17	-0,02	-0,04	0,04	0,24	0,13	-0,16	-0,24	-0,16	-0,03	-0,17	0,05	0,49	0,01	0,10	-0,15	0,11
7	0,31	-0,14	-0,25	-0,18	0,53	-0,18	0,36	-0,10	-0,61	-0,15	0,25	-0,07	-0,31	0,01	-0,19	0,03	0,14	0,16	-0,31	-0,41	-0,24	-0,30	-0,33	-0,19	0,09	0,56	-0,05	0,02	-0,26	0,05
8	0,15	0,01	-0,63	-0,18	0,22	-0,05	0,24	0,04	-0,09	-0,15	0,28	0,03	-0,56	-0,02	-0,31	0,15	0,04	0,20	-0,23	-0,18	0,12	-0,33	-0,05	-0,37	-0,12	0,92	0,01	0,03	-0,47	0,01
9	0,09	-0,23	-0,41	0,09	0,17	-0,17	-0,12	0,03	0,08	-0,01	0,21	-0,06	-0,38	0,43	-0,40	0,02	-0,16	-0,01	-0,22	-0,15	-0,12	-0,23	0,08	-0,34	-0,05	0,72	-0,20	0,11	-0,37	-0,53
10	-0,19	-0,05	-0,36	-0,18	0,35	0,08	0,02	-0,88	-0,19	-0,14	0,44	-0,12	0,46	-0,11	-0,37	0,21	0,08	0,21	-0,46	-0,44	-0,25	-0,23	0,10	-0,32	-0,09	0,13	-0,12	0,03	-0,31	0,01
11	0,08	-0,04	-0,17	-0,06	0,22	-0,03	0,11	0,16	-0,36	0,06	-0,20	0,02	-0,17	0,00	-0,02	0,18	-0,01	-0,01	-0,34	-0,40	-0,10	0,00	0,37	0,00	0,07	0,37	-0,29	-0,01	-0,37	-0,01
12	-0,01	0,04	-0,22	-0,17	0,35	-0,08	0,12	-0,37	0,04	-0,14	0,48	-0,20	0,13	-0,37	0,06	-0,20	-0,07	0,57	-0,01	-0,36	0,31	-0,01	-0,08	0,22	0,05	0,73	-0,10	0,15	-0,43	0,09
13	-0,27	-0,15	-0,22	-0,20	0,47	-0,19	0,01	-0,09	-0,23	-0,18	0,34	0,02	0,28	-0,35	-0,25	-0,16	0,01	0,30	-0,03	-0,18	-0,30	0,10	-0,18	0,00	0,35	0,37	0,59	-0,01	-0,39	0,04
14	-0,24	-0,13	-0,22	-0,20	0,99	0,09	-0,39	-0,37	-0,32	0,09	-0,05	0,05	0,41	0,07	-0,35	0,11	-0,05	0,20	-0,44	-0,57	-0,16	0,21	-0,17	0,54	0,04	0,53	0,11	0,00	-0,38	0,16
15	0,04	0,06	-0,16	-0,23	1,78	-0,01	-0,25	-0,11	-0,10	-0,23	0,43	-0,08	-0,27	-0,01	-0,28	0,38	-0,01	-0,03	-0,30	-0,28	-0,10	0,01	0,11	0,29	-0,02	0,46	0,13	0,02	-0,49	0,06
16	0,01	-0,08	-0,36	-0,41	1,72	-0,36	0,36	-0,10	-0,61	-0,07	0,37	-0,08	0,18	-0,02	-0,01	0,27	-0,03	0,09	-0,42	-0,20	0,17	-0,16	-0,03	-0,17	-0,01	-0,32	-0,32	0,02	-0,43	0,03
17	-0,11	-0,18	-0,07	-0,12	0,90	0,10	0,24	0,04	-0,09	-0,15	0,25	-0,07	-0,29	0,07	-0,26	0,08	-0,02	0,34	-0,17	0,07	0,12	-0,30	-0,33	-0,19	0,04	0,07	-0,07	-0,02	-0,45	0,02
18	0,06	0,15	-0,17	0,09	0,04	0,21	-0,12	0,03	0,08	-0,15	0,28	0,03	-0,41	0,31	-0,28	0,07	-0,15	-0,03	-0,34	-0,10	-0,04	-0,33	-0,05	-0,37	0,01	0,26	-0,04	0,06	-0,49	0,06
19	-0,08	0,02	-0,28	-0,07	0,99	0,09	0,12	-0,37	0,04	-0,01	0,21	-0,06	-0,31	0,46	-0,04	-0,06	-0,04	0,30	-0,17	0,10	0,02	-0,23	0,08	-0,34	0,08	0,12	0,05	-0,04	-0,48	-0,01
20	0,04	0,02	-0,27	-0,23	1,78	-0,01	0,01	-0,09	-0,23	-0,14	0,44	-0,12	-0,14	-0,03	-0,18	0,11	0,05	-0,15	-0,29	-0,32	-0,15	-0,23	0,10	-0,32	0,10	0,14	-0,07	-0,01	-0,52	0,03
21	-0,03	-0,14	-0,31	-0,41	1,71	-0,36	-0,39	-0,37	-0,32	-0,07	0,37	-0,08	-0,35	-0,16	-0,13	-0,11	0,02	0,07	-0,42	-0,20	0,17	-0,16	-0,03	-0,17	0,06	0,28	0,10	-0,07	-0,46	-0,01
22	0,27	-0,06	0,01	-0,12	0,90	0,10	-0,25	-0,11	-0,10	-0,15	0,25	-0,07	-0,14	0,10	-0,18	0,11	0,06	0,12	-0,17	0,07	0,12	-0,30	-0,33	-0,19	0,01	0,26	-0,04	0,23	-0,49	-0,06
23	-0,03	-0,18	-0,12	-0,23	1,62	-0,01	0,36	-0,10	-0,61	-0,15	0,28	0,03	-0,23	-0,08	-0,29	0,22	-0,07	0,13	-0,34	-0,10	-0,04	-0,33	-0,05	-0,37	0,08	0,12	0,05	-0,11	-0,34	0,03
24	0,19	-0,19	0,08	-0,41	1,60	-0,36	0,24	0,04	-0,09	-0,01	0,21	-0,06	-0,20	0,29	-0,09	0,09	-0,42	0,07	-0,17	0,10	0,02	-0,23	0,08	-0,34	0,10	0,14	-0,07	-0,01	-0,52	0,03
25	-0,07	-0,21	-0,31	-0,12	0,90	0,10	-0,12	0,03	0,08	-0,14	0,44	-0,12	0,02	-0,15	-0,21	0,13	-0,11	-0,02	-0,29	-0,32	-0,15	-0,23	0,10	-0,32	0,06	0,28	0,10	-0,07	-0,46	0,02
Individual mean set-up error $m_{individual}$	0,03	-0,06	-0,24	-0,15	0,79	-0,05	0,01	-0,17	-0,18	-0,10	0,27	-0,05	-0,11	0,03	-0,17	0,06	-0,02	0,18	-0,24	-0,22	-0,04	-0,13	-0,02	-0,08	-0,01	0,22	-0,07	0,02	-0,38	0,01
Population mean set-up error M_{pop}	-0,06	0,04	-0,07																											
Population systematic error $\sum_{set-up}$	0,10	0,33	0,11																											
Individual random error $\sigma_{individual}$	0,15	0,11	0,15	0,14	0,58	0,16	0,24	0,27	0,22	0,09	0,2	0,07	0,29	0,21	0,16	0,15	0,11	0,19	0,17	0,27	0,18	0,17	0,18	0,28	0,2	0,56	0,23	0,07	0,12	0,12
Population random error σ_{set-up}	0,17	0,26	0,18																											
Margin $2,5\sum+0,7\sigma$	0,36	1	0,41																											

APPENDIX B

NAL	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7			Patient 8			Patient 9			Patient 10		
Fraction	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat
1	-0,03	0,07	-0,32	-0,18	0,47	0,01	-0,88	0,19	0,06	-0,20	0,02	0,55	-0,22	-0,48	-0,10	-0,02	0,24	-0,07	0,45	0,05	0,00	0,37	0,00	-0,60	-1,30	-0,71	0,10	0,00	0,09	
2	0,08	0,01	-0,13	-0,04	0,35	-0,19	0,11	0,16	-0,36	-0,14	0,48	-0,20	-0,15	0,20	-0,12	0,08	-0,01	0,37	-0,05	-0,93	-0,29	-0,01	-0,08	0,22	-0,63	-1,53	-0,41	0,03	-0,35	-0,11
3	-0,03	0,05	-0,35	-0,02	0,22	-0,05	0,12	-0,37	0,04	-0,18	0,34	0,02	-0,16	0,03	0,11	0,22	0,08	0,01	-0,50	-0,44	0,19	0,10	-0,18	0,00	0,00	0,48	-0,08	-0,02	-0,39	-0,01
4	0,15	0,13	-0,36	0,07	0,59	-0,17	0,11	-0,09	-0,23	-0,09	-0,05	0,05	-0,16	0,04	-0,01	-0,21	0,02	0,64	0,02	-0,44	0,16	0,21	-0,17	0,54	-0,02	0,53	-0,16	0,02	-0,26	0,04
5	0,19	0,03	-0,29	-0,18	0,42	-0,07	-0,39	-0,37	-0,32	-0,23	0,43	-0,08	-0,29	0,07	0,11	-0,16	0,02	0,38	-0,36	-0,17	-0,35	0,01	0,11	0,29	0,03	0,57	-0,12	0,03	-0,35	0,02
6	0,15	-0,25	0,16	-0,09	0,07	0,28	-0,24	0,20	0,04	0,05	0,17	-0,04	-0,26	0,15	0,06	-0,01	0,02	-0,09	0,32	0,15	-0,19	-0,22	-0,04	-0,38	0,29	0,74	0,31	0,07	0,12	0,10
7	0,24	-0,20	0,04	-0,11	0,12	-0,09	0,37	0,21	-0,47	-0,03	0,05	-0,03	-0,27	-0,01	-0,11	0,06	0,12	-0,17	-0,12	-0,10	-0,19	-0,36	-0,34	-0,40	0,33	0,81	0,25	-0,01	0,01	0,04
8	0,08	-0,05	-0,34	-0,11	-0,19	0,04	0,25	0,35	0,05	-0,03	0,08	0,07	-0,52	-0,04	-0,23	0,18	0,02	-0,13	-0,04	0,13	0,17	-0,39	-0,06	-0,58	0,12	1,17	0,31	0,00	-0,20	0,00
9	0,02	-0,29	-0,12	0,16	-0,24	-0,08	-0,11	0,34	0,22	0,11	0,01	-0,02	-0,34	0,41	-0,32	0,05	-0,18	-0,34	-0,03	0,16	-0,07	-0,29	0,07	-0,55	0,19	0,97	0,10	0,08	-0,10	-0,54
10	-0,26	-0,11	-0,07	-0,11	-0,06	0,17	0,03	-0,57	-0,05	-0,02	0,24	-0,08	0,50	-0,13	-0,29	0,24	0,06	-0,12	-0,27	-0,13	-0,20	-0,29	0,09	-0,53	0,15	0,38	0,18	0,00	-0,04	0,00
11	0,01	-0,10	0,12	0,01	-0,19	0,06	0,12	0,47	-0,22	0,18	-0,40	0,06	-0,13	-0,02	0,06	0,21	-0,03	-0,34	-0,15	-0,09	-0,05	-0,06	0,36	-0,21	0,31	0,62	0,01	-0,04	-0,10	-0,02
12	-0,08	-0,02	0,07	-0,10	0,01	0,13	-0,06	0,18	-0,02	0,28	-0,16	0,17	-0,39	0,14	-0,17	-0,09	0,24	0,18	-0,05	0,36	-0,07	-0,09	0,01	0,29	0,98	0,20	0,12	-0,16	0,08	
13	-0,34	-0,21	0,07	-0,13	0,06	-0,10	0,02	0,22	-0,09	-0,06	0,14	0,06	0,32	-0,37	-0,17	-0,13	-0,01	-0,03	0,16	0,13	-0,25	0,04	-0,19	-0,21	0,59	0,62	0,89	-0,04	-0,12	0,03
14	-0,31	-0,19	0,07	-0,13	0,58	0,18	-0,38	-0,06	-0,18	0,21	-0,25	0,09	0,45	0,05	-0,27	0,14	-0,07	-0,13	-0,25	-0,26	-0,11	0,15	-0,18	0,33	0,28	0,78	0,41	-0,03	-0,11	0,15
15	-0,03	0,00	0,13	-0,16	1,37	0,08	-0,24	0,20	0,04	-0,11	0,23	-0,04	-0,23	-0,03	-0,20	0,41	-0,03	-0,36	-0,11	0,03	-0,05	-0,05	0,10	0,08	0,22	0,71	0,43	-0,01	-0,22	0,05
16	-0,06	-0,14	-0,07	-0,34	1,31	-0,27	0,37	0,21	-0,47	0,05	0,17	-0,04	0,22	-0,04	0,07	0,30	-0,05	-0,24	-0,23	0,11	0,22	-0,22	-0,04	-0,38	0,23	-0,07	-0,02	-0,01	-0,16	0,02
17	-0,18	-0,24	0,22	-0,05	0,49	0,19	0,25	0,35	0,05	-0,03	0,05	-0,03	-0,25	0,05	-0,18	0,11	-0,04	0,01	0,02	0,38	0,17	-0,36	-0,34	-0,40	0,28	0,32	0,23	-0,05	-0,18	0,01
18	-0,01	0,09	0,12	0,16	-0,37	0,30	-0,11	0,34	0,22	-0,03	0,08	0,07	-0,37	0,29	-0,20	0,10	-0,17	-0,36	-0,15	0,21	0,01	-0,39	-0,06	-0,58	0,25	0,51	0,26	0,03	-0,22	0,05
19	-0,15	-0,04	0,01	0,00	0,58	0,18	0,13	-0,06	0,18	0,11	0,01	-0,02	-0,27	0,44	0,04	-0,03	-0,06	-0,03	0,02	0,41	0,07	-0,29	0,07	-0,55	0,32	0,37	0,35	-0,07	-0,21	-0,02
20	-0,03	-0,04	0,02	-0,16	1,37	0,08	0,02	0,22	-0,09	-0,02	0,24	-0,08	-0,10	-0,05	-0,10	0,14	0,03	-0,48	-0,10	-0,01	-0,10	-0,29	0,09	-0,53	0,34	0,39	0,23	-0,04	-0,25	0,02
21	-0,10	-0,20	-0,02	-0,34	1,30	-0,27	-0,38	-0,06	-0,18	0,05	0,17	-0,04	-0,31	-0,18	-0,05	-0,08	0,00	-0,26	-0,23	0,11	0,22	-0,22	-0,04	-0,38	0,30	0,53	0,40	-0,10	-0,19	-0,02
22	0,20	-0,12	0,30	-0,05	0,49	0,19	-0,24	0,20	0,04	-0,03	0,05	-0,03	-0,10	0,08	-0,10	0,14	0,04	-0,21	0,02	0,38	0,17	-0,36	-0,34	-0,40	0,25	0,51	0,26	0,20	-0,22	-0,07
23	-0,10	-0,24	0,17	-0,16	1,21	0,08	0,37	0,21	-0,47	-0,03	0,08	0,07	-0,19	-0,10	-0,21	0,25	-0,09	-0,20	-0,15	0,21	0,01	-0,39	-0,06	-0,58	0,32	0,37	0,35	-0,14	-0,07	0,02
24	0,12	-0,25	0,37	-0,34	1,19	-0,27	0,25	0,35	0,05	0,11	0,01	-0,02	-0,16	0,27	-0,01	0,12	-0,44	-0,26	0,02	0,41	0,07	-0,29	0,07	-0,55	0,34	0,39	0,23	-0,04	-0,25	0,02
25	-0,14	-0,27	-0,02	-0,05	0,49	0,19	-0,11	0,34	0,22	-0,02	0,24	-0,08	0,06	-0,17	-0,13	0,16	-0,13	-0,35	-0,10	-0,01	-0,10	-0,29	0,09	-0,53	0,30	0,53	0,40	-0,10	-0,19	0,02
Σ_{set-up}	0,10	0,21	0,11																											
Individual random error $\sigma_{individual}$	0,16	0,13	0,20	0,13	0,55	0,17	0,24	0,33	0,23	0,10	0,20	0,07	0,29	0,21	0,16	0,16	0,11	0,27	0,17	0,31	0,18	0,19	0,18	0,34	0,27	0,61	0,31	0,07	0,12	0,12
Population random error σ_{set-up}	0,18	0,27	0,21																											
Margin $2,5\Sigma+0,7\sigma$	0,38	0,71	0,41																											
Mean shift of Nmax	0,07	0,06	-0,29	-0,07	0,41	-0,09	-0,01	-0,31	-0,14	-0,12	0,20	-0,04	-0,04	0,02	-0,08	-0,03	0,02	0,33	-0,19	-0,31	-0,05	0,06	0,01	0,21	-0,24	-0,25	-0,30	0,03	-0,27	0,01

APPENDIX C

e-NAL	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7			Patient 8			Patient 9			Patient 10		
Fraction	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat
1	-0,03	0,07	-0,32	-0,18	0,47	0,01	0,02	-0,88	0,19	0,06	-0,20	0,02	0,55	-0,22	-0,48	-0,10	-0,02	0,24	-0,07	0,45	0,05	0,00	0,37	0,00	-0,60	-1,30	-0,71	0,10	0,00	0,09
2	0,08	0,01	-0,13	-0,04	0,35	-0,19	0,11	0,16	-0,36	-0,14	0,48	-0,20	-0,15	0,20	-0,12	0,08	-0,01	0,37	-0,05	-0,93	-0,29	-0,01	-0,08	0,22	-0,63	-1,53	-0,41	0,03	-0,35	-0,11
3	-0,03	0,05	-0,35	-0,02	0,22	-0,05	0,12	-0,37	0,04	-0,18	0,34	0,02	-0,16	0,03	0,11	0,22	0,08	0,01	-0,50	-0,44	0,19	0,10	-0,18	0,00	0,00	0,48	-0,08	-0,02	-0,39	-0,01
4	0,15	0,13	-0,36	0,07	0,59	-0,17	0,11	-0,09	-0,23	-0,09	-0,05	0,05	-0,16	0,04	-0,01	-0,21	0,02	0,64	0,02	-0,44	0,16	0,21	-0,17	0,54	-0,02	0,53	-0,16	0,02	-0,26	0,04
5	0,19	0,03	-0,29	-0,18	0,42	-0,07	-0,39	-0,37	-0,32	-0,23	0,43	-0,08	-0,29	0,07	0,11	-0,16	0,02	0,38	-0,36	-0,17	-0,35	0,01	0,11	0,29	0,03	0,57	-0,12	0,03	-0,35	0,02
6	0,15	-0,25	0,16	-0,09	0,07	0,28	-0,24	0,20	0,04	0,05	0,17	-0,04	-0,26	0,15	0,06	-0,01	0,02	-0,09	0,32	0,15	-0,19	-0,22	-0,04	-0,38	0,29	0,74	0,31	0,07	0,12	0,10
7	0,24	-0,20	0,04	-0,11	0,12	-0,09	0,37	0,21	-0,47	-0,03	0,05	-0,03	-0,27	-0,01	-0,11	0,06	0,12	-0,17	-0,12	-0,10	-0,19	-0,36	-0,34	-0,40	0,33	0,81	0,25	-0,01	0,01	0,04
8	0,08	-0,05	-0,34	-0,11	-0,19	0,04	0,25	0,35	0,05	-0,03	0,08	0,07	-0,52	-0,04	-0,23	0,18	0,02	-0,13	-0,04	0,13	0,17	-0,39	-0,06	-0,58	0,12	1,17	0,31	0,00	-0,20	0,00
9	0,02	-0,29	-0,12	0,16	-0,24	-0,08	-0,11	0,34	0,22	0,11	0,01	-0,02	-0,34	0,41	-0,32	0,05	-0,18	-0,34	-0,03	0,16	-0,07	-0,29	0,07	-0,55	0,19	0,97	0,10	0,08	-0,10	-0,54
10	-0,25	-0,05	-0,10	-0,15	0,05	0,17	0,04	-0,68	-0,11	-0,06	0,27	-0,08	0,55	-0,20	-0,25	0,23	0,09	-0,01	-0,30	-0,21	-0,20	-0,23	0,08	-0,40	0,08	0,18	-0,11	-0,01	-0,07	0,09
11	0,02	-0,04	0,09	-0,03	-0,08	0,06	0,13	0,36	-0,28	0,14	-0,37	0,06	-0,08	-0,09	0,10	0,20	0,00	-0,23	-0,18	-0,17	-0,05	0,00	0,35	-0,08	0,24	0,42	-0,06	-0,05	-0,13	0,07
12	-0,07	0,04	0,04	-0,14	0,05	0,01	0,14	-0,17	0,12	-0,06	0,31	-0,16	0,22	-0,46	0,18	-0,18	-0,06	0,35	0,15	-0,13	0,36	-0,01	-0,10	0,14	0,22	0,78	0,13	0,11	-0,19	0,17
13	-0,33	-0,15	0,04	-0,17	0,17	-0,10	0,03	0,11	-0,15	-0,10	0,17	0,06	0,37	-0,44	-0,13	-0,14	0,02	0,08	0,13	0,05	-0,25	0,10	-0,20	-0,08	0,52	0,42	0,82	-0,05	-0,15	0,12
14	-0,30	-0,13	0,04	-0,17	0,69	0,18	-0,37	-0,17	-0,24	0,17	-0,22	0,09	0,50	-0,02	-0,23	0,13	-0,04	-0,02	-0,28	-0,34	-0,11	0,21	-0,19	0,46	0,21	0,58	0,34	-0,04	-0,14	0,24
15	0,03	0,08	0,06	-0,18	1,42	0,04	-0,18	0,09	0,00	-0,19	0,32	-0,06	-0,26	-0,08	-0,15	0,38	0,01	-0,21	-0,12	-0,04	-0,04	-0,02	0,12	0,15	0,10	0,42	0,28	-0,01	-0,26	0,10
16	0,00	-0,06	-0,14	-0,36	1,36	-0,31	0,43	0,10	-0,51	-0,03	0,26	-0,06	0,19	-0,09	0,12	0,27	-0,01	-0,09	-0,24	0,05	0,23	-0,19	-0,02	-0,31	0,11	-0,36	-0,17	-0,01	-0,20	0,07
17	-0,12	-0,16	0,15	-0,07	0,54	0,15	0,31	0,24	0,01	-0,11	0,14	-0,05	-0,28	0,00	-0,13	0,08	0,00	0,16	0,01	0,32	0,18	-0,33	-0,32	-0,33	0,16	0,03	0,08	-0,05	-0,22	0,06
18	0,05	0,17	0,05	0,14	-0,32	0,26	-0,05	0,23	0,18	-0,11	0,17	0,05	-0,40	0,24	-0,15	0,07	-0,13	-0,21	-0,16	0,15	0,02	-0,36	-0,04	-0,51	0,13	0,22	0,11	0,03	-0,26	0,10
19	-0,09	0,04	-0,06	-0,02	0,63	0,14	0,19	-0,17	0,14	0,03	0,10	-0,04	-0,30	0,39	0,09	-0,06	-0,02	0,12	0,01	0,35	0,08	-0,26	0,09	-0,48	0,20	0,08	0,20	-0,07	-0,25	0,03
20	0,04	0,03	-0,07	-0,18	1,39	0,02	0,05	0,10	-0,16	-0,11	0,33	-0,10	-0,10	-0,14	-0,07	0,12	0,07	-0,33	-0,13	-0,15	-0,11	-0,23	0,10	-0,38	0,18	0,09	0,04	-0,03	-0,29	0,06
21	-0,03	-0,13	-0,11	-0,36	1,32	-0,33	-0,35	-0,18	-0,25	-0,04	0,26	-0,06	-0,31	-0,27	-0,02	-0,10	0,04	-0,11	-0,26	-0,03	0,21	-0,16	-0,03	-0,23	0,14	0,23	0,21	-0,09	-0,23	0,02
22	0,27	-0,05	0,21	-0,07	0,51	0,13	-0,21	0,08	-0,03	-0,12	0,14	-0,05	-0,10	-0,01	-0,07	0,12	0,08	-0,06	-0,01	0,24	0,16	-0,30	-0,33	-0,25	0,09	0,21	0,07	0,21	-0,26	-0,03
23	-0,03	-0,17	0,08	-0,18	1,23	0,02	0,40	0,09	-0,54	-0,12	0,17	0,05	-0,19	-0,19	-0,18	0,23	-0,05	-0,05	-0,18	0,07	0,00	-0,33	-0,05	-0,43	0,16	0,07	0,16	-0,13	-0,11	0,06
24	0,19	-0,18	0,28	-0,36	1,21	-0,33	0,28	0,23	-0,02	0,02	0,10	-0,04	-0,16	0,18	0,02	0,10	-0,40	-0,11	-0,01	0,27	0,06	-0,23	0,08	-0,40	0,18	0,09	0,04	-0,03	-0,29	0,06
25	-0,09	-0,18	-0,16	-0,04	0,42	0,16	-0,12	0,18	0,15	-0,11	0,33	-0,10	0,08	-0,27	-0,12	0,12	-0,05	-0,16	-0,15	-0,20	-0,12	-0,20	0,09	-0,33	0,11	0,23	0,19	-0,08	-0,22	0,04

Individual mean set-up error $m_{individual}$																														
	0,00	-0,06	-0,05	-0,11	0,50	0,00	0,04	0,00	-0,10	-0,05	0,15	-0,03	-0,07	-0,03	-0,08	0,07	-0,01	0,00	-0,10	-0,04	0,00	-0,14	-0,03	-0,17	0,10	0,24	0,08	0,00	-0,19	0,04

Population mean set-up error M_{pop}																														
	-0,03	0,05	-0,03																											

Population systematic error Σ_{setup}																														
	0,08	0,20	0,07																											

Individual random error $\sigma_{individual}$																														
	0,15	0,12	0,18	0,13	0,55	0,17	0,24	0,31	0,23	0,10	0,20	0,07	0,30	0,22	0,16	0,15	0,10	0,24	0,17	0,30	0,18	0,18	0,18	0,32	0,24	0,60	0,28	0,07	0,12	0,14

Population random error σ_{set-up}																														
	0,18	0,27	0,20																											

Margin $2,5\Sigma+0,7\sigma$																														
	0,33	0,68	0,32																											

Mean shift of N4																														
	0,07	0,06	-0,29	-0,07	0,41	-0,09	-0,01	-0,31	-0,14	-0,12	0,20	-0,04	-0,04	0,02	-0,08	-0,03	0,02	0,33	-0,19	-0,31	-0,05	0,06	0,01	0,21	-0,24	-0,25	-0,30	0,03	-0,27	0,01

Mean shift of N5																														
	0,06	0,00	-0,26	-0,03	0,30	-0,09	-0,02	-0,20	-0,08	-0,08	0,17	-0,04	-0,09	0,09	-0,12	-0,02	-0,01	0,22	-0,16	-0,23	-0,05	0,00	0,02	0,08	-0,17	-0,05	-0,23	0,04	-0,24	-0,08

Mean shift of N6																														
	0,01	-0,02	-0,22	-0,05	0,36	-0,05	-0,07	-0,20	-0,10	-0,04	0,11	-0,02	-0,01	0,07	-0,13	0,00	-0,02	0,18	-0,18	-0,25	-0,06	0,03	-0,01	0,14	-0,12	0,04	-0,15	0,03	-0,23	-0,04

Mean shift of N7																														
	0,00	-0,01	-0,20	-0,05	0,39	-0,03	-0,04	-0,19	-0,07	-0,03	0,11	-0,02	-0,04	0,11	-0,11	-0,01	-0,02	0,18	-0,16	-0,17	-0,04	0,00	0,00	0,06	-0,08	0,05	-0,11	0,02	-0,23	-0,03

Mean shift of N8																														
	0,02	-0,03	-0,15	-0,08	0,48	-0,06	0,00	-0,15	-0,07	-0,03	0,11	-0,02	-0,06	0,12	-0,09	0,01	-0,06	0,14	-0,14	-0,12	-0,03	-0,03	0,01	0,01	-0,05	0,05	-0,09	0,01	-0,24	-0,02

APPENDIX D

Online	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7			Patient 8			Patient 9			Patient 10		
Fraction	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat	Vrt	Lng	Lat
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,06	-0,20	0,02	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,10	0,00	0,09
2	0,08	0,01	-0,13	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,15	0,20	-0,12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,16	0,03	0,11	0,00	0,00	0,00	0,00	0,00	0,10	-0,18	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
4	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,09	-0,05	0,05	-0,16	0,04	-0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
6	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,16	-0,03	-0,17	0,00	0,00	0,00	0,10	-0,15	0,11	
7	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,03	0,14	0,16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
8	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,15	0,04	0,20	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
9	0,00	0,00	0,00	0,09	0,17	-0,17	-0,12	0,03	0,08	0,00	0,00	0,00	0,00	0,00	0,00	0,02	-0,16	-0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
10	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,09	0,13	-0,12	0,00	0,00	0,00	0,00
11	0,08	-0,04	-0,17	0,00	0,00	0,00	0,00	0,00	0,00	0,06	-0,20	0,02	-0,17	0,00	-0,02	0,18	-0,01	-0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
13	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,10	-0,18	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
14	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,09	-0,05	0,05	0,00	0,00	0,00	0,00	0,11	-0,05	0,20	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
15	0,04	0,06	-0,16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,18	-0,02	-0,01	0,00	0,00	0,00	0,00	0,00	-0,16	-0,03	-0,17	0,00	0,00	0,00	0,00	0,00	0,00	0,00
17	-0,11	-0,18	-0,07	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,17	0,07	0,12	0,00	0,00	0,04	0,07	-0,07	0,00	0,00	0,00	0,00
18	0,06	0,15	-0,17	0,00	0,00	0,00	-0,12	0,03	0,08	0,00	0,00	0,00	0,00	0,00	0,00	0,07	-0,15	-0,03	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
19	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,17	0,10	0,02	0,00	0,00	0,08	0,12	0,05	0,00	0,00	0,00	0,00
20	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,14	-0,03	-0,18	0,11	0,05	-0,15	0,00	0,00	0,00	0,00	0,00	0,10	0,14	-0,07	0,00	0,00	0,00	0,00
21	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,11	0,02	0,07	0,00	0,00	-0,16	-0,03	-0,17	0,00	0,00	0,00	0,00	0,00	0,00	0,00
22	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,14	0,10	-0,18	0,11	0,06	0,12	-0,17	0,07	0,12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
23	-0,03	-0,18	-0,12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,08	0,12	0,05	0,00	0,00	0,00	0,00
24	0,19	-0,19	0,08	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	-0,17	0,10	0,02	0,00	0,00	0,10	0,14	-0,07	0,00	0,00	0,00	0,00
25	0,00	0,00	0,00	0,00	0,00	0,00	-0,12	0,03	0,08	0,00	0,00	0,00	0,00	0,00	0,00	0,13	-0,11	-0,02	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Individual mean set-up error $m_{individual}$	0,01	-0,01	-0,03	0,00	0,01	-0,01	-0,01	0,00	0,01	0,00	-0,02	0,01	-0,03	0,01	-0,02	0,03	-0,01	0,02	-0,03	0,01	0,01	-0,01	-0,02	0,01	0,03	-0,01	0,01	-0,01	0,01	
Population mean set-up $error M_{pop}$	0,00	0,00	0,00																											
Population systematic error Σ_{set-up}	0,02	0,02	0,02																											
Individual random error $\sigma_{individual}$	0,05	0,07	0,07	0,02	0,03	0,03	0,04	0,01	0,03	0,03	0,06	0,01	0,08	0,05	0,06	0,06	0,06	0,08	0,06	0,03	0,03	0,06	0,05	0,06	0,04	0,05	0,04	0,03	0,03	0,03
Population random error σ_{set-up}	0,05	0,04	0,04																											
Margin $2,5\Sigma+0,7\sigma$	0,08	0,07	0,07																											