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
"Stereotactic body radiotherapy for treatment of liver metastasis"

UDC 615.849:616.36-006.6

Student

Group	Full name	Signature	Date
0AM8M	Laime Mamani Zuleida Angelica		

Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Date
Chief Medical Physicist of Tomsk Regional Oncology Center	Sukhikh Evgeniya Sergeevna	Candidate of physical and mathematical sciences		

ADVISERS:

Scientific adviser

Position	Full name	Academic degree, academic rank	Signature	Date
Medical Physicist of Tomsk Regional Oncology Center	Tatarchenko Mariya A.	Medical Physicist		

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	Menshikova Ekaterina Valentinovna	Ph. D.		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	Verigin Dan Alexandrovich	Ph.D.		

ADMITTED TO DEFENSE:

Director of programme	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Cherepennikov Yury Mikhailovich	Ph.D.		

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

_____ ___ Cherepennikov Yury Mikhaylovich
(Signature) (Date) (Full name)

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Master's thesis

For a student:

Group	**Full name**
0AM8M	Laime Mamani Zuleida Angelica

Topic of research work:

"Stereotactic body radiotherapy for treatment of liver metastasis"	
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 VMAT plans of radiation therapy. The role of the patient preparation, the treatment planning, the quality control plans, and the delivery of treatment to five patients with liver metastasis in the Tomsk Regional Oncology Center. Application area: oncology, radiotherapy.
List of the issues to be investigated, designed and developed:	A review of literary sources on the subject under study; creation and verification of dosimetric plans; analysis of the results; section "Financial management, resource efficiency and resource saving" (Calculation of the cost of research and development); section "Social Responsibility", and review of "Foreign language".

Advisors to the sections of the master's Graduation Thesis	
Section	**Advisor**
Financial management, Resource efficiency resource saving	Menshikova Ekaterina Valentinovna
Social Responsibility	Verigin Dan Alexandrovich
Foreign language	Smirnova, Uliana Aleksandrovna

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
Chief Medical Physicist of Tomsk Regional Oncology Center	Sukhikh Evgeniya Sergeevna	Candidate of physical and mathematical sciences		
Medical Physicist of Tomsk Regional Oncology Center	Tatarchenko Mariya A.	Medical Physicist		

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM8M	Laime Mamani Zuleida Angelica		

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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«Национальный исследовательский Томский политехнический университет» (ТПУ)

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: 2018/2019 and 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 the section (module) / type of work (research)	Maximum score of the section (module)
14.02.2020	Literature analysis and study	15
10.03.2020	Exploring hardware and software	15
15.03.2020	Creating, verifying treatment plans for SBRT	20
06.04.2020	Analysis and processing of the data obtained	20
15.05.2020	Issuing an explanatory note	15
31.05.2020	Preparing to defend the dissertation Work	15

COMPILED BY:
Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Date
Chief Medical Physicist of Tomsk Regional Oncology Center	Sukhikh Evgeniya Sergeevna	Ph. D. in Physical and Mathematical Sciences		

Advisor

Position	Full name	Academic degree, academic rank	Signature	Date
Medical Physicist of Tomsk Regional Oncology Center	Tatarchenko Mariya A.	Medical Physicist		

AGREED BY:
Director of the programme

Position	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Cherepennikov Yury Mikhailovich	Candidate of technical sciences		

TASK FOR SECTION
"FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING"

For a student:

Group	Full name
0AM8M	Laime Mamani Zuleida Angelica

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

Input data to the section «Financial management, resource efficiency and resource saving»:	
1. The cost of scientific research resources (RR): material, technical, energy, financial, information and human	Work with information presented in Russian and foreign scientific publications, analytical materials, statistical bulletins and editions, regulatory documents
2. Norms and standards for spending resources	
3. The used system of taxation, tax rates, deductions, discounts and loans	
The list of subjects to study, design and develop:	
1. Assessment of the commercial potential, prospects and alternatives for conducting research from the standpoint of resource efficiency and resource conservation	Competitive Technical Scorecard
2. Planning and budgeting for research	Hierarchical structure of work Calendar schedule of the project
3. Assessment of the resource, financial, budgetary, social and economic effectiveness of the study	Project Resource Efficiency Definition
A list of graphic material (with list of mandatory blueprints):	
1. Evaluation map of competitive technical solutions 2. Hierarchical structure of work 3. Organizational structure of the project 4. Schedule of the project 5. Budget of the project 6. Matrix of responsibility 7. Determination of resource efficiency of the project	

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

The task issued by adviser:

Position	Full name	Academic degree	Signature	Date
Associate Professor	Menshikova Ekaterina Valentinovna	PhD		

The task was accepted by the student:

Group	Full name	Signature	Date
0AM8M	Laime Mamani Zuleida Angelica		

TASK FOR SECTION
«SOCIAL RESPONSIBILITY»

For a student:

Group	Full name
0AM8M	Laime Mamani Zuleida Angelica

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

Topic of research work:

"Stereotactic body radiotherapy for treatment of liver metastasis"	
Initial data for section «Social Responsibility»:	
1. Information about object of investigation	The VMAT plans of radiation therapy. The role of the patient preparation, the treatment planning, the quality control plans, and the delivery of treatment to five patients with liver metastasis in the Tomsk Regional Oncology Center. Application area: oncology, radiotherapy.
List of items to be investigated and to be developed:	
1. Legal and organizational issues to provide safety: - Special 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;

Assignment date for section according to schedule	

The task was issued by consultant:

Position	Full name	Scientific degree	Signature	Date
Associate Professor	Verigin D.A.	Ph.D.		

The task was accepted by the student:

Group	Full name	Signature	Date
0AM8M	Laime Mamani Zuleida Angelica		

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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REVIEW
of the supervisor about master's thesis work

Student	Laime Mamani Zuleida Angelica

Field of training/programme	14.04.02 Nuclear Physics and Technology / Nuclear Medicine

Division	Division for Nuclear-Fuel Cycle	**School**	School of Nuclear Science & Engineering

Topic of research work
"Stereotactic body radiotherapy for treatment of liver metastasis"

The work presented for review contains an explanatory part of 114 sheets, and 9 sheets of appendices; in total, the work contains 123 sheets.

Characteristic of work in general.

The opinion of the supervisor about the work as a whole is indicated: the subject of work, the goals and objectives of the work, the degree of disclosure of the topic, relevance, practical significance, etc., an assessment of the achievement of each of the planned learning outcomes of the educational program is given. It should be noted the quality of the Master's Graduation Thesis registration and the degree of compliance with the Regulation on the Master's Graduation Thesis. It is necessary to indicate the scientific novelty for the master's work.
At the present time, research in the area of radiation therapy is given special attention. The problem of case definition and treating malignant disease is a priority both in Russia and abroad. Also the delivery of care of palliative care and comfortable maintenance of the standard of living of patients is a priority. The purpose of research work is studying methods of treating liver metastases for using stereotactic body radiation therapy (SBRT). The total number of patients with liver metastases is approximately one third of the total number of patients with malignant tumors, therefore this topic is important. The gold standard for the treatment of liver metastases is liver resection, this procedure is possible only in 30-40% of patients. For those patients who remain incurable, it remains possible to conduct sessions of SBRT. This method of radiation therapy has been introduced into routine practice at the Tomsk Regional Oncology Center since September 2018, this method has been successfully used and gives good data on local monitoring.

Characteristics of student work.

The author analyzes the literature about the treatment of liver metastases using SBRT, studies optimal fractionation, and acceptable doses for risk organs. The student participated in the dosimetric planning at the Monaco Planning Station.

Negative aspects of work.

The following remarks apply to the work: 1. verification and treatment data are not processed accurately enough; 2. the task of studying motion management of internal organs has not been fully completed; 3. incorrect design of theoretical formulas in the literature review and the practical part; 4. some spelling errors and stylistic errors; 5. in some cases, the author uses the generally accepted terms somewhat incorrectly; 6. the student has no publications of this theme.

Positive aspects of work.

This study is an important vector of development in the regional oncology center. The introduction of this methodology was a laborious and complex process, but was successfully completed in accordance with international recommendations.

Completed work can be recognized as completed qualification work that meets all the requirements, and its author:

Laime Mamani Zuleida Angelica

Deserves a mark:

And awarding the degree/master in:

Division	Division for Nuclear-Fuel Cycle

Supervisor:

Chief Medical Physicist of Tomsk Regional Oncology Center — Sukhikh Evgeniya Sergeevna

«____» _____ 2020 г.

Advisor:

Medical Physicist of Tomsk Regional Oncology Center — Tatarchenko Mariya A.

«____» _____ 2020 г

REVIEW
of master's thesis

Student	Laime Mamani Zuleida Angelica

Education program	14.04.02 Nuclear Physics and Technology / Nuclear Medicine

Division	Nuclear fuel cycle facilities	School	Nuclear Engineering School

Topic of research work
“Stereotactic body radiotherapy for treatment of liver metastasis”

The work presented for review contains an explanatory part of 114 sheets, and 9 sheets of appendices; in total, the work contains 123 sheets.
The work was performed in accordance with the assignment and in full.

The reviewed work contains 6 sections.

First section:
In the first section developed the "theoretical part"; described the literature review about stereotactic body radiation therapy (SBRT); considered specific information related to the topic (dose, calculation of biologically effective dose, normal tissue tolerance, liver and movement management in radiotherapy); and presented the general description of the equipment (immobilization devices, active breathing coordinator, Elekta Synergy linear accelerator, Monaco Planning System and ArcCHECK).

Second section:
In the second section, developed the "practical part"; determined the patient selection criteria; described the planning, verification, and administration of therapy; and developed the therapy results.

Third section:
In the third section developed the "financial management, efficiency and conservation of resources"; presented pre-project analysis, Ishikawa graph, SWOT analysis, project control events, project plan, Budget for scientific and technical research, calculation of materials costs, calculation of the depreciation cost of equipment for experimental works, cost of the workforce of the executors of technical scientific research, a benchmark in financial management, efficiency and resource saving.

Fourth section:
In the fourth section developed the "social responsibility"; described legal and organizational elements to provide safety, basic ergonomic requirements for the correct location and arrangement of the investigator's workplace, occupational safety, ecological safety, and emergency safety.

Fifth section:
The fifth section included the conclusion and future work, pointed out the main aspects of the work; emphasized the importance of the subject and the results; determined a reason to continue researching on the topic and take a next action through suggestions.

Sixth section:

The sixth section developed the 4 appendices, which complement important aspects of the practical part of the work (isodose curves shown on CT images (liver), data of DVH for all 5 patients, ArcCHECK QA of Dose Distribution, and CT / RMI of the abdominal cavities with contrasting dynamics).

Topic of research work
“Stereotactic body radiotherapy for treatment of liver metastasis”

Assessment of the work of the reviewer as a whole:

Disadvantages and comments of work:

Completed work can be recognized as completed qualification work that meets all the requirements, and its author:

Laime Mamani Zuleida Angelica

Deserves a mark:

And awarding the degree/master in:

Division	Division for Nuclear-Fuel Cycle

Position, place of work of the reviewer **Full name of reviewer**

«____» _____ 2020 г.

ABSTRACT

Master's Graduation work 123 sheets, 32 fig., 26 tab., 91 total sources.

Keywords: Stereotactic body radiation therapy, liver metastases, Elekta Synergy, VMAT, DVH, ArcCHECK.

The aim of this work is to study the planning methodology of VMAT. the role of pre-treatment topometry, treatment planning, quality control plans, and delivery of treatment to five patients with liver metastasis in the Tomsk Regional Oncology Center.

The basic constructive, technological, technical, and operational characteristics: Volumetric-modulated arc therapy (VMAT) is a highly sophisticated linear accelerator-based treatment method and allows dose rate-changing intensity modulation with gantry rotation. In this work, it is described our clinical experience with stereotactic body radiation therapy (SBRT) using a VMAT technique for five patients with liver metastases.

Elekta Synergy is a high-energy linear accelerator with an intensity modulation function. The accelerator is designed to supply therapeutic X-ray beams and has a wide energy range for photon beams (6 MeV, 10 MeV). The system also includes: Multi-leaf collimator (MLC), iViewGT portal imaging system, XVI imaging system.

To conduct topometric preparation for all patients, a Toshiba Aquilion spiral scanner (Toshiba, Japan) with a cut thickness of 0.5 mm was used, a reconstruction index of 2.0 mm; DICOM data was sent to the contouring station MonacoSim; contouring of critical organs and tissues, targets was carried out, planned volumes of exposure were determined; stage 3-D planning of the exposure program was carried out. Based on the obtained computed tomographic scans, a three-dimensional patient model was built, several treatment plans were calculated on the Monaco planning system. Based on the dose-volume histogram (DVH), the plans were evaluated, the most optimal treatment plan was selected taking into account the tolerant levels of radiation of critical organs and the tumor; and the verification of the exposure plans was carried out using the ArcCHECK dosimetric phantom (Sun

Nuclear Corporation, Melbourne, Florida, USA) with SNC Patient software (version 6.7.4). In addition, to verify the position before each treatment session, the image system of portal XVI was used for verification. The complex of means for immobilizing patients during topometric preparation and the treatment consisted with vacuum mattress and Active Breathing Coordinator (ABC), this system consists of 3 main parts: ABC cart, laptop interface, mouthpiece w / flow meter and valve.

An analysis of the results of therapy obtained during work for the five patients suggests a favorable outcome of treatment of liver metastasis with SBRT.

Application area: Radiotherapy, oncology

Cost effectiveness/significance: Liver metastases in Russia represents a significant clinical unmet need. Approximately, 9000 patients are diagnosed annually representing a significant human toll and cost burden for a health care system with limited resources. Despite this high prevalence, investigations of practice patterns and knowledge level among Russian radiation oncologists and medical physicists for treating this disease are lacking, since stent radiation therapy directed to the liver is not commonly used in Russia in the treatment of patients with liver metastases, because few centers are equipped for movement management. To achieve our objective, we carried out the measures related to the evaluation of patients with liver metastases and the application of the established protocol for the management of this disease, in order to improve the patient's quality of life.

DEFINITIONS, DESIGNATIONS, ABBREVIATIONS, REGULATORY REFERENCE

3D - Three dimensions / Three-dimensional

MRI - Magnetic Resonance Imaging

AAA - Anisotropic Analytical Algorithm

AAPM - American Association of Physicists in Medicine

ABC - Active Breathing Coordinator ™

Accelerator - Linear Electron Accelerator

DNA - Deoxyribonucleic Acid

ASTRO - American Society for Radiation Oncology

BED - Biological effective Dose

CBCT - Cone Beam Computed Tomography

CS - Convolution-Overlay

CTV - Clinical Target Volume

DIBH - Deep Inspiration Breath Hold

DICOM - Digital Imaging and Communication in Medicine

DRR - Digital Reconstructed Radiography

GTV - Gross Tumor Volume

HDR - High Dose Rate

IAEA - International Atomic Energy Agency

IC - Conformance Index

IC50 - Compliance Index for 50% of the prescribed absorbed dose

IGRT - Image Guided Radiation Therapy

IH - Homogeneity Index

IM - Internal Margin

IMRT - Intensity Modulated Radiotherapy

ITV - Internal Target Volume

kVCT - Kilovoltage Computed Tomography

LQM - Linear Quadratic Model

MC - Monte Carlo

MLC – Multileaf Collimator

MU – Monitor Units

MVCT - Megavoltage Computed Tomography

OAR - Planar variation off-axis. Off-axis factor

OR - Risk Organ

PDD - Percent Depth Dose

PET - Positron Emission Tomography

PET-CT Multimodal imaging equipment PET and CT

PTV - Planning Target Volume

MR - Magnetic Resonance

ROI - Region of interest

RTOG - Radiation Therapy Oncology Group

RX - X-Ray

SBRT - Stereotactic Body Radiation Therapy

Sc - Collimator Factor

Scp - Factor of total dispersion / Field factor

SEFM - Spanish Society of Medical Physics

SEOR - Spanish Society of Radiation Oncology

SM - Setup Margin

Sp - Dummy dispersion factor

SUV - Standard Uptake Value

CT - Computed tomography / CT simulator

TCP - Tumor Control Probability

TG- Task Group

TPR - Tissue Phantom Ratio

UM - Monitor Units

VMAT - Volumetric Intensity Modulated Radiotherapy

QA - Quality Guarantee.

DVH – Dose Volume Histogram.

LINKS TO THE FOLLOWING STANDARDS ARE USED IN THIS PAPER

1. GOST 7.1-2003 System of standards for information, library and publishing business. Bibliographic description. General requirements and rules compilation.
2. GOST 7.9-95 System of standards for information, library and publishing case. Abstract and abstract. General requirements.
3. GOST 7.32-2017 System of standards for information, library and publishing business. Research Report. Structure and rules execution.
4. GOST 7.80-2000 System of standards for information, library and publishing business. Bibliographic record. Heading. General requirements and compilation rules.
5. GOST 7.82-2001 System of standards for information, library and publishing business. Bibliographic description of electronic resources. Are common requirements and rules.
6. GOST 8.009-84 State system for ensuring the uniformity of measurements. Normalized metrological characteristics of measuring instruments.
7. GOST R 7.0.5-2008 System of standards for information, library and publishing business. Bibliographic reference. General requirements and rules compiling.
8. GOST R 7.0.12-2011 System of standards for information, library and publishing business. Bibliographic record. Abbreviations for words and phrases in Russian language. General requirements and rules.
9. GOST R 15.011-96 Development and production system for production. Patent research. Content and procedure.

TABLE OF CONTENTS

INTRODUCTION

National working groups in several different countries have reported their definitions of SBRT. The definitions of SBRT provided by the American Association of Physics in Medicine (AAPM) Task Group 101; the American Society for Therapeutic Radiology and Oncology and the American College of Radiology (ASTRO and ACR); the Canadian Association of Radiation Oncology—Stereotactic Body Radiotherapy (CARO-SBRT) and the National Radiotherapy Implementation Group of the UK [1-5] all agree on the following items: SBRT is (1) a method of external beam radiotherapy (EBRT) that (2) accurately delivers a (3) high dose of irradiation in (4) one or few treatment fractions to an (5) extracranial target.

These essential components of the SBRT definition are specified in more detail below:

1. SBRT can be adequately performed with either traditional linear accelerators equipped with suitable image-guidance technology, accelerators specifically adapted for SBRT or dedicated delivery systems. Additionally, the principles of SBRT apply for both photon and particle therapy;
2. it is of fundamental importance that the entire SBRT workflow be systematically optimized and that appropriate quality assurance (QA) measures are implemented. From a clinical perspective, the term “accurate” covers disease staging; multidisciplinary discussion of the indications for SBRT; tumor site adjusted imaging with appropriate spatial and temporal resolution for target and organ at risk (OAR) definition; highly conformal treatment; image-guided patient setup; active or passive intrafraction motion management and follow-up (preferably at the treating institution). From a physics perspective, SBRT requires additional and more sophisticated QA procedures compared to conventional radiotherapy.

   SBRT developed about a decade later than SRS but was based on similar principles. The first paper on clinical results of SBRT was published by a research

group from the Karolinska Institute, Stockholm [6] and since then the technique has evolved dramatically and it is now one of the important cornerstones in modern radiation oncology. The early publication from Stockholm reported a local control rate of treated tumors that was much higher than expected, but a large number of publications confirm the high probability of local control after hypofractionated radiotherapy with high biological equivalent doses.

1 Stereotactic body radiotherapy application for liver metastases

Metastatic lesions to the liver from other primary sites are not uncommon and can be a significant burden for patients, caregivers, and health care providers. Liver metastases can cause significant morbidity with pain and anorexia, adversely affecting health-related quality of life. In addition, more extensive liver disease can cause hepatic dysfunction and worsening performance status limiting systemic therapy and increasing mortality [7]. The most common metastatic lesion in the liver is from colorectal adenocarcinoma [8]. In 2017, the incidence of colorectal cancer (CRC) in the United States is estimated to be approximately 135,430 new cases, with half of these patients going on to develop liver metastasis in their lifetime [8,9]. Clinical series and autopsy studies have shown that as many as 40–50% of patients with metastatic CRC have disease confined to the liver [10], many oligometastatic [11], making these patients amenable for liver-directed therapies. Surgical hepatic metastatectomy has a long track record with 5-year survival rates of 50%–60% and up to 20% can achieve long-term disease-free survival in carefully selected patients [12,13,14]. However, only 10%–20% of liver metastases are amenable to resection, leaving systemic therapy as the traditional recourse for majority of patients. For unresectable tumors, despite advances in combination chemotherapy and targeted agents resulting in a doubling of median survival from approximately 10 to 20 months, it is not without significant toxicity [15]. Chemotherapy has also been used to downstage lesions, potentially allowing patients to become eligible for surgery [16]. Since most patients with liver metastases remain ineligible for surgery, alternative liver-directed therapies, such as stereotactic body radiotherapy (SBRT), radiofrequency ablation, microwave ablation, radiolabeled microspheres, transarterial chemo embolization, cryoablation, and alcohol injection, have shown some benefit [17].

Historically, radiation therapy has had a limited role in the treatment of hepatic metastasis because of the low tolerance of the liver to radiation. A major

concern is the risk of radiation-induced liver disease (RILD) [18]. However, the liver obeys the parallel architecture model of radiobiology and the risk of RILD is proportional to the mean dose of radiation delivered to normal liver tissue; therefore, it becomes safe to treat small hepatic lesions with high doses, limiting the mean dose to normal liver [19].

In the past decade, improvements in tumor imaging, radiation therapy planning, delivery, and motion management, have contributed to the development of stereotactic body radiation therapy (SBRT). Intensification of tightly focused radiation to small lesions, while significantly limiting dose to the surrounding tissues, in either a single or limited number of dose fractions have resulted in the delivery of a highly biological effective dose. SBRT requires a high level of accuracy, and recommendations and treatment quality control guidelines have been established.

In past years, several prospective and retrospective studies have reported effective local tumor control of hepatic metastases through stereotactic body radiotherapy (SBRT), with tolerable toxicity [22]. Improvements have been made in patient positioning and immobilization methods; image acquisition, integration, and transfer to radiotherapy systems; respiratory motion management; high-dose output and fast radiation delivery; and steep dose gradients from target lesions to surrounding normal tissues. Because of these advances, SBRT achieves highly precise and accurate radiotherapy with minimal serious toxicity [23,24].

Table 1 gives the results of the prospective and the largest retrospective cohort studies in SBRT for liver metastases. The survival of patients in nonrandomized SBRT-studies depends in part on how well they are selected. However, studies of large cohorts of patients with metastatic cancer treated with SBRT have reported favorable survival rates even in negatively selected patients who were not eligible for surgery or radiofrequency ablation (Table 1).

Table 1- RESULTS FROM PROSPECTIVE AND LARGE RETROSPECTIVE STUDIES OF SBRT FOR LIVER METASTASES

Author; year	Design	Pts with liver metastases	Frx x dose	m-FU mts	Local control 2 years (%)	Survival 1-2 years (%)	Severe morbidity
Schefter 2005	Phase I	18	3 x 12-20 Gy	NR	NR	NR	None
Katz 2007	Retrospect	69	5 x 10 Gy	14.5	57	68, 24	None
McCammon 2009	Retrospect	81/141[a]	3 x 12 Gy 3 x 16 Gy 3 x 20 Gy	8.2	89 59 8	NR	8grade >=3: pneumonitis, dermatitis, soft tissue Inflammation/fibrosis, vertebral fracture
Rusthoven 2009	Phase I/II	47	3 x 12-20 Gy	16	92	77,30	1 grade 3: soft-tissue necrosis
Lee 2009	Phase I	68	6 x 4.6-10 Gy	11	71 (1-yr)	79, 41 (3 yrs.)	7 grades >=3: thrombocytes[b], hepatic[b], gastritis, lethargy, nausea
Goodmam 2010	Phase I	19	1 x 18-30 Gy	17	75	62, 49	2 grades >=3: duodenal ulceration, bowel obstruction
Rule 2010	Phase I	27	3 x 10 Gy 5 x 10 Gy 5 x 12 Gy	20	56 89 100	90, 50 78, 67 75,56	1 grade 3: hepatic[b]
Van der Pool 2010	Retrospect	20	3 x 10-12.5 Gy	26	74	100, 74	3 grade 3: hepatic[b] and lethargy
Chang 2011	Retrospect	65	2-3 x 20 Gy	55	38 (2-yr)	77, 45	Acute: 2 grade 3 hepatic[b] Late: 4 grade 3 hepatic[a] and gastritis

Table 1 continuation

Comito 2014	Phase II	42	4 x 12 Gy – 3x 25 Gy	24	80	80, 65	None
De Vin 2014	Retrospect	77/309[a]	10 x 4-5 Gy	12	33	32 (3-yr)	NR
Fode 2015	Retrospect	225/321[a]	3 x 15-22.5	29	LR; 13	80, 58	Acute: 11 grades >= 3: hepatic[b], nausea pain, gastritis, skin, deterioration of performance status Late: 3 grades >= 3: gastritis and skin
Scorsetti 2015	Phase II	42	3 x 25 Gy	24	91	81, 65	No grade >= 3
Meyer 2016	Phase I	14	1 x 35-40 Gy	30	100	85, 78	No grade >= 3

mFU median follow-up; NR not reported; LR local recurrence in competitive risk analysis

[a]Mixed p atient material included other than liver metastasis patients

[b]Biochemical tests

For liver SBRT, integration of imaging (CT, MRI, PET-CT) is required in order to properly define the metastases, as is highly conformed dosimetry to further minimize radiation dose to healthy liver and surrounding tissues. Due to uncertainty of liver positioning during the breathing, the effectiveness and safety of SBRT depends on the accuracy to treat a moving organ. Various image-guided methods, the use of internal markers, breathing control and intra-fraction control of tumor position (Gating or Tracking) increase SBRT precision, allowing the delivery of cytotoxic high dose to the metastases, while maintaining whole-liver doses within acceptable limits [25, 26].

The feasibility and potential utility of SBRT in selected patients with liver metastases, has been evaluated with encouraging results. SBRT has resulted as a safe and effective treatment, with minimal toxicity and high rates of local control [27-

34]. Therefore, it can be considered a noninvasive treatment to deliver ablative treatments [35,36,37]. Most of the retrospective and prospective clinical experiences and studies of liver metastases (using high-dose SBRT) have generally selected patients with a limited number of lesions. However, there are also patients with more than 3 liver metastases or patients with liver oligo-progression that in the course of their disease could be treated safely and benefit from ablative local treatments with sequential SBRT, thus improving their metastatic sites, decreasing morbidity and prolonging survival [38].

In the last 3 years there are international studies with important results on the Body Stereotactic Radiation in liver metastases and interesting conclusions about it:
1) The study "Stereotactic body radiation therapy for liver metastasis - The linac-based Greater Poland Cancer Centre practice" published by Fundowicz M, Adamczyk M, Kołodziej-Dybaś A. in April 2017. It concludes that the literature validation of the assumptions concerning the steps of the GPCC linac-based liver SBRT procedure show their potential for an effective and patient friendly implementation.
2) In the study "Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage" published in August 2017, Hiroshi Doi, Norihisa Masai, Kenji Uemoto, Osamu Suzuki, Hiroya Shiomi, Daisaku Tatsumi, and Ryoong-Jin Oha refer that the actual mean doses appropriate for liver irradiation in modern radiotherapy techniques have not been adequately investigated, although SBRT is sometimes alternatively performed using fractionated regimens; and that is why more studies are required to define the optimal application of SBRT in cancer therapy and normal tissue tolerance.

Liver metastases in Russia represents a significant clinical unmet need. Approximately, 9000 patients are diagnosed annually representing a significant human toll and cost burden for a health care system with limited resources. Despite this high prevalence, investigations of practice patterns and knowledge level among Russian radiation oncologists and medical physicists for treating this disease are lacking, since stent radiation therapy directed to the liver is not

commonly used in Russia in the treatment of patients with liver metastases, because few centers are equipped for movement management.

This research work on stereotactic radiotherapy in liver metastases is carried out based on the current patterns of this disease in Russia; since this disease serves as a relevant case study among Russians due to its high prevalence in the population, which in itself is due to epidemiological risk factors, including a high rate of alcohol abuse and endemic hepatitis infection in this population. To achieve our objective, we carried out the measures related to the evaluation of patients with liver metastases and the application of the established protocol for the management of this disease, in order to improve the patient's quality of life.

2 General information

2.1 Dose

The data that are published show considerable heterogeneity in the dose-fractionation schedules delivered. Nonetheless, there is a clear dose-response relationship.

McCammon et al [39] report 3-year local control rates of 89.3% for lesions receiving 54-60 Gy in 3 fractions, compared to 59% (36-53.9 Gy/3 fractions), and 8.1% (less than 36 Gy). Similarly, Chang estimate that the dose required to achieve a 90% likelihood of local control at 1 year is 46-52 Gy in 3 fractions (or a BED (assuming an α/β of 10) of more than 75 Gy).

A 10-fraction regimen may be useful for the palliation of larger volume disease and has been shown to be effective and well tolerated, even in heavily pre-treated patients.

However, in comparing dose regimen, it is important to note that the use of biological effective dose (BED) calculations when using small number of large fractions may not be as reliable as when used for conventionally fractionated radiotherapy.

Suggested fractionations and dose distribution requirements:

1) 40-60 Gy in 3 fractions (Alternate days) e.g. 45Gy in 3 fractions. Prescribed to the prescription isodose covering at least 95% of the PTV (usually 80-95%). DMax within PTV<133%.

2) 50-60 Gy in 5 fractions (Alternate days or daily) This may be used when a larger PTV volume is being treated in order to achieve OAR constraints (<=6cm), when the PTV is within 1 cm of small bowel/visceral OAR/bile duct or adjacent to chest wall/ribs. ≥95% of the PTV will receive the prescription dose.

3) 30-60 Gy in 10 fractions Consider use when target volume does not meet true SABR eligibility criteria (e.g. single lesion >6cm, multiple lesions where unable to meet 5# planning constraints or extrahepatic disease).

10 equal fractions delivered over 2 weeks. The total dose prescribed will be individualized according to the effective liver volume treated as follows:

1) 40-60 Gy if less than 30% of effective volume of liver irradiated;

2) 35-50 Gy if between 30%-50% of effective volume of liver irradiated;

3) 30 Gy if between 50%-70% of effective volume of liver irradiated.

Table 2- LIVER DOSE CONSTRAINTS

Description	Constraint	3 fractions		5 fractions		Source	End point
		Optimal	Mandatory	Optimal	Mandatory		
Normal Liver (Liver minus GTV)	V10Gy	-	-	< 70%	-	3 fractions: AAPM / Wulf et al/ Rusthoven et al 5 fraction: ABC-07/ SPARC protocols	Grade 3+ liver function dysfunction/ radiation induced liver disease (classic or non-classic)
	Mean liver dose	-	-	< 13Gy	< 15.2Gy		
	D50%	< 15Gy	-	-	-		
	Dose to ≥700cc	< 15Gy	< 19.2 Gy	-	-		

2.2 Biologically Effective Dose calculation [40]

When using Biologically Effective Dose **(**BED) calculations to estimate the biological dose to tumors rather than normal tissues, the main differences are that:

a) the numerical range of α/β ratios is wider in tumors and data are lacking for many specific tumor types.

b) a repopulation correction factor should be included in the case of tumors that contain rapidly proliferating clonogens, for which there are several possible patterns of repopulation to consider.

These requirements are now considered in turn.

Tumor alpha/beta (α/β) Ratios

These vary from the accepted values of 10–30 Gy for squamous cell cancers to much lower values of 4–5 Gy in breast cancer [35]. Other slower growing cancers, such as of the prostate, appear to have very small α/β ratios (0.8–2.5 Gy), although there remains concern that there are no established generic values for many tumor types and there is no predictive assay for α/β for individual tumors. Melanoma is another instance where very low values have been reported by some authors. For these reasons, it is prudent to perform multiple BED calculations, as for normal tissues, in order to achieve some general conclusion about which fractionation policy is to be recommended. If the α/β ratios are not well documented for a particular histological tumor type, we would recommend the use of α/β = 5, 10 and 15 Gy in most situations. Table 3 shows the subtle difference between schedules that are equivalent to 60 Gy in 30 fractions for tumor control.

Table 3- CALCULATED SCHEDULES THAT ARE APPROXIMATELY ISOFFECTIVE TO 60 GY IN 30 FRACTIONS (SEE TEXT).

α/β =5 Gy	α/β =10 Gy	α/β =15 Gy
10 x 4.4 Gy	11 x 4.4 Gy	12 x 4.4 Gy
16 x 3.25 Gy	17 x 3.25 Gy	17 x 3.25 Gy

The results are calculated to the nearest whole fraction by rearrangement of equation to give:

$$n=\mathrm{BED}/d(1+d/(\alpha/\beta)) \qquad (1)$$

In this case, as an alternative to the approach used previously in calculations of normal tissue isoeffects, we calculate values of n for assumed values of d (3.25 and 4.4 Gy respectively in table 3) and choose the final value of n to the nearest whole number.

In general, for tumors that have high α/β values, the total dose is reasonably predictive of local control; whereas, if the α/β values are low, the total dose and the fraction size together determine the outcome.

2.3 Normal tissue tolerance

SBRT of liver tumors is generally tolerated well. However, the esophagus, the stomach, the duodenum, and the large bowel should be considered in the selection of patients and in the treatment planning process because of their limited tolerance to radiation and the risk of severe adverse effects when they are exposed to large radiation doses. The liver tolerates large doses to relatively large volumes as long as a sufficient volume of liver is spared. Gastritis, gastric- or intestinal ulceration, chronic skin reaction, rib fracture, and hepatic failure seldom occur as late effects after SBRT for liver metastases. There is growing use of SBRT for treatment of liver metastases. The results of prospective phase I/II trials and retrospective cohort studies are encouraging, but we are still missing high level evidence to prove its efficacy.

Table 4- DOSE VOLUME CONSTRAINTS FOR ORGANS AT RISK WITH BIOLOGIC EQUIVALENT DOSE (BED) FROM SELECTED STUDIES.

Organ at risk	Study	Dose-volume constraint (V Gy)	Biologic Equivalent Dose
Liver (alpha/beta 3)	Herfarth (2001) Wulf (2006) Mendez Romero (2006)	V12< 30% V7 < 30% D30 < 7 Gy/ 5 Gy V21 < 33% V15< 50%	V60 < 30% V29.3 < 50% 3 fx V12.4 < 30%/V7.8<50%
Duodenum (alpha/beta8)	Wulf (2006) Mendez Romero (2006) Tse (2008)	D100< 7 Gy D5 cc < 21 Gy V3 0 < 0.5 cc	1 fx 13.1 Gy max/3 fx 9 Gy max 3 fx V39 < 5cc/5 fx V32 < 5cc V48.8 <0.5 cc
Bowel (alpha/beta 8)	Herfarth Wulf Mendez Romero Tse	12 Gy max D100<7Gy D5cc <21Gy V30 < 0.5	30 Gy max 1 fx 13.1 Gy max/3 fx 9 Gy max 1 fx V39.4 <5cc/5 fx V32 < 5cc V 48.8 Gy<0.5 cc

Table 4 continuation

Stomach (alpha beta 5)	Herfarth Wulf Mendez Romero Tse (2008)	12 Gy max D100 < 7 Gy D5 cc <21 Gy V30 < 0.5 cc	40.8 Gy max 1 fx l6.8 Gy max/3 fx10.3 Gy max 3 fx V50. 5 < 5 cc/5 fx V38.6 <5 cc
Spinal cord (alpha/beta 3)	Shefter (2005) Hoyer (2006) Mendez Romero (2006) Tse (2008)	18 Gy max 18 Gy max 15 Gy max V27 <0.5 cc	54 Gy max 54 Gy max 3 fx 40 Gy max 5 fx 30 Gy max V 67.5 <0.5 cc

2.4 Liver

a) Hepatic toxicity

The main organ at risk for irradiation of hepatic tumors is the liver itself [41,42]. Radiation-induced liver disease (RILD) is the main radiotherapy toxicity [41,43-45]. Hepatic lesions have the character of veno-occlusive diseases (VOD). For classical RILD, symptoms occur 4 weeks after hepatic irradiation, with an increased weight, a fatigue, a non-icteric ascitis and a predominant increase of PALK. In general, the radiologic presentation on CT scan is a hypodensity which disappears a few months later [46,47]. In contrast, patients with a pre-existent hepatopathy, as cirrhosis or viral hepatitis, may present a transaminases increase and a jaundice within three months following hepatic irradiation corresponding to a non-classical post-radiation-hepatopathy.

Hepatic functions and tumor type

Classical data show that the whole healthy liver can receive 30 Gy per fractions of 2 Gy [48] and has the feature of a parallel structured organ from a radiobiological point of view [41,43]]. The comparison of studies should take into account the treatment duration and the doses per fraction according to the quadratic linear model [43, 49-51]. The alpha/beta ratio for healthy liver is quite low, from 1.5 [52] to 3 [68]. Murphy et al. [45] postulates that the risk of hepatic toxicity for hypofractionated irradiation is overestimated in clinical practice when biological

normalization is omitted. While analyzing 2O3 patients treated with conformational RT and intra-hepatic chemotherapy, Dawson et al. [54] showed in 2002 that the radiation-induced liver disease (RILD) threshold dose is 30 Gy, the 5% risk of RILD corresponding to a 32 Gy dose (2 Gy/fraction) for patients carrying metastasis and 28 Gy for primary hepatic tumors [55]. Andolino et al. [56] described a population of 60 patients treated from 2006 to 2009 for HCC associated with an A (36 patients) or B (24 patients) Child–Turcotte Pugh (CTP) score cirrhosis. Four patients out of the 8 patients with a CTP B score higher than 8, developed a hepatic failure during or immediately following the treatment. In this center, the indications of liver SBRT for this population are actually restricted to being a bridge for transplantation. For the other patients, it is proposed to limit the SBRT indications to patients with an A or B CTP score lower than or equal to 7 with a maximum tumor diameter lower than 6 cm and one to three lesions to be treated.

Taking these data into account, Pan et al. [43] proposed constraints for prescription on the liver minus GTV volume for non-uniform irradiation on healthy and pathological liver. For 3 fractions treatment: less than 15 Gy for metastasis, less than 13 Gy for HCC and less than 6 Gy for HCC with a CPT equal to or lower than B. In terms of critical volume, 700 ml of healthy liver should receive less than 15 Gy.

b) Biliary tract toxicity

Few papers are dedicated to biliary complications of SBRT. Eriguchi et al. [57] studied 50 patients irradiated on the central biliary tract in 5 fractions for hepatic tumors at a total dose of 50 Gy for metastasis, 40 Gy for Child A HCC and 35 Gy for Child B HCC. The delineation of biliary tract was standardized and the dose volume histograms (DVH) of the biliary ducts were normalized for the length of the biliary duct irradiated. In this study, 2 grade I biliary stenosis occurred, one patient having received more than 20 Gy on 7 mm of the biliary duct presented a asymptomatic stenosis while the other one was treated twice and received more than 80 Gy on 13 mm of the left hepatic duct. The 7 patients who received more than 20 Gy on the gallbladder did not present any toxicity. In another article, Osmundson et al. [51] presented a population of 96 patients irradiated for primary or metastatic

hepatic lesions treated between 2006 and 2013. The central biliary system was defined by the authors as a 15 mm expansion of the portal veina from the splenic convergence to the portal bifurcation. Fifty-one patients presented biliary or hepatic tumors and 45 metastases. The median fraction number was 5 and 51% of patients received three fractions. Sixty-seven percent of patients had a Child A score, 28.1% a B score. Hepatobiliary grade 2 toxicities were observed for 23 patients (24%) and grade 3 toxicities for 18 patients (18.8%). The most frequent grade 3 toxicities were stenosis or biliary obstruction, the frequency being 20-fold higher for patients with cholangiocarcinoma (CCA). Two deaths related to biliary obstruction were observed, one of them for a patient with cholangiocarcinoma. The predictive factors in a univariate analysis were the cholangiocarcinoma and HCC histology, the presence of a stent during treatment and dosimetric factors. In a multivariate analysis, V_{BED10} 72 > 21 cc, V_{BED66} > 24 cc and a mean equivalent dose > 14 Gy on the central biliary hepatic tract were correlated with a toxicity risk > 3, as well as CCA histology and the presence of the stent. The authors propose 3 fractions treatment with the following constraints on the central biliary tract: V_{BED10} 72 < 21 cc and a V_{BED66} < 24 cc. [51]

c) Stomach, duodenal and bowel toxicities

The toxicity on the digestive tube is the one most frequently observed with hepatic SBRT. In general, these side effects are limited to a limited and transient bleeding, but some severe hemorrhages have been observed as well as perforations. Some data on duodenal SBRT toxicities have been identified with pancreatic tumor SBRT studies. In terms of radiobiology, the signification of doses is different for stomach (alpha/beta 5) and for bowel (alpha/beta 8). For stomach, the proposed constraints in various studies range from 7 to 30 Gy maximum dose with a BED of 10.3–90 Gy [58,46,59,60,61]. Mendez Romero et al. constrained 5 cc of stomach to less than 21 Gy [47]. A few gastric acute toxicities have been reported. Kopek [62] describes an acute gastric toxicity with two grade 3 nausea for 44 patients. Herfarth et al. [46] also describes nausea and anorexia for 11 patients on the 37 accrued. Wulf

et al. [59] proposes a prophylactic IPP or anti-H2 treatment during treatment of hepatic metastasis closed to the stomach.

Hoyer et al. [63] in a population of 22 patients receiving 45 Gy in 3 fractions delivered in 5–10 days for non-operable pancreatic tumor whose size was higher than 6 cm, evaluated toxicity for the duodenum. Seventy-nine percent of the patients presented an acute toxicity, four patients (18%) developed a severe mucositis or a duodenal or gastric ulceration and one of them developed a perforation. In this study, the median volume receiving more than 30 Gy was 136 ml. In another work, the same team [69] analyzed a population of 64 patients with 141 hepatic metastasis from colorectal carcinoma. They received 3 fractions of 15 Gy delivered in 8 days. Two patients who received more than 30 Gy on the duodenum presented ulcerations with a favorable issue with medical treatment. One grade 3 toxicity among 15 diarrheas was reported in this study [64].

For pancreatic tumor stereotaxis, Murphy et al. [45] have proposed a dosimetric model of duodenal toxicity. The duodenal delineation was specified with precision for 73 patients irradiated with a single 25 Gy dose 14 days after the last Gemcitabine treatment administration. Twelve patients presented grade 2–4 duodenal toxicities with a median interval of 6.3 months. The predictive dosimetric parameters were a V15 < 9.1 cc, a V20 < 3.3 cc and a Dmax > 23 Gy. Applying the same prescription to 27 cholangiocarcinoma, Kopek et al. [62] observed 22% of gastric or duodenal ulcerations after a median delay of 6.7 months requiring hospitalization and blood transfusion, a duodenal stenosis for 4 patients (11%), two of them requiring dilatation. The probability of grade higher or equal to 2 ulceration was correlated to the maximal dose delivered to 1 cc of the duodenum. The constraint followed by this group is one cc of the duodenum to get no more than 21 Gy in 3 fractions (V21Gy < 1 cc).

Bae et al. [45] evaluated the abdominal or pelvic SBRT toxicities delivering 33–60 Gy in three fractions for 202 patients. The grade 3 toxicity on the digestive tract was highly correlated to the V and to the overall time treatment. The severe bowel toxicity decreases from 50% to 4% when the V_{25} value is respectively higher

or lower than 20 ml. In the same way, the grade 3 toxicity raised from 0 to 18% for an overall treatment time decreased from 8 to 4 days.

For small bowel, multiple proposals of limiting constraints have been defined in different studies: 12 Gy maximum, 30 Gy maximum, [60] D100 < 7 Gy [59], D5 < 21 Gy[66], V30 < 0.5 cc[67]. However, no major toxicity has been reported.

d) Chest wall

As observed using lung SBRT, chest wall pains and sometimes rib fracture are observed after liver SBRT. They are of course more frequent after treating tumors close to the chest wall, and for doses above 50 Gy. Andolino et al. [68] proposes a Dmax less than 50 Gy and that less than 5 cc of the chest wall receive 40 Gy if these objectives are compatible with adequate tumor coverage.

e) Less exposed organs at risk

Dose limitation proposals have also been formulated for less exposed organs at risk, and observing these constraints, no clinical toxicity have been documented.

Esophagus

A death due to bleeding on esophageal varices, probably linked to cirrhosis without any other esophageal toxicity, has been observed [66].

Some liver SBRT protocols define constraints for esophagus. Méndez Romero et al. limits to 5 cc the esophageal volume receiving more than 21 Gy in 3–5 fractions.

A maximal dose of 14 Gy is proposed by Herfarth et al., and for Tse et al. [61] the V30 must be less than 0.5 cc.

Heart

Wulf et al. [59] proposed to limit the dose delivered to the hearth to 7 Gy and Tse et al. [61] proposed a V_{40} < 0.5 cc. No cardiac toxicity has been described.

Kidney

Constraints proposed for the two kidneys are V_{15} lower than 35%, and for the right kidney lower than 33% [60,66].

Spinal cord

The dose has to be restricted to 18 Gy [69,60] or the V_{27} must be inferior to 0.5 cc.

f) Treatment assessments and clinical follow-up

Acute toxicity [70]

Radiation-induced liver disease (RILD) is defined as anicteric elevation of alkaline phosphatase (ALP) to greater than twice the upper limit of normal, with nonmalignant ascites (Classical RILD), or elevation of transaminases to more than 5 times the upper limit of normal or pre-treatment levels (Non-classical RILD). The rates of RILD are notably very low in all published series (<1% in modern series). Childs Pugh B and Hep B/C carriage is associated with a higher incidence of RILD.

Late toxicity

Caution should be noted regarding late effects since several studies of liver SABR have observed poor survival. Only one study has durable follow up – 4.3 years. Most others have followed up of around 16-18 months and, therefore, the extent of late radiation effects may be underestimated. However, the rates of high-grade toxicity (G3 or worse) are generally low (2-5%). Reported severe late toxicities are rare and include GI bleeding and rib fractures.

2.5 Motion management in radiation therapy

These techniques have been accepted as effective radiation therapies for tumors that are subject to respiratory motion, as techniques that allow precise targeting of the tumors with prescribed radiation dosages, while reducing the dosage of irradiation to unaffected tissue surrounding tumors. Using respiratory motion management (RMM) makes it possible to reduce the irradiated area and lower the incidence of adverse effects in principle. However, it is necessary to bear in mind that, without great care, this kind of treatment poses risks that may lead to unintended treatment results.

2.5.1 RMM requirements [72]

a) The treatment detailed here may only be applied when the length of respiratory tumor motion exceeds 10 mm without RMM being implemented. When the three-dimensional length of motion exceeds 10 mm, the evaluation must be that 'the length of respiratory-induced motion exceeds 10 mm'. For example, if the lengths of motion in the craniocaudal, right left, and dorsoventral directions are 9 mm, 4 mm, and 4 mm, respectively, the three-dimensional length is calculated as:

$$\sqrt{9^2 + 4^2 + 4^2} = 10.6\ mm \quad (2)$$

So fulfilling the requirements of these Guidelines. The length of the respiratory-induced tumor motion must be measured under free, unforced breathing, and irregularities in the respiration due to hiccups, coughs, sneezes, and deep respiration are to be excluded. Some institutions stipulate in the medical fee regulatory standards that treatment of 'tumors whose length of respiratory motion is 10 mm or longer' must be categorized as Tokkei-Shinryo (therapies covered by special schedules). However, the Guidelines detailed here assume that RMM is applicable to tumors where the length of respiratory motion exceeds 10 mm;

b) In the treatment plans, it must be ascertained and recorded that the expansion of area of irradiation required to compensate for respiratory motion can be reduced to≤5 mm in any direction, three dimensionally. In regulations for medical treatment fees and institutional standards, two different expressions are used: 'expansion of field of irradiation required due to respiratory motion', and 'expansion of area of irradiation required to compensate for respiratory motion'. However, the present guidelines use only the expression: 'expansion of area of irradiation required to compensate for respiratory motion'. 'Expansion of area of irradiation required to compensate for respiratory motion' applies to both the length of the respiration-induced tumor motion, as well as to the uncertainties related to RMM, and is equivalent to a part of the internal margin defined in ICRU (International Commission on Radiation Units and Measurements) Report 62 [71]. The three-

dimensional direction refers to six directions: the cranio, caudal, right, left, dorso, and ventral directions, and the expansion of the irradiated area necessary in each direction must be 5 mm or less. If the expansion of area of irradiation required in order to compensate for respiratory motion is 5 mm or less in any one direction, then, where the irradiated area does not contract when compared with areas where RMM is not performed, it cannot be regarded as effective RMM;

c) At every instance of irradiation treatment, it is necessary to ascertain and record that the tumor is included in the irradiated area determined in (b), immediately prior to and during the irradiation. 'Immediately prior to the irradiation' refers to the time from placing the patient on the treatment table in the room where the irradiation will take place until the start of the first beam of irradiation of the treatment. 'During the irradiation' refers to the time during which each treatment beam takes place. 'A tumor is included in the irradiated area' means that a tumor is included in the planning target volume (PTV), three-dimensionally. However, 2D confirmation is acceptable during the irradiation.

When it is difficult to directly verify that the tumor is included in the irradiated area, it is acceptable to confirm this based on a marker in the body that represents the tumor positions, such as a marker in the vicinity of the tumor. In such cases, it is assumed that the method of predicting tumor positions based on the particular marker has been verified. It is necessary to verify that a tumor is included in the irradiated area immediately prior to the irradiation. Furthermore, it is recommended to verify this state, the inclusion of the tumor in the irradiated area, during the irradiation. (According to the description in the document for medical treatment fees, this verification should be performed immediately prior to the irradiation OR during the irradiation; however, these Guidelines specify the performance of the verification immediately prior to the irradiation as indispensable).

2.5.2 Examples of measures that may be considered with RMM

The following six methods are described as examples of measures to include with RMMs in the 2008 Guidelines for Radiotherapy Planning [73]:

a) inhalation of oxygen;

b) abdominal compression: a method to secure a part of the abdomen by a band or shell, a method that uses an abdominal compression board, and others;

c) learning of regular respiratory patterns (the metronome method);

d) breath hold technique: active breathing control, self-respiratory cessation in deep inspiration;

e) self-respiratory breath-monitoring measured at two thoraco-abdominal points; gating with respiration;

f) real-time tumor-tracking: pursuing irradiation and intercepting irradiation.

If a technique satisfies the requirements listed in the definition of RMMs, it may be accepted for inclusion as an RMM. However, it is generally difficult to meet the requirements if (i) inhalation of oxygen, or (iii) learning of regular respiratory patterns, is used alone.

Measure (vi) is regarded as a ‘real-time tumor-tracking irradiation technique’, and techniques to pursue and intercept correspond to Real-time tumor-tracking irradiation techniques (i) and (ii), respectively.

3 Overview of equipment

3.1 Immobilization devices

Patient immobilization and control of organ motion are crucial for the success of SBRT in this setting. A variety of body frame systems are available, most relying on vacuum cushions, with or without abdominal compression [74,75].

Abdominal compression is a convenient mean of reducing tumor motion by applying a compressive plate or a breath belt during both planning CT and treatment. High levels of forces are required to compress the abdomen [76], and subxiphoid compression is advised for better breathing management, reducing craniocaudal liver motion to within 5 mm [77]. However, liver deformation and gross tumor volume positional deviation are important consequences of abdominal compression, necessitating rigid liver-to-liver registrations to minimize variations [78].

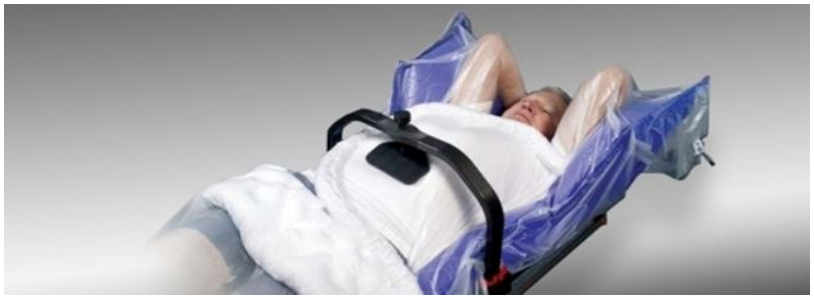

Figure 1 - Abdominal compression (BodyFIX)

Motion is a major cause of artifacts in modern imaging and errors in high-precision therapy. BodyFIX enables accurate, precise patient positioning and immobilization, providing the foundation for successful imaging and treatment in radiation therapy.

The patented BodyFIX dual vacuum technology maximizes repositioning accuracy and intra-treatment patient stability by reducing both involuntary and voluntary patient movement. Manufactured entirely from radiotranslucent materials,

BodyFIX provides artifact-free image clarity with minimal beam attenuation. The unique cover sheet nestles around the patient and produces a uniform pressure, securely immobilizing the patient's body parts.

The immobilization system requires only one radiation therapist for first and daily patient set-up. The BlueBAG BodyFIX Vacuum Cushions create a comfortable, stable and precise mold of the patient's position for up to six weeks. They can be used for different clinical set-ups and indications such as thorax, hip or total body.

Whenever precise localization and targeting are required, non-invasive stereotactic reference frames are available for extracranial stereotaxis.

Figure 2 - Vacuum Cushions (BlueBAG BodyFIX)

3.2 Active breathing coordinator (ABC)

The ABC or Active breathing coordinator system is the respiratory gating system used with the Elekta treatment machine. Unlike the Varian, this system uses a spirometer to track the patient's actual lung volume. Consists of 3 main parts: ABC cart, laptop interface, mouthpiece w / flow meter and valve.

Methods controlling breathing motion include active breathing control (ABC), abdominal compression, respiratory gating, and real-time tumor tracking. ABC involves a modified spirometer, with two pairs of flow monitors and scissor valves to control respiration. Activation is triggered at a predefined lung volume,

“freezing” all breathing motion for 15-20 s by closing both valves. ABC-assisted SBRT is quick, generating the smallest planning target volume by comparison. However, pretreatment training is required, and it may be unsuitable for some patients, especially those with reduced lung function [79].

With respiratory gating, SBRT dose is delivered only in specific phases of the respiratory cycle to avoid unnecessary dosing of normal tissue and underdosing of the target. Treatment time is longer with gating, but it is an acceptable alternative to ABC.

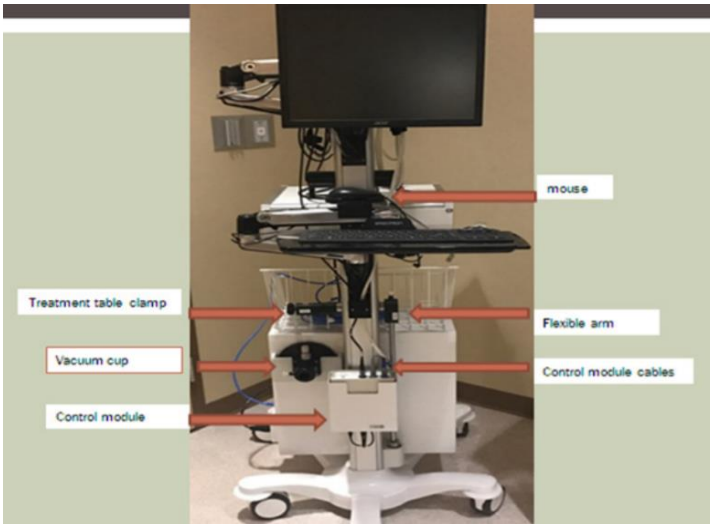

Figure 3 - Trolley

When the button is released the balloon, valve is deflated. If the patient presses the button twice is one second it will send a distress signal that will show up on the laptop screen.

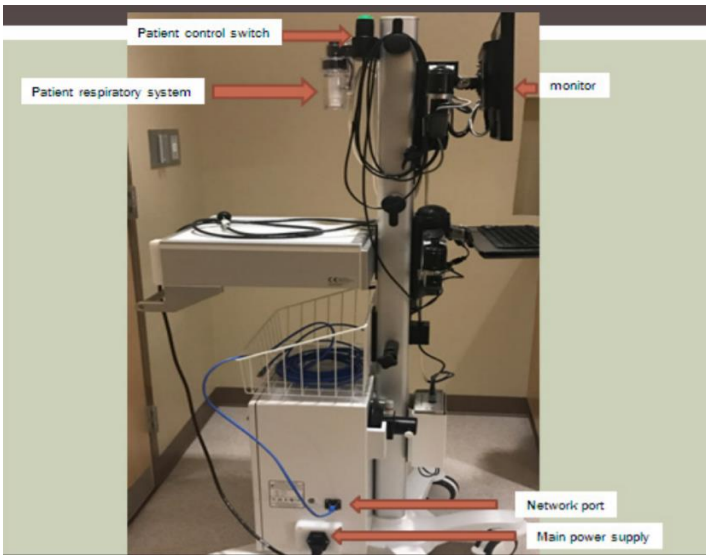

Figure 4 - Patient control switch: Patient presses the button during treatment and releases it to stop the breath hold.

3.3 Linear accelerator Elekta Synergy

Linear accelerator (Figure 5) equipped with imaging systems that help locate structures and their structures and their inter and intrasession movement to optimize the patient's position before treating.

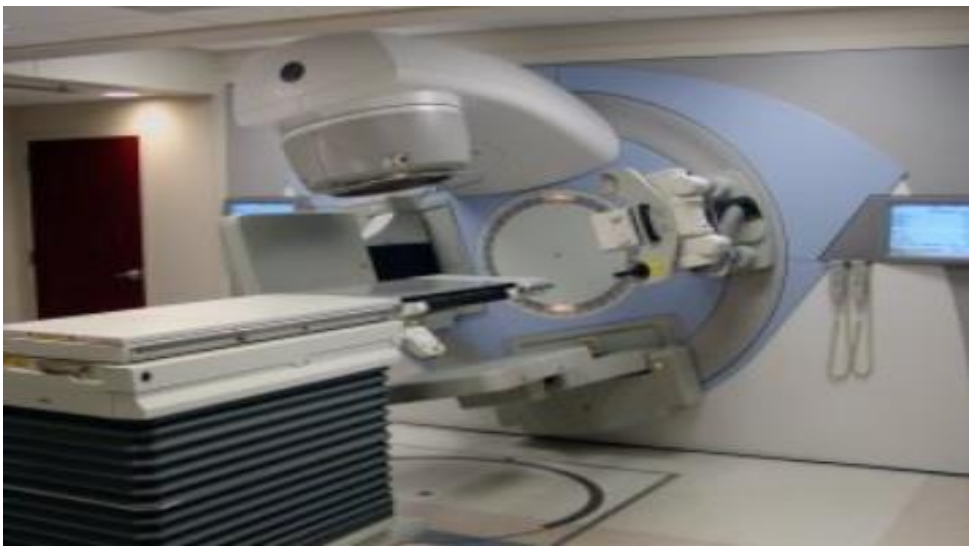

Figure 5 - Linear accelerator Elekta Synergy.

It has a multilayer collimator (MLC) of 80 sheets of 1 cm wide in the isocenter optimized for use in IMRT. This includes a maximum displacement per sheet of up to 32.5 maximum per sheet of up to 32.5 cm (for large treatment fields) and higher primary collimators for minimizing the dose between sheets.

Main Features:

a) double focus plates;
b) fields up to 40x40 cm2;
c) rapid placement of complex irregular fields;
d) compatibility with most planners;
e) optimized adjustment tools: AUTOCAL.

AUTOCAL is an application that coordinates several field sequences with different conformations for quality control of the MLC (Figure 6).

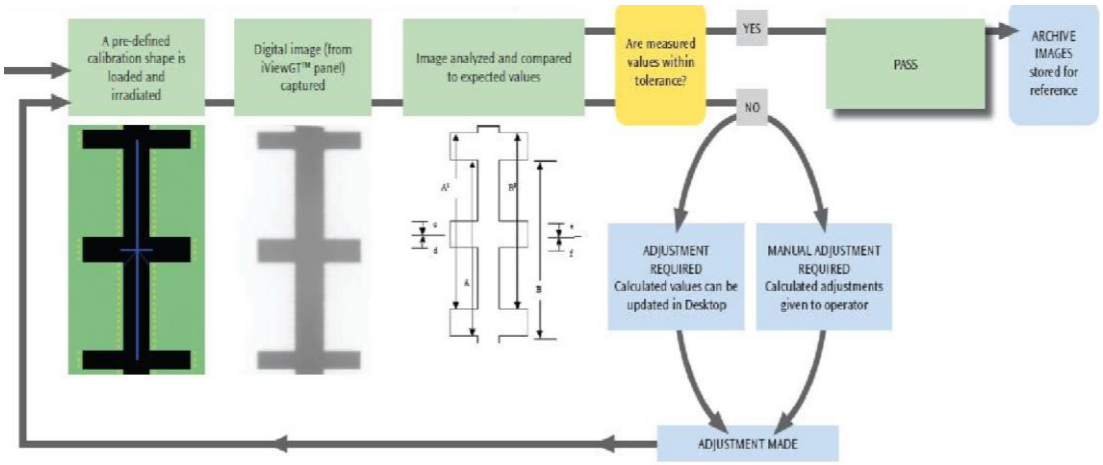

Figure 6 - AUTOCAL

The method of image-guided radiotherapy in its most advanced form was introduced into practice by the company Elekta with the new design of linear accelerator Elekta Synergy™XVI and it is intended for radiotherapy departments, which strive to improve their radiation therapy programs. Image-guided radiotherapy (IGRT) adds time as the fourth dimension to conformal radiotherapy and its excellent spatial resolution together with the ability to reconstruct the volume in any direction makes it ideal for positional registration [80].

Elekta Synergy™XVI, and other types derived thereof - Synergy S, Infinity, Axesse etc. along with the modern information system Elekta MOSAIQ have a full range of functions to enable the provision of treatment and medical procedures for the benefit of the patient:

a) precise targeting of the determined volume;
b) excellent organ imaging;
c) minimization of the exposure to healthy tissue.

Elekta is continuously improving the irradiation treatment methods and techniques for better shaping of the radiation field based on the exact 3D size of the target while eliminating inaccuracies caused by physiological movements of organs

and any errors during the setup. To fully utilize the potential of radiotherapy and the treatment of oncological patients, Elekta is working with clinical partners in the further development of accurate, real-time image-guided radiotherapy [80].

Elekta Synergy™XVI was the first linear accelerator to introduce into practice integrated imaging that allows the visualization of targets in the same frame of reference as the radiation system [80].

Imaging methods that use one or two 2-D X-ray images are good for identification of bones or markers, but they cannot differentiate soft tissue, show details of risk organs or provide images of cross sections of the body. For this purpose, Elekta Synergy ™ XVI uses the kilovoltage X-ray volume imaging XVI with an extended perspective by the fourth dimension and displaying in real time [80].

XVI does not scan and add up individual sections together but reads and reconstructs the data as a total volume in a single cycle. This results in an excellent image quality. Accurate imaging of the XVI model can be used for any part of the body and produces images which are much easier to interpret for the purposes of radiation treatment than images from other imaging modalities. It has spatial resolution, which is normally associated with the MRI image, but because it uses kilovolt X-rays, it does not have problems with spatial distortion which is sometimes attributed to MRI. Similar contrast to that of the CT enables the identification of structures such as tumors or organs at risk without the need to resort to implanted markers [80].

The XVI model has the potential for accurate and revolutionary changes in the localization of tumors and critical organs in the course of radiotherapy. Excellent spatial resolution and integrity-submillimetre isotropic resolution and the ability to reconstruct the volume in any direction makes it ideal for positional registration. Elekta Synergy™XVI can capture a large volume of 3-D data even during a fast scanning cycle. This means that it can be used to capture images of the patient in the irradiation position immediately before the irradiation procedure is commenced. The movement and changes in the tumor and organs are clearly visible and the target can

be located using the relationship of the overall anatomy with the irradiation beam without the need to use markers on the skin or calibrated movements of the irradiation table. The full potential of the image-guided radiotherapy is reached when irradiation is individually adapted to each patient in accordance with anatomical conditions varying in time. In cooperation with clinics around the world, Elekta is developing integrated and specialized tools for workflows with the linear accelerator Elekta Synergy™XVI and with other models derived from it (Table 5) - Synergy S, Infinity, Axesse, thereby creating an efficient and qualified infrastructure for further improvements in therapeutic irradiation and of its effectiveness. Once the daily target is accurately defined, the application of irradiation must be executed with the same accuracy in the subsequent fractions. In order to make sure that this condition is fulfilled, Elekta fulfills all the prerequisites of beam shaping with high levels of customization to the target and with the view from the beam in real time [80].

Table 5 - ELEKTA LINEAR ACCELERATORS* COMPARISON CHART

Model	Versa HD	Infinity / Axesse	Synergy / S	Synergy Platform	Precise	Compact
Years Manufactured	2013 & newer	2009 & newer	2002 & newer	2002 & newer	1997-2005	2008 & newer
Power Source	Magnetron	Magnetron	Magnetron	Magnetron	Magnetron	Magnetron
Photon Energy Configuration	6&10/15/18	6&10/15/18	6&10/15/18	6&10/15/18	6&10/15/18	6&10/15/18
Electron Energies	Yes	Yes	Yes	Yes	Yes	No
Multi-Leaf Collimator (MLC)**	160 Agility MLC (Field size 40x40cm, leaf thickness-5mm)	80 MLC (Field size 40x40cm, leaf thickness-10mm) Optional: 160 Agility	80 MLC (Field size 40x40cm, leaf thickness-10mm)	80 MLC (Field size 40x40cm, leaf thickness-10mm)	80 MLC (Field size 40x40cm, leaf thickness-10mm)	80 MLC (Field size 40x40cm, leaf thickness-10mm)
Portal Imager (EPID)**	iViewGT (Amorphous Silicon)	iViewGT (Amorphous Silicon)	iViewGT (Amorphous Silicon)	iViewGT (Amorphous Silicon)	iViewGT (Amorphous Silicon), iView (camera based)	Optional

Table 5 continuation

Treatment Delivery	3D, IMRT, VMAT, SRS/SBR, SRT,SABR	3D, IMRT, VMAT, SRS/SBRT (Axesse)	3D, IMRT, VMAT, SRS/SBRT (Optional)	3D, IMRT, VMAT, SRS/SBRT (Optional)	3D, IMRT, SRS/SBRT (Optional)	3D, IMRT, SRS/SBRT (Optional)
KV Imaging for IGRT**	XVI	XVI	XVI	N/A	N/A	N/A
CBCT	FOV 50x26cm	XVI	XVI	N/A	N/A	N/A
VMAT	Yes	Yes	Yes	Only with XVI	N/A	N/A
Treatment Couch	Hexapod (6 degrees of motion)	Precise, Hexapod (optional)	Precise	Precise	Precise	Precise
Pros	Latest, cutting-edge technology Competes with Varina True Beam Integrates VMAT, gating, CBCT	Digital System	Reliable, digital technology Includes the XVI-imaging	Relatively inexpensive in secondary market	Many systems available market Relatively inexpensive to acquire Some are dismantled and used for parts	Good, budget system for international markets Reliable
Cons	More expensive than other devices None available in the secondary market yet	Few installed in the U.S.	Few	Does not include XVI component Fewer trained service engineers U.S. than Varian	Installation costs can double the cost of equipment	None available in the U.S. Single photon energy only

*Data shown here may not be accurate and is based on equipment seen in the secondary market. See manufacturers for exact data.
**Similar devices are manufactured by vendors other than the linear accelerator manufacturer.

3.4 Monaco Planning System

When a new Treatment Planning System (TPS) has been purchased, initial testing is necessary. National and international protocols describe a set of tests to

evaluate its image and anatomy handling, the accuracy of its calculations, the completeness of its reporting capabilities and its connectivity features.

The Monaco treatment planning system combines Monte Carlo dose calculation accuracy with robust optimization tools to provide high-quality radiotherapy treatment plans for three-dimensional conformal radiotherapy (3D CRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT). Recent technology advances have allowed for fast calculation speeds, which allow clinicians and patients to benefit from the accuracy of the Monte Carlo algorithm while reducing overall planning time. A collection of biological and physical dose-based planning tools and templates simplify the planning process and allow for consistent results across organizations. At the same time, multicriteria optimization (MCO) ensures critical organs are spared to the greatest possible degree while maintaining target coverage. Monaco encompasses a full suite of treatment modalities, including conventional radiotherapy and particle therapy, and is paving the way for real-time adaptive treatments with developments in magnetic resonance (MR)-guided radiation therapy [81].

Monaco 5.11 templates further increase efficiency by allowing users to easily import and export treatment plans, facilitating best practice sharing across departments and organizations (Figure 7). The ability to create multiple prescription plans simultaneously reduces overall planning time as well. Improved data sharing creates opportunities to optimize individual treatment plans.

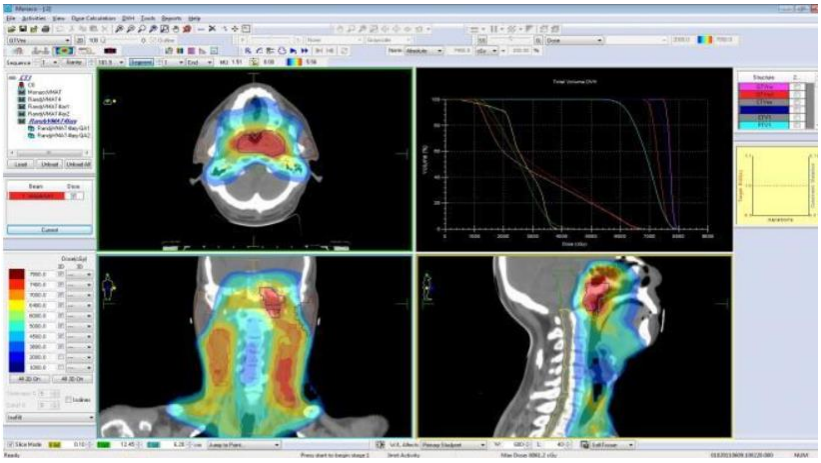

Figure 7 - Monaco 5.11

3.5 ArcCHECK

ArcCHECK is the only true 4D array specifically designed for QA of today's modern rotational deliveries. At its heart are over 1300 SunPoint® Diode Detectors providing consistent and highly sensitive measurements for all gantry angles, with no additional hardware required. Independent absolute dose measurements enable the gold standard for stringent and efficient patient plan and machine QA testing.

Figure 8 - ArcCHECK.

This phantom has the following characteristics:

a) ease of installation (no more than 5 minutes);

b) the sensitivity of the detectors does not depend on the angle of incidence of the radiation beam (information on the complete dose distribution is not lost, in contrast to the two-dimensional matrix, for which the loss of information at gantry angles of 90 and 270 degrees reaches 20%);

c) high spatial resolution, which allows verification of small fields with a high dose gradient (diode size 0.64 mm2, in contrast to the size of the ionization chamber 3 mm2);

d) registration of both the input and output doses (which is important when assessing the total dose load on the patient);

e) the ability to calibrate every three years by the user;

f) the diode is 10 times more sensitive than the ionization chamber (more precisely, it measures the dose);

g) geometric characteristics close to the patient's body.

3.5.1 An Ideal Geometry

Phantoms are ideally shaped like a patient. The cylindrical design of ArcCHECK intentionally simulates patient geometry to better match reality.

ArcCHECK detectors are always facing the delivery beam regardless of gantry angle. The detector geometry relative to the BEV remains constant. Detection of very small gantry angle errors is possible. In contrast, when a 2D array is irradiated obliquely, the geometry collapses to 1D. Even when there is no detector shadowing effect, significant information is lost on a 2D array, and errors up to 10° are missed 75% of the time.

With ArcCHECK, gantry angle, leaf-end position, absolute dose, and time (4D) are measured and correlated to identify sources of error. Dose accuracy is improved and errors can be traced to the treatment planning system, the delivery system, or the imaging system.

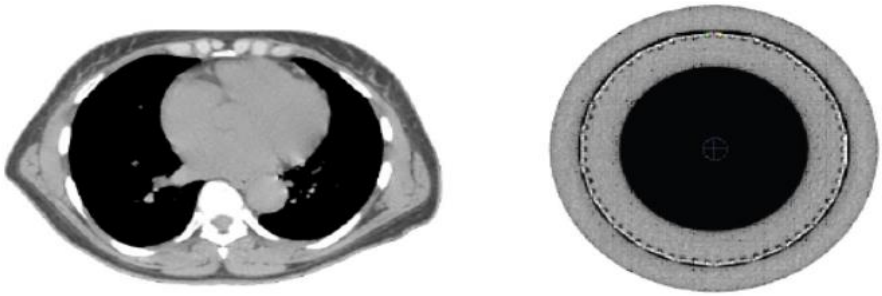

Figure 9 - ArcCHECK. An Ideal Geometry.

3.5.2 What You See with ArcCHECK

ArcCHECK displays BEV dose distribution throughout the entire arc delivery. More data is available to perform a more thorough QA analysis.

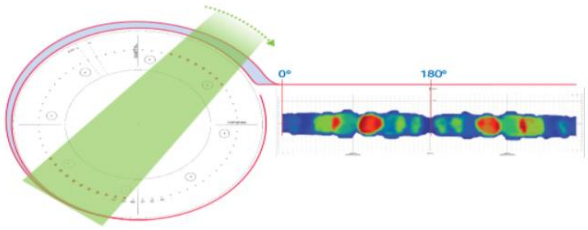

Figure 10 - ArcCHECK Measurement

4 PRACTICAL PART

The practical part of the work was carried out on at the Tomsk Regional Oncology Center. For the study, 5 patients were treated with body stereotactic radiotherapy. Table No.6 presents the input data of the selected patients.

4.1 Patient selection criteria

Selection criteria for patients with liver metastases candidate to SBRT are controversial and a multidisciplinary board discussion is recommended.

Table 6- SELECTION CRITERIA FOR SBRT.

Selection criteria for SBRT	Patients categories		
	Suitable	Cautionary	Unsuitable
Lesion number	<3	4-6	>7
Lesion diameter (cm)	1-3	>3 and ≤6	>6
Distance from OARs (mm)	>8	5-8	<5
Liver function	Child A	Child B	Child C
Free liver volume (cc)	>1,000	<1,000 and ≥700	<700

Histopathology is not considered an inclusion or exclusion criteria. Similarly, age is not a selection criterion. SBRT, indeed, is a non-invasive and safe therapy ideal for elderly patients, who are often unsuitable for surgery.

Recommended selection criteria:

a) tumors that are inoperable (a solution to hepatobiliary MDT) or are medically inoperative.

b) maximum individual tumor diameter <6 cm (only speculation);

c) life expectancy> 3 months;

d) > 800cc normal / not involved liver;

e) adequate organ function: hemoglobin ≥ 9 g / dL, neutrophils ≥ 1.0×109/L, platelets ≥ 80 x 109/L, AST or ALT <6 x ULN, reasonable renal function.

Recommended exclusion criteria:

a) previous radiation therapy of the upper abdominal region, which would prevent partial re-irradiation of the liver due to dose limits on normal tissues;

b) progressive extrahepatic malignant disease that cannot be controlled by surgery, radiation therapy, or systemic therapy;

c) previous anticancer therapy within four weeks after SBRT;

d) uncontrolled bleeding (disorders extrahepatic disease).

e) patients with signs of liver failure, including hepatic encephalopathy;

f) class C for Child-Pugh (in patients with liver dysfunction);

g) active hepatitis;

h) positive primary node;

i) gross ascites;

j) pregnant women.

4.2 Planning, verification, and delivery of therapy

Since September 2018, stereotactic radiotherapy for liver metastases has been introduced in the usual practice of the Tomsk Regional Oncology Center. Elekta Synergy linear accelerator is operated in this center, with the help of which the VMAT dose delivery technique is implemented. Elekta Synergy is a high-energy linear accelerator with an intensity modulation function.

To conduct topometric preparation for all patients, a Toshiba Aquilion spiral scanner (Toshiba, Japan) with a cut thickness of 0.5 mm was used, a reconstruction index of 2.0 mm; DICOM data was sent to the contouring station MonacoSim; Later, contouring of critical organs and tissues, targets was carried out, planned volumes of exposure were determined; Stage 3-D planning of the exposure program was carried out. Based on the obtained computed tomographic scans, a three-dimensional

patient model was built, several treatment plans were calculated on the MonacoSim planning system. Based on the dose-volume histogram (DVH), the plans were evaluated, the most optimal treatment plan was selected taking into account the tolerant levels of radiation of critical organs and the tumor; and the verification of the exposure plans was carried out using the ArcCHECK dosimetric phantom (Sun Nuclear Corporation, Melbourne, Florida, USA) with SNC Patient software (version 6.7.4). In addition, to verify the position before each treatment session, the image system of portal XVI was used for verification. The complex of means for immobilizing patients during topometric preparation and the treatment consisted of system ABC.

Dosimetric radiation plans had the same technical calculation parameters for all 5 patients:

a) photon radiation energy of 10 MV;

b) VMAT irradiation technique;

c) design grid 0.2 cm;

d) maximum beamlet width 0.2 cm;

e) maximum segment width 1 cm;

f) Monte Carlo calculation algorithm, statistical calculation uncertainty of 0.8%.

The dosimetric exposure plans created in the Monaco planning system were evaluated using dose-volume histograms (DVH) for the target and critical organs and based on the criteria of conformity (CI, Conformal Index) and homogeneity (HI, Homogeneity Index) to cover volumes the target. Further, all plans were optimized to achieve maximum approximation of CI and HI to unity, and according to the (DVH) graphs, optimization was carried out to create the most uniform and conformal dose distribution (equal to the value of the prescribed dose for the SBRT course) in terms of PTV (CTV) and so that the tolerant levels of radiation exposure to critical organs are not exceeded.

To ensure that the dosimetric treatment plan in the accelerator corresponds to the plan presented in the planning system, the verification procedure was carried out in the therapeutic accelerator itself. This procedure is especially important when

conducting SBRT due to extremely high single doses, it allows you to see the real picture of the dose distribution in the patient's body, taking into account all the features of the therapeutic apparatus. The specific quality control for every patient was performed with quality assurance system ArcCHECK. For pre-therapeutic tests, the dose distributions of all VMAT plans were obtained by the ArcCHECK diode array. Detector arrays come with their own software for calculating dosimetric analysis profiles or calculating the gamma index value.

Using gamma analysis, the isodose map, taking into account the correction factor, in the matrix plane is compared in the DICOM format with the isodose map calculated on the Monaco planning system. Method allows analyzing discrepancies between measured and calculated by spatial and dosimetric deviations. When assessing dose deviation and spatial deviation, the points are compared: calculated (rc, Dc) and measured (rm, Dm) (Figure 11).

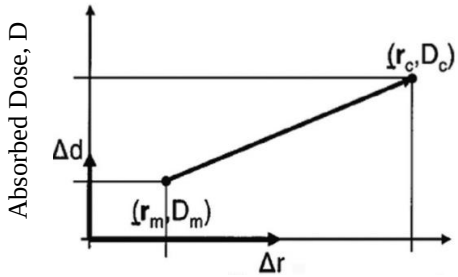

Figure 11 - The dose-distance vector space shows the measured dose of Dm at rm and the calculated dose of Dc at rc

For all points (rc, Dc), the difference between the calculated and measured doses d (i) = Dm (i) -Dc and the distance between points r (i) = rm (i) -rc are determined. The gamma index is calculated by the formula:

$$\gamma(i) = min\sqrt{\left(\frac{d(i)}{\Delta d}\right)^2 + \left(\frac{r(i)}{\Delta r}\right)^2} \quad (3)$$

If the gamma index is less than unity, then the calculated dose is within the accepted criterion (for example, 3% or 2 mm) and it is considered that the dose distributions at this point coincide within this criterion.

4.3 Results of the therapy

For this study, 5 patients (2 men and 3 women) who meet the inclusion criteria have been taken into account; the average age of the patients is 57 years (ranging from 43 to 71 years); of the 5 patients, 3 were initially diagnosed with rectal cancer, 1 with ovarian cancer and 1 with breast cancer; however, all patients were taken into account for this study because they have liver metastases in common. The average volume of metastasis is 38.9 cc. (from 2.4 to 75.4 cc or cm^3). The average number of fractions 3 (range from 1 to 5), the average single dose of 11 Gy (range from 8 to 15 Gy), the average total dose of 42 Gy (range from 39 to 45 Gy). The most common treatment regimen with a total dose of 45 Gy delivered over 3 fractions. The dose was prescribed at 98,94% isodose to 100% of the target volume. The data of each patient are shown in Table 7.

Table 7 - GENERAL DATA OF PATIENTS UNDERGOING SBRT, ACCORDING TO THE PATHOLOGY OF ORIGIN, NUMBER OF LIVER METASTASES AND TREATMENT CARRIED OUT

Patient	Sex (Male or Female)	Age	Pathology of origin	Number of liver metastases	Total Dose (Gy)	Single Dose (Gy)	BED α/β ratio (Gy)
1	Male	46	Rectal adenocarcinoma	1	45	15	112.50
2	Male	69	Rectal adenocarcinoma Prostate cancer	2	45	15	112.50
3	Female	58	Ovarian cancer	3	42	14	100.80

Table 7 continuation

4	Female	71	Cancer of the rectosigmoid junction	3	39	13	89.70
5	Female	43	Right breast cancer	6	40	8	72.00

Biological effective dose (BED)

In SBRT the most used model to describe the biological effect of radiotherapy on the tumor cell and on healthy tissues is the linear quadratic model (LQM) [82, 83]. This calculates the biological effective dose (BED) using a ratio that considers the number of sessions, the dose absorbed per session and an α/β ratio that is a function of the radiosensitivity of each type of tissue. Although the model quadratic linear is the most widely used tool, there is controversy in favor, and against it being able to predict cytotoxicity at a single absorbed dose, underestimating tumor cell death, and overestimating the toxicity of healthy tissues.

Consequently, it is advisable to apply protocols already in progress that are known about the absorbed dose schemes, the number of fractions and the values of absorbed dose restrictions to the risk organs.

In SBRT treatment schemes with more than one session, such as those of the Radiation Therapy Oncology Group (RTOG 813), which administers 50 Gy in 5 sessions or 60 Gy in 5 sessions, and RTOG 915, which delivers 60 Gy in 3 sessions, when calculating the BED of each one of them we can see that it varies between 100 Gy and 180 Gy.

Therefore, the α / β ratio of each tissue determines the biological effect of ionizing radiation on it, and it is theoretically possible to modify this effect by altering the fractionation. The dose received by the tumor in healthy tissue based on its α / β, the dose per fraction and the number of fractions is the biological effective dose (BED) which, according to Barendsen's basic formula [84], is equal to the total dose (D) multiplied by the effectiveness relative (ER):

$$BED = n.d.\left(1 + \frac{d}{\frac{\propto}{\beta}}\right) \quad (4)$$

Where n is the number of fractions and d is the dose per fraction.

The table 7 shows the results of the calculations made in the five patients, which are developed below:

a) patient number 1: 3 x 15 Gy x (1+1.5) = 112.5 Gy

b) patient number 2: 3 x 15 Gy x (1+1.5) = 112.5 Gy

c) patient number 3: 3 x 14 Gy x (1+1.4) = 100.80 Gy

d) patient number 4: 3 x 13 Gy x (1+1.3) = 89.70 Gy

e) patient number 5: 5 x 8 Gy x (1+0.8) = 72.00 Gy

One of the characteristics of SBRT treatments, with more than one session, is that the BED of the treatment is equal to or greater than 100 Gy for an α/β of 10. However, in this study 3 of the 5 patients meet this characteristic.

Table 8- RECOMMENDED DOSE CONSTRAINTS FOR THE ORGAN AT RISK (OARS) [12]

	3 fractions	5 fractions
coverage		
PTV	$D_{110\%}$<2%	
	$V_{95\%}$≥95%	
OAR		
Normal liver volume	>700 cm^3 at <15 Gy	mean <15 Gy
Stomach, duodenum, small bowel	D 3 cm^3 at <21 Gy	D 0.5 cm^3 at <32 Gy
Both Kidneys	V 15 Gy at <35%	mean <12 Gy
Spinal cord	D 1 cm^3 at <18 Gy	D 0.5 cm^3 at <28 Gy
Heart	D 1 cm^3 at <30 Gy	V 32 Gy at <15 cm^3
Both lungs	V 12,4 Gy at <1.000 cm^3	V 11,4 Gy at <1.000 cm^3
Rib	D 30 cm^3 at <30 Gy	nil

For the five patients undergoing SBRT, the radiation exposure to critical organs was within the following limits (Table 8).

These indicators comply with international requirements for permissible heterogeneity of tumor irradiation.

4.1.1 Treatment plans

For the five patients with liver metastases, treatment plans were compiled and verified using a high volumetric modulation of radiation intensity dose delivery technique in the fractionated radiation mode. Figures 12-16 show the dosimetric treatment plans created in the Monaco system for the 5 patients respectively, which fully comply with the international requirements for the degree of local tumor control and the degree of damage to critical organs and normal tissues.

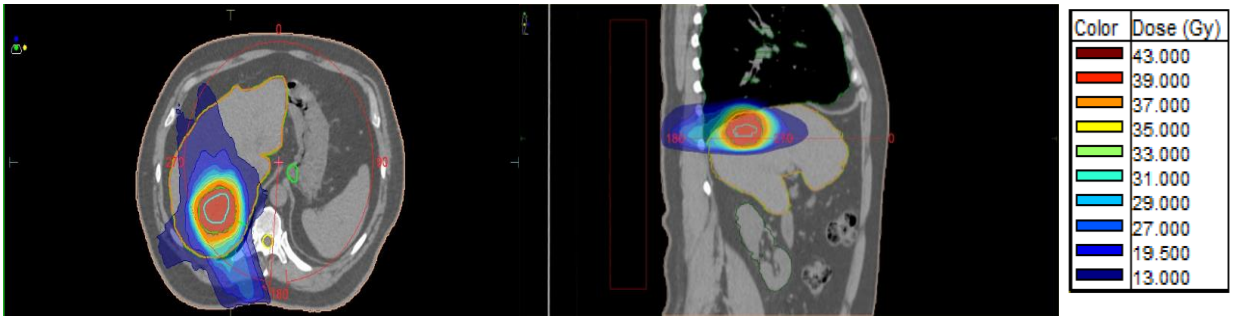

Figure 12- Treatment plan using VMAT to target 1 tumor in the liver. The orange contours represent the PTV volume, and the blue represent the 50% isodose lines. (Patient 1).

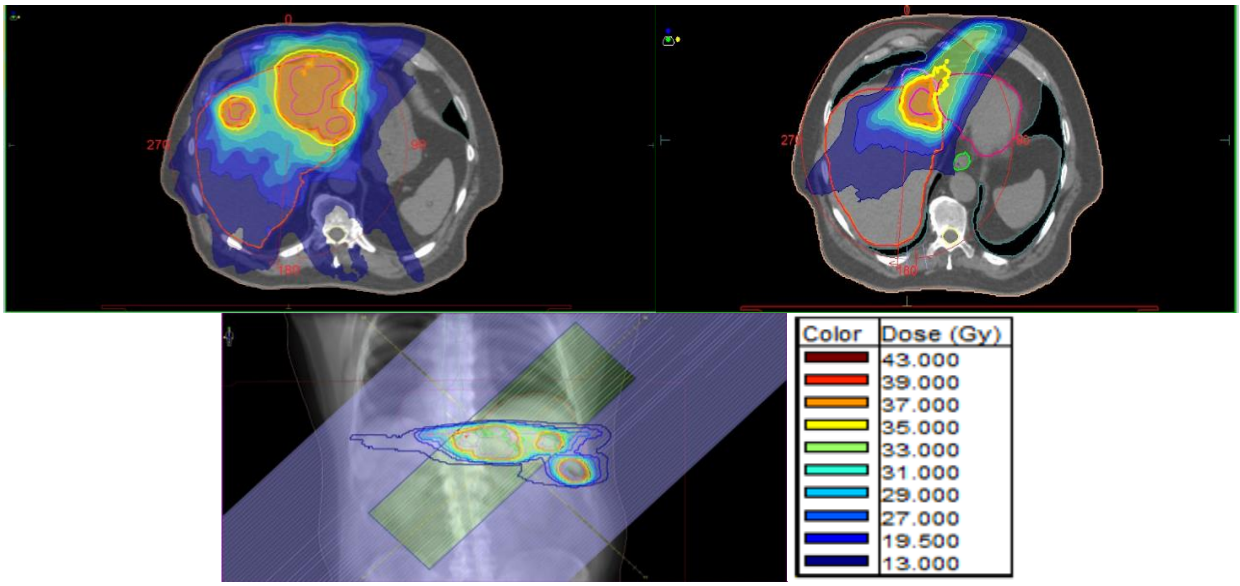

Figure 13- Treatment plan using VMAT to target 3 tumors in the liver. The orange contours represent the PTV volume, and the blue represent the 50% isodose lines (Patient 2).

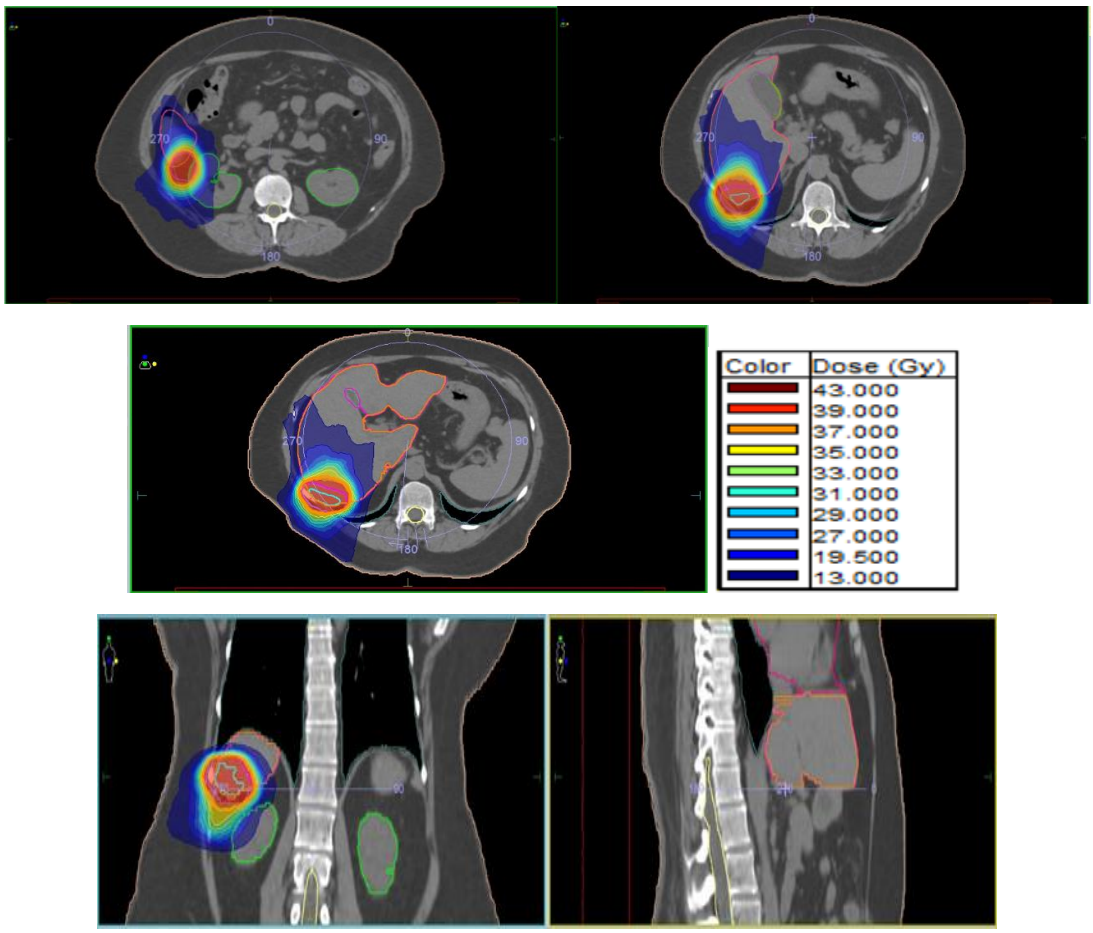

Figure 14- Treatment plan using VMAT to target 2 tumors in the liver. The orange contours represent the PTV volume, and the blue represent the 50% isodose lines (Patient 3).

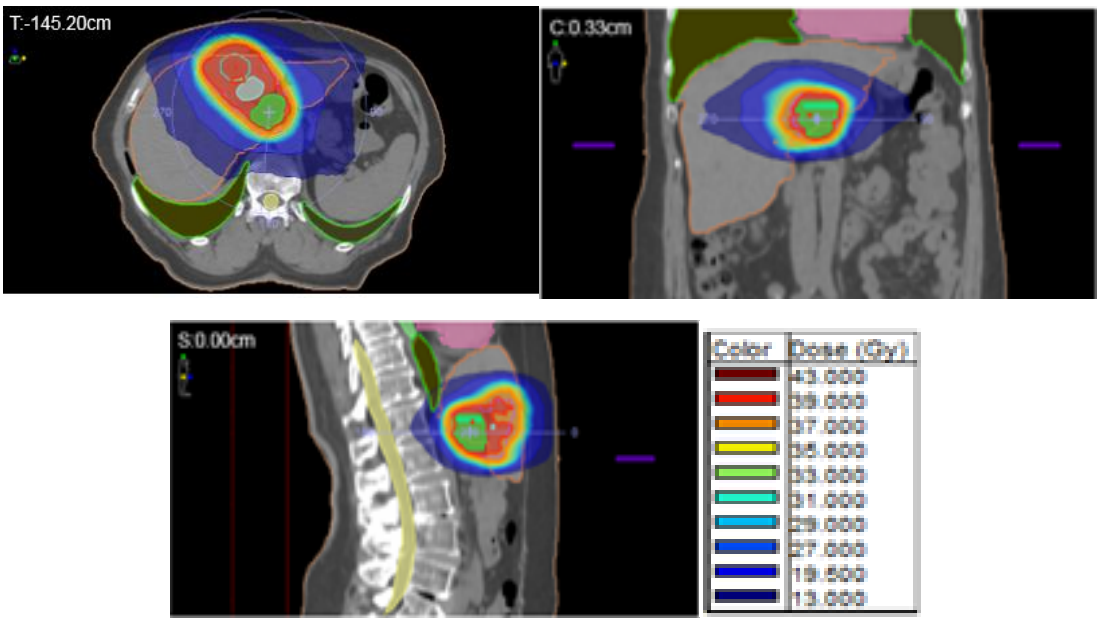

Figure 15- Treatment plan using VMAT to target 3 tumors in the liver. The orange contours represent the PTV volume, and the blue represent the 50% isodose lines (Patient 4).

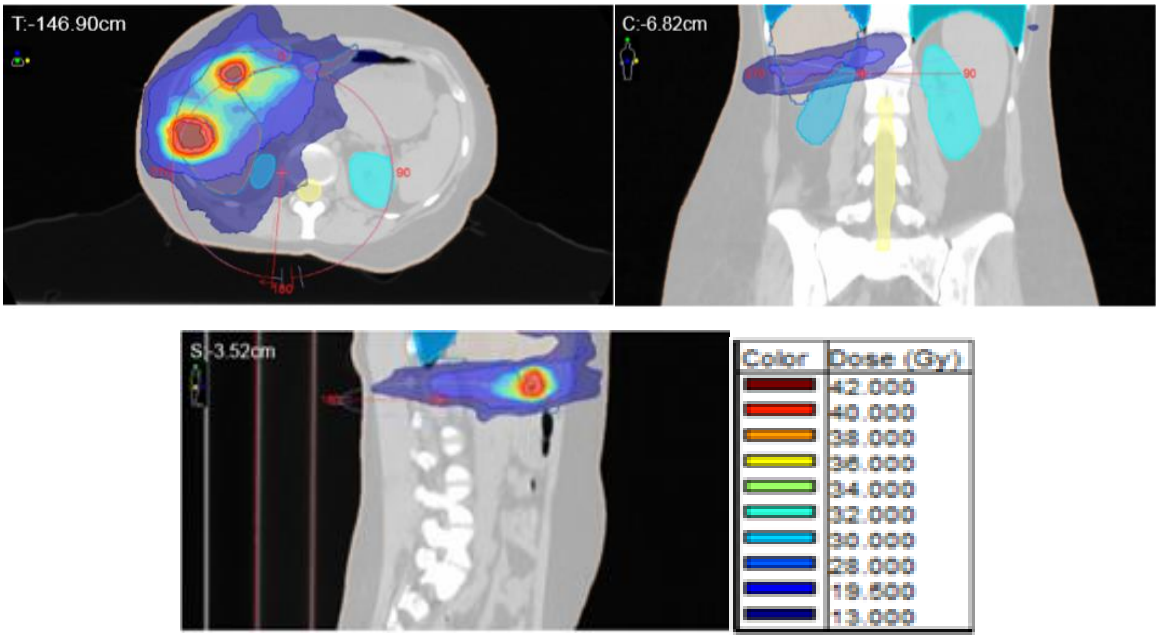

Figure 16- Treatment plan using VMAT to target 6 tumors in the liver. The orange contours represent the PTV volume, and the blue represent the 50% isodose lines (Patient 5).

In all patients, contouring of critical organs and tissues, objectives were performed, and planned exposure volumes were determined.

4.1.2 DVH and statistics

For each plan, Dose-Volume Histograms (DVH) were obtained, which allow a qualitative assessment of the optimality of the plan. A line of a certain color reflects a percentage of the volume of a certain structure that has received a specific dose. Histograms are presented in cumulative form for simplified perception. The figures 16-20 below shows the DVH for each patient (Appendix 1).

As a result of the analysis of measured and calculated dose-volume (DVH) histograms, conclusions were drawn about the most important structures (targets and critical organs) that are most exposed to radiation exposure. In this study, the maximum (median 49.02 Gy), mean (median 46.49 Gy) and min (median 39.33 Gy) doses of PTV (represented by the purple lines); the maximum (median 48.46 Gy), mean (median 46.91 Gy) and min (median 45,67 Gy) doses of GTV (represented

by red lines); the maximum (median 48.68 Gy), mean (median 7.88 Gy) and min (median 0.19 Gy) doses of Liver margin (represented by the orange lines) and OAR were evaluated (such as lung sum the maximum 48.52 Gy, mean 0.49 Gy and min 0.02 Gy was respectively; kidney right the maximum 48.24 Gy, mean 9.78 Gy and min 0.54 Gy was respectively; heart the maximum 41.45 Gy, mean 4.11 Gy and min 0.59 Gy was respectively; and spinal cord the maximum 7.25 Gy, mean 1.39 Gy and min 0.02 was respectively); Regarding the % volume in all the structures, the mean value 99.84 was obtained; Whereby, the radiation doses to the OARs were within the constraints in all patients. Data of DVH for all 5 patients are presented in table 9 (Appendix 1 and 2).

According table 9 (Appendix 2)., we can conclude that the obtained percentage values of cold and hot zones are within acceptable limits for all created plans. All plans have acceptable tumor coverage (100% PTV is coated at the prescribed dose).

On the other hand, the study “Patient-Specific Quality Assurance Protocol for Volumetric Modulated Arc Therapy using Dose Volume Histogram” carried out by Christopher Low, suggests that DVH should also be considered as a research tool that can be useful to diagnose the cause of failed plans, since it allows dose errors to be related to the patient's anatomy.

This study has evidenced the integration of DVH metrics into a VMAT protocol to provide clinically meaningful results that complement point doses and gamma index measurements.

4.1.3 ArCHECK QA of Dose Distribution

Dynamic deliveries have become increasingly common and these techniques require great diligence during Quality Assurance (QA) prior to treatment. ArcCHECK is an accurate and efficient tool for pretreatment verification.

According to the quality control to verify compliance with the specified criteria of geometric characteristics and doses for the measured and calculated points of the plan, in the 5 patients, all areas meet the eligibility criteria for the location in question.

Verification of the exposure plan was carried out using the ArcCHECK system, figures 21-25 show them for each patient (Appendix 3).

The cylindrical phantom ArcCHECK, allowed verifying treatment plans by comparing the actual plan issued by the treatment unit and calculated by the planning system. As a result of the comparison, two dose volume histograms were compiled, after the application of which it was possible to find out the dose received by one or the other organ.

Gamma Analysis (verification method of volumetric modulated arc therapy plans)

The quantitative analysis of dose distributions is achieved by directly comparing the planned isodose distributions to the measured dose planes using gamma analysis.

Dose metrics are most applicable in regions of low dose-gradient, where the difference between calculated and measured doses at a point are determined and have a pass/fail criterion based on designated acceptance tolerances. In regions of high dose gradient, a small geometric shift could result in a large dose disparity. Here distance metrics are used to determine the distance between a measured dose point and the nearest calculated data point with a matching dose, known as distance-to-agreement (DTA).

According to the data on the dose distribution for VMAT for localization (the regions of liver metastasis), the Summary (Gamma Analysis) coincidence was greater than 97.7% for the 3% / 2 mm criterion. Table 10 shows the reliability results of the gamma analysis.

Table 10. RESULTS OF THE GAMMA ANALYSIS

Summary (Gamma Analysis) Gamma criterion of 3%/2mm for the VMAT technique.				
Patient	Total Points	Passed	Failed	% Passed
1	129	126	3	97,7
2	390	386	4	99
3	144	144	0	100
4	512	512	0	100
5	301	295	6	98

The gamma index method can be summarized mathematically as follows [85].
DM is the dose-difference criterion (a value of 3 % is used in this study) and dM is the DTA criterion (a value of 2 mm is used in this study) and are evaluated for a single measurement point rm located at the origin of the geometric representation. The x and y axes represent the spatial location of the calculated distribution relative to the measured point rc. The vertical axis, δ, displays the difference between the measured dose, Dm(rm), and calculated dose, Dc(rc). An ellipsoid surface represents the acceptance criterion.
The surface is defined as:

$$1 = \sqrt{\frac{r^2}{\Delta d_M^2} + \frac{\delta^2}{(\Delta D_M^2)}} \tag{5}$$

where $r = |r - r_m| \quad \delta = D(r) - D_m(r_m)$ is the dose difference at position rm.
If any part of the calculated distribution surface intersects the defined ellipsoid the calculated point rm passes the criteria. This equation can be used to determine the gamma index, γ, at each point in the evaluation plan rc-rm for the point rm hence

$$\gamma = \min(\Gamma)\, \forall(r_c) \tag{6}$$

where:

$$\Gamma = \sqrt{\frac{r^2}{\Delta d_M^2} + \frac{\delta^2}{(\Delta D_M^2)}} \quad (7)$$

And hence the pass/fail criteria can be defined by:

$\gamma \leq 1$, calculation passes

$\gamma > 1$, calculation fails

Figure 27 shows that for the 5 patients, the pass/fail criteria were defined by $\gamma \leq 1$, thus, calculation passes at each point in the evaluation plan.

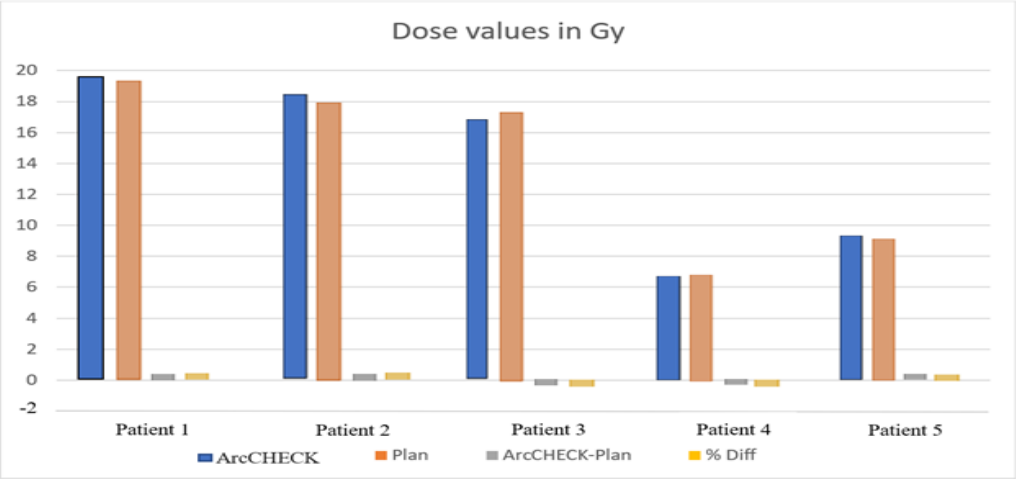

Figure 27- ArcCHECK QA comparison.
Comparison of the planning station with the verification data.

The advantages of gamma index methods are that they allow for a general comparison that simultaneously considers dose differences and DTA, the γ values can be displayed as an iso-distribution and the degree to which a point fails known. Modern software displays dose planes and highlights the locations of failed points or regions and indicates whether the calculated dose is lower or greater (colder or hotter) than the measured dose. The quality of agreement of a beam can thus be assessed on either the absolute number or percentage of points that pass the criteria. Gamma analysis is the comparison metric used by the commercially available Sun Nuclear Corporation SNC Patient software. This software was used throughout this project to establish dosimetric % differences between five dose planes (Figure 27- ArcCHECK QA comparison). The department's version of software (version 6.2.3)

uses an initial simplified approach, first checking if the dose difference is less than or equal to the prescribed 3 % criteria, and if this fails, checking if the nearest point on the calculated grid of the same dose is within the prescribed 2 mm criteria. In this case, the point is considered a passing detector point. In the event these simplified methods both fail to produce a passing point, Low's method described above is used to find a passing point of the gamma value less than or equal to 1. If a gamma value is found to be greater than 1, the detector point fails.

Quality Assurance (QA) is very important in ensuring the stable, safe and accurate operation of the system. In order to identify exactly the real dose into the target volume, it's necessary to use dose measure and control equipment.

To consider if the patient position set-up is the same as planned CT, cone beam CT was taken before the treatment by XVI systems. Information was transferred back to the software after the radiation oncologist completed the check, and then transferred again to the LINAC for treatment in the 5 patients.

4.3.4 Rapid delivery of radiotherapy

Finally, the radiation beam was delivered using Volumetric Arc Therapy (VMAT). This highly conformal, powerful x-ray beam is swept around the patient, into the liver tumor, without interruption. This fast delivery of radiation reduces the treatment time of respiratory gated treatment (Figure 28).

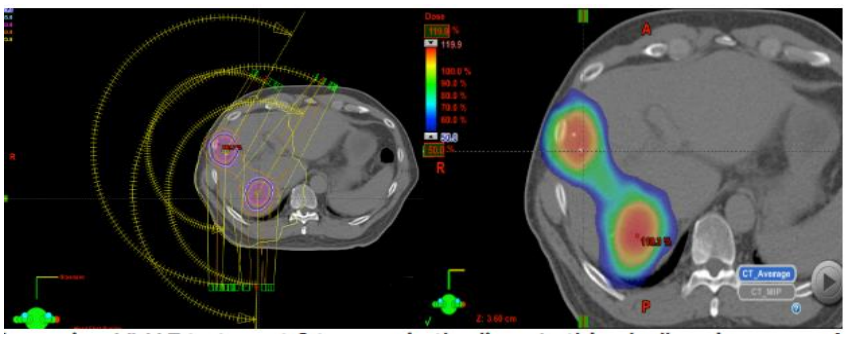

Figure 28- Example of a treatment plan using VMAT to target 2 tumors in the liver. In this challenging case, 4 arcs were used to achieve a highly conformal

dose coverage around both tumors. Each arc takes less than 1-2 minutes for delivery.

4.3.5 Effect of SBRT

Effect of radiotherapy in each patient:

a) patient No. 1 - targeted stabilization, the emergence of a new;
b) patient No. 3 - complete regression of the target focus, the emergence of a new;
c) patient No. 2 - stabilization by targeted lesions;
d) patient No. 4 - stabilization by targeted foci, the emergence of new;
e) patient No. 5 - not evaluated, not related to treatment.

The expected response to targeted therapy is stabilization of the tumor process; According to the results in our patients, a local control of 100% of the cases was obtained, and only one patient presented complete regression.

4.3.6 Medical considerations post-treatment SBRT

The early side effects of SBRT to the liver include fatigue, nausea (rarely vomiting) and mild skin changes. These are temporary and resolve within a month of radiation therapy. The normal liver cells can be damaged by radiotherapy, with the effects seen only a few weeks after SBRT. With attention to technique in avoiding as much normal liver as possible, this usually shows up as mild to moderate abnormalities in the liver blood tests without any symptoms. The blood tests tend to normalize with time. For patients with underlying unhealthy liver, there is a higher risk of having radiation-induced liver disease that is severe enough to cause liver failure. Patient selection is therefore very important.

In the 5 patients, body stereotactic radiotherapy was satisfactory, without serious complications or hepatoxicity.

Median follow-up - 5.9 months. The level of local control was 100%. The treatment was accompanied by minimal toxic effects, nausea and vomiting after an irradiation session - 27%, abdominal pain - 18%, fever - 9%, absence of symptoms 46%. Toxicity of 3-4 degrees was not observed.

4.3.7 Post-SBRT medical recommendations

1) General clinical tests (hematological control) 7-10 days after the end of treatment;

2) Observation and evaluation with an oncologist / chemotherapist, for the decision on the continuation of the special treatment (targeted chemotherapy);

3) 3-8 weeks after completing treatment (depending on each patient): check the MRI of the liver with contrast for evaluation of the effect;

4) Continuation of special treatment, pharmacological therapy as planned;

5) Symptomatic treatment by a general practitioner / oncologist;

To carry out aspect 3) it is important to take into account the following considerations:

3) Analysis of treatments data and results of MRI exams

Liver - Segmental Anatomy on cross-sectional images (Figure 29) [86]

Left lobe: lateral (II / III) vs medial segment (IVA / B). Extrapolate a line along the superior sickle ligament to the confluence of the left and middle hepatic veins in the IVC (blue line).

Left versus right lobe: VAT / B vs V / VIII. Extrapolate a line from the gallbladder fossa superiorly along the middle hepatic vein to the IVC (red line).

Right lobe: anterior (V / VIII) vs posterior segment (VI / VII). Extrapolate a line along the right hepatic vein from the inferior IVC to the lateral hepatic margin (green line).

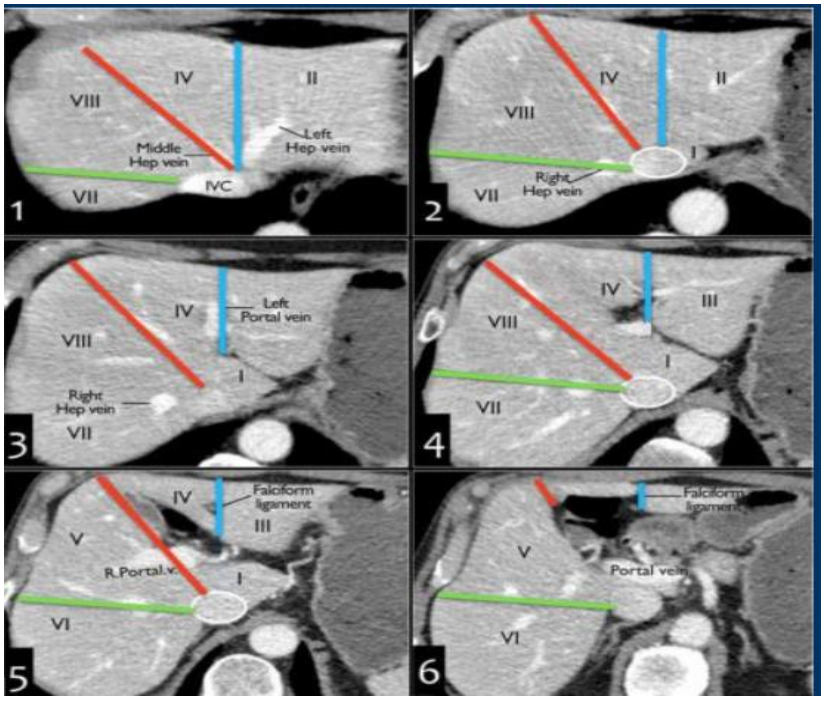

Figure 29- Couinaud's classification of liver anatomy divides the liver into eight

This figure was used to investigate which segment of the liver is affected in a total of 5 patients who were included in this study.

The liver is known to be the primary target of metastasis in colorectal cancer. However, we do not know enough from the literature to describe the segmental distribution of metastatic liver lesions in colorectal cancers, prostate cancer, ovarian cancer, and right breast cancer.

When the total number of metastatic lesions was evaluated, excluding segment I, the highest number of lesions was observed in segment VIII. The liver segments with the highest number of metastatic lesions were, respectively, VI, VII and VIII. In this case, the least number of metastatic lesions was observed in segment IV (Appendix 4).

This analysis concludes that liver metastases are more common in the right lobe than in the left lobe in this study.

5 FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE CONSERVATION

5.1 Pre-project analysis

At present, the prospect of scientific research is determined not so much by the scale of the discovery, which is difficult to assess at the first stages of the life cycle of a high-tech and resource-efficient product, but rather the commercial value of development. Evaluation of the commercial value of the development is a prerequisite in the search for funding sources for scientific research and commercialization of its results. This is important for developers who need to represent the state and prospects of ongoing research.

The objective of this work is to carry out the planning, verification and administration of the Stereotactic Body Radiation Therapy (SBRT) treatment to five patients of the Tomsk Regional Oncology Center with a diagnosed liver metastases, as well as an analysis of the results of the treatment with conclusions about the prospects for greater use of this method in the treatment of liver metastases in Tomsk Regional Oncology Center. The area is medicine. The sphere is radiotherapy, treatment of malignant tumor processes. The final consumer is the oncology centers and departments. Studies have shown a significant advantage of the SBRT in liver metastases.

5.2 Ishikawa Chart

The Ishikawa cause-effect diagram (Cause-and-Effect-Diagram) is a graphical method for the analysis and formation of cause-effect relationships, a tool

for the systematic determination of the causes of a problem and subsequent graphical presentation. The diagram created as part of this work is presented in Figure 30.

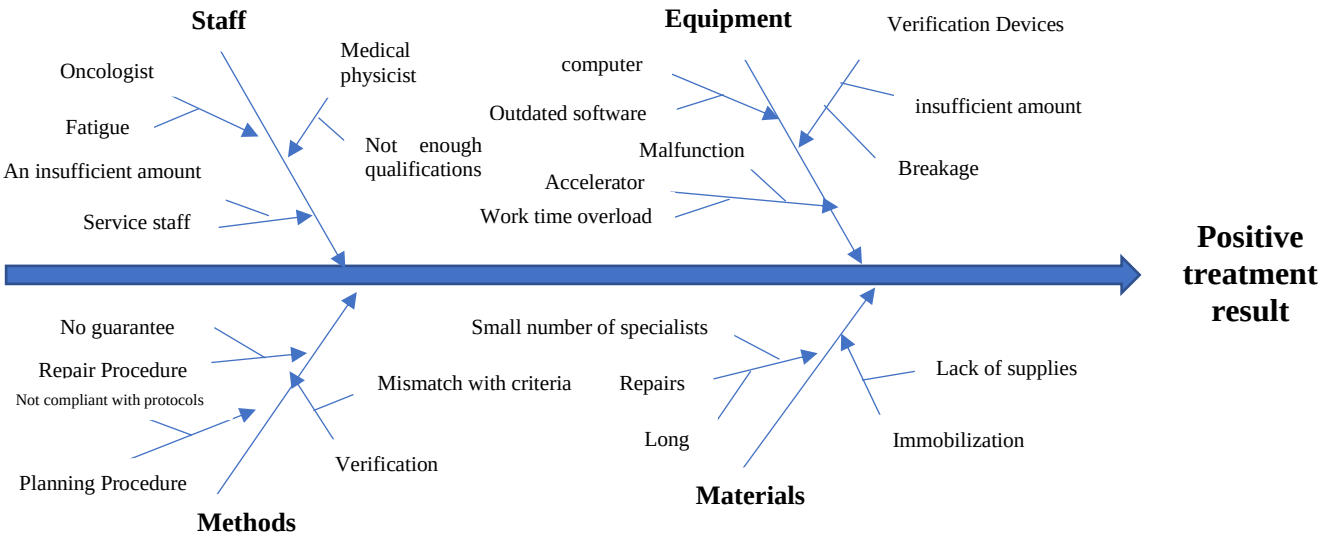

Figure 30- Cause and effect diagram of Ishikawa.

The Ishikawa cause-effect diagram consists of four main areas:

a) staff;

b) equipment;

c) methods;

d) materials.

Each area contains factors influencing the object of analysis. Table 12 provides a description of the chart with suggested solutions to the problems. Each of the selected factors can affect the outcome of the study and treatment, so that their decision will provide a positive result, both within the framework of this work, and for future studies.

Table 12 - DESCRIPTION OF THE ISHIKAWA DIAGRAM.

Area	Factors	Problem	Decision
Staff	Oncologists	Fatigue	To prevent unnecessary fatigue is possible to either connect additional oncologists, or break working hours into shifts.
	Medical Physicists	Lack of qualifications	To solve the problem, it is possible to either send staff to receive additional education or organize advanced training courses directly on the basis of

Table 12 continuation

			the LLP. You can also hire more qualified professionals to transfer experience.
	Service staff	Lack of quantity	The only solution is to recruit additional staff
Equipment	computer	Outdated software	As a solution to this problem, you can either contact the software provider or switch to using another, alternative software package.
	Verification Devices	Lack of quantity or breakdown	It is necessary to purchase additional units of equipment, as well as find out the most vulnerable elements and pre-order components in case of unexpected breakdown.
	Accelerator	Malfunction or overload	It is necessary to clearly follow the instructions for use and in time to carry out the necessary procedures for inspection and health checks, as well as plan treatment taking into account the maximum load on the system.
Methods	Repair Procedure	No guarantee	It is necessary during the time to carry out the necessary procedures for examining and verifying the operability of equipment, as well as use the services of only certified specialists to maintain warranty service.
	Verification	Mismatch with criteria	It is necessary to re-carry out planning until all requirements are met.
	Planning	Protocol mismatch	It is necessary to draw up a clear documentation of the criteria with which all plans will have to check and follow this instruction for each patient.

5.3 SWOT analysis

SWOT - Strengths Weaknesses Opportunities Threats - is a comprehensive analysis of a research project. The purpose of its implementation is to identify the strengths and weaknesses of the project, as well as an understanding of the opportunities and threats that affect the process of performing work. The first stage of the SWOT analysis is presented in table 13.

Table 13 - FIRST PHASE SWOT ANALYSIS

	Strengths of a research project: C1. Shipping Modern treatment C2. Use hypofractionation C3. High Performance Center C4. High effectiveness of treatment C5. High Qualification Involved Staff	**Weaknesses of a research project:** Sl1. The need for high-tech equipment Sl2. The need for high precision planning Sl3. The involvement of a large number of staff Sl4. High risk of error Sl5. The need for additional checks
Opportunities: B1. Infrastructure use in Tomsk Regional Oncological Center B2. Decrease in treatment time B3 Improvement of the effectiveness of treatment in general B4 Tomsk Regional Oncological Center Competitiveness Improvement B5 Formation of new recommendations.		
Threats: U1. Treatment mismatch U2. Plan failure U3. Equipment breakdown U4. Lack of qualifications U5. Congestion center		

The second stage is to identify the strengths and weaknesses of the research project with environmental conditions. This correspondence or inconsistency should help to identify the extent to which strategic change is needed. The result of the second stage is presented in Table 14.

Table 14- INTERACTIVE PROJECT MATRIX

		The strengths of the project				
		C1	C2	C3	C4	C5
Possibilities Project	B1	+	+	+	+	+
	B2	+	+	+	+	+
	B3	+	+	0	-	-
	B4	+	+	-	+	+
	B5	+	+	0	+	+

The third is the final SWOT-analysis matrix Table 15.

Table 15 - SWOT FINAL ANALYSIS MATRIX

	Strengths of a research project: C1. Shipping Modern treatment C2. Use hypofractionation C3. High Performance Center C4. High effectiveness of treatment C5. High Qualification Involved Staff	**Weaknesses of a research project:** Sl1. The need for high-tech equipment Sl2. The need for high precision planning Sl3. The involvement of a large number of staff Sl4. High risk of error Sl5. The need for additional checks
Opportunities: B1. Infrastructure use in Tomsk Regional Oncological Center. B2. Decrease in treatment time B3 Improvement of the effectiveness of treatment in general B4 Tomsk Regional Oncological Center Competitiveness Improvement B5 Formation of new recommendations	1. The ability to accept more patients 2. The growth of the prestige of the center	1. When planning, it is possible to make independent control 2. Availability of necessary equipment in Tomsk Regional Oncological Center
Threats: U1. Treatment mismatch U2. Plan failure U3. Equipment breakdown U4. Lack of qualifications U5. Congestion center	1. Ability to improve procedures and standards	1. Timely procedures for inspection and verification of equipment performance will reduce the risk of breakdown and the need for repairs

This section identifies the key strengths and weaknesses of the project, as well as factors affecting the outcome of the work, such as project opportunities and threats. A combined analysis of these factors helped to understand how the project should be developed and what situations should be avoided in the future.

5.4 Control events of the project

Within the framework of this section, the key events of the project are identified, their dates and results, which were obtained as of these dates. Information is presented in table 16.

Table 16 - PROJECT CONTROL EVENTS

No.	Control event	Date	Result (confirming document)
1	Develop a technical task	10.02.2020- 13.02.2020	Graduation Qualification Orders
2	Determining the direction of the study	13.02.2020- 15.02.2020	-
3	Literature analysis and study	14.02.2020- 15.03.2020	Literary review data-list (Literature)
4	Exploring hardware and software	10.03.2020- 15.03.2020	-
5	Creating, verifying treatment plans for SBRT	15.03.2020- 06.04.2020	-
6	Analysis and processing of the data obtained	06.04.2020- 26.04.2020	Report
7	Comparison Results international requirements	26.04.2020- 15.05.2020	-
8	Making an explanatory note	15.05.2020- 30.05.2020	Explanatory Note
9	Preparing to defend the dissertation work	31.05.2020- 15.06.2020	Presentation

5.5 Project Plan

5.5.1 Hierarchical structure of project work

In the process of creating a hierarchical structure of the project structured the contents of the entire project, which presented in Figure 31.

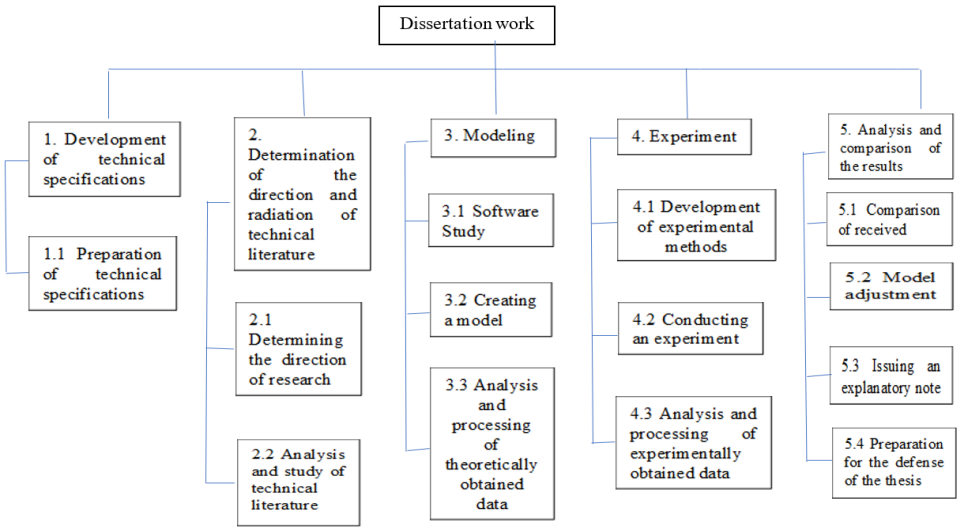

Figure 31 - Hierarchical structure of works.

A group of planning processes consists of processes carried out to determine the overall content of work, clarify goals and develop a sequence of actions required to achieve these goals. Hierarchical structure of work (HSW) - detailing the enlarged structure of work.

As part of the planning of a scientific project, it is necessary to construct a project schedule presented in table 17. Next, using the Grant chart in table 18, the project schedule is illustrated, on which the work on the topic is characterized by the start and end dates of these works.

Table 17 - PROJECT CALENDAR PLAN

No	Name	Calendar time in days	Date	Composition Participants
1	Development of technical specifications	3	10.02.2020 - 13.02.2020	Head
2	Determining the direction of research	2	13.02.2020 - 15.02.2020	Head Master
3	Analysis and study of literature	30	14.02.2020 - 15.03.2020	Master
4	Studying hardware and software	4	10.03.2020 - 15.03.2020	Head Master
5	Creation, verification of treatment plans for SBRT	21	15.03.2020 - 05.04.2020	Head Master
6	Analysis and processing of data	20	06.04.2020- 26.04.2020	Master
7	Comparison of results with international requirements	20	26.04.2020- 15.05.2020	Master

Table 17 continuation

8	Issuing an explanatory note	15	15.05.2020- 30.05.2020	Head Master
9	Preparation for the defense of the thesis	16	31.05.2020- 15.06.2020	Master

Table 18 - CALENDAR CHART IN THE FORM OF GRANT CHART.

-Head - Master -Head + Master

No.	Type of work	Performers	Calendar time in days	Duration of work												
				Ф		М			А			М			И	
				2	3	1	2	3	1	2	3	1	2	3	1	2
1	Development of technical specifications	Head	3													
2	Determining the direction of research	Head Master	2													
3	Analysis and study of literature	Master	30													
4	Studying hardware and software	Head Master	4													
5	Creation, verification of treatment plans for SBRT	Head Master	21													
6	Analysis and processing of data	Master	20													
7	Comparison of results with international requirements	Master	20													
8	Issuing an explanatory note	Head Master	15													
9	Preparation for the defense of the thesis	Master	16													

5.6 Budget for scientific and technical research (RST)

When planning the budget for RST, a full and reliable reflection of all types of expenses associated with its implementation should be ensured. In the process of budgeting the RST, the following cost grouping is used by items:

a) materials.

b) the cost of labor of employees directly involved in the final qualification work of the master.

c) contributions to extrabudgetary funds.

d) work performed by third parties.

e) special equipment for scientific and experimental work.

f) other direct costs.

g) overhead.

5.7 Calculation of material costs

The main costs in this research work are the costs of electricity when working on a planning system, personal computer and a linear accelerator. The cost of electricity was also included in the material costs of the STI. Electricity costs are calculated by the formula 8:

$$C_{элэкт} = Ц_{эл} * P * F_{об} \quad (8)$$

where $Ц_{эл}$ - tariff for industrial electricity (5.8 rubles per 1 kilowatt per hour);

P - equipment power is measured in kW;

$F_{об}$ - the time of use of the equipment in hours.

When performing the work, a stationary computer with an average power of 550 W (0.55 kW) was used. All work was performed on it for 4 hours a day all the time the work was done 91 days 364 hours.

$$C_{элэкт} = 5.8 * 0.55* 364 = 1161 \text{ rub}$$

The cost of electricity consumed by the accelerator and related elements are:

$$C_{элэкт} = 5.8 * 30 * 2 = 348 \text{ rub}$$

The results of calculations for the costs of materials are shown in table 19.

Table 19- MATERIALS COST RESULTS.

Name	Power of equipment	Quantity, hour	Unit price, rub	Amount, rub
Electricity consumed by dosimetric equipment (ArcCHECK)	30	2	5.8	348
Electricity consumed by the accelerator and related systems (Elekta Synergy linear accelerator)	30	2	5.8	348
Electricity consumed by a personal computer and related device	0.55	364	5.8	1161
Name				
Paper	SvetoCopy	1 paquete	280	280
Printer ink	-	2 cartridge	150	300
Pen	Bic	1	200	200
Internet	Tomtel	4 months	450	1800
Total for materials				2580
Transportation and procurement costs (3-5%)				0
Total for Article				7017

5.8 calculation of the cost of depreciation for equipment for experimental work

The equipment used in the scientific work was already available in the radiology department, so this article describes the costs in the form of depreciation. In this thesis, the special equipment necessary for conducting experimental work includes:

a) Elekta Synergy linear accelerator, the cost is 182,000,000 rubles for a designated life of 30 years;

b) a cylindrical dosimetric phantom ArcCHECK, the cost is 6,000,000 rubles for a designated life of 15 years.

The cost of depreciation of equipment is calculated by the formula 9:

$$C_{аморт} = \frac{C_{об} * H_а\%}{T_{год} * 100\%} T, \quad (9)$$

Where: $C_{об}$ - the cost of equipment in rubles;

H_a% - the rate of amortization;

$T_{год}$ - Number of working days per year

T - lifespan, in the number of days.

The depreciation rate is calculated as the reciprocal of the life of the equipment, multiplied by 100%. The number of working days in a year is equal to 2020 - 251.

The equipment was used with stops for 4 months, but not continuously, for the accelerator 76 working days, and for the phantom 25 working days.

$$C_{аморт} = \frac{C_{об}}{T} = \frac{182000000}{30 * 251} * 76 + \frac{6000000}{15 * 251} * 25 = 1836919+39841=1876760 \text{ rub.}$$

5.9 The cost of labor of performers Scientific Technical Research

This article includes the basic salary of scientific and engineering workers directly involved in the implementation of work on this topic. The amount of expenses on wages is determined on the basis of the complexity of the work performed and the current system of remuneration. The fee is calculated according to the formula 10:

$$C_{зп} = З_{ос} + З_{доп}, \quad (10)$$

Where $З_{ос}$ is the basic salary;

$З_{доп}$ - additional salary

The basic salary of a supervisor is calculated on the basis of industry wages. The industry system of remuneration in TPU involves the following composition of wages:

a) Salary - determined by the company. In TPU, salaries are distributed in accordance with the positions held, for example, assistant, teacher, assistant professor, professor.

b) Incentive payments - are established by the head of departments for effective work, the performance of additional duties, etc. Additional wages include payment for unworked time (regular and study leave, fulfillment of state duties, payment of remuneration for seniority, etc.) and is calculated based on 10-15% of the basic wage, employees directly involved in the implementation of the theme are calculated by formula 11:

$$З_{доп} = К_{доп} * З_{осн}, \quad (11)$$

where $З_{доп}$ - additional salary in rubles;

$К_{доп}$ - additional salary ratio;

$З_{осн}$ - basic salary in rubles.

The main salary of the head is calculated by the formula 12:

$$З_{осн} = З_{дн} * Т_{раб}, \quad (12)$$

Where $З_{осн}$ - is the basic salary of one employee;

$Т_{раб}$ - the duration of the work performed by the scientific and technical worker in working days;

$З_{дн}$ - the average daily salary of the employee in rubles.

The average daily wage is calculated by the formula 13:

$$З_{дн} = \frac{З_{М} М}{F_{д}} = \frac{З_{б} K_{р} М}{Fд} \quad (13)$$

where $З_{м}$ - the monthly official salary of the employee, rubles;

M - the number of months of work without vacation during the year;

when you leave at 24 workday M = 11.2 months, 5-day week,

when leaving at 48 workday M = 10.4 months, 6-day week;

$F_{д}$ - the actual annual fund of working time of scientific and technical personnel (in working days);

$З_{б}$ - base salary;

$к_{р}$ - a district coefficient of 1.3 for Tomsk.

The base salary of an engineer at the department of NI TPU, having the degree of candidate of technical sciences and the title of “teacher” is 35 120 rubles. The main salary of the head for the period of work (38 working days) is:

$$З_{дн} = \frac{З_{м}М}{F_{д}} = \frac{З_{б}К_{р}М}{F_{д}} = \frac{35120*1,3*10,4}{299-48} = 1892\ rub/per\ day$$

$$З_{осн} = З_{дн} * Т_{раб} = 1892 * 38 = 71896\ rub$$

$$З_{доп} = К_{доп} * З_{осн} = 0,15 * 71896 = 10784,4\ rub$$

$$С_{зп} = 71896 + 10784,4 = 82680,4\ rub$$

Master's salary is 17 310 rubles / month. The work was carried out for four months (80 working days), which means the total wage rate is equal to:

$$З_{дн} = \frac{З_{м}М}{F_{д}} = \frac{З_{б}К_{р}М}{F_{д}} = \frac{17310*1,3*10,4}{247-24} = 1049,4\ rub/per\ day$$

$$З_{осн} = З_{дн} * Т_{раб} = 1049,4 * 80 = 83952\ rub$$

$$З_{доп} = К_{доп} * З_{осн} = 0,15 * 83952 = 12593\ rub$$

$$С_{зп} = 83952 + 12593 = 96545\ rub$$

5.9.1 Contributions to extrabudgetary funds

The amount of contributions to extrabudgetary funds is 27.1% in 2020 of the total cost of labor of employees directly involved in the performance of work.

$$С_{внеб} = К_{внеб} * (З_{ос} + З_{доп}) \quad (14)$$

Where $К_{внеб}$ is the coefficient of contributions to social funds.

$$С_{внеб} = 0,271 * (74098,3 + rub, 4) = 22819\ \text{rub}$$

5.9.2 General expenses

To take into account the general costs, it is necessary to take into account the costs of maintaining the management apparatus and the general economic services (university), which apply equally to all scientific research work carried out. This article takes into account the remuneration of administrative staff, the maintenance of buildings, office equipment and household goods, depreciation of property, labor protection and training costs.

General expenses take into account other expenses of the organization that are not included in the items of previous expenses: printing and photocopying of research materials, payment for communication services, electricity, postal and telegraphic costs, reproduction of materials, etc. Its value is determined by the following formula:

$$З_{накл} = К_{нр} * (сумма\ статей\ 1 \div 6) \quad (15)$$

where $К_{нр}$ is the coefficient taking into account overhead costs.

The value of the overhead coefficient is taken in the amount of 15%.

$$З_{накл} = 0{,}15 * (74098{,}3 \div 10104{,}4) = 12630{,}4\ \text{rub}$$

5.9.3 Formation of the budget for the costs of scientific and technical research (STR)

The calculated value of the research work is the basis for the formation of the project cost budget. The definition of the budget for the research project for each implementation option is given in table 20.

Table 20 - CALCULATION OF THE BUDGET EXPENDITURES STR

Title of the article	Cost of expenses in rubles
1. Material costs of STR	7017
2. The cost of equipment	1907153
3. Main staff costs involved in the interpretation of the subject	179225.4
4. Extra Budgetary contributions (funds)	22819
5. General expenses	12630,4
Total cost of budget STR	2128844.8

The planned cost of work is 2128844.8 rub.

5.9.4 Organizational structure of the project

The structure most appropriate to this work is the project structure, which includes all its participants and is created to successfully achieve the goals of the project. The organizational structure of this project is shown in Figure 32.

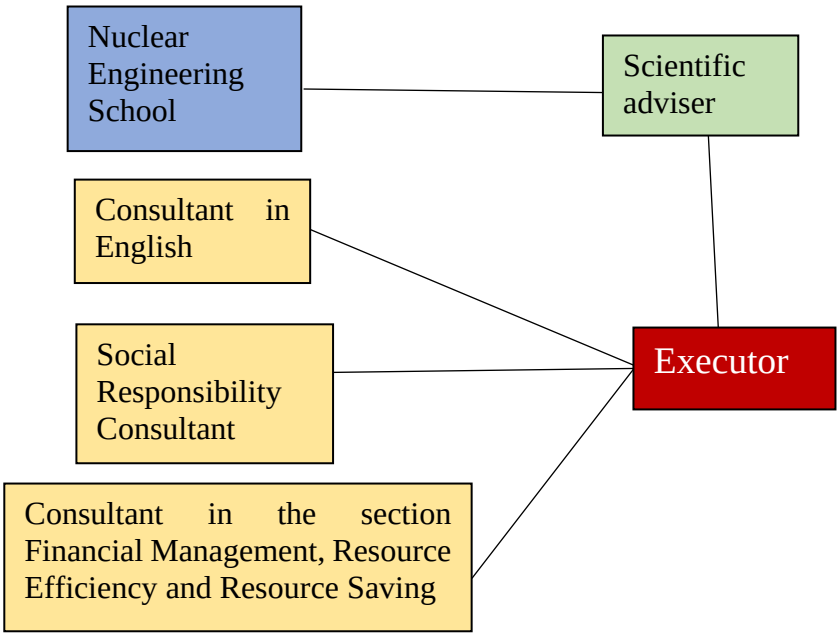

Figure 32- The organizational structure of the project

5.9.5 Responsibility Matrix

The liability matrix determines the degree of responsibility of each member of the project for a task, if he has something to do with it.

Table 21- RESPONSIBILITY MATRIX

Project stages	Scientific adviser	Consultant English language	Consultant management	Consultant Social Respons.	Master
Analysis and study of literature	O				И
Hardware and software study	O				И
Creation, verification of treatment plans for SBRT	O				И
Analysis and processing of data	O				И
Comparison of results with international requirements	O				И
Issuing an explanatory note	C				И
Preparation for the defense of the thesis	C				И
Resource Efficiency and Resource Evaluation			C		И
Social Responsibility Section				C	И
English translation		C			И

Responsible (O) - the person responsible for the implementation of the project phase and monitoring its progress. Contractor (I) - the person (s) performing work as part of the project phase. Approver (U) - the person who approves the results of the project stage (if the stage provides for approval). Coordinator (C) - a person who analyzes the results of the project and participates in the decision on whether the results of the stage meet the requirements.

5.9.6 Calculation of scientific and technical effect

Recently, to assess the scientific value, technical significance and effectiveness of planned and performed work, the method of point estimates has been widely used, on the basis of which it is concluded that R&D is appropriate. The

essence of this technique is that based on the assessment of the signs of work, the coefficient of the scientific and technical effect of R&D is determined by the formula 16:

$$H = \sum_{i=1}^{3} К_I * n_i \quad (16)$$

where H is an indicator of the Scientific and Technical Level (STL);

k is the weight coefficient of the i-th attribute of STL;

n is the score (in points) of the i-th attribute.

Table 22 shows the assessment of STL Graduation work (WRC).

Table 22- ASSESSMENT OF STL GRADUATION WORK (WRC).

Sign of STL	weight coefficient	Characteristic development	Selected point
Novelty level	0.6	New	8
Theoretical Results	0.4	Statement of experience	1
Possibility of implementation	0.2	During the first years	10
		industry	4

$$H = 8 * 0{,}6 + 1 * 0{,}4 + 10 * 0{,}2 + 4 * 0{,}2 = 8$$

According to the STL scale, this scientific and technical work corresponds to a relatively high level.

5.10 Reference of financial management, resource efficiency and resource saving

1. Financial management, resource efficiency and resource conservation: a training manual / I.G. Vidyaev, G.N. Serikova, N.A. Gavrikova, N.V. Shapovalova, L.R. Tukhvatulina Z.V. Krinitsyna; Tomsk Polytechnic University. - Tomsk: Publishing house of Tomsk Polytechnic University, 2014. - 36 p.

6 SOCIAL RESPONSIBILITY

6.1 Introduction

The objective of the work was to prepare and describe the VMAT plans, to carry out evaluation qualitative for the critical organs and evaluation qualitative of the quality control plans for five patients with liver metastases.

The process of research was carried out on at the Tomsk Regional Oncology Center. Application area: Radiotherapy, oncology.

For 5 patients with metastases liver, RT planning, an independent verification of radiation plans, and treatment delivery using fractionated SBRT with a VMAT dose delivery technique were performed. To conduct topometric preparation for all patients, Elekta Synergy is a high-energy linear accelerator with an intensity modulation function was used. The complex of means for immobilizing patients during topometric preparation and the treatment itself consisted of a system ABC. To create an exposure plan, a dosimetric planning system was used with a dose calculation algorithm based on the Monte Carlo Monaco method (version 5.1).

An analysis of the results of therapy obtained during work for the five patients suggests a favorable outcome of treatment of liver metastasis with SBRT.

To achieve our objective, we carried out the measures related to the evaluation of patients with liver metastases and the application of the established protocol for the management of this disease, in order to improve the patient's quality of life.

6.2 Legal and organizational items in providing safety

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 [1].

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

a) to have a workplace that meets Occupational safety requirements;

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

c) 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;

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

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

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

g) 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;

h) 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;

i) 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.

6.3 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.

6.4 Occupational safety

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

The object of investigation is “to prepare and describe the VMAT plans, to carry out evaluation qualitative for the critical organs and evaluation qualitative of the quality control plans for five patients with liver metastases”. Therefore, object of investigation itself cannot cause harmful and dangerous factors.

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

The main elements of the production process that form dangerous and harmful factors are presented in Table 23.

Table 23 - POSSIBLE HAZARDOUS AND HARMFUL FACTORS

Factors (GOST 12.0.003-2015)	Work stages			Legal documents
	Develop-ment	Manu-facture	Exploi-tation	
1. Deviation of micro-climate 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. Sanitary rules GOST 12.1.038-82 SSBT. Electrical safety. Maximum permissible levels of touch voltages and currents.
2. Excessive noise		+	+	
3.Increased level of electromagnetic radiation	+	+	+	
4. Insufficient illumination of the working area		+	+	
5. Abnormally high voltage value in the circuit, the closure which may occur through the human body	+	+	+	

Table 23 continuation

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:

a) Physical:

1) temperature and humidity;
2) noise;
3) static electricity;
4) electromagnetic field of low purity;
5) illumination;
6) presence of radiation;

b) Psychophysiological:

1) 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 optimum and permissible values of the microclimate characteristics are established in accordance with [2] and are given in Table 24.

Table 24 - 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

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 [2], the intensity of the electromagnetic field at a distance of 50 cm around the screen along the electrical component should be no more than:

a) in the frequency range 5 Hz - 2 kHz - 25 V / m;
b) in the frequency range 2 kHz - 400 kHz - 2.5 V / m.

The magnetic flux density should be no more than:

a) in the frequency range 5 Hz - 2 kHz - 250 nT;
b) 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.

Table 25 -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.

Table 26 – RADIATION INDEX

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.

6.4.3 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:

a) at least 30 m^3 per hour per person for the volume of the room up to 20 m^3 per person;
b) 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:

a) increase the distance from the source (the screen should be at least 50 cm from the user);
b) 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 [2], 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.

Increased levels of ionizing radiation

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:

a) radiation characteristics of radiation sources, pollution in air, liquid and solid wastes.
b) radiation factors developed with technological processes in working places and environment.
c) radiation factors of contaminated environment.
d) irradiation dose levels of personnel and population.

The main controlled parameters are:

a) annual effective and equivalent doses
b) intake and body content of radionuclides

c) volume or specific activity of radionuclides in air, water, food products, building materials and etc.

d) radioactive contamination of skin, clothes, footwear, working places and etc.

e) dose and power of external irradiation.

f) 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.

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.

6.5 Ecological safety

6.5.1 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.

6.5.2 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 goes 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.

6.5.3 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.

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.

6.6 Safety in emergency

6.6.1 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:

a) malfunction of current-carrying parts of installations;

b) work with open electrical equipment;

c) short circuits in the power supply;

d) non-compliance with fire safety regulations;

e) presence of combustible components: documents, doors, tables, cable insulation, etc.

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

6.6.2 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.

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:

a) elimination of the formation of a flammable environment (sealing equipment, control of the air, working and emergency ventilation);
b) use in the construction and decoration of buildings of non-combustible or difficultly combustible materials;
c) the correct operation of the equipment (proper inclusion of equipment in the electrical supply network, monitoring of heating equipment);
d) correct maintenance of buildings and territories (exclusion of the source of ignition - prevention of spontaneous combustion of substances, restriction of fire works);
e) training of production personnel in fire safety rules;
f) the publication of instructions, posters, the existence of an evacuation plan;
g) compliance with fire regulations, norms in the design of buildings, in the organization of electrical wires and equipment, heating, ventilation, lighting;
h) the correct placement of equipment;
i) well-time preventive inspection, repair and testing of equipment.

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

a) inform the management (duty officer);
b) call the Emergency Service or the Ministry of Emergency Situations - tel. 112;
c) take measures to eliminate the accident in accordance with the instructions.

6.7 Conclusions of social responsibility

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.

6.8 References of social responsibility

1 Federal Law "On the Fundamentals of Labor Protection in the Russian Federation" of 17.07.99 № 181 – FZ.

2 SanPiN 2.2.2 / 2.4.1340-03. Sanitary-epidemiological rules and standards "Hygienic requirements for PC and work organization".

3 GOST 12.1.038-82 Occupational safety standards system. Electrical safety.

4 Fire and explosion safety of industrial facilities. GOST R12.1.004-85 Occupational safety standards system. Fire safety.

CONCLUSION

Five patients with liver metastases were treated at the Tomsk Regional Oncology Center, thanks to the range of equipment for remote radiotherapy with support for VMAT dose delivery technology, which includes the Elekta Synergy linear accelerator and the Monaco dosimetric planning system, the SBRT procedure was possible for the treatment of liver metastases. Based on the dose-volume histogram (DVH), the plans were evaluated, the most optimal treatment plan was selected taking into account the tolerant levels of radiation of critical organs and the tumor. Using the ArcCHECK cylindrical dosimetric phantom supported by 3DVH software, verification of the treatment plan was produced undistorted and provided an analysis of the reasons for mismatch / plan mismatch according to the necessary selection criteria. The ABC or Active breathing coordinator system is the respiratory gating system used with the Elekta treatment machine. Importance is highlighted of respiratory management during radiotherapy treatment to ensure optimal dose delivery to both the tumor volume and surrounding organs. Although breathing evaluation was not described in this study, an analysis is recommended of the measured dose distributions to determine if the level of coverage is similar in dependence on the breathing rates from other studies.

Analysis of treatments data and results of MRI exams concludes that liver metastases were more common in the right lobe than in the left lobe in this study.

Finally, it is concluded that SBRT technique gets much advantages in clinical practice, ensuring delivering prescribed dose to the target and minimizing dose to the surrounding normal tissues, so it requires high accuracy and synchronous facilities. Although it takes much time for planning, the duration of treatment is short. This is an accurate and safe technique in modern radiation therapy.

FUTURE WORK

While this project has established that VMAT is a viable treatment option for liver metastases, no testing procedures were performed using respiratory management to determine which method provides optimal dose restrictions. In the plans created for the five patients of this investigation, the VMAT plan developed adequate dose coverage without higher doses for organs at risk. A planning study should be undertaken by experienced planning staff to determine which technique offers the best dosimetric outcomes. These outcomes should also be weighed against other factors including reduced treatment delivery time for VMAT, planning and calculation times, VMAT patient verification measurements and inability to use the 6D positioning system with current 4D techniques.

A novel investigation to follow this project is to repeat the investigation with a flattening filter-free (FFF) treatment method. FFF is currently being commissioned for use in the Prince of Wales Radiation Oncology department. An investigation into the viability of FFF treatment would be required to assess the effect of the forward peaked beam and significantly faster dose delivery times (approximately 4 times faster for 10 MV Elekta beams).

Finally, measurements should be repeated for each of the treatment techniques following implementation of gating within the department.

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2. WHAT IS NUCLEAR MEDICINE? // XII Materials of the international scientific-practical conference, "Modern Intellectual Transformation of Socio-Economic Systems, Russia, Saratov, February 15, 2018.

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Appendix 1.

Isodose curves shown on CT images (liver)

The figures 16-20 below shows the DVH for each patient.

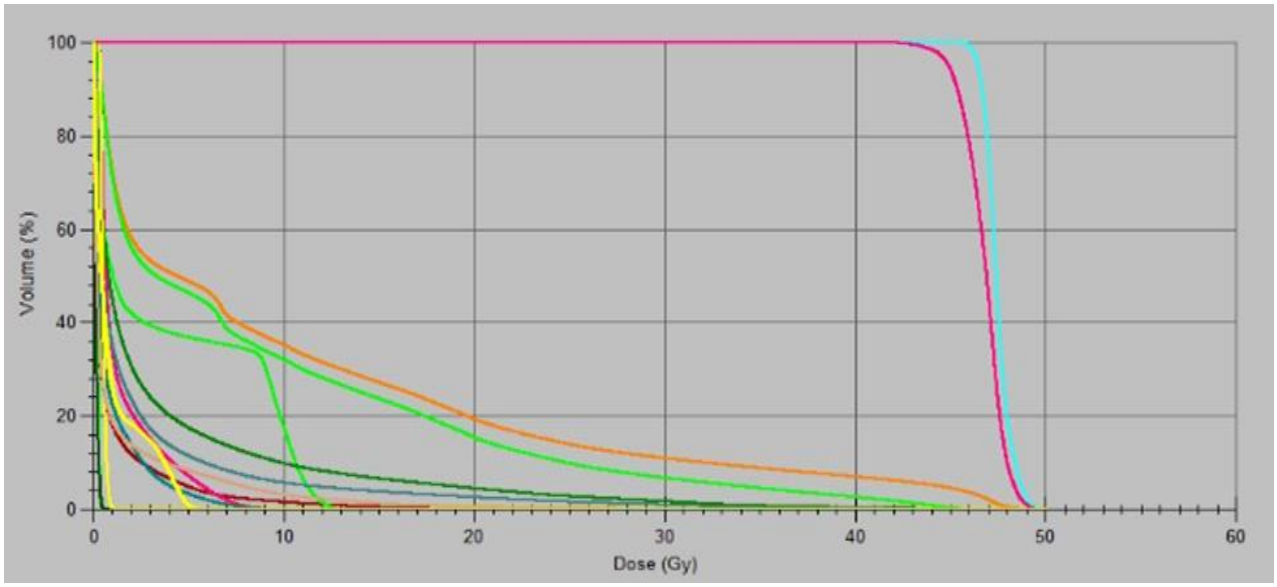

Figure 17- DVH for the patient 1

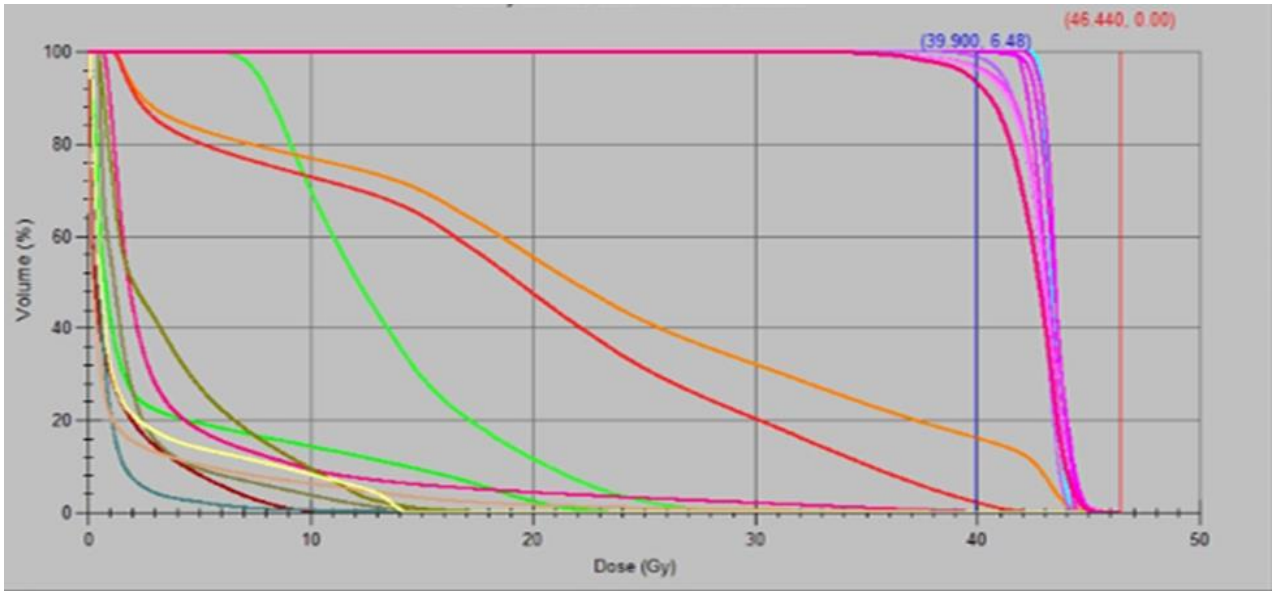

Figure 18- DVH for the patient 2

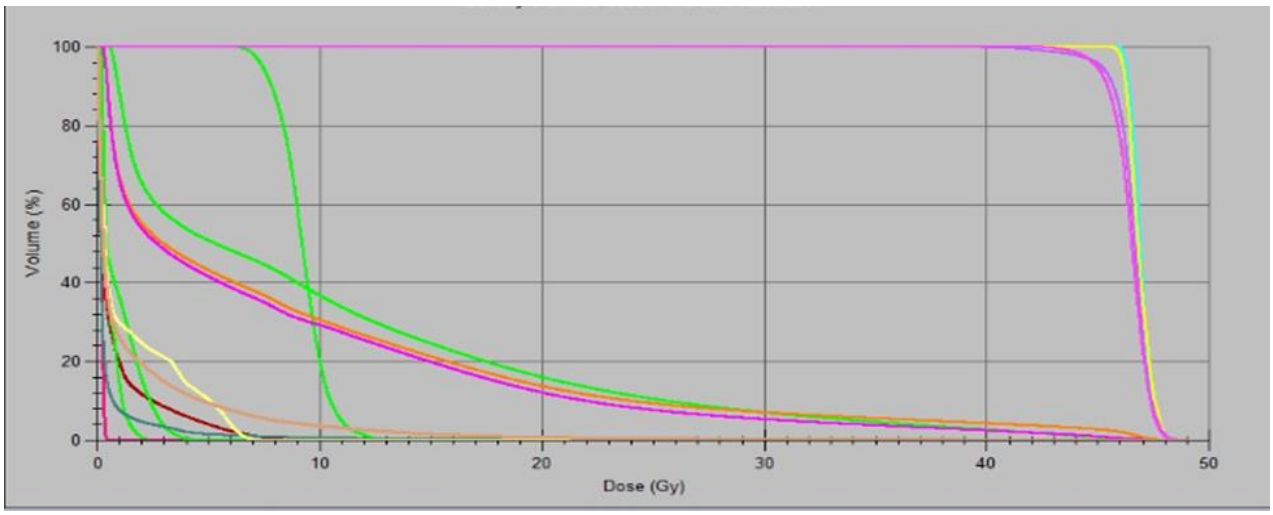

Figure 19- DVH for the patient 3

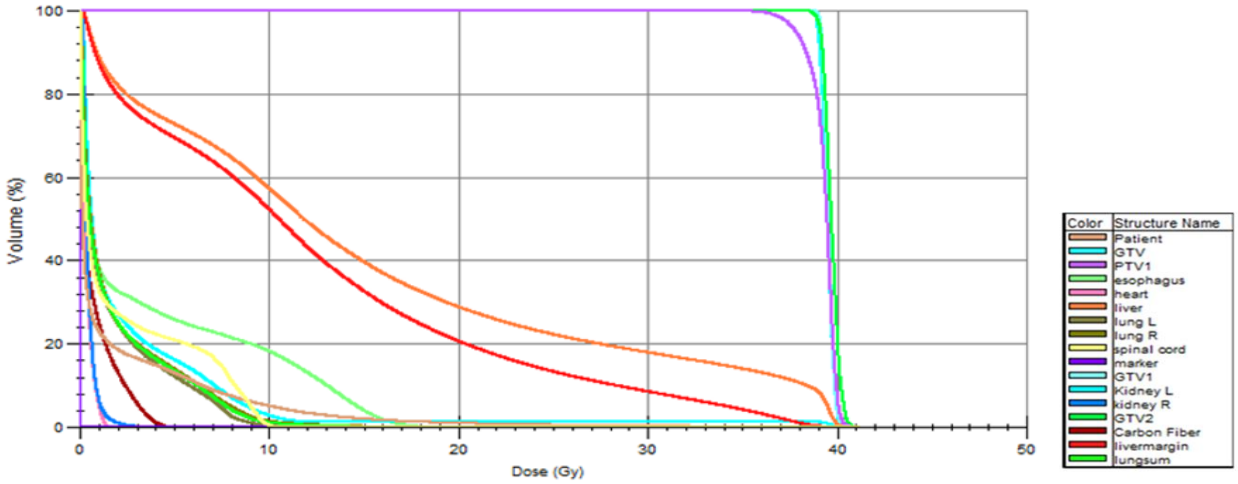

Figure 20- DVH for the patient 4

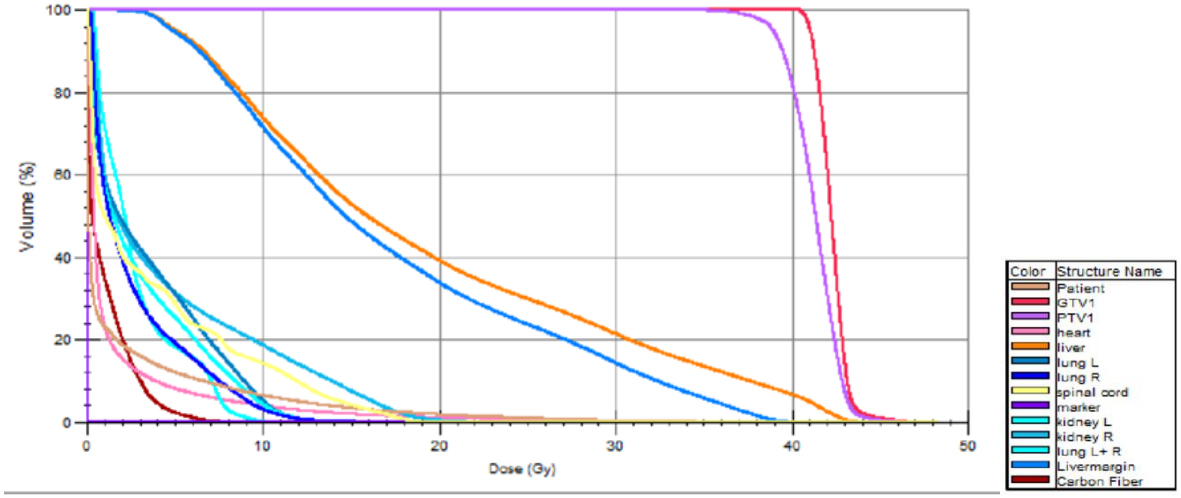

Figure 21- DVH for the patient 5

Appendix 2.

Table 9 – DATA OF DVH FOR ALL 5 PATIENTS

Patient	Structure	Volume (cm^3)	Min. Dose (Gy)	Max. Dose (Gy)	Mean. Dose (Gy)	% in Volume	% Vol < Cold Ref	% Vol > Hot Ref
1	GTV	37.008	45.091	50.016	47.479	100.00	0.00	0.14
	PTV	102.098	40.188	50.016	46.769	100.00	1.73	0.05
	Liver Margin	2183.910	0.080	47.271	8.827	100.00		16.85
	Lung S.	5098.790	0.050	48.868	2.360	99.46	-	4.90
	Spinal C	62.918	0.001	5.827	1.019	99.13	-	-
	Kidney R	246.558	0.019	0.569	0.147	100.00	-	0.00
	Heart	611.386	0.220	10.160	1.466	100.00	-	-
2	GTV1	2.859	42.239	44.501	43.369	100.00	100.00	0.00
	GTV2	75.432	38.215	46.082	43.439	100.00	99.04	0.00
	GTV3	4.140	41.973	45.241	43.570	100.00	99.53	0.00
	PTV	306.699	19.539	46.440	42.752	100.00	38.23	0.00
	Liver Margin	1540.839	1.082	43.807	18.881	100.00	-	50.44
	Lung S.	4572.417	0.058	22.824	0.874	99.58	-	0.29
	Heart	622.395	0.596	41.452	4.111	100.00	-	2.04
	Spinal C.	112.557	0.075	14.463	2.142	99.73	-	0.00
	Kidney R	224.064	0.381	20.649	3.753	100.00	-	42.10
	PTV1	17.958	37.258	44.828	42.747	100.00	39.68	0.00
	PTV2	258.396	19.814	46.440	42.839	100.00	35.40	-
	PTV3	22.437	33.082	46.056	42.422	100.00	6.48	0.00
3	GTV1	4.872	45.768	48.500	46.939	100.00	0.00	0.00
	GTV2	2.406	45.576	48.425	46.873	100.00	0.00	0.00
	PTV1	28.428	37.287	48.966	46.548	100.00	1.20	0.00
	PTV2	18.840	41.365	49.074	46.447	100.00	0.26	0.00
	Liver Margin	1512.192	0.198	48.685	7.888	100.00	-	13.13
	Lung S	2918.076	0.018	48.520	0.494	99.33	-	0.44
	Spinal C.	82.920	0.019	7.246	1.389	99.51	-	0.00
	Kidney R	124.914	0.544	48.241	9.779	100.00	-	24.58

Table 9 continuation

4	GTV1	26.643	38.571	40.526	39.490	100.00	0.01	0.00
	GTV2	8.136	38.650	40.446	39.545	100.00	0.00	0.00
	GTV3	16.833	38.246	41.167	39.707	100.00	0.25	0.00
	PTV	177.972	32.734	41.167	39.292	100.00	1.75	0/00
	Liver Margin	1377.012	0.118	40.582	12.250	100.00	-	21/95
	Kidney R	113.208	0.105	3.408	0.458	100.00	-	0.10
	Lung S	3734.130	0.048	20.557	1.761	98.59	-	0.37
	Spinal C	45.030	0.025	10.391	2.136	99.53	-	0.00
5	GTV	32.370	39.864	48.239	42.260	100.00	0.01	2.15
	PTV	107.103	28.732	48.239	41.247	100.00	2.04	1.31
	Liver Margin	1150.644	0.974	42.263	17.173	100.00	-	
	Kidney R	100.302	0.242	23.829	4.563	100.00	-	40.54
	Lung	2911.248	0.081	29.198	3.043	99.12	-	-
	Spinal cord	78.519	0.059	19.693	3.692	99.69	-	0.00

Appendix 3.

ArcCHECK QA of Dose Distribution

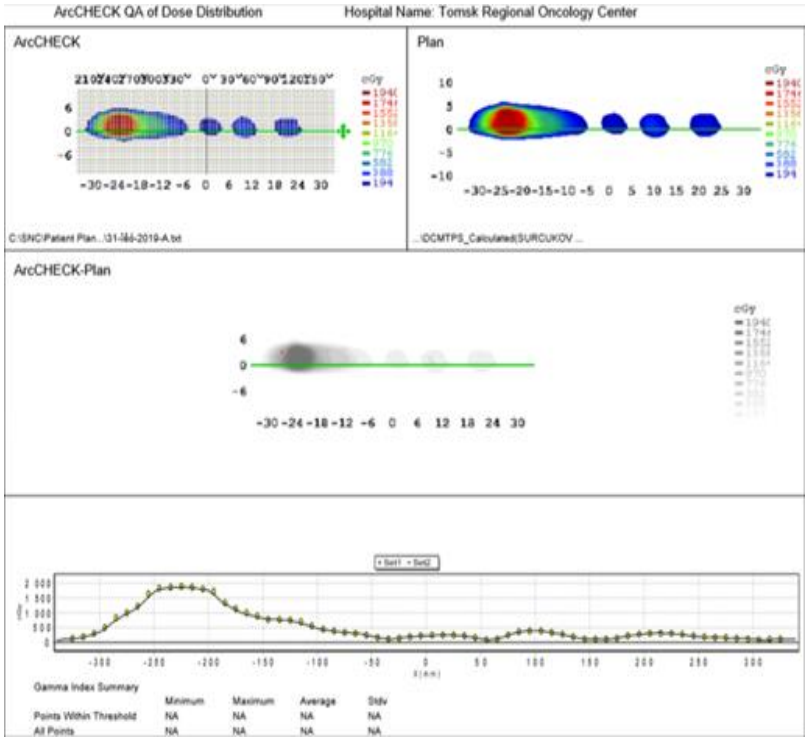

Figure 22- Patient 1

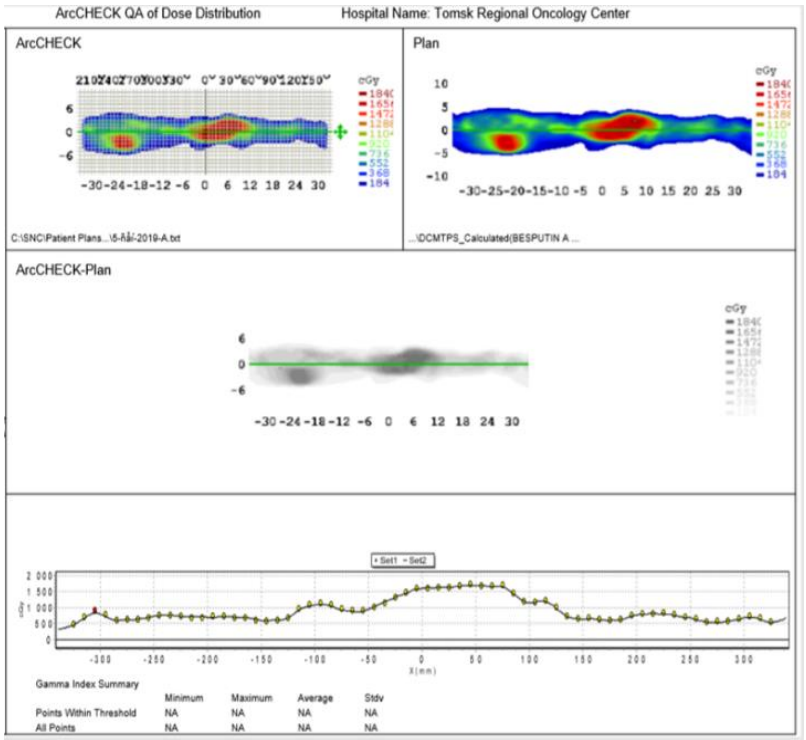

Figure 23- Patient 2

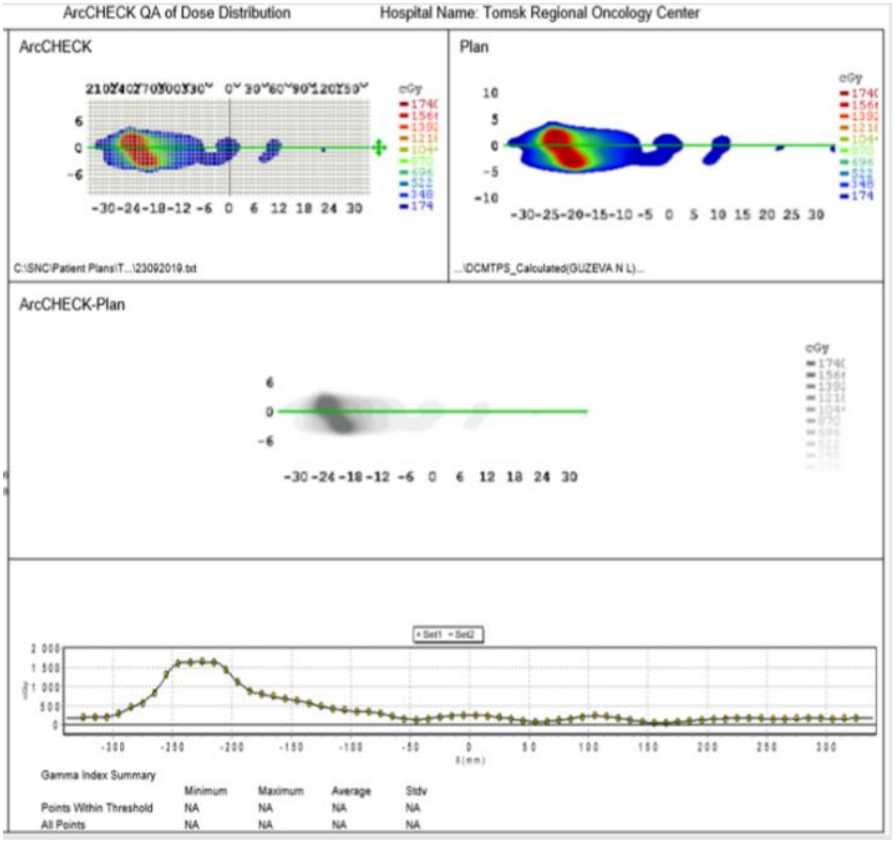

Figure 24- Patient 3

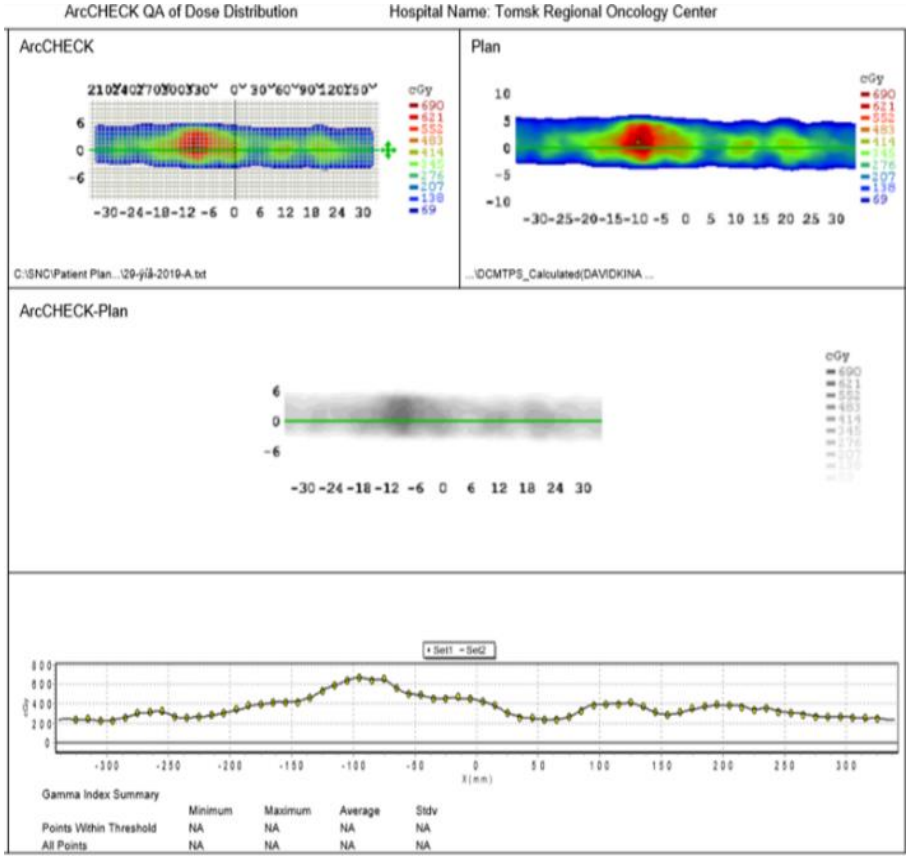

Figure 25- Patient 4

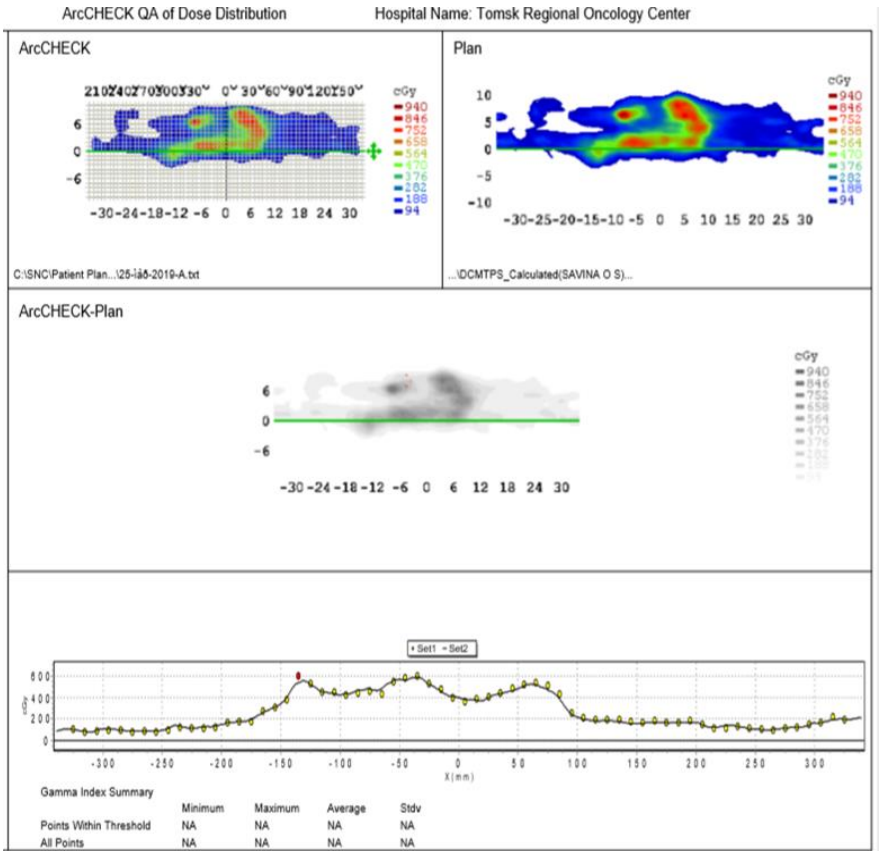

Figure 26- Patient 5

Appendix 4.

Table 11- CT / RMI of the abdominal cavities with contrasting dynamics

Patient	Conclusions	
	Data provided 2019 year	Data provided 2020 year
1	09.10.2019 Liver segment 7- as of 07/28/2018 negative dynamics in the form of an increase in total size by 100%, changes in the nature of contrast gain. Liver segment 6- formation of fluid without gas probably a hemangioma.	16.02.2020 Segment 6 liver, probably hemangioma. For the period of 09/10/2019 - negative dynamics. Signs of distal obstruction of both ureters with the formation of hydronephrosis of both kidneys and ectasia of the ureters. Recommended: oncologist consultation, dynamic control of MRI in dynamics, ultrasound / MRI.
2	01.06.2019 Liver segment 2, 3, 6 and 8 - solid formations in the liver. As of March 13, 2019 - stabilization of formations in the form of an increase in total size by a maximum of 8% (segment 2). - Choledochoectasia 25.12.2019 Segments 2, 3, 6 and 8 - solid formations in the liver - mts. As of 31.10.2019 progression in the form of an increase in non-target formations by a maximum of 40%. - Choledochoectasia	Not yet done -

Table 11 continuation

3	26.07.2019 Liver segment 6- hypovascular liver formation Liver segment 7- cystic formation. Hepatomegaly, fatty hepatosis. 05.12.2019 Hepatic Mts (Liver segment 4), secondary damage of the abdominal lymph nodes - negative dynamic of 27.07.2019. Moderate hepatomegaly. Steatosis of the liver.	Not yet done - -
4	09.09.2019 CT- In the liver parenchyma, hypodense lesions with weak peripheral accumulation of the contrast agent are determined: in liver segment 4a - the lesion 15x11x17 mm (previously 5x5 mm), in liver segment 8 - two discharge lesions with a total size of 34x30x44 mm (previously 30x20x27 mm), in liver segment 5 - lesions 31x36x30 mm (previously 14x14x17 mm) and 13x10x11 mm (previously 6x7x7 mm). The gates of the liver are differentiated, the portal vein is 12 mm. The hepatic veins are not dilated, their contours without features. Choledoch up to a diameter of 6. Bile ducts without filling defects, somewhat enlarged in the left lobe of the liver.	Not yet done
5	05.03.2019 CT- The structure of the liver is disturbed due to multiple different-sized hyperactive focal changes, with fuzzy contours, diameters from 0.7 cm to 3.7 * 3.3 cm, the largest: in liver segment 2- 1.3 cm, in liver segment 3- 3.3 * 3.6 cm, in liver segment 8- 1.4cm, in liver segment 5-2.0cm, in liver segment 7-2.5cm.	Not yet done