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 and Engineering
Field of training (Specialty): 14.04.02. Nuclear Physics and Technology
Division: Nuclear Fuel Cycle

MASTER'S GRADUATION THESIS

Topic of research work
The probability of complications of organs at risk (OAR) of the Head-and-neck with Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy Techniques

UDC:615.47: 615.849: 616.831

Student

Group	Full name	Signature	Date
0AM8M	**Tawfik Helmy Tawfik Abdelmalak**		

Scientific supervisors

Position	Full name	Academic degree, academic rank	Signature	Date
Associate professor	Evgeniia Sukhikh.	PhD		
Professor	Dr.Ehab Mostafa	MD		

Adviser

Position	Full name	Academic degree, academic rank	Signature	Date
Radiation Oncologist	Alexander Taletsky			

ADVISERS:

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate professor	Menshikova E.V.	PhD		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Date
Senior lecturer	Verigin D.A	Cand.of Sc		

ADMITTED TO DEFENSE:

Director of the programme	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Cherepennikov Yu.M.	PhD		

Tomsk – 2020

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Division: Nuclear Fuel Cycle

APPROVED BY:
Director of the programme
_____CherepennikovYu.M.
«____» _____ 2020

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Magister's Dissertation

For a student:

Group	Full name
0AM8M	Tawfik Helmy Tawfik Abdelmalak

Topic of research work:

The probability of complications of organs at risk (OAR) of the Head-and-neck with Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy Techniques	
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 date for research work: *(the name of the object of research or design; performance or load; mode of operation (continuous, periodic, cyclic, etc.); type of raw material or material of the product; requirements for the product, product or process; special requirements to the features of the operation of the object or product in terms of operational safety, environmental impact, energy costs; economic analysis, etc.)*	Using Monaco software to create radiotherapy plans for patients with head and neck cancers to compare between two different techniques of radiotherapy.
List of the issues to be investigated, designed and developed *(analytical review of literary sources with the purpose to study global scientific and technological achievements in the target field, formulation of the research purpose, design, construction, determination of the procedure for research, design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).*	1. literature review about Head and Neck cancer (risk factor, pathology, clinical picture, diagnosis, treatment) 2. literature review about different techniques of radiotherapy and radiobiological evaluation.

	3. Create radiotherapy plans for selected patients and analysis thee data.

Advisors to the sections of the Master's Graduation Thesis
(with indication of sections)

Section	Advisor
1. Literature review	Evgeniia Sukhikh/Ehab Mostafa/Alexander
2. Practical part	Evgeniia Sukhikh/Ehab Mostafa/Alexander
3. Financial management	Menshikova E.V.
4. Social Responsibility	Verigin D.A

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

Assignment issued by a scientific supervisors/advisors:

Position	Full name	Academic degree, academic status	Signature	Date
Associate professor	Evgeniia Sukhikh	PhD		
Professor	Dr.Ehab Mostafa	MD		
Radiation Oncologist	Alexander Taletsky			

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM8M	Tawfik Helmy Tawfik Abdelmalak		

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

To the student:

Group	Full name
0AM8M	Tawfik Helmy Tawfik Abdelmalak

School	Nuclear Science & Engineering	**Division**	Nuclear-Fuel Cycle
Degree	Master	**Specialization**	14.04.02 Nuclear physics and technology / Nuclear medicine

Input data to the section «Financial management, resource efficiency and resource saving»:	
1. *Resource cost of scientific and technical research (STR): material and technical, energetic, financial and human*	– Salary costs – 319,289; – STR budget –509,060;
2. *Expenditure rates and expenditure standards for resources*	– Electricity costs – 5,8 rub per 1 kW
3. *Current tax system, tax rates, charges rates, discounting rates and interest rates*	– Labor tax – 27,1 %; – Overhead costs – 30%;
The list of subjects to study, design and develop:	
1. *Assessment of commercial and innovative potential of STR*	– comparative analysis with other researches in this field;
2. *Development of charter for scientific-research project*	– SWOT-analysis;
3. *Scheduling of STR management process: structure and timeline, budget, risk management*	– calculation of working hours for project; – creation of the time schedule of the project; – calculation of scientific and technical research budget;
4. *Resource efficiency*	– integral indicator of resource efficiency for the developed project.
A list of graphic material *(with list of mandatory blueprints):*	
1. *Competitiveness analysis* 2. *SWOT- analysis* 3. *Gantt chart and budget of scientific research* 4. *Assessment of resource, financial and economic efficiency of STR* 5. *Potential risks*	

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

Task issued by adviser:

Position	Full name	Scientific degree, rank	Signature	Date
Associate professor	E.V. Menshikova	PhD		

The task was accepted by the student:

Group	Full name	Signature	Date
0AM8M	Tawfik Helmy Tawfik Abdelmalak		

Task for section
«Social responsibility»

To student:

Group	Full name
0AM8M	Tawfik Helmy Tawfik Abdelmalak

School	Nuclear Science and Engineering	Department	Nuclear fuel cycle
Degree	Master programme	Specialization	14.04.02 Nuclear physics and technology / Nuclear medicine

Title of graduation thesis:

The probability of complications of organs at risk (OAR) of the Head-and-neck with Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy Techniques	
Initial data for section «Social Responsibility»:	
1. Information about object of investigation (matter, material, device, algorithm, procedure, workplace) and area of its application	– Effect of exposure to ionizing radiation in radiation oncology centers on patients and health care workers due to exposure to radiation machines (e.g Elekta machine). – Application area: radiation oncology centers.
List of items to be investigated and to be developed:	
1. Legal and organizational issues to provide safety: – Special (specific for operation of objects of investigation, designed workplace) legal rules of labor legislation; – Organizational activities for layout of workplace.	– Labour 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	– Enchanced 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, rank	Signature	date
assistant professor	Verigin D.A.	Cand.of Sc.		

The task was accepted by the student:

Group	Full name	Signature	date
0AM8M	Tawfik Helmy Tawfik Abdelmalak		

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 (PC-1,2, 3, 6, UC-1,3), Criterion 5 RAEE (p 1.1)
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-2,6,9,10,14, UC-2,3,4, BPC1,2), Criterion 5 RAEE (p 1.2)
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-4,5,6,9,22, UC-1,2,5,6), Criterion 5 RAEE (p 1.3)
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-7,10,11,12,13, UC-1-3,BPC1,3), Criterion 5 RAEE (p 1.4)
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-8,11,14,15, BPC-1), Criterion 5 RAEE (p 1.3)
LO6	To demonstrate ability to develop multi-option schemes for achieving production goals with the effective use of available technical means and resources.	FSES HE Requirements (PC-12,13,14,16, BPC-2), Criterion 5 RAEE (p 1.3)
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 (PC-2,6,9,10,14, UC-1,2,3), Criterion 5 RAEE (p 1.2,2.4,2.5)
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 (PC-16,17,21, UC-5,6, BPC-1), Criterion 5 RAEE (p 2.6) coordinated with

		the requirements of the international standard EURACE & FEANI
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 (BPC-3, UC-2,4), Criterion 5 RAEE (p 2.2)
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-18,20,21,22,23, UC-1,4, BPC-2), Criterion 5 RAEE (p 1.6,2.3) coordinated with the requirements of the international standard EUR-ACE & FEANI

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School School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 «Nuclear Physics and Technology»
Level of education Master Degree Program
Division Division for Nuclear-Fuel Cycle
Period of completion 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 section (module) / type of work (research)	Maximum score for the section (module)
27.01.2020	1. Preparation of technical specifications and selection of research areas	
24.02.2020	2. Development of a common research methodology	
23.03.2020	3. Selection and study of materials on the topic	
13.04.2020	4. Obtaining necessary data and verification of the obtained results	
27.04.2020	5. Processing received data	
18.05.2020	6. Registration of the work performed	
29.05.2020	7. Preparation for defending a dissertation	

COMPILED BY:
Scientific supervisors:

Position	Full name	Academic degree, academic rank	Signature	Date
Associate professor	Evgeniia Sukhikh	Ph.D		
Professor	Dr.Ehab Mostafa	MD		

Adviser

Position	Full name	Academic degree, academic rank	Signature	Date
Radiation Oncologist	Alexander Taletsky			

AGREED BY:
Director of the programme

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	Cherepennikov Yu.M.	Ph.D		

Abstract

Master's Graduation work includes 121 pages, 7figures, 22 tables, 167 sources.

Key- Words: radiotherapy, intensity modulated radiotherapy, head and neck tumour, boost, biological effective dose.

Purpose of work: Compare prescription dose coverage of PTV and complication of OAR based on DVH (dose volume histogram) from SEQ and SIB plans delivered with volumetric modulated arc therapy (VMAT) for patients with squamous cell cancer of the head and neck.

Field of application: treatment of patients.

Economic efficiency / significance of work: high.

Practical assignment of the work:

1. Based on different techniques of radiotherapy are used in treatment of head and neck cancers.
2. Create treatment plans for patients by two different techniques SEQ and SIB.
3. Analysis plans based on DVH and Evaluate received physical dose.
4. Asses plans based on BED.

The results of the conducted research have been presented at the TPU conference” X All-Russian scientific-practical conference "Scientific initiative of foreign students and graduate students of Russian universities" In April 22-24, 2020.

List of Abbreviations

BED - Biological Equivalent Dose
CT Scan - Computerized Tomography
CTV-N - Cervical lymph node Clinical Target Volume
CB - Concomitant Boost
CBCT - Cone-Beam CT
CTV-T - Primary Tumour Clinical Target Volume
DPF - Dose Per Fraction
EBV - Epstein-Barr virus
EUA - Examination Under Anaesthesia
EBRT - External Beam Radiation Therapy
FNA - Fine Needle Aspiration
GTV - Gross Target Volume
Gy - Gray
HNC - Head and Neck Cancer
HNSCCs - Head and Neck Squamous Cell Carcinomas
HSV - Herpes Simplex Virus
HIV - Human Immunodeficiency Virus
HPV - Human Papilloma Virus
IGART - Image Guided Adaptive Radiation Therapy
IGRT - Image Guided Radiation Therapy
IgM - Immunoglobulin M
IMRT - Intensity-Modulated Radiation Therapy
IORT - Intra-Operative Radiation Therapy
LRC - Loco-Regional Control
LQM - Linear Quadratic Model
MRI - Magnetic Resonance Imaging
MMMF - Man-Made Mineral Vitreous Fibers
MLC - MultiLeaf-Collimator
Mus - Monitor Units
NCCN - National Comprehensive Cancer Network
ND - Neck Dissection
NTD - Normalized Total Dose
OARs - Organs at Risk
OS - Overall Survival
OTT - Overall Treatment Time
PEG - Percutaneous Endoscopic Gastrostomy
PD - Physical Dose
PTV - Planning Target Volume
PET - Positron Emission Tomography

PET/CT - Positron Emission Tomography/ Computerized Tomography
PRV - Planning Organ at Risk Volume
RT - Radiation Therapy
RTOG - Radiation Therapy Oncology Group
RE - Relative Effectiveness
SD - Standard Deviation
SEQ - Sequential Boost
SIB - Simultaneous Integrated Boost
SCC - Squamous Cell Carcinoma
SABR - Stereotactic Ablative Body Radiation therapy
SBRT - Stereotactic Body Radiation Therapy
TV - Target Volumes
TPS - Treatment Planning System
3DCRT - Three-Dimensional Conformal Radiation Therapy
TCP - Tumour Control Probability
VMAT - Volumetric Modulated Arc Therapy

Table of Contents

Introduction

Head and neck cancer belong to the most prevalent cancers and are the sixth leading cause of cancer worldwide. Most of the cases represent squamous cell carcinoma (SCC) arising in the stratified epithelium of the oral cavity, pharynx, and larynx. Head and neck squamous cell carcinomas (HNSCCs) develop in the mucosal linings of the upper aerodigestive tract(1).

Head and neck cancer encompass malignant tumours of the upper aerodigestive tract including the pharynx, larynx, oral cavity, nasal cavity, paranasal sinuses, and salivary glands. Head and neck cancer are widespread in several regions of the world. Worldwide, head and neck cancer account for more than 550,000 cases and 380,000 deaths annually (2).

Tobacco and alcohol abuse are two important risk factors associated with oral, pharyngeal and laryngeal cancer (3). Viral infection also plays a role, with associations between the human papillomavirus (HPV) and oropharyngeal cancer (4), as well as the Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (5).

Treatment options include surgery, chemotherapy and radiation. Most of early-stage I and II patients can be treated with single modality therapy using either surgery or radiation alone, and survival rates are similar for both treatment types (6). By contrast, when advanced stage III and IV cancer is treated to cure the patient, this needs multimodality therapy to include surgery with adjuvant radio(chemo)therapy or organ preservation chemoradiation (7),or chemotherapy as induction treatment followed by surgery or radio(chemo)therapy.

Radiotherapy is an effective treatment modality in head and neck cancer. It may be used as a definitive treatment (with or without chemotherapy), as an adjuvant treatment after surgery, or after surgery to treat local failure. In recent years new radiotherapy methods have been developed. These techniques aim to reduce the radiation dose to critical tissues near the tumour while still providing an adequate dose

to the tumour volume so that control rates are not compromised. This allows a high dose to be delivered to the tumour while sparing organs at risk, resulting in less acute and late toxicity compared to 3DCRT, in particular xerostomia (8).

The IMRT technique is characterized by a highly conformal dose distribution to targets, while a constraint dose to organs at risk (OARs)(9). Sequential boost (SEQ) intensity-modulated radiation therapy regimens for head and neck cancer (HNC) consist of elective irradiation followed by a series of reduced boost fields aiming at the various overall doses required for tumour control or OARs tolerance. By contrast, IMRT with a simultaneous integrated boost technique allows the simultaneous delivery of individualized dose levels of selective target volumes (TV) by creating one single treatment plan. Simultaneous integrated boost (SIB) technique became popular as it improved planning efficiency and escalated the dose per fraction delivered to the gross target volume (GTV) to potentially improve tumour control(10).

Several studies have reported that SIB-IMRT is a safe and effective treatment for HNC, while it provides the following advantages: (1) shortening of the treatment time; (2) increased biologically equivalent dose (BED) to the tumour with dose per fraction slightly >2 Gy; and (3) more conformal dose distributions compared to that of SEQ-IMRT which is divided into a large-field phase and a boost phase(11).

Some studies showed that SIB-IMRT could present a risk of locoregional failure because of the lower marginal doses. Thus, patients undergoing SIB-IMRT were liable to side effects when the doses given to the adjacent critical structures or other normal tissues were the main concern in the high-dose region(12).

Volumetric arc therapy (VMAT) is an IMRT extension, that allows irradiation with simultaneously changing multileaf-collimator (MLC) position, gantry position, and dose rate (13).Volumetric-modulated arc therapy (VMAT) has been shown to provide similar plan quality with respect to fixed-field IMRT but with a significant reduction in treatment time leading to improved patient comfort and probably smaller intra-fraction movements and also reduction in monitor units (MUs) number (14).

Dual arc VMAT is a quick and accurate treatment technique for head and neck cancer. VMAT plans including double arcs for simultaneous-integrated boost treatments of head-and-neck cancer have been found to be improved compared to static-beam step-and-shoot IMRT plans including 5–9 beam ports regarding dose to OARs and dose conformity, although delivery times were significantly reduced by 50%(15). Stromberger et al study compared the two VMAT boost techniques (SEQB vs. SIB) and found that the SIB technique was associated with a lower rate of acute and late toxicities(16).

1.Literature review

1.1. Epidemiology

Worldwide, head and neck cancer represent more than 550,000 cases and 380,000 deaths every year (2). In the United States, head and neck disease represents 3 percent of malignancies, with around 63,000 Americans developing head and neck disease every year and 13,000 dying from the disease (17). In Europe, there were around 250,000 cases (an estimated 4 percent of the cancer incidence) and 63,500 deaths 2012 (18). Males are affected significantly more than females, with a ratio ranging from 2:1 to 4:1.

1.2. Risk Factors

Smoking, alcohol consumption, human papillomavirus (HPV) infection (especially for oropharyngeal cancers), and Epstein-Barr virus (EBV) infection (especially for nasopharyngeal cancers in Asia) are the most frequently associated risk factors for head and neck cancer(5).

Tobacco items: Smoking tobacco products (cigarettes, stogies, pipes) is a significant hazard factor for the development of head and neck cancer. In heavy cigarette smokers, there is an increased risk of cancer of 5 to 25 times greater than that of non-smokers (19). Smokeless tobacco (both chewing tobacco and snuff) is associated with an increased risk of developing oral and pharyngeal cancer(20).

Alcohol: Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract, although it is frequently hard to isolate the impacts of smoking and alcohol. Alcohol intake and tobacco smoking seem to have an interactive and multiplicative impact on the risk of developing head and neck cancer (21).

Numerous sorts of viral infections have been related to an increased risk of head and neck cancer, including especially EBV, HPV, and human immunodeficiency infection (HIV).

Epstein-Barr virus: Nasopharyngeal carcinoma is a moderately uncommon malignancy in most populations but is one of the most well-known cancers in southern China. A large body of evidence supports the role of EBV as the essential etiologic agent in the pathogenesis of nasopharyngeal carcinoma(22).

Human papillomavirus: Epidemiologic and molecular evidence has established a causal job for HPV, primarily type 16, in patients with head and neck cancer, especially that originating in the base of the tongue and the tonsils. HPV associated oropharyngeal tumors are usually seen in younger men who do not use tobacco and alcohol(23).

Herpes simplex virus: Herpes simplex virus (HSV) is less strongly correlated with the development of oral carcinomas than EBV or HPV. Serologic studies have shown that patients with head and neck cancer have more significant levels of the immunoglobulin M (IgM) antibody to HSV type 1(24). HSV can convert cells in vitro into a malignant phenotype. This may be because of an HSV-encoded peptide that increases the mutagenicity of infected cells(25).

Immunodeficiency: Immunodeficiency because of infection with HIV has been related to an increased risk of cancer in the head and neck region. There is an approximately two- to three-fold increase in the incidence of squamous cell carcinoma of the head and neck for people infected with HIV, with variation depending upon the particular site of origin. Other histologic types of cancer may also be increased in the head and neck region, including lymphoepithelial carcinoma of the salivary gland, nasopharyngeal carcinoma, and Merkel cell carcinoma(26). Between 24 and 40 percent of the head and neck cancers in patients infected with HIV are related to human papillomavirus (HPV), which is not significantly different than in the general population(27).

Betel nut chewing: which is widespread in specific districts of Asia, is an independent risk factor for the development of squamous cell head and neck cancer (28).

Multiple other occupational or environmental toxins: have been studied for a potential association with head and neck cancer. These include asbestos, pesticides, man-made mineral vitreous fibers (MMMF), polycyclic aromatic hydrocarbons (29), textile workers, wood workers (30), manufacturers of mustard gas, plastic and rubber products, naphthalene refiners, ethanol, sulfuric acid mist, leather and paint workers, automobile mechanics, construction workers (cement) (31).

Radiation: Prior irradiation for either malignant or benign disease has been connected to thyroid cancer, salivary gland tumours, SCCs, and sarcomas (32).

Diet: Numerous studies indicate that the risk of nasopharyngeal carcinoma is increased in frequent consumers of preserved meats that contain high levels of added nitrites (33).

Different hereditary factors: and pathways may contribute to an increase in the risk of head and neck cancer, and these factors may interact with other known risk factors. Examples of these factors include metabolic polymorphisms that influence exposure to the carcinogens in tobacco smoke, DNA repair gene polymorphisms, and variations in other pathways contributing to carcinogenesis (34).

Different factors: also, may contribute to the development of head and neck cancer in selected patients. These include poor oral hygiene and periodontal disease, which has been related to carcinoma of the oral cavity (35). On the other hand, dental prostheses or poorly fitting dentures do not appear to be independent risk factors for the development of oral carcinoma (36).

1.3. Anatomic Subsites

Cancer of the head and neck includes a number of cancers, mainly squamous cell carcinoma, originating from a variety of sites classified into five main areas:

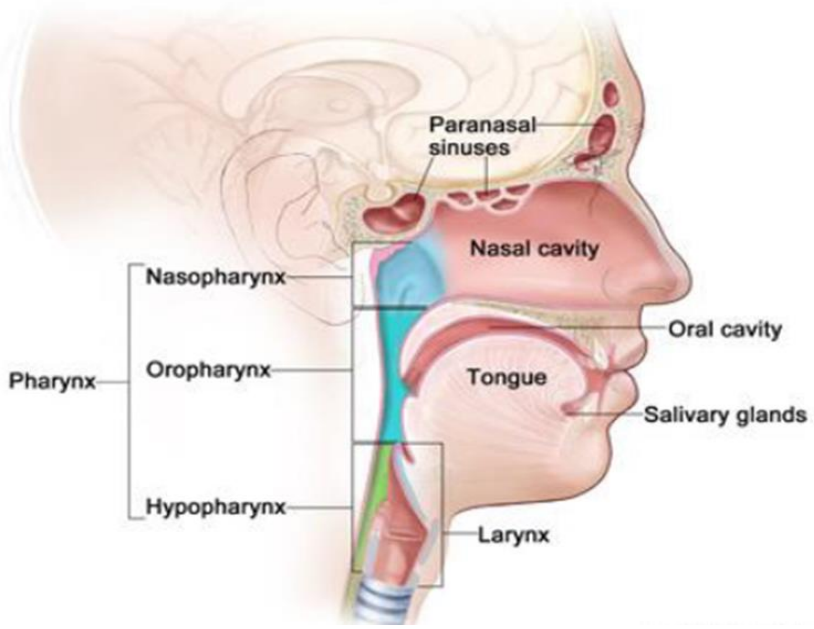

Figure 1– Anatomy of head and neck.

The lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, and upper and lower gingiva are included in the oral cavity. The vermilion of the lips determines the anterior boundary of the oral cavity. The posterior boundary is defined by the tongue's circumvallate papillae, the anterior tonsillar pillars (palatoglossus muscles), and the posterior hard palate margin. The hard palate defines the upper boundary of the oral cavity. The oral cavity is inferiorly defined by the mylohyoid muscles. The oral cavity's lateral boundary is defined by the buccomasseteric region (the cheeks ' buccal mucosa) and the retromolar trigone (located behind the third mandibular molar).

The pharynx is divided into the nasopharynx, oropharynx, and hypopharynx:

1. The nasopharynx forms the nasal cavity continuation. The boundary between the nasal cavity and nasopharynx is determined by the posterior choanae of

the nasal cavity. The nasopharynx is superiorly defined by the basisphenoid and basiocciput (clivus) and inferiorly by the hard and soft palate. The posterior edge of the nasopharynx is the prevertebral muscle and the anterior margin of the cervical spine at C1 and C2 levels. The posterolateral boundary of the nasopharynx includes many essential structures. The lateral wall of the nasopharynx is elevated by the torus tubarius, a cartilaginous structure that forms the opening of the Eustachian tube. The Eustachian tube allows communication between the middle ear and the nasopharynx through a pharyngobasilar fascia defect (sinus of Morgagni), which lines the nasopharynx. The Morgagni sinus may give nasopharyngeal cancer access to the skull base. The Rosenmüller fossa (lateral nasopharyngeal recess), a typical site of nasopharyngeal cancer, is located posterior to the torus tubarius. Also, the nasopharynx contains the adenoids (nasopharyngeal tonsils), located in the midline roof of the nasopharynx.

2. The soft palate determines the boundary between the nasopharynx and oropharynx. The circumvallate papillae and the anterior tonsillar pillars divide the oropharynx anteriorly from the oral cavity. The oropharynx structures are the palatine tonsils, posterior tonsillar pillars, tongue base (a posterior one-third of the tongue), valleculae, soft palate and the posterior pharyngeal wall. The oropharynx is inferiorly defined by the hyoid and the pharyngoepiglottic folds.

3. The hypopharynx consists of the pyriform sinuses, the posterior surface of the larynx (post cricoid area), and the inferior, posterior, and lateral pharyngeal walls.

The larynx divided into three anatomical regions: the supraglottic region, the glottic larynx (true vocal cords and mucosa of the anterior and posterior commissures), and the subglottic larynx extending to the lower border of the cricoid cartilage.

The nasal cavity and the paranasal sinuses (maxillary, ethmoidal, sphenoidal, and frontal).

The major (parotid, submandibular, and sublingual) and minor salivary glands. Minor salivary glands are located within the submucosa throughout the oral cavity,

palate, paranasal sinuses, pharynx, larynx, trachea and bronchi, but are most prominent in the buccal, labial, palatal, and lingual regions (37).

1.4. Pathology:

The neoplastic processes are extremely varied and extensive in the H&N. Most of H&N epithelial tumours are Squamous Cell Carcinoma as the normal epithelial lining in the oral, oropharyngeal cavities and larynx is composed of squamous epithelium. Squamous metaplasia occurs frequently as a result of damage to the respiratory type epithelium normally present in the nasal cavity, paranasal sinuses and upper aero-digestive tract and pre-neoplastic changes (squamous dysplasia) are well known as a result of tobacco smoke and alcohol consumption.

Viruses are essential in the pathogenesis of nasopharyngeal and oropharyngeal tumours. Epstein Barr Virus (EBV) presents as non-keratinising SqCC (nasopharyngeal carcinoma).

SqCC is generally classified into non-keratinizing and keratinizing subtypes. They can be classified according to the amount of keratinization present (Broders classification) as well-differentiated (keratinization greater than 75%), moderately differentiated (keratinization between 25 and 75%), and poorly differentiated (keratinization less than 25%).

Respiratory type (pseudostratified columnar ciliated) epithelium that lines the nasal cavity and paranasal sinuses may result in adenocarcinomas.

Normal salivary glands consist of serous and mucinous acinar cells and ducts with surrounding myoepithelial cells and supporting stroma.

In the salivary glands, neoplasia consists of a number of benign and malignant tumours, some of which have similar morphological and immunohistochemical appearances such as Mucoepidermoid carcinoma (most common malignant primary salivary gland neoplasm), Adenoid cystic carcinoma, Acinic cell carcinoma.

Metastases to H&N are rare and usually caused by primaries that originate in the kidney, colon, breast, lung, thyroid, prostate or melanoma. Identification often involves immunohistochemistry as well as a detailed clinical history and radiological correlation (38).

Premalignant pathology:

Leukoplakia is characterized by hyperparakeratosis and is commonly associated with underlying epithelial hyperplasia. the possibility of malignant transformation is less than 5 percent in the absence of underlying dysplastic changes.

Erythroplakia has red superficial patches adjacent to normal mucosa. It is usually associated with epithelial dysplasia and up to 40 percent of cases are associated with carcinoma in situ or invasive tumours (39).

1.5. Clinical Presentation

The majority of H&N cancers are more frequent in the 50–70 age group. They typically present with the effects of a local tumour in the organ of origin or with enlarged malignant nodes. The clinical presentation of head and neck cancer varies widely depending on the primary site and exposure to different risk factors.

Nasopharyngeal carcinoma: The most common presenting complaint is a neck mass because of regional lymph node metastasis. Symptoms because of the primary tumour may include hearing loss (associated with serous otitis media), tinnitus, nasal obstruction and pain, and its associated growth into adjacent anatomical structures, which may result in muscle involvement and impaired function of cranial nerves II to VI. Adults with a unilateral effusion must have a nasopharynx examination.

Oropharyngeal tumours: Presenting complaints may include dysphagia, pain (odynophagia, otalgia), obstructive sleep apnoea or snoring, bleeding, or mass of the neck.

Hypopharyngeal tumours: Patients with these tumours frequently remain

asymptomatic for a longer period of time and are thus more likely to be seen in the later stages of the disease. Dysphagia, odynophagia, otalgia, weight loss, haemoptysis, dyspnoea, and neck mass are typically presenting symptoms.

Laryngeal cancer: The symptoms associated with cancer of the larynx depend on location. The initial complaint of glottic cancers may be persistent hoarseness; Subsequent symptoms may include dysphagia, referred otalgia, chronic cough, haemoptysis, and stridor. Supraglottic cancers are frequently discovered later and may present with airway obstruction or palpable metastatic lymph nodes. Primary tumours in the subglottis are rare. Affected patients usually present with stridor or complaints of dyspnoea on exertion.

Sinus tumours: Epistaxis, proptosis, diplopia, swelling, trismus, and unilateral nasal obstruction are common symptoms of sinus tumours. Facial and/or head pain may be seen in later stages, because of pressure or tumour infiltration into nerves or periosteum. Malignant enlarged nodes manifest in 5% at presentation.

Oral cavity tumours: Patients may have mouth pain or nonhealing mouth ulcers, loosening of teeth, ill-fitting dentures, dysphagia, odynophagia, weight loss, bleeding, or referred otalgia.

Tongue cancer may develop as an infiltrative and/or exophytic lesion. The presenting symptom is always a pain, with or without dysarthria. Dysarthria means deep muscle invasion of the advanced tumour stage. Maybe there is a long history of leukoplakia or erythroplakia.

Lip cancer typically presents as an exophytic or ulcerative lesion of the lower lip that is sometimes associated with bleeding or pain. Many patients complain of numbness of the skin of the chin because of the involvement of the mental nerve.

Salivary gland tumours: The patient usually presents with a painless mass or swelling. Parotid tumours typically present as a lump in the gland.

Systemic symptoms such as anorexia and weight loss are uncommon in H&N cancer unless the tumour site affects swallowing directly.(40)

1.6. Diagnosis and Staging Evaluation

Initial evaluation: The initial evaluation of the primary tumour is based on a thorough history and combination of inspection, palpation, indirect mirror examination, or direct flexible laryngoscopy. Physical examination must include careful evaluation of the nasal cavity and oral cavity with visual examination and/or palpation of mucous membranes, the floor of the mouth, the anterior two-thirds of the tongue, tonsillar fossae and tongue base (best seen on mirror examination or flexible laryngoscopy), palate, buccal and gingival mucosa, posterior pharyngeal wall and external auditory canal examination.

An examination under anaesthesia: An examination under anaesthesia often is done to best characterize the extent of the tumour, to check for synchronous second primary tumours, and to take biopsies for tissue diagnosis. Symptom-directed pan endoscopy (laryngoscopy, bronchoscopy and esophagoscopy) shows a 2.4 to 4.5 percent incidence of second primary tumours of the upper aerodigestive tract, but not of the lower airways (41). There is evidence that positron emission tomography (PET) may augment or replace pan endoscopy in the detection of synchronous primary cancers there is still a risk of false negatives. pan endoscopy can find synchronous primaries that are too small to be identified with PET, whereas PET can identify tumours of a lower aerodigestive tract not seen with pan endoscopy(42).

Fine needle aspiration biopsy: Fine needle aspiration (FNA) biopsy is often used to make an initial tissue diagnosis of a head and neck cancer when a patient has a mass of neck (metastatic cervical lymph node) without an obvious primary mucosal upper aerodigestive tract site. This technique has a high degree of sensitivity and specificity and a diagnostic accuracy that ranges from 89 to 98 percent (43).

sentinel lymph node biopsy: is usually done at the same time with surgical tumour resection for staging the clinically and radiologically N0 neck in patients with early-stage head and neck cancer. Sentinel lymph node biopsy is technically feasible,

efficient, oncologically safe, and associated with less morbidity than an elective dissection of the neck (44).

Imaging studies: may augment the physical exam and evaluation of squamous cell carcinoma of the head and neck, especially to evaluate the degree of local invasion, the involvement of regional lymph nodes, and the presence of distant metastases or second primary malignancies. The most common metastatic sites are the lungs, liver, and bone, (45) whereas the most common sites of second primary malignancies are the head and neck, followed by the lungs and oesophagus.

CT scan: CT can identify head and neck tumours based on either anatomic distortion or specific tumour enhancement. Tumours typically enhance more than normal head and neck structures except for mucosa, extraocular muscles, and blood vessels. Compared to MRI, CT provides greater spatial resolution, and can be done with faster acquisition times, thereby virtually eliminating motion artefact, and it is better for bone destruction assessment (46).CT is especially useful for upstaging cancers with deeper local invasion or infiltration into adjacent structures that are difficult to detect on physical examination. CT evaluation of regional lymph nodes primarily relies on size criteria as well as the appearance of lymph nodes to discriminate involved from uninvolved lymph nodes and also to detect extracapsular tumour spread. Pathologic lymphadenopathy is generally defined radiologically as a node greater than 10 to 11 mm in minimal axial diameter or a node with central necrosis(47).Other features suggesting pathological lymph nodes include rounded shape, loss of normal fatty hilum, increased or heterogeneous contrast enhancement, clustering of lymph node, and location of sentinel lymph node (48).

Magnetic resonance imaging: MRI provides superior soft-tissue description compared to CT (49) MRI is also better than CT to discriminate tumour from mucus and to detect invasion of bone marrow (50). On the other hand, CT scanning is better than MRI to detect invasion of the bone cortex because MRI reveals no bony detail. MRI is superior to CT for determining perineural spread, invasion of the skull base, and

intracranial extension. MRI scan is the imaging modality recommended by the National Comprehensive Cancer Network (NCCN) guidelines for evaluating skull base erosion(51).

Integrated PET/CT: have greatly replaced other tests because PET/CT is effective for the identification of occult regional nodal metastases, as well as occult distant metastases, unknown primary lesions, and synchronous second primary tumours. PET/CT is sensitive and superior for deep lesions assessment (52).

1.7. Overview of Treatment

Integrated approach to management:

For optimal decision making, treatment planning, and posttreatment response assessment, a multidisciplinary approach is needed. This must include surgeons, medical oncologists, and radiation oncologists, as well as dentists, speech/swallowing pathologists, dieticians, and rehabilitation therapists (53).

Management of Squamous Cell Carcinomas:

Localized (early stage) disease: About 30 to 40 percent of patients with head and neck squamous cell carcinomas present with stage I or II (early stage) disease. Such patients are generally treated with either primary surgery or definitive radiation therapy (RT). In situ carcinoma patients are usually surgically treated the same way as T1 patients. RT and surgery result in similar local control and survival rates for many sites; the choice of therapy is usually based on the specific site and its requirements, surgical accessibility of the tumor, and the functional outcomes and morbidity associated with each modality. For patients initially treated with surgery for clinically early-stage cancers, postoperative RT with or without concurrent chemotherapy is recommended for those that are pathologically locoregionally advanced, and have close or positive margins and other factors, including perineural invasion and lymphovascular invasion that increase the risk of local recurrence. The finding of

multiple lymph nodes on elective lymph node dissection in the clinically N0 patient is also an indication for radiation. (51).

Locoregionally advanced disease: Locoregionally advanced (stage III/IV) squamous cell carcinoma of the head and neck is associated with a high risk of local recurrence as well as distant metastases. Combined modality approaches (surgery, RT, and/or chemotherapy) are usually required to improve the chances for long-term disease control(54). These combined modality methods include primary surgery followed by either postoperative RT or concurrent chemoradiotherapy, induction chemotherapy (the addition of chemotherapy before surgery and/or RT), concurrent chemoradiation treatment without surgery, and sequential therapy (induction chemotherapy followed by concurrent chemoradiation treatment) without surgery. Definitive RT, combined chemoradiotherapy, and sequential therapy are usually reserved for patients who are medically inoperable, who have unresectable disease, or who have a resectable disease where surgical resection cannot be done with acceptable long-term functional consequences (e.g., total glossectomy that may require tubal ligation to avoid aspiration)(51).

Definitive RT alone, often using a modified fractionation schedule, remains a treatment option for older adult patients and those with poor performance status, as the meta-analysis found a lack of benefit for concurrent chemotherapy in those in their 70's and a possible detriment for those in their 80's (54).

Surgery:

Simple excision without reconstruction is often enough for small cancers and depending on site and surgical expertise it may be with a knife, transoral laser or robotic operation. One potential benefit of primary surgery over primary radiotherapy is that there is a definitive pathological assessment that can assist with prognosis and guide adjuvant treatments for those at higher risk of local recurrence (55). Adjuvant radiotherapy to the primary site may be prescribed with close/involved excision margins when further surgery is not possible. With larger cancers, the need for full

microscopic excision is counterbalanced by the challenge of functional restoration, especially when a large excision necessitates the reconstruction of bone and/or soft tissue(56).For people with positive excision margins, adjuvant radiotherapy to the primary site is usually recommended for T3/T4 tumors, and concurrent chemotherapy.

Neck dissection (ND) is the cornerstone of neck therapy. Two key factors determine the extent of the surgery. Firstly, nodal levels with involved nodes identified by imaging at staging will be dissected. Therefore, ND is recommended for nodal levels at risk of occult metastases based on knowledge of tumour biology and spread routes, even though there is no imaging evidence of node metastases. Adjuvant neck radiotherapy (+/− concomitant chemotherapy) is recommended where adverse pathological features indicate higher rates of recurrence ,such as extra-capsular nodal spread or more than one involved node (57).

Curative and Adjuvant Chemotherapy:

Concomitant chemotherapy means weekly or three weekly cisplatin during a radiotherapy course for stage III/IV disease. This potentiates the effect of radiation, increasing cure rates by about 6.5% but also increasing acute and late side effects (54). Other drugs are also used. Cetuximab is especially well-proven (58)

Neoadjuvant or induction chemotherapy is the use of chemotherapy as the initial treatment, usually prior to definitive radiation. The response is common but there is insufficient evidence that tumour shrinkage results in increases in overall cure rates. So, this method has currently been especially used in “organ preservation” techniques where a response to neoadjuvant chemotherapy enables a non-surgical approach to laryngeal and hypopharyngeal cancers to potentially preserve speech and swallowing (59).

Radiation therapy (RT)**:**

Radiotherapy is an effective and potentially curative treatment for head and neck cancers. RT yields better functional outcomes than surgery for many primary sites within the head and neck and, thus, is often favoured for localized disease. RT is often

used in combination with chemotherapy as a definitive organ function-preserving strategy for locoregionally advanced lesions, or as an adjuvant following surgery.

External beam radiation therapy (EBRT): is used to treat most head and neck cancers RT treatment at least requires a three-dimensional conformal technique. Highly conformal radiation methods, such as intensity-modulated RT (IMRT) and image-guided RT (IGRT), have showed reduced morbidity and represent the current standard of care (62).

Three-dimensional conformal RT: The current minimum standard for RT delivery to head and neck cancer is 3D-CRT.With 3D-CRT, the anatomical relationship between the tumor of the patient and normal anatomy is used to deliver a radiation dose that conforms to the target volume and reduces exposure to other structures. 3D-CRT requires an accurate definition of anatomy, a sophisticated treatment planning system that can measure the dose in three dimensions, and a treatment device that can deliver the specified dose(60).

Intensity-modulated RT(IMRT): an advanced form of 3D-CRT, is indicated for treating cancers of head and neck. IMRT uses nonuniform radiation beam intensities to optimize the delivery of radiation to the planned target volume while reducing the irradiation of normal tissue outside the target (64).

Volumetric Modulated Arc Therapy (VMAT): With the advent of volumetric modulated arc therapy (VMAT), where the gantry moves around the patient as the beam is being modulated, the delivery of each IMRT dose to the tumor has become much quicker. Usually, IMRT plans take 20 to 25 minutes for delivery of the daily treatment, while a VMAT plan can now be delivered in about three to five minutes (about 1.5 minutes per gantry rotational arc), which is better for patients. Randomized studies now show that IMRT can decrease side effects (especially xerostomia) compared with older three-dimensional conformal techniques, even in the setting of concurrent chemotherapy(61). Additionally, the improved ability to deliver more conformal RT

while still sparing normal organs has also enhanced tumor-related outcomes in some head and neck cancer patients with tumors of the paranasal sinus or nasopharynx (62).

Image-guided RT: Image-guided radiation therapy (IGRT):is a technique that complements IMRT in that improved pretreatment imaging on a daily basis allows margins to be minimized to ensure that the target is accurately treated in spite of daily tumor motion and setup error. IGRT uses high-resolution on-board imaging to direct radiation delivery immediately before each radiation treatment, not just during the treatment-planning process. These methods include onboard kilovoltage radiation imaging and cone beam CT scan(63).

Image-Guided Adaptive Radiation Therapy (IGART): More improvement of the IGRT enables the radiation treatment plan to be modified according to changes in tumor size or normal organ shifts during the six to seven weeks of treatment (68). Adaptive replanning can be used to increase the accuracy of treatment delivery when major anatomical changes have occurred due to patient weight loss, tumor shrinkage, or normal tissue change (69).

Stereotactic Body Radiation Therapy: Large doses of RT administered over one to five fractions to specific targets is called stereotactic body radiation therapy (SBRT) or stereotactic ablative body radiation therapy (SABR). This method has provided good local tumor control in a variety of tumor settings. With SBRT, it typically attacks only the gross tumor without prophylactic nodal irradiation. The procedure is more effective for smaller tumors and is usually well tolerated due to the smaller volume of treatment. The treatment can be performed with IGRT technology on most modern machines but requires special quality assurance and machine calibration. SBRT can be especially useful for patients with recurrent head and neck tumors who have had previous RT, where further conventional RT is limited (70). the short one- to two-week course of treatment may also be attractive for patients with a poor overall prognosis. Adding a systemic agent like cetuximab to these treatments can also improve local control rates (71).

Charged particle radiation: Heavy charged particles, such as protons or carbon ions, are being increasingly used for cancers of head and neck, especially those requiring high doses adjacent to critical organs at risk, such as the base of the skull, or in the reirradiation setting. proton therapy provides better dosimetric sparing of normal organs or structures for well-defined and relatively small lesions (64). Other particle beams, such carbon ions, are being investigated in other indications (eg, for tumors of the salivary gland)(65).

Brachytherapy: Brachytherapy uses a radioactive source inserted inside or next to the tumor using either an interstitial implant or an intracavitary device. Temporary implants, rather than permanent implants, are used for cancers in the head and neck region. Placing intracavitary brachytherapy radiation source in the lumen of cavitary structures, such as the nasopharynx or oral cavity. Brachytherapy may be used as a boosting technique after external beam treatment or as the sole treatment in carefully selected, small oral cavity or oropharynx tumors (66). Brachytherapy can administer high doses of radiation to the target and spare surrounding tissues.

Intraoperative Radiation Therapy: a larger dose of RT can be given during the operation. Orthovoltage or electron machines are usually used to deliver superficial treatments. This may be useful in recurrent head and neck tumors that have had prior RT, in which further RT is limited as part of salvage treatment. The benefit of intraoperative radiation therapy (IORT) is the ability to deliver the treatment directly to the surgical bed without having to deliver the dose through surrounding normal tissues. If the recurrence is amenable to surgical salvage, surgery with IORT is performed, and then followed by a lower dose of external beam radiation therapy (67).

1.8. Dose and Fractionation of Radiotherapy:

Daily radiation therapy (RT) using a dose of 2 Gy to gross tumour on a five-days-per-week schedule with a total dose of 66 to 70 Gy in seven weeks is the standard treatment regimen for definitive treatment of cancer of head and neck. For adjuvant radiotherapy 60 Gy has been the standard dose with 66 Gy if there are positive margins of resection or extra nodal spread. The prophylactic dosage to uninvolved nodal levels has often been 50 Gy.Nevertheless, there is evidence that alternative fractionation schedules can improve the outcomes (68)(51).

Alternative regimens are divided into categories:

Hypofractionation: Hypofractionation attempts to increase tumor control by increasing the biological effectiveness of the treatment by using higher daily doses of radiation and reducing the duration of the treatment course. it has most often been used in earlier-stage disease. Although increasing the dose per fraction usually causes concern about an increased risk of late effects, the relatively smaller radiation volumes in early-stage disease and the lack of concurrent chemotherapy use have mitigated those concerns. Increased daily doses for head and neck stereotactic body radiation therapy (SBRT) can range from 2.2 Gy per fraction up to 8.5 Gy per fraction. Although SBRT is usually used in the reirradiation setting, studies are emerging that will assess its role in the upfront setting, either for early-stage larynx cancer(69) or for patients who are too old or frail for a conventional extended course of RT for more-advanced disease(70).

This technique has become a standard for patients with early larynx cancer, with 63 Gy in 28 fractions usually used for stage T1 cancers and 65.25 Gy in 29 fractions used for T2 cancers with mobile vocal cords(71). The National Comprehensive Cancer Network (NCCN) guidelines recommend either conventionally fractionated RT (2 Gy per fraction to 66 to 70 Gy) or hypofractionated RT (2.25 Gy per fraction to 63 to 65.25 Gy) for early-stage, node-negative (T1-2, N0) cancer of glottis.

Another widely used hypofractionated regimen for radiation alone in earlier-stage oropharyngeal cancer is 66 Gy in 30 fractions (2.2 Gy per fraction), which was evaluated in the Radiation Therapy Oncology Group (RTOG) 0022 trial in T1-2N0-1 oropharyngeal cancer(72).

Hyperfractionation: Hyperfractionation attempts to increase tumor control by increasing the total radiation dose. Hyperfractionation uses multiple daily treatments with smaller-than-conventional fraction sizes given over about the same treatment duration. Typical hyperfractionation schedules use 1.1 to 1.2 Gy per fraction, two fractions per day (with a peroid of six hours or more between fractions), to total doses of 74 to 82 Gy. Long-term toxicity to normal tissues partly depends on the size of each treatment fraction, as well as the total radiation dose. Reducing the size of each radiation fraction must permit higher total doses without increasing late morbidity compared to conventionally fractionated irradiation (73). Hyperfractionation is now preferred over concomitant boost as the preferred regimen for intensified radiation therapy (RT) to exploit the benefits of tumor control without significantly increasing late effects (81)(82).

Concurrent chemoradiotherapy with hyperfractionated RT results in increased efficacy compared with hyperfractionated RT given without chemotherapy(74).

Accelerated fractionation: Accelerated fractionation attempts to decrease tumor repopulation as a prominent cause of radiation therapy (RT) failure during the course of RT by reducing the total time over which the radiation is administered. Accelerated fractionation administers the same or a slightly reduced total dose to the tumor but over a shorter course of treatment by giving multiple smaller doses (1.5 to 1.6 Gy) per day or administering additional standard-size doses (2 Gy) per week (e.g., six or seven fractions versus five fractions per week).

An older method widely used in the pre-intensity-modulated radiation therapy (IMRT) era was called "concomitant boost," in which 54 Gy was delivered in 30 fractions of 1.8 Gy once daily and a boost was provided by a second RT plan directed

to the gross disease only to a dose of 18 Gy in 12 fractions given as a second daily fraction. This method is not widely used in the IMRT era.

Accelerated regimens that employ continuous rather than split-course schedules and conventional without reducing the total dose of radiation do seem to improve local control (75)(76)(73).Concurrent chemoradiotherapy using accelerated RT doesn't seem to be superior to chemoradiotherapy with conventional fractionation of the RT (77).

Simultaneous integrated boost technique with IMRT : With the advent of intensity-modulated radiation therapy (IMRT) and its widespread adoption in the treatment of locally advanced head and neck cancer, the ability to increase the dose focally per fraction to the tumour itself while maintaining lower doses to elective areas of interest has gained popularity as a novel way of radiation therapy (RT) intensification. This has been studied most closely in the nasopharyngeal cancer setting, where the Radiation Therapy Oncology Group (RTOG) 0225 and 0615 trials using a regimen of 70 Gy in 33 fractions using 2.12 Gy per fraction. More recent results of this technique show excellent locoregional control and favourable toxicity profiles(78).

1.9. Local Control and Overall Survival

A meta-analysis has found improvements in both LRC (7% at 5 years) and absolute survival (3% at 5 years) with modified fractionated RT(79). And also another study has shown that there is a link between a change in LRC and a change in OS, with a 10% improvement in LRC at 2 years expected to lead to a 6.7% improvement in OS at 5 years(80).

Hyperfractionation and accelerated fractionation continuous reduced 5-year local-regional failure by 19% when compared to standard fractionation for patients with locally advanced head and neck squamous cell cancer treated with radiation therapy alone. At 5 years, LRC and overall survival were improved by Hyperfractionation only for patients with locally advanced SCC without increasing late toxicity (81).

Overall survival:

With respect to conventional radiotherapy, an improved overall survival can be achieved either through concomitant chemoradiotherapy, hyperfractionated RT with increased total dose. Accelerated radiotherapy regimens can achieve a smaller potential benefit in overall survival(82) (83)(84).

Loco-regional control:

An improved loco-regional control can be obtained either through moderate accelerated radiotherapy regimens delivered with a partial reduction in OTT, high total dose and no split course planned, hyperfractionation with an increased total dose, chemoradiotherapy with concomitant approach(82)(83)(75).

1.10. Complications of Radiotherapy

Most of the toxicity of radiation therapy (RT) can be divided into acute toxicity, which is mostly inevitable but transient, and late toxicity, which can be reduced but usually sustained. Acute toxicity is defined as events that occur during RT or within 90 days of treatment starting and late toxicity is defined as any changes noted after 90 days. Understanding of dose-response relationships for normal tissues of interest (e.g., parotid gland, larynx, pharyngeal constrictors) may reduce late toxicity. The simplest and most effective way of reducing acute toxicity is to avoid overtreatment (i.e., not treat unnecessarily large target volumes)(85).

Salivary gland damage and xerostomia: The salivary glands would be considered to be a late responding tissue with little acute effects due to their slow cellular turnover (60 to 120 days). Nevertheless, changes in the quantity and composition of saliva that occur shortly after the initiation of radiation therapy (RT) suggest that these glands exhibit both an acute response and a late response(86).

Temporary reduction in saliva production becomes evident within one to two weeks following the initiation of RT, and permanent reduction may be noted with

cumulative radiation doses as low as 10 to 15 Gy to the parotid gland (87).

Mean doses of radiation to the parotid glands greater than 24 to 26 Gy cause permanent damage to the parotid glands, which typically leads to more than a 75 percent reduction in salivary gland function (97). The radiation dose response of the oral cavity's submandibular gland and minor salivary glands is less well known than that of the parotid, but it is recommended that these organs be avoided in a manner that does not compromise target coverage. Xerostomia is the most prevalent late effect of RT for head and neck cancer (98). The degree of xerostomia largely depends on the volume of irradiated salivary tissue. A significant advantage of highly conformal RT strategies such as intensity-modulated RT (IMRT) is reduced salivary irradiation and thus less long-term damage (98)(99).

Mucositis: Mucositis is a common severe complication of radiation therapy (RT) and chemoradiotherapy. The loss of stem cells in the basal layer caused by radiation interferes with the replacement of cells in the superficial mucosal layers when they are lost through normal physiologic sloughing. Mucositis usually becomes clinically evident in the second or third week of RT. Its incidence and severity depending on the radiation treatment volume, dose fractionation schedule, and the use of induction and/or concomitant chemotherapy. The most effective ways of minimizing mucositis are to better restrict the volumes of normal mucosal tissues within the high dose radiation treatment volumes(88).

Dental issues: Dental status has a significant effect on the posttreatment quality of life between patients with head and neck cancer. Patients with head and neck cancer often have preexisting poor dental and oral hygiene, which can lead to increased risks of complications from their cancer treatment, including osteoradionecrosis and infection in particular(89).Indications for tooth extraction before RT are compromised teeth in an area that is expected to receive a minimum dose of 50 Gy. Healthy tooth extraction does not seem to prevent the development of osteoradionecrosis (90).All indicated extractions and/or restorative work must be completed before RT. A delay of

about two weeks is ideal between extractions and the beginning of RT to allow proper healing. If the extracted teeth are outside the volume of the treatment, treatment can be started sooner. RT may lead to total dental destruction if the teeth after radiation are not treated with a stricter treatment regime (91).

Osteoradionecrosis: Patients who need dental extractions in a previously irradiated area of mandible or maxilla are at risk for developing osteoradionecrosis. Osteoradionecrosis in the absence of a recurrent or residual tumor is defined as exposed, irradiated bone. Osteoradionecrosis is a complication of radiation therapy (RT) because of vascular obliteration and decreased vascular supply of the irradiated tissues (104). It results in hypo vascular areas with associated tissue hypoxia. The period at which osteoradionecrosis begins is quite variable. In some cases, it can be diagnosed shortly after RT completion, while in other patients it may not be diagnosed for years following the original cancer treatment. The mandible is the most commonly affected bone because, in a lot of patients treated for head and neck cancer, a large portion of the mandible is exposed to high doses of radiation(92). Maxillary osteoradionecrosis is rare and most often occurred in the setting of irradiation for nasopharyngeal cancer(93).

RT targets oral cavity generally administer higher doses of radiation to larger volumes of the mandible than treatment of targets in the pharynx and larynx. As a consequence, osteoradionecrosis most often occurs in patients treated for tumors of the oral cavity(94).The crude incidence of osteoradionecrosis with reirradiation is only slightly higher than that seen during the initial course of RT which is possibly due to minor expansions in the reirradiation setting (95).When using IMRT, failure to limit "hot-spots" in the mandible may deposit excess dose and causing osteoradionecrosis(96). careful attention to decreasing the volume of mandible receiving high doses of RT has the potential to minimize the risk. In patients undergoing cancer therapy, dental illness found that post-RT patients had the highest incidence of decayed, missing, and filled teeth (97).

Radiation Dermatitis: Radiation dermatitis in the field of treatment is common

during radiation therapy (RT). The severity of injuries varies from hyperpigmentation and dry desquamation of the epithelial layers to moist desquamation and skin necrosis. Before initiating RT, patients must be instructed about appropriate skincare and avoidance of exposure to skin irritants. They must also limit direct sun (UV) exposure(98).

Dysgeusia: Dysgeusia is defined as an abnormal or impaired sense of taste; the sense of taste may also be affected by impaired olfaction. An altered sense of taste and/or smell may contribute to nutritional difficulties and weight loss. Both chemotherapy and radiation therapy (RT) may impair the sense of taste by their effects on the receptors in the tongue and nasal epithelium(99).

Trismus: Trismus is a condition characterized by a reduced ability to open the jaw, usually caused by a combination of spasm, fibrosis, and contraction of the muscles responsible for movement at the temporomandibular joint. The incidence of trismus has varied widely in patients receiving radiation therapy (RT) for head and neck cancer. The mean prevalence of trismus was about 25 percent using older RT techniques (113). However, newer techniques that minimize the radiation dose to the muscles of mastication seem to significantly reduce the incidence of trismus. Using intensity-modulated RT (IMRT) has found that the incidence of trismus was about 5 percent (114) (115).

Weight Loss And Malnutrition: Xerostomia, mucositis, dental problems, abnormalities in taste and smell, and orofacial pain can all lead to difficulties in maintaining adequate nutrition during and after treatment(100).

Stroke: Ischemic stroke may be a late complication of neck irradiation (101). Multiple factors may contribute to this increased risk in patients with head and neck cancer, including carotid artery stenosis and increased plaque deposition, as well as other preexisting risk factors for cerebrovascular disease, especially smoking(102).

Carotid Artery Rupture: Carotid artery rupture is most common in the surgically exposed carotid artery with insufficient normal residual tissue to cover it, recurrent

tumor, infection or extreme radiation damage (119) The occurrence of carotid blowouts in the reirradiation setting indicated that the syndrome was more common in accelerated fractionation reirradiation techniques(103).

Dysphagia: In addition to the effects of radiation, other causative factors including xerostomia, surgical disorders, and concurrent chemotherapy. A mean dose of radiation greater than 50 Gy to the larynx and inferior pharyngeal constrictor has been found to correlate with stricture and aspiration(104).

Oesophageal Toxicity: Oesophageal toxicity seems to be multifactorial in patients treated for head and neck cancer. Factors that may contribute include mucositis from RT or chemoradiotherapy, muscle fibrosis, or changes due to changes in bacterial flora or pH changes due to xerostomia (105). patients who developed an oesophageal stricture after RT. Factors associated with a significantly increased risk of an oesophageal stricture include the use of a percutaneous endoscopic gastrostomy (PEG) tube and/or nasogastric tube during treatment and the use of a dose of radiation greater than 45 Gy to the upper oesophagus(106).

Thyroid Disease: The incidence of thyroid disease after radiation therapy (RT) for head and neck cancer varies widely but tends to be dose dependent. Hypothyroidism after radiotherapy occurs at a median period of 1.4–1.8 years(107). The higher incidence of hypothyroidism with intensity-modulated RT (IMRT), but this increased risk can be avoided with proper technique that minimizes the dose of radiation to the thyroid gland(108).

Myelitis: Radiation damage to the spinal cord is one of the most feared complications of cancer treatment with radiation therapy (RT). The radiation myelitis syndrome usually begins 9 to 15 months following the end of RT with paraesthesia and other sensory disturbances. Then evolving to involve motor signs. It is fatal in about 50 percent of cases (109). Myelitis risk of can be reduced with proper technique that minimizes the radiation dose to spinal cord such as a spinal cord PRV (planning organ at risk volume) with a 6-mm margin leads to maintain the maximum spinal cord dose

below 45 Gy(110).

Retinopathy and Optic Neuropathy: Radiation-induced optic neuropathy is caused by radiation-induced ischemia to the optic nerve The incidence of optic neuropathy increases significantly with doses greater than 50 Gy. This incidence of optic neuropathy can be reduced by sparing optic structures with IMRT. The dose constraint of the optic nerve and chiasm is a maximum dose 54 Gy (111).

Ototoxicity: Both cisplatin and ionizing radiation may cause sensorineural hearing loss regardless of other comorbidities. The toxicity can be additive when combined (129). The apparatus of the inner ear is located in the petrous part of the temporal bone and must be contoured as an avoidance structure for radiation therapy (RT) planning (130). an increase in the mean dose to the inner ear was associated with increased hearing loss so the mean dose <45 Gy to the inner ear limits the frequency of hearing loss (131).

Lacrimal Gland: Dry eye syndrome is a disorder that results from deficiencies or defects in the components of lubrication that can cause structural and functional abnormalities of the eye's surface. Mild to moderate dry eye syndrome respond to conservative measures, however, severe dry eye syndrome can cause many symptoms including compromised vision, severe pain, and eye loss. Therapeutic radiation therapy (RT) doses to the entire globe may cause severe dry eye syndrome. It seems this is dose dependent. the mean dose <34 Gy to the lacrimal gland limits the incidence of severe dry eye syndrome (112).

Dysphonia: Dysphonia may be caused by treatment of head and neck cancer when the larynx is targeted by radiation therapy (RT) and/or surgical instruments (ie, laryngeal cancer) and when the larynx is near to targets (ie, neck lymphatics)(113). Patients receiving either elective or therapeutic nodal irradiation must have a contoured larynx and avoided, because of the dose-related toxicity (114). With careful treatment planning, the ability to limit the mean dose to the larynx to be less than 35 Gy is similar between different RT techniques(115).

Orofacial Pain: Orofacial pain occurs frequently in patients with head and neck cancer. In these cases, orofacial pain tends to be multifactorial. Mucositis, which is common during radiation therapy (RT) with or without concurrent chemotherapy, leads to some of the observed worsening of pain during treatment (136).

1.11. Special Circumstances:

Nasopharyngeal carcinoma: Radiation therapy (RT) is the mainstay of locoregional nasopharyngeal cancer treatment, however, the integration of chemotherapy has been instrumental in increasing survival for most stage II and advanced-stage disease (III and IV)(116). Normally, surgery is not used because of the nasopharynx's deep anatomical location and its close proximity to vital neurovascular structures and skull base (117).

The nasal vestibule and nasal cavity cancers: Nasal vestibule tumors are essentially cancers of the skin and are treated with surgery and/or RT depending on the size and location of the nasal vestibule. Nasal cavity cancers are similar to those in the paranasal sinuses and have a wide range of histologies. Both early and moderately advanced nasal cavity tumours are treated with resection and postoperative radiation (118).

Paranasal sinus cancer: Paranasal sinus cancers include several histologies, with adenocarcinoma and squamous cell carcinoma become dominant. Aggressive surgical resection remains the mainstay of treatment(119), but multimodality approaches with surgery, RT, and chemotherapy may be suitable for specific histologies and for advanced-stage cancers(120).

Salivary gland cancers: Salivary gland tumours consist of a wide range of benign and malignant histologies that occur in salivary gland tissue throughout the head and neck (142). Surgical salivary gland resection is important to both diagnosis and treatment. Patients with benign and low-grade tumours are usually treated with surgery

alone, while patients with high-grade carcinomas and other high-risk features are usually treated with surgery and postoperative RT (143).

Locally recurrent disease: Patients with recurrent local cancer of the head and neck previously treated with radiation have a poor prognosis (121). Locoregional recurrences occur in 15 to 50 percent of patients with squamous cell carcinoma of the head and neck, and this is the main factor contributing to deaths from head and neck cancer(122). All patients with the recurrent locoregionally disease must be evaluated for distant metastases before initiating retreatment. Those with good performance status and whose disease is limited to the head and neck may benefit from surgical salvage(123), and/or radiation or reirradiation(103), despite treatment options are limited by the previous treatment received.

Metastatic disease: The cosmetic, social, psychological and functional impacts of metastatic H&N cancers require a multidisciplinary supportive approach to management. Palliative treatment and supportive care are the most appropriate choices. Palliative surgery may be useful in certain cases, such as debulking tumors that obstruct airways(124), while palliative radiotherapy is particularly useful to improve pain(125). Palliative chemotherapy may be used to improve the quality of life(126).

1.12. Reconstruction and Rehabilitation:

Surgical resection of the mandible, palate, and larynx can cause problems in airway management, mastication, deglutition, speech, and cosmesis. The function is also impaired by RT and chemoradiotherapy. The type of reconstruction will often depend on comorbidities and functional purposes. Dieticians, speech and language therapists and restorative dentists must meet the person before surgery (127)(96). Speech and swallowing rehabilitation are very important in restoring function and quality of life following both surgery and RT(128).

Prosthetic rehabilitation of patients with the defective hard palate (the result of

tumour resections involving the maxilla) consists of placement of an obturator prosthesis, which serves to restore the function of orofacial, including deglutition, control of secretions, mastication, and phonetics, and to aesthetically replace the missing orofacial structures. The obturator filling defect in the palate that causes velopharyngeal incompetence (VPI), which would otherwise allow a food bolus to go into the Sino nasal cavity, and results in a hypo resonant, non-intelligible speech quality. Surgical reconstruction alone or combined with an obturator prosthesis can be used to repair palatal defects (129). Furthermore, a diversity of reconstruction options, including free flaps and autogenous (fibular) bone flaps, are available to restore mandibular defects(130)(131).

1.13. Posttreatment Evaluation and Surveillance:

Regular posttreatment follow-up is an important part of the care of patients after potentially curative treatment of head and neck cancer. Patients must be educated about possible signs and symptoms of second primary cancer and local-regional recurrence, including hoarseness, pain, dysphagia, bleeding, and enlarged lymph nodes. After completion of treatment, posttreatment imaging is important to evaluate for residual disease and establish a baseline (132). clinical evaluation around six weeks after RT or chemoradiotherapy and then a complete evaluation, including imaging (CT or MRI and generally a PET/CT) around 3-4 months to document the primary tumor regression (133).

Obtaining imaging studies, particularly PET/CT, prior to 12 weeks after treatment may lead to an increased frequency of false-positive results(134). CT or MRI can be done at four to six weeks if needed as part of the clinical evaluation(133). Following treatment, follow-up intensity is greatest in the first two to four years. About 80 to 90 percent of all recurrences occur within this time period (135). the risk of second

primary malignancy is higher than the risk of relapse for most patients beyond three years(136).

1.14. Immobilization:

The main goal of radical radiotherapy is to deliver a high radiation dose to a target while minimizing the dose to surrounding healthy tissues. In order to optimize radiotherapy delivery, it should be the aim to minimize margins as much as possible. This can be obtained by improving patient setup and immobilization. Devices of immobilization are widely used in radiation therapy to ensure accurate positioning and repositioning of patients with minimal patient movement during their fractionated radiotherapy(137).

Headrests**:** used for patient positioning and immobilization Fig. 2. The importance of accuracy of radiation delivery is reflected in the process of the treatment planning process. An immobilization shell or mask is made of deformable thermoplastics to ensure the person and tumor are in the same position throughout a course of treatment.

Thermoplastic sheets are available in various sizes and thicknesses, as perforated or solid sheets and Head masks or Head and neck masks. Thermoplastic is stiff at room temperature, but when heated in a water pan to temperatures in the range of 55° to 70 C, the material softens and becomes soft. The softened sheet can be shaped around the body part to be treated and the ends of the mask clamped to the supporting board. When thermoplastic cools down, it hardens to form a rigid mask. Patients in a supine position on a headrest are immobilized by a thermoplastic mask that attaches to a carbon fiber base plate fixed to the treatment couch. The combination of a base plate and mask provides an accurate patient immobilization system.

Gilbeau et al. have analysed the accuracy of the setup of three different types of thermoplastic masks. The first type of mask Fig. 3 A patient's head tied with three

fixation points, two fixation points on both sides of the head and one on top of the head. The second type of mask Fig. 3 B has four fixation points, two on the sides of the head and two around the shoulder. As shown in Fig. 3 C, the third type has five fixation points. Gilbeau et al. found that for the isocentre located in the head and neck, there was no major difference in the setup deviation among the 3 masks. The reproducibility of setup was found to be better at the shoulder level with a four- and five-point mask(138).

Figure 2– Head rests (immobilization devices).

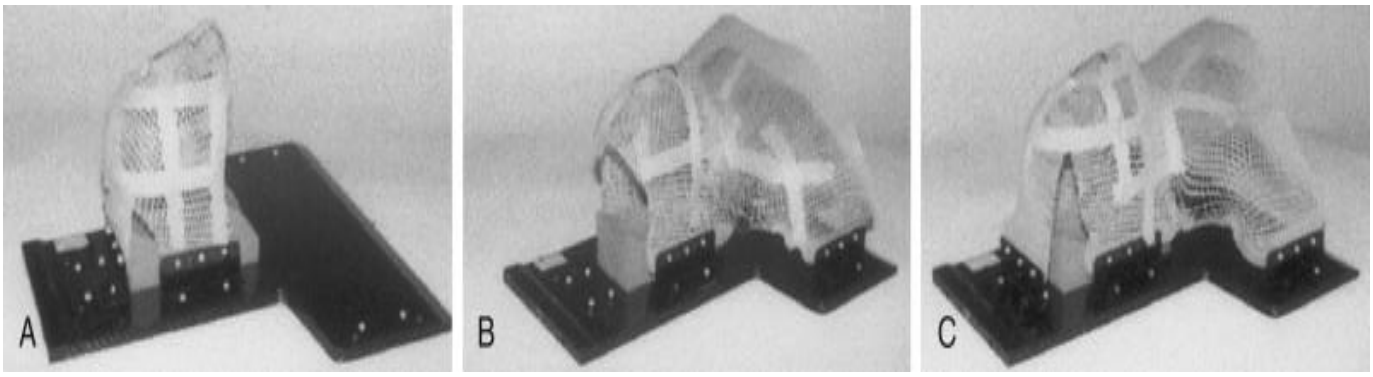

Figure 3– Thermoplastic masks (three fixation points (A), four fixation points (B), five fixation points (C)).

1.15. Target Volume Definition:

General principles for the definition of the target volume that can be applied throughout the head and neck.

GTV: The GTV is defined as the primary tumour and any lymph nodes more than 10 mm in short axis dimension or smaller nodes with necrotic centres or suspected to contain tumour rounded contours. The diagnostic images and records and

photographs of initial evaluation (in a clinic or in examination under anaesthesia [EUA]) are very important to assess the extent of the primary tumour and the exact site of involved lymph nodes (139). If induction chemotherapy has been used, the post chemotherapy GTV is contoured, but the pre-chemotherapy extent of the tumour must be included in the CTV70(140)(141).

Primary tumour CTV (CTV-T): CTV delineation by growing the GTV by an isotropic margin of 10 mm unless there are natural tissue barriers on the basis that a surgical margin of 10 mm is considered adequate for local excision. The CTV is then edited slice by slice – again starting in the centre of the volume to subtract air and adjacent structures such bone which is definitely not involved. The CTV margin can be locally expanded by more than 10 mm if local structures such as muscle or soft tissue which are at risk of involvement (139).

Postoperative primary tumour CTV: It is more difficult to specify guidance for CTV definition postoperatively because the anatomy is distorted by the resection and by any reconstructive myocutaneous flaps. Radio-opaque clips are used for marking close or involved margins can be helpful. It is sometimes useful to determine the site of the preoperative GTV on the planning CT to orientate the possible sites of microscopic disease, but this is less helpful when the anatomy is very different after major resection. If there is a bulky residual disease a GTV can be determined and expanded to form the CTV as above(142).

Cervical lymph node CTV (CTV-N): Defining nodal CTVs requires both the proper selection nodal levels and the delineation of those levels on the CT dataset. it would be different for each site and stage of the disease. Often two nodal CTVs are selected a high-risk volume containing involved nodes or those close to the primary site and a lower risk volume containing levels that considered to be at risk of microscopic disease. These are classified according to dose, e.g. CTV44(143).

For postoperative neck irradiation, the entire operative field is usually defined in the CTV, especially when there was extracapsular spread. Where nodes abutted

muscles or other structures not removed at operation, those structures must be included in the CTV(144).

PTV: Each CTV is grown isotropically to develop a PTV. CTV-PTV margins for each centre can be determined, with the assumption that there is no intra-fractional organ motion in the head and neck. as usually a 3-5 mm margin (139).

OAR and PVR: OAR described in the same manner as GTV on serial axial CT slices. Depending on the location of the PTV, OAR contours will include the spinal cord, parotid glands, optic nerves and chiasm, lacrimal glands and lenses. With more information about how DVHs associated with adverse effects. Because of the catastrophic effect of late spinal cord damage, the spinal cord PRV is usually defined either by adding a margin of 5 mm isotropic round the cord or by contouring the bony spinal canal as a surrogate for the cord PRV(145).

1.16. Elekta Synergy:

Modulated and Image-Guided Radiation Therapy (IMRT and IGRT) system is designed to provide automated workflow tools and 3D volumetric imaging at treatment time. This new technology delivers targeted radiation, with the help of highly sophisticated software, such as a missile from a computerized satellite. It provides IMRT, IGRT, SRS, SRT, and SBRT with Arc Therapy. It provides personalized, safe, efficient and high-quality radiation with enhanced dose conformity according to tumour size, shape, and pathology. With this new technology, the total dose of radiation integral has been reduced to one-tenth and treatment time to only 2 - 3 minutes as against 30 minutes with older technology. This leads to higher tumour control probability, reduces the possibility of secondary tumours and minimal side effects(146).

Multileaf Collimator: MLC is a completely integrated unit into the accelerator head, which provides the ability to determine irregularly shaped fields without the need to manufacture individual shielding blocks. The fully integrated leaf collimator with 80

segments for the field size at isocentre 40 x 40 cm ensures that the user does not have to resort to any compromises even in the most complicated cases of irradiation. The position of all leaves continues to be monitored and controlled by an optical camera located in the collimator. The leaf movement is done by high-performance high-torque electric motors. This prohibits the leaf from assuming an incorrect position. The collimator provides an exceptional 45 cm distance from the patient, which is important for non-coplanar beams and intensity-modulated rotational therapy (IMRT) or volume modulated arc radiation therapy (VMAT). For static and dynamic techniques up to 18 MV and field size 14 x 12 cm, Elekta is provided with a micro-multileaf collimator with model designation APEX with 24 pairs of 2.5 mm wide leaves in the isocentre and interdigitations possibility and multiple fields formation (147).

Imaging and positioning: The Linear Accelerator is provided with both MV, KV, and XVI (CT) imaging during treatment time. Modalities of High conformance radiation treatment require precise positioning, immobilization and organ motion management.

1.17. Monaco Planning System:

Because radiation therapy treatments become faster and more complex, with increasingly higher doses, shorter fractionation schemes, and smaller target margins, treatment planning systems are required to be more accurate, more automatic, more sensitive to patient biology and integrated with the treatment machine.

Monaco has been developed to meet the key treatment planning challenges of modern radiation oncology clinics. The Monaco treatment planning system combines Monte Carlo dose calculation accuracy with robust optimization tools to achieve 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 advances in technology 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 throughout organizations. At the same time, multicriteria optimization (MCO) ensures vital organs are spared to the greatest possible degree while maintaining target coverage. Monaco includes a complete range 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 (148).

Monaco templates further increase efficiency by enabling users to easily import and export treatment plans, facilitating best practice sharing across departments and organizations. The ability to create multiple prescription plans simultaneously reduces overall planning time also. Improved data sharing provides opportunities to optimize individual treatment plans(149).

Patient Contouring: Fast, accurate contouring is important in planning efficiency and productivity. Elekta is provided with an integrated suite of automated, easy-to-use visualization capabilities and improved contouring tools for rapid delineation and modification of critical planning structures.

Image Fusion: Advanced image registration and fusion tools allow effective utilization of all diagnostic imaging modalities available. Fast and reliable automated fusion helps ensure that planning structures have the best possible delineation options.
Virtual Simulation: Advanced visualization tools and increase staff efficiency, fully integrated CT simulation, planning accuracy and patient convenience.

IMRT Planning: An intuitive prescription-based inverse planning solution accelerates DVH prescription modification, optimization and dose calculation for dynamic and segmental (step-and-shoot) IMRT delivery.

Conformal Planning: 2D and 3D conformal treatment planning capabilities include customizable templates that support an efficient generation of the plan(148).

1.18. Technic Delivery of Prescription Dose (3DCRT, IMRT, VMAT):

Radiation therapy is a standard therapeutic option for many head and neck cancer (HNC) patients but presents many technical challenges. Primary head and neck tumours are often located near numerous critical structures and delivering an adequate radiation dose to the primary and regional lymph nodes requires special attention to protect these organs at risk (OARs). HNC treatment planning methods using external-beam radiotherapy have evolved from the traditional three-field technique in the early days to intensity-modulated radiotherapy (IMRT), and recently to the more efficient volumetric modulated arc therapy (VMAT). IMRT and VMAT require higher precision and accuracy in patient setup than conventional radiotherapy because of a highly conformal dose distribution and steep dose gradients. Therefore, image guidance for head and neck radiotherapy has also evolved from weekly 2D portal imaging to daily 3D CT or cone-beam CT (CBCT) imaging(150).

Three-field technique(3DCRT):

Head and neck tumors are most often treated with 6 MV photon beams. The three-field technique consists of two opposed lateral fields to irradiate the primary tumor and cervical lymph nodes in the upper and lower neck, and a third anterior field to irradiate the supraclavicular lymph nodes. The bilateral fields and the anterior field share the same isocenter and are matched at the isocenter plane to avoid overlapping fields at the field junction line. It is also desirable to move the line of junction during the treatment course to feather the junction dose distribution(150).

Intensity-modulated radiation therapy (IMRT):

In contrast to the three-field treatment planning technique, IMRT delivers non uniform beams across the tumor through a sequence of field segments with varying intensities which, in sum, provide the desired dose distribution. IMRT can produce a

conformal dose distribution and has steep dose fall-off at the boundary between the tumor and the normal structures. IMRT enables dose-escalation without increasing toxicity to the critical organs, potentially improving the therapeutic ratio. HNC is the ideal disease site for IMRT because of the complex tumor shape, nearby critical structures, and minimum organ motion in the region. Furthermore, IMRT capability to produce inhomogeneous dose distribution allows the primary and secondary target volumes to be treated simultaneously.

Techniques of Head and neck IMRT planning include the split-field and the extended-field IMRT techniques. To split field IMRT technique, the primary and the upper neck above the vocal cords are treated by IMRT, and the lower neck and the supraclavicular fossae are treated by the conventional anterior field. The fields of IMRT are matched with the anterior field at the isocenter with a half-beam block technique. One concern of the split-field technique is underdosage possibility of the tumor at the field junction. Alternatively, extended field IMRT treats all tumor volumes simultaneously with different prescription doses to the primary tumor and the regional lymph nodes. This technique avoids field matching as in the split-field technique but may increase the dose to the larynx if a special dose constraint is not applied to protect the larynx. The extended-field technique can also provide a high dose to any involved lymph nodes in the lower neck and supraclavicular region(150).

The typical beam arrangement for bilateral tumors treatment consists of 9 coplanar 6 MV photon beams evenly distributed around the patient (0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320°). The typical beam arrangement for unilateral cases treatment consists of 7 coplanar beams, angled from the tumor side. The gantry angle must avoid the lateral directions and can be adjusted slightly to avoid the shoulder or to minimize the beam path through the shoulder. Given that the field size is often large relative to head and neck treatments, the isocenter is usually selected at the center of the irradiated region(150).

IMRT optimization has evolved from forward planning in the early days to inverse planning currently used by most of treatment planning systems. Forward planning uses the field-in-field technique to obtain a simple intensity-modulated dose distribution. With forward planning, a planner manually adjusts the shape of block and the beam intensity of each field through a process of trial-and-error. On the other hand, inverse planning is a computer algorithm that adjusts the beam weighting and blocking to achieve an optimal plan based on dose objectives applied to the tumor targets and critical organs. Compared with forward planning, the technique of inverse planning provides more conformal-dose distributions to the tumor volumes with significantly better sparing of critical structures. However, care should be taken as marginal failure in the spared parotid gland has been reported because of potentially inadequate dose to possible microscopic disease(150).

Volumetric-modulated arc therapy (VMAT):

VMAT is an advanced form of IMRT. With a number of fixed gantry angles, the conventional IMRT plan delivers a number of small fields (segments) formed by the multileaf collimator (MLC) either by sequentially moving the MLC leaves to various positions and then delivering the radiation dose (step-and-shoot method), or to continue move the leaves during the beam-on time (sliding window method). VMAT delivery allows motion of the MLC and gantry at the same time adjusting MLC leaf speed, gantry speed, and dose rate while the radiation beam is on. VMAT has emerged as a mainstream treatment option for HNC. Due to the complexity of the anatomy in the head and neck region, a VMAT plan usually consists of 2-3 full or partial arcs, depending on whether the treatment targets are bilateral or unilateral.

VMAT plans increase the number of beam angles, and are therefore able to create a more conformal dose distribution to the target volume when compared to traditional IMRT. VMAT plans provide similar PTV coverage as the fixed gantry IMRT plans with improved homogeneity. Most importantly, the delivery time for a VMAT plan is much shorter (about 5 minutes) compared with fixed gantry IMRT plan

(10-15 minutes). Both VMAT and IMRT achieve adequate coverage of PTV dose. OAR sparing degree is comparable for VMAT and IMRT, although sometimes the contralateral OAR sparing may be improved with VMAT(150).

1.19. Recalculation for Regimen of Fractionation by Means BED (LQM):

The linear quadratic model is a popular radiobiological model that facilitates to quantify the biological effect in terms of cell kill with respect to dose (Gy)(151).in order to get Tumour Control Probability (TCP), equivalent to that of a conventional fractionation, the total dose simultaneously delivered to the targets must be determined according to the Linear Quadratic Model (LQM) to be used with the SIB technique(152). Thus, the dose per fraction to PTVs and/or boost might differ by 2 Gy per fraction. Based on the Biological Equivalent Dose (BED) formalism, a new total dose and the fraction dose can be calculated in order to get the same biological effect, named IsoBED herein (153). The sensitivity to changes in FS for each tissue can be quantified with the use of the α/β ratio, which value marks the shape of the fractionation response. A high α/β ratio (range, 7–20 Gy), as in acutely responding tissues and in tumours, indicates a more linear survival response of the target cells; a low α/β ratio (range, 0.5–6 Gy), as in late responding tissues, defines a survival curve of the target cells that is significantly curved. For that reason, the effects of fractionation are relatively larger in the latter than in the former tissues(11).

Linear quadratic (LQ) model and iso-effect formalisms:

The measure of the effect of a course of fractionated RT, can be done by using the LQ model, widely accepted in radiobiology.

In this model the biologically effective dose (BED) is defined as:

$$\mathrm{BED} = nd\ \mathrm{RE} \qquad (1)$$

where RE is the relative effectiveness:

$$\mathrm{RE} = 1 + d/(a/\beta) \qquad (2)$$

where n is the number of fractions; d the fraction dose and α and β coefficients represent the contribution to cell killing from linear and quadratic components, respectively. The value of α/β, which is given in Gy is the dose at which the cell killing is to the same extent produced by the two mechanisms. The BED formula provided a simple and convenient way to calculate isoeffective RT schedules. Different treatments in fractionation regimes are defined as equivalent if they have the same BED, being iso-effective in terms of survival cells. RT radiobiological effects of the strategy should be considered for any different effect, both for cancer and normal tissue cells and for anyone of these a value of BED must be calculated. Due to the sensitivity of different fractionation of the acutely and late responding tissues, the iso-effective total dose increases more rapidly by decreasing the dose per fraction for late effect than for early effect, providing that late reactions are those mainly dose limiting. The use of the Eq. (1) is justified only under the following conditions: complete repair between two successive fractions and no proliferation during treatment. It follows that in SIB-IMRT strategy this formula can be used for late normal responding tissues only, while for H&N cancers and acutely responding tissues the proliferation process is relevant and it should be taken into account in the BED calculation. Following Fowler formulation, the effect of OTT can be included in the BED formula:

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right) - \frac{\ln 2}{\mathrm{nd}\alpha}\frac{\mathrm{T}-\mathrm{T_k}}{\mathrm{T_{pot}}}\ , \tag{3}$$

$$\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{ln2}{nd\alpha}\frac{T - T_k}{T_{pot}} = RE \tag{4}$$

where Tpot, T and Tk are time parameters previously defined as the doubling time, the OTT and onset of proliferation time, respectively. When multiple fractions per day are used, to ensure a complete repair of sublethal damage to take place after each dose, the interfraction interval must be at least 6 h. In fact, for many normal tissues this time is enough to allow a full recovery between fractions. If this interval is observed, we can use the Eqs. (1) and (3) for accelerated hyperfractionation with CB also, and no

correction needs to be made. The total BED value for CB schedule can be the result of the sum between the two BED components, each one relating to a treatment phase: one relating to wide volume, to which Eq. (1) can be applied, and one relating to boost volume, to which Eq. (3) can be applied. Unfortunately, the comparison among BEDs across treatment using different fraction sizes is not very intuitive. Therefore, each calculated BED value can be normalized to produce an equivalent dose applied in 2Gy fractions or normalized total dose (NTD2Gy) as defined by:

$$NTD2Gy = BED/\ RE2Gy, \ , \qquad (5)$$

where RE2Gy is the relative effectiveness of 2Gy per fraction(11).

2.practical part

2.1. Patients and methods:

2.1.1Patients selection and contouring:

Ten patients with Head and Neck squamous cell carcinoma (HNSCC) were randomly selected from a list of patients previously treated with VMAT plan (Monaco planning system, Elekta Synergy) in the Radiotherapy Department at Tomsk Regional Oncology Centre. Patient and tumour characteristics are summarized in Table 1. All patients were simulated and treated supine, immobilized by a thermoplastic head and shoulder mask fixed to the treatment couch. Patients were treated using 6-MV photons, and treatment was given in 5 daily fractions per week. seven patients with Stage III-IVB disease treated with concurrent chemoradiation (cisplatin 100mg/m² every 3weeks).

The high-risk TV consisted of the gross tumour volume (GTV)and a 10-mm margin surrounding GTV, which are equal to the clinical target volume (CTV), CTV1. CTV2 consisted of elective nodal regions at risk(154). Expanding the CTVs by an isotropic margin of 5 mm gave the corresponding PTVs. All TV and OAR (parotid gland, mandible, oesophagus, spinal cord, brainstem, cochlea, thyroid gland, oral cavity, and submandibular gland) were contoured by a radiation oncologist on an intravenous (80 ml, Ultravist) enhanced planning-CT on axial slices with 3 mm slice thickness in the Monaco Treatment Planning System (TPS), version 5.10(Elekta Synergy Medical Systems).

Table 1–Patients' and tumour characteristics.

Characteristics		Total, n = 10
Mean age, years		59.2 (Range 45-70)
Tumour site	oropharyngeal cancer	6
	larynx cancer	1
	base of tongue cancer	1
	hypopharyngeal cancer	2
Tumour	*T1*	2
	T2	3
	T3	4
	T4a	1
Nodes	N0	4
	N1	2
	N2	3
	N3	1
Metastases	M0	10
Bilateral neck irradiation		10

2.1.2. Linear-quadratic model:

The linear-quadratic model with a/b values (e.g.10 Gy for tumour; 2 Gy for spinal cord;2 Gy for brain stem) was employed to calculate biologically effective doses. SEQ (sequential boost technique) dose prescription for all datasets was 25 single fractions of 2 Gy for TD (total dose) 50 Gy to PTV2 followed by 10 single fractions of 2 Gy for TD 70 Gy to PTV1, a total time of treatment 7 weeks. SIB (simultaneous integrated boost technique) dose consisted of 25 daily single fractions of 2 and 2.8 Gy to PTV 2 and PTV 1 respectively, resulting in TDS of 50, 70 Gy and a total time of treatment 5 weeks.

2.1.3. VMAT planning:

The goal was to deliver the prescribed doses to the PTVs while keeping the dose to the OARs (SC, BS, PGs, OC, SMGs, larynx within the constraints (Table 2). Treatment was carried out with Elekta synergy accelerators. Treatment plans consisted of two 358° arcs running clockwise/counterclockwise between gantry angles of 181° and 179°. The corresponding collimator angles lay between 10–30° and 350–330°, depending on the PTV length.

Table 2– Summary of dose-volume constraints.

Target volume/organ at risk	Mean prescription Dose		Planning goals
	SIB	SEQ	
PTV1	70	70	V95 % ≥ 95%, D_{max} 107 % (not >2% of PTV)
PTV2	50	50	V95 % ≥ 95 %, D_{max} 107 % (not >2% of PTV)
spinal cord			Max < 45 Gy, <50 Gy (limit) [1 cc of the PTV cannot exceed 50 Gy].
Brainstem			Max < 54 Gy, <60 Gy (limit) [1 cc of the PTV cannot exceed 60 Gy].
submandibular gland			D_{mean} ≤ 39 Gy
parotid gland			D_{mean} ≤ 26 Gy (a) Mean ≤ 26 Gy in one gland (b) Or at least 20 cc of the combined volume of both parotid glands will receive < 20 Gy (c) Or at least 50 % of one gland will receive < 30 Gy
Mandible			Max < 70 Gy outside high dose PTV, avoid hot spots
Oesophagus			Mean < 45 Gy
Thyroid			V45 Gy < 50%

2.1.4. Plan evaluation:

Quantitative comparisons used a DVH analysis, with parallel qualitative visual comparisons of the axial isodose curves. The mean volumes of PTV1–2, the D_{mean}, D_{max} (maximal dose to the PTV), D2 (dose delivered to at most 2 % of the PTV), D100 (dose delivered to 100 % of the PTV), D98 (dose delivered to 98 % of the PTV) and D95 (dose delivered to 95 % of the PTV) for PTV1–2 were also evaluated.

Regarding OARs, the D_{mean} for the ipsilateral (IL) and contralateral (CL) parotids gland, submandibular gland and oesophagus, the D_{max} for the spinal cord, brain stem and Mandible, V50 (volume in percent receiving 50 Gy) for the oral cavity, and V45 (volume in percent receiving 45 Gy) for the thyroid gland were assessed (114).

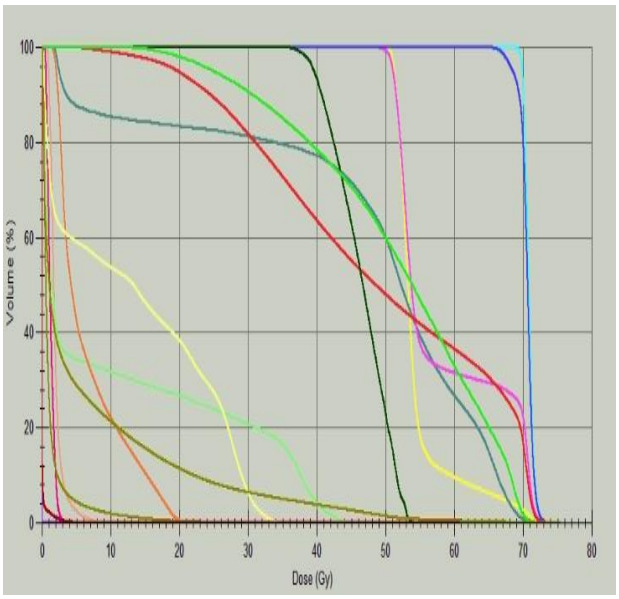

Figure 4– SIB DVH

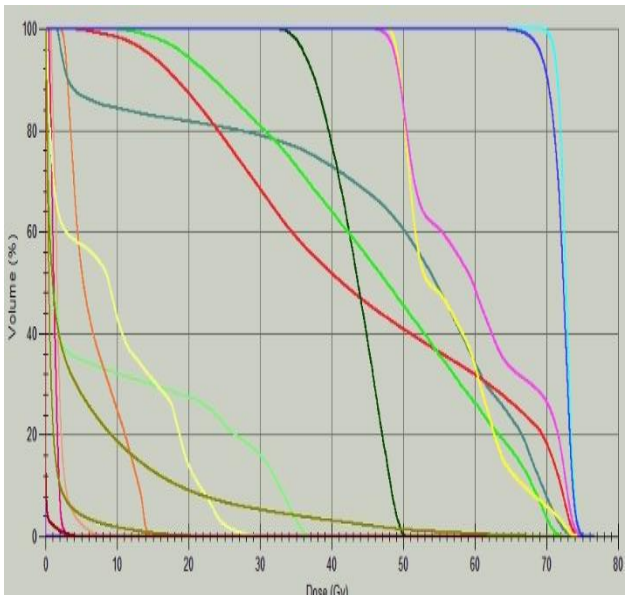

Figure 5–SEQ DVH

2.1.5. Biological Plan Evaluation:

BED: The concept of biologically effective dose (BED) is commonly used for iso-effective dose fractionation calculation(155). It is derived from the LQ model and is defined as:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad (1)$$

The BED calculations were performed using an equation written in an excel sheet. Each dose was converted to the corresponding BED using equation (1) and taking into account the number of fractions and the different α/β values for tumours and OARs. For all OARs, e.g brain stem and spinal cord $\alpha/\beta = 2$ Gy was used in all plans. For PTV1 and PTV2 in SEQ and SIB plans, $\alpha/\beta = 10$ Gy were used to calculate the BED (BED10).

2.1.6. Statistical analysis:

Microsoft Excel 2010 and IBM SPSS Version 20 were used for calculations and for descriptive statistics. Descriptive statistics of the data are presented as mean ±standard deviation (SD).

The differences in the mean between the two schemes were compared and analysed using the Wilcoxon ranked sign test.Statistically significant differences were assumed for a significance level of $p < 0.05$.

2.2. Results:

Target coverage and dose:

Both techniques achieved the planning objectives in tumour coverage 95 % of tumour volume received ≥ 95%of the dose, D_{max} not more than 107 % of the dose (not >2% of PTV).

Measured mean volumes (± standard deviation, SD) were 157.3±104.1 and 427.8±121.8 cm^3 for PTV70, PTV50 respectively for SIB and 157.3±104.1 and 427.75±121.8 cm^3 for PTV70, PTV50 respectively for SEQ.

Measured D_{mean} were 71.9±0.7 and 61.11±2.95 for PTV70 and PTV50 respectively for SIB, and 72.6±0.3 and 62.9±3.2 for PTV70 and PTV50 respectively for SEQ ($p = 0.002$ for PTV70 and $p = 0.006$ for PTV50).

In our study, the BED to PTV70 was higher in SIB- VMAT than SEQ-VMAT, 92.52±1 Gy10 and 87.58± 0.4 Gy10, respectively. the BED to PTV50 was lower in SIB-VMAT

than SEQ-VMAT, 75.97±4.38 Gy10 and 78.7±4.8Gy10, respectively (p = 0.002 for PTV70 and p = 0.006 for PTV50).

There are significant statistical differences were seen in the physical mean dose and BED for PTV70 and PTV 50 between both techniques which can translate into increasing tumour control probability with high BED in the SIB technique.

OAR:

Both techniques also respected the planning objectives for OAR.OAR in both techniques were within constraints. Both techniques also respected the planning objective of D_{max} < 45 Gy,<50 Gy (limit)[1 cc of the PTV cannot exceed 50 Gy] for the spinal cord and D_{max} < 54 Gy, <60 Gy (limit) [1 cc of the PTV cannot exceed 60 Gy] for brain stem.

Our study which showed that the mean dose of D_{max} to the spinal cord and brain stem in SIB-VMAT (39.6. ± 3.7 Gy and 31.3 ± 17.3 Gy) and in SEQ-VMAT (40.8± 5.6 Gy and 30.5 ± 17.6 Gy) respectively(p= 0.14 for spinal cord and p = 0.25 for brain stem).BEDs were calculated for the spinal cord and brain stem in SIB-VMAT (70.33 ± 9.3 Gy and 55.7± 36.1 Gy) and in SEQ-VMAT (64.97± 11.5 Gy and 47.8 ± 32.2 Gy) respectively (p = 0.1 for spinal cord and p = 0.12 for brain stem).

No significantly statistical differences were seen in the physical mean dose of D_{max} and BED for both SC and BS in both techniques. However, the SEQ gave lower BED to the SC and BS in comparison to SIB, which may translate into less incidence of complications in the SEQ technique such as myelopathy.

Results are presented in table (3).

Table 3– Dose-volume histogram parameters and treatment efficiency for SeqB and SIB plans (mean ± SD).

		SIB	SEQ	P-value
PTV70	Reference dose	70	70	
	Volume	157.3±104.1	157.3±104.1	
	D_{mean}	71.9±0.7	72.6±0.3	0.002
	BED	92.52±1.07	87.58±0.4	0.002
PTV50	Reference dose	50	50	
	Volume	427.8±121.8	427.75±121.8	
	D_{mean}	61.11±2.95	62.9±3.2	0.006
	BED	75.97±4.38	78.7±4.8	0.006
Spinal cord	D_{max}	39.6±3.7	40.8±5.6	0.14
	BED	70.33±9.3	64.97±11.5	0.1
Brain stem	D_{max}	31.1±17.3	30.5±17.6	0.25
	BED	55.7±36.1	47.8±32.2	0.12

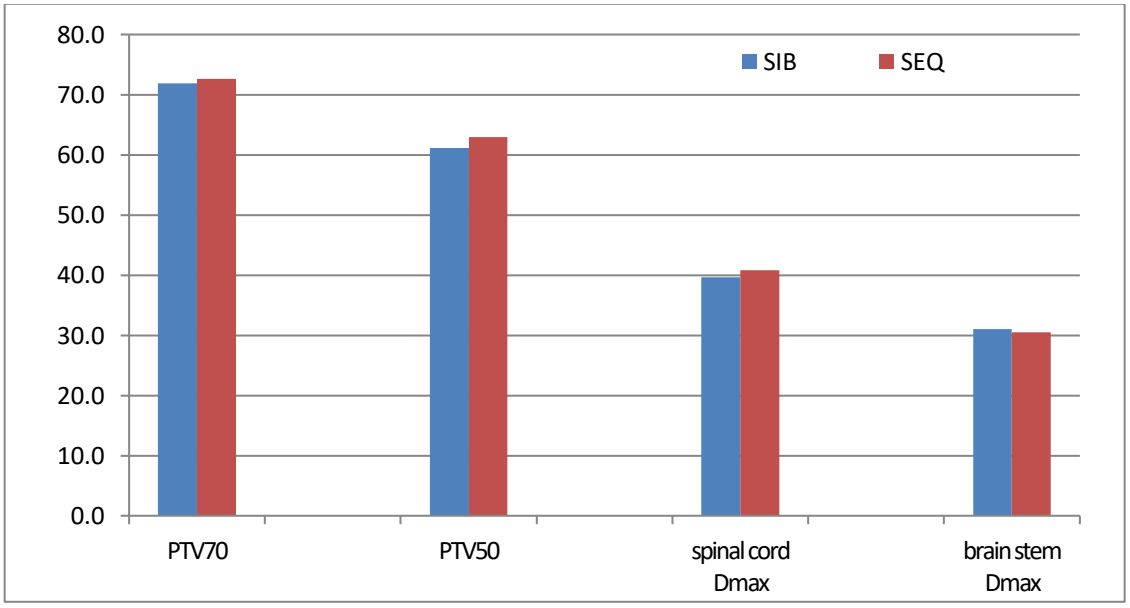

Figure 6–this figure shows a comparison between both techniques SIB and SEQ regarding physical dose. physical doses for PTV70, PTV50 and spinal cord are slightly higher in SEQ technique than SIB technique but not for the brain stem.

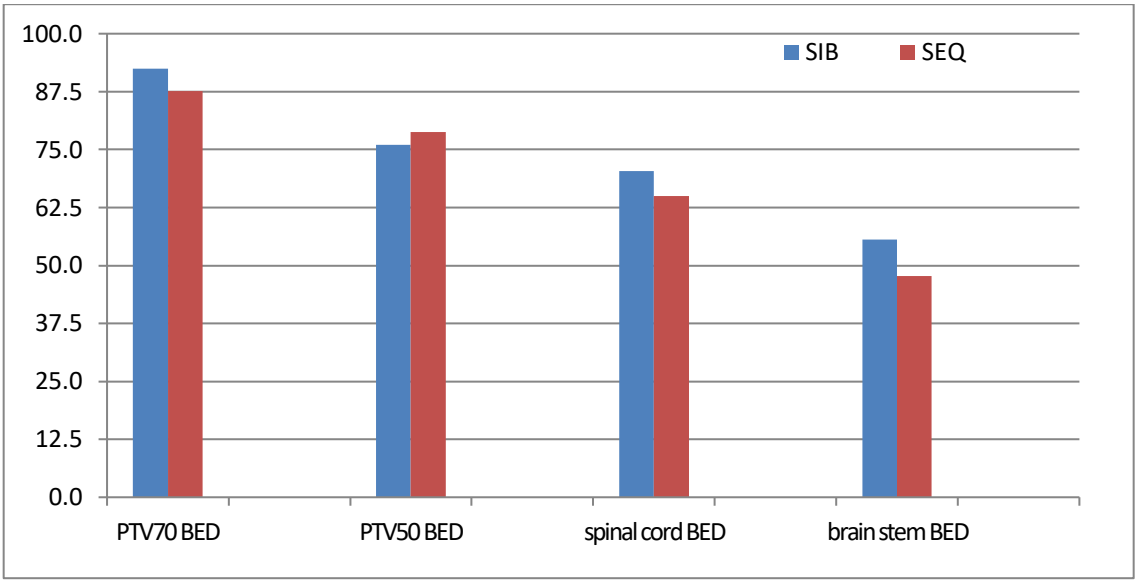

Figure 7– this figure shows a comparison between both techniques SIB and SEQ regarding BED. BEDs for PTV 70, spinal cord and brain stem are higher in SIB technique than SEQ technique.

2.3. Discussion:

Many studies have shown the effectiveness and advantages of the advanced radiation technique, IMRT(VMAT), which can achieve dose escalation to the tumour and also reduce the dose to the surrounding normal tissue(156). IMRT(VMAT) can be applied in either sequential (SEQ) technique or simultaneous integrated boost (SIB) technique. The IMRT(VMAT) technique, which is called the SEQ boost, has been applied using a shrinking field to make a sequential boost without increasing the dose to OARs, resulting in the development of 2 to 3 treatment plans for each patient. The simultaneous integrated boost (SIB) allows a single plan with different doses suitable for selective TVs; meanwhile, the normal tissues within or adjacent to the PTV-boost may receive higher doses per fraction compared to the doses provided by SEQ-IMRT(VMAT) (157).

On the one hand, some studies have shown that SIB-IMRT(VMAT) can provide more conformal dose distribution, including both better coverage of boost volume and non-target tissues sparing. A treatment comparative planning study found that both SIB-

IMRT(VMAT) and SEQ-IMRT(VMAT) provided excellent performances in terms of coverage, conformity, and dose to the PTV, while SIB-IMRT could be associated with a lower rate of toxicity(16). Chen et al also reported that SIB-IMRT(VMAT) could allow for better distribution in the elective nodal area, while two-phase SEQ-IMRT(VMAT) could lead to higher doses to OARs regarding the parotid gland and inner ear(158).

An evaluation of different IMRT(VMAT) boost strategies was carried out and the results showed that conformality and OARs sparing of the SIB IMRT(VMAT) plans were superior compared with SEQ-IMRT(159). On the contrary, 2 studies showed that the SEQ-IMRT(VMAT) plan, compared with the SIB-IMRT plan, not only appeared to provide higher dose coverage, conformity, and homogeneity, but also significantly reduced the monitor units (MUs)(160). Both IMRT(VMAT) techniques can reach equal dose coverage of PTV, as in our study both techniques achieved equal dose coverage of PTV.

When comparing two radiation techniques with distinct biological effects, the BED, rather than the physical dose, provides a potentially better method for comparison. The BED reflects the radiobiological effectiveness of the physical dose (PD) deslivered with a unique fractionation scheme(161).

There are four major factors of BED that provide the capability of quantitatively estimating the biological response to the delivered dose: (1) cellular radio-sensitivity; (2) treatment dose-per-fraction (DPF); (3) total delivered dose; and (4) overall treatment time. The radio-sensitivity of cells is quantitatively defined by two constants, α and β, both of which represent the frequency of lesions within the low- and high-dose regions of the survival curve using the linear-quadratic model (LQ-model)(161).

It is well known in the treatment of H&N cancers that FS, total dose and OTT impact on tumour control and acute and late toxicity in a complex way. However, the most significant change associated with the SIB technique compared to the sequential approach is related to the fractionation strategy, concerning mostly with two time-dose

parameters: (1) the shortening of the OTT; and (2) the increase of FS to the boost volume. Moreover, both the total prescribed dose (PD) and the biologic dose may be increased. High TCPs are associated with large BEDs, which are a result of a small number of large dose fractions (11).

SIB-IMRT (VMAT) can increase the BED of delivery to the tumour with a dose per fraction >2 Gy while achieving shorter treatment time. It is well known that increasing BED in HNC for local tumour control can lead to significant clinical benefits, which is associated with improved survival. When assuming that a/b is 10 Gy for HNC, it has been found that enhancing local control in HNC is approximately 1.7% per 1% change in the total dose (equivalent to 2Gy/ fraction), with that being translated to 1.2% change in BED(162).

The BED of SIB-IMRT(VMAT) was higher than that of SEQ-IMRT(VMAT), which could have caused a different biological effect by SIB-boost. In our study, the BED to PTV70 was higher in SIB-VMAT than SEQ-VMAT which leads to increase tumour control probability in the SIB technique. This higher fraction size may have an effect on cellular death and regeneration of acutely responding normal tissue surrounding target volumes. the optimum fractionation and prescribed dose are still uncertain when using SIB-IMRT(VMAT).

In a SIB-IMRT(VMAT) plan, Normal tissues outside the PGTV may receive low BED due to the low dose per fraction; however, normal tissues embedded in or near the PGTV may receive a higher dose(163). Generally, a higher prescribed dose, higher dose per fraction, and shorter treatment course may increase the killing effect of radiation on tumours as well as on normal tissues. the dose per fraction delivered to PGTV was higher in the SIB-IMRT(VMAT) group than that in the SEQ-IMRT(VMAT) group which could provide a survival benefit(164). our study showed a slight difference in the mean dose of D_{max} to the spinal cord and brain stem in both techniques. However, BEDs were higher for the spinal cord and brain stem in SIB-VMAT due to high dose per fraction and reduction in overall treatment time which increase the risk of

myelopathy.

From a socioeconomic prospective, fewer treatment fractions (i.e., 25 fractions in SIB-VMAT as compared to 35 fractions in SEQ-VMAT) also lead to time and cost savings as well as reducing the workload of health care providers. Furthermore, from the radiobiological point of view, reduction in overall treatment time is supposed to reduce the risk of tumour clonogens regrowth during the late phase of radiation treatment and possibly to improve tumour control probability and decrease normal tissue complication probability (156).

The results of the conducted research have been presented at the TPU conference” X All-Russian scientific-practical conference "Scientific initiative of foreign students and graduate students of Russian universities" In April 22-24, 2020.

3.Financial management, resource efficiency and resource saving.

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

3.1. Competitiveness analysis of technical solutions.

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

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

Evaluation map analysis presented in Table 1. The position of your research and competitors is evaluated for each indicator by you on a five-point scale, where 1 is the weakest position and 5 is the strongest. The weights of indicators determined by you in the amount should be 1. Analysis of competitive technical solutions is determined by the formula:

$$C = \sum W_i \cdot P_i, \qquad (1)$$

C - the competitiveness of research or a competitor;

Wi– criterion weight;

Pi – point of i-th criteria.

SIB: Simultaneous integrated boost technique.

SEQ: sequential boost technique.

Because We compare two different techniques of radiotherapy.

Table 4 – Evaluation card for comparison of competitive technical solutions.

Evaluation criteria	Criterion Weight	Points		Competitiveness Taking into account weight coefficients	
		P_{SIB}	P_{SEQ}	C_{SIB}	C_{SEQ}
Technical criteria for evaluating resource efficiency					
1. Risk of radiotherapy side effects	0.18	4	3	0.72	0.54
2. Dose homogeneity	0.13	4	5	0.52	0.65
3. Dose on organs at risk	0.2	5	4	0.90	0.54
4. Easy planning	0.14	4	2	0.56	0.28
5.Risk of treatment failure	0.1	4	4	0.40	0.40
Economic criteria for performance evaluation					
1. Competitive methods	0.08	5	5	0.40	0.40
2. Power application	0.07	3	5	0.21	0.35
3. Price	0.1	4	4	0.40	0.40
Total	1	33	32	4.11	3.56

As the analysis showed, the application of the technique of simultaneous integrated boost in intensity-modulated radiation therapy is more competitive because it is easier in creating a plan and reduced risk of side effects.

3.2. SWOT analysis:

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

Table 5 – SWOT Analysis.

	Strengths: S1. Decrease dose to critical organs. S2. Increase dose to tumor lead to increase tumor control. S3. Short treatment time	Weaknesses: W1. Difficulty in assessing late toxicity of radiation because it needs long period of follow up. W2. Lack of necessary software in oncology clinics.
Opportunities: O1. treatment of patients with head and neck cancer. O2. Reduction in patient's treatment time that leads to decrease in the cost of staying patient in hospital.	Strategy which based on strengths and opportunities: 1. Acceleration of the entire course of Radiotherapy. 2. There is no risk of developing radioresistance due to a decrease in patient failure from radiotherapy due to short treatment time.	Strategy which based on weaknesses and opportunities: 1. Conducting long term studies aimed at the study of late radiation reactions 2. Training of medical physicists to work with the inverse planning program to become interested in this product and, therefore, acquiring software in a clinic
Threats: T1. Lack of commercial interest in the project due to the availability of other IMRT techniques.	Strategy which based on strengths and threats: 1. Implementation of the methodology as standard in the Tomsk Regional Oncology	Strategy which based on weaknesses and threats: 1. Creation of a statistical database showing the benefits of using the simultaneous boost

T2. The lack of demand in the market, due to the lack of a evidence base clinical research customers.	Center. 2. calculation of biological effective dose (BED) for different techniques of IMRT to choose technique with better tumor control and better in sparing organs at risk.	technique and sequential boost. 2. Conducting multiple studies with long period of patient follow-up. 3. Evaluation of the five-year survival of patients with head and neck cancer who treated with both techniques of IMRT.

Based on the results of the analysis, it can be concluded that the Interest in the use of simultaneous boost for the treatment of head and neck tumors can be increased due to increase dose to tumor and short treatment time.

3.3. Project Initiation and Organizational Structure.

The initiation process group consists of processes that are performed to define a new project or a new phase of an existing one. In the initiation processes, the initial purpose and content are determined, and the initial financial resources are fixed. The internal and external stakeholders of the project who will interact and influence the overall result of the research project are determined.

Table 6– Stakeholders of the project.

Project stakeholders	Stakeholder expectations
Russian oncological clinics and patients	Availability of Radiotherapy Equipment. The method of radiation therapy and simplified stages of treatment for patients.
Medical Physicists	Create radiotherapy plans. Reduction mistakes in planning.
Oncologists	Approve radiotherapy plans, regular examination of patient and Treat any side effects.

Table 7 – Purpose and results of the project.

Purpose of project:	To compare between simultaneous integrated boost (SIB) and sequential boost (SEQ) techniques of intensity modulated arc therapy in treatment of head and neck tumors.
Expected results of the project:	1. Increased local tumor control and survival statistics. 2. Dose reduction for organs at risk. 3. Reducing the exposure time per session and the entire treatment course.
Criteria for acceptance of the project result:	1. maintenance dose to organs at risk within constraints 2. Maintenance of adequate coverage of target at the level V95> 95%.
Requirements for the project result:	1. The project must be completed by June 1, 2020 of the year. 2. The results obtained must meet the acceptance criteria for the project result. 3. The results of scientific research should be presented at one of the all-Russian / regional conferences and have a publication in one of scientific journals.

Table 8 – The organizational structure of the project.

№	Participant	Role in the project	Functions	Labor time, hours.
1	Supervisor “Associate Professor”	Head of project	Consultations. Creating plans. Review master's dissertation.	480 hours
2	Master’s student	Executor	Writing master's dissertations. Compare between both techniques as regard target coverage and dose to organs at risk based on dose volume histogram. Calculate biological effective dose (BED) for both techniques. Statistical analysis of data.	894 hours

Table 9– Project limitations

Factors	Limitations / Assumptions
3.1. Project's budget	550,000 rubs
3.1.1. Source of financing	TPU
3.2. Project timeline:	22/07/2019 to 20/05/2020
3.2.1. Date of approval of plan of project	20/02/2020
3.2.2. Completion date	1/06/2020

Table 10 –Project Schedule.

Job title	Duration, working days	Start date	Date of completion	Participants
General Technical supervision	40 days	22/07/2019	15/09/2019	Supervisor
Research and analysis of literature	47 days	16/09/2019	19/11/2019	Supervisor/ Student
Collection of cases and creating radiotherapy plans	111 days	20/11/2019	22/04/2020	Supervisor/ Student
Analysis and evaluation of results	9 days	23/04/2020	05/05/2020	Supervisor/ Student
Preparing of dissertation	22 days	06/05/2020	04/06/2020	Student

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

Table 11 – Gantt chart of Project Schedule

№	Activities	Participants	T_c, Days	Duration of the project											
				July	August	Septembe	October	Novembe	December	January	February	March	April	May	June
1	General Technical supervision	Supervisor	40												
2	Research and analysis of literature	Supervisor / Student	47												
3	Collection of cases and creating radiotherapy plans	Supervisor / Student	111												
4	Analysis and evaluation of results	Supervisor / Student	9												
5	Preparing of dissertation	Student	22												

3.4. Scientific and technical research budget.

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

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

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

- Material costs of scientific and technical research;

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

The budget for scientific and technical research is shown in table:

Name	Material costs	Costs of special equipment	Basic salary	Additional salary	labor tax	Overhead	Total cost
Cost, rubles	9,030	15,000	290,263.6	29,026.36	78,661.4	87,079.1	509,060.46

3.4.1. Calculation of material costs.

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

$$C_m = (1 + k_T) \cdot \sum_{i=1}^{m} P_i \cdot N_{consi} \quad (2)$$

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

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

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

k_T – coefficient taking into account transportation costs.

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

Energy costs are calculated by the formula:

$$C = P_{el} \cdot P \cdot F_{eq} \quad (3)$$

where P_{el} − power rates (5.8 rubles per 1 kWh);

P − power of equipment, kW;

F_{eq} − equipment usage time, hours.

Table 12 – Material Costs.

Name	Unit	Amount	Price per unit, rub.	Material costs, rub.
Electricity of PC	kWh	100	5.8	580
Papers		200	1	200
Printing on A4 sheet		500	4	2000
Pen		1	150	150
Transportation and procuring expenses		100	21	2100
Internet	Month	4	1000	4000
Total				9030

3.4.2Cost of special equipment.

Equipment was not specifically purchased for this work, therefore, it is necessary to calculate costs associated with this special equipment (instrumentation, devices and mechanisms fixation, special Software necessary to carry out work for example in this work Monaco Treatment Planning System (TPS)) all of those cost about 15000 rubles.

3.4.2. Basic salary.

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

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

$$S_b = S_a \cdot T_w \quad (4)$$

where Sb – basic salary per participant;

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

Sa - the average daily salary of participant, rub.

The average daily salary is calculated by the formula:

$$S_d = S_m \cdot M \,/\, F_v \quad (5)$$

where S_m – monthly salary of a participant, rub.;

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

at holiday in 48 days, M = 11.2 months, 6 day per week;

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

Table 13 – The valid annual fund of working time

Working time indicators	
Calendar number of days	365
The number of non-working days - weekend - holidays	 52 14
Loss of working time - vacation - sick absence	 48
The valid annual fund of working time	251

Monthly salary is calculated by formula:

$$S_{month} = S_{base} \cdot (k_{premium} + k_{bonus}) \cdot k_{reg} \quad (6)$$

where S_{base} – base salary, rubles;

$k_{premium}$ – premium rate;

k_{bonus} – bonus rate;

k_{reg} – regional rate.

3.4.3.a. Supervisor base salary

The basic salary of the supervisor is calculated on the basis of the sectoral labor payment. The sectoral wage system in TPU assumes the following composition of wages. The salary is determined by the enterprise.

In TPU, salaries are distributed in accordance with the positions held. The head of this research work is an employee with the position of a associate professor The salary of the senior teacher is 35120 rubles.

The wage increments are 10000 rubles (surcharges of the academic council), and the district coefficient for Tomsk Region is 1.3.

Basic Salary of Supervisor: 35,120 *1.3 = 45,656 rub.

(45,500 * 10.4)/251 = 1,891.7 rub/day.

In total of days: 1,891.7 rub/day * 80 days = 151,336.0 rub.

3.4.3.b master student salary.

Since master student basic salary is 17,310.

Basic Salary of master student: 17,310*1.3 = 22,503 rub.

(22,503 *10.4)/251 = 932.4 rub/day.

In total of days: 932.4 rub/day * 149 days = 138,927.6 rub.

Table 14– Calculation of basic salary.

Participant	Basic salary, rubles
Head of project	151,336.0
Executor	138,927.6
Total	290,263.6

3.4.3. Additional salary.

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

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

$$W_{add} = k_{extra} \cdot W_{base} \quad (7)$$

where W_{add} – additional salary, rubles;

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

W_{base} – base salary, rubles.

Table 15– Calculation of Additional Salary.

Participant	Additional salary, rubles
Head of project	15,133.6
Executor	13,892.76
Total	29,026.36

3.4.4. Labor tax.

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

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

$$P_{social} = k_b \cdot (W_{base} + W_{add}) \quad (8)$$

where k_b – coefficient of deductions for labor tax.

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

Table 16– Calculation of Labor tax.

Participant	Labor tax, rubles
Labor rate	27.1%
Head of project	41,012
Executor	37,649.4
Total	78,661.4

3.4.5. Overhead costs.

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

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

Overhead is calculated according to the formula:

$$C_{ov} = k_{ov} \cdot (W_{base} + W_{add}) \quad (9)$$

where k_{ov} – overhead rate.

Table 17 – Calculation of overhead

Participant	Overhead costs, rubles
overhead rate	30%
Head of project	45,400.8
Executor	41,678.3
Total	87,079.1

3.4.6. Formation of budget costs.

The calculated cost of research is the basis for budgeting project costs.

Determining the budget for the scientific research is given in the table.

Table 18 – budget for scientific and technical research.

Name	Cost, rubles
1. Material costs	9030
2. Costs of special equipment	15000
3. Basic salary	290,263.6
4. Additional salary	29,026.36
5. Labor tax	78,661.4
6. Overhead	87,079.1
Total planned cost	509,060.46

3.5. Conclusion

Thus, in this section was developed stages for design and create competitive development that meet the requirements in the field of resource efficiency and resource saving.

These stages include:

- development of a common economic project idea, formation of a project concept;
- organization of work on a research project;
- identification of possible research alternatives;
- research planning;
- assessing the commercial potential and prospects of scientific research from the standpoint of resource efficiency and resource saving;
- determination of resource (resource saving), financial, budget, social and economic efficiency of the project.
-

4.Social responsibility

4.1. Introduction

Radiation therapy is one of the main modalities of cancer treatment (e.g. external beam radiotherapy). Medical staff and patients are at risk of exposure to ionizing radiation, so limitation exposure is necessary to reduce any harmful hazardous and make it as low as reasonably achievable.

4.2 Legal and organizational items in providing safety

Nowadays one of the main way to radical improvement of all prophylactic work referred to reduce Total Incidents Rate and occupational morbidity is the widespread implementation of an integrated Occupational Safety and Health management system. That means combining isolated activities into a single system of targeted actions at all levels and stages of the production process. Occupational safety is a system of legislative, socio-economic, organizational, technological, hygienic and therapeutic and prophylactic measures and tools that ensure the safety, preservation of health and human performance in the work process (165).

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

- to have a workplace that meets Occupational safety requirements;
- to have a compulsory social insurance against accidents at manufacturing and occupational diseases;
- to receive reliable information from the employer, relevant government bodies and public organizations on conditions and Occupational safety at the workplace, about the existing risk of damage to health, as well as measures to protect against harmful and (or) hazardous factors;
- to refuse carrying out work in case of danger to his life and health due to violation of Occupational safety requirements;

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

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

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

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

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

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

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

4.3 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.

4.4. Occupational safety

A dangerous factor or industrial hazard is a factor whose impact under certain conditions leads to trauma or other sudden, severe deterioration of health of the worker(165).A harmful factor or industrial health hazard is a factor, the effect of which on a worker under certain conditions leads to a disease or a decrease in working capacity.

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

The object of Investigation is investigation of effect of Exposure to ionizing radiation in radiation oncology centers on patients and health care workers due to exposure to radiation machines (e.g. Elekta machine).Exposure to ionizing radiation can cause many harmful hazards (e.g. cataract, genetic mutation, cancer) so limit exposure is an important but within beneficial range to be as low as reasonably achievable.

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

The working conditions in the workplace are characterized by the presence of hazardous and harmful factors, which are classified by groups of elements: physical, chemical, biological, psychophysiological. The main elements of the production process that form dangerous and harmful factors are presented in Table 19.

Table 19 – Possible hazardous and harmful factors.

Factors (GOST 12.0.003-2015)	Work stages			Legal documents
	Development	Manufacture	Exploitation	
1. Deviation of microclimate indicators	+	+	+	Sanitary rules 2.2.2 / 2.4.1340–03. Sanitary and epidemiological rules and regulations "Hygienic requirements for personal electronic computers and work organization." Sanitary rules 2.2.1 / 2.1.1.1278–03. Hygienic requirements for natural, artificial and combined lighting of residential and public buildings. Sanitary rules 2.2.4
2. Excessive noise		+	+	
3.Increased level of electromagnetic radiation	+	+	+	
4.Insufficient illumination of the working area		+	+	

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

The following factors effect on person working on a computer:

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

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

Deviation of microclimate indicators:

The air of the working area (microclimate) is determined by the following parameters: temperature, relative humidity, air speed. The optimum and permissible values of the microclimate characteristics are established in accordance with(166) and are given in Table 20.

Table 20 – Optimal and permissible parameters of the microclimate.

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

Excessive noise:

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

Increased level of electromagnetic radiation:

The screen and system blocks produce electromagnetic radiation. Its main part comes from the system unit and the video cable. According to (166), the intensity of

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

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

The magnetic flux density should be no more than:

- in the frequency range 5 Hz - 2 kHz - 250 nT;
- in the frequency range 2 kHz - 400 kHz - 25 nT.

Abnormally high voltage value in the circuit:

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

- with direct contact with current-carrying parts during computer repair;
- when touched by non-live parts that are under voltage (in case of violation of insulation of current-carrying parts of the computer);
- when touched with the floor, walls that are under voltage;
- short-circuited in high-voltage units: power supply and display unit.

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

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

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 22– Dose limits

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.

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

Deviation of microclimate indicators:

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

- at least 30 m^3per hour per person for the volume of the room up to 20 m^3 per person;

- natural ventilation is allowed for the volume of the room more than 40 m^3 per person and if there is no emission of harmful substances.

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

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

Excessive noise:

In research audiences, there are various kinds of noises that are generated by both internal and external noise sources. The internal sources of noise are working equipment, personal computer, printer, ventilation system, as well as computer equipment of other engineers in the audience. If the maximum permissible conditions are exceeded, it is sufficient to use sound-absorbing materials in the room (sound-absorbing wall and ceiling cladding, window curtains). To reduce the noise penetrating outside the premises, install seals around the perimeter of the doors and windows.

Increased level of electromagnetic radiation:

There are the following ways to protect against EMF:

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

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

When working with a computer, the ionizing radiation source is a display. Under the influence of ionizing radiation in the body, there may be a violation of

normal blood coagulability, an increase in the fragility of blood vessels, a decrease in immunity, etc. The dose of irradiation at a distance of 20 cm to the display is 50 μrem / hr. According to the norms (166), the design of the computer should provide the power of the exposure dose of x-rays at any point at a distance of 0.05 m from the screen no more than 100 μR / h.

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

Increased levels of ionizing radiation:

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

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

The radiation control is control of:

- Radiation characteristics of radiation sources, pollution in air, liquid and solid wastes.
- Radiation factors developed with technological processes in working places and environment.
- Radiation factors of contaminated environment.
- Irradiation dose levels of personnel and population.

The main controlled parameters are:

- Annual effective and equivalent doses.
- intake and body content of radionuclides.

- volume or specific activity of radionuclides in air, water, food products, building materials and etc.
- radioactive contamination of skin, clothes, footwear, working places and etc.
- dose and power of external irradiation.
- particles and photons flux density.

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

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

- characteristics of radioactive contamination of the environment;
- probability of radiation accidents and scale of accidents;
- degree of readiness to effective elimination of radiation accidents and its aftermathches;
- number of persons irradiated with doses higher than controlled limits of doses;
- analysis of actions for providing radiation safety, meeting requirements, rules, standards of radiation safety;
- analysis of irradiation doses obtained by groups of population from all ionizing radiation sources.

Abnormally high voltage value in the circuit:

Measures to ensure the electrical safety of electrical installations:

- disconnection of voltage from live parts, on which or near to which work will be carried out, and taking measures to ensure the impossibility of applying voltage to the workplace;

- posting of posters indicating the place of work;
- electrical grounding of the housings of all installations through a neutral wire;
- coating of metal surfaces of tools with reliable insulation;
- inaccessibility of current-carrying parts of equipment (the conclusion in the case of electroporating elements, the conclusion in the body of current-carrying parts)(167).

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.

4.5 Ecological safety

4.5.1 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.

4.5.2 Analysis of the environmental impact of the research process

Process of investigation itself in the thesis do not have essential effect on

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

4.5.3 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.

4.6 Safety in emergency

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

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

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

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

4.6.2 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:

- elimination of the formation of a flammable environment (sealing equipment, control of the air, working and emergency ventilation);
- use in the construction and decoration of buildings of non-combustible or difficultly combustible materials;
- the correct operation of the equipment (proper inclusion of equipment in the electrical supply network, monitoring of heating equipment);

- correct maintenance of buildings and territories (exclusion of the source of ignition - prevention of spontaneous combustion of substances, restriction of fireworks);
- training of production personnel in fire safety rules;
- the publication of instructions, posters, the existence of an evacuation plan;
- compliance with fire regulations, norms in the design of buildings, in the organization of electrical wires and equipment, heating, ventilation, lighting;
- the correct placement of equipment;
- well-time preventive inspection, repair and testing of equipment.

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

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

4.7 Conclusion

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

Possible negative effect on environment were given in compact form describing main ecological problem of using nuclear energy. It could be stated that with respect to all regulations and standards, investigation itself and object of investigation do not pose special risks to personnel, other equipment and environment.

Conclusion:

The SIB technique is a more effective way of planning and delivering VMAT, because it involves the use of the same plan for the entire course of treatment. It may have biologic advantages: the ability for dose/fraction escalation to a tumour and conformal avoidance of normal tissues. However, tissues embedded in the target volume may be at higher risk, and caution must be observed when applying higher than conventional fraction sizes.

Furthermore, there may be an advantage in terms of higher biologically effective tumour dose and/or lower biologically effective dose normal tissues outside the tumour volume. SIB-VMAT may be superior to SEQ-VMAT in its convenience and short-course of treatment, but there is still confusion in terms of optimum fractionation and prescribed dose. However, there is an increased risk of complication due to the high dose per fraction and reduction in overall treatment time which leads to increase BED for SC and BS so the risk of complications are increased such as myelopathy.

In contrast, sequential boost VMAT is more time consuming and requires the summation of 2 or more treatment plans, which can theoretically lead to more potential uncertainty in true dose distribution, but less risk of complications in comparison to SIB such as myelopathy.

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