Kaunas University of Technology

Faculty of Mathematics and Natural Sciences

The impact of the contrast material on dose planning for volumetric arc treatment of head and neck tumours

Master's Final Degree Project

Medical physics (6213GX001)

Simas Jankauskas
Project author

Lect. dr. Jurgita Laurikaitienė
Supervisor

Kaunas, 2020

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Declaration of Academic Integrity

I confirm that the final project of mine, Simas Jankauskas, on the topic „The impact of the contrast material on dose planning for volumetric arc treatment of head and neck tumours“ is written completely by myself; all the provided data and research results are correct and have been obtained honestly. None of the parts of this thesis have been plagiarised from any printed, Internet-based or otherwise recorded sources. All direct and indirect quotations from external resources are indicated in the list of references. No monetary funds (unless required by Law) have been paid to anyone for any contribution to this project.

I fully and completely understand that any discovery of any manifestations/case/facts of dishonesty inevitably results in me incurring a penalty according to the procedure(s) effective at Kaunas University of Technology.

Simas Jankauskas

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Kaunas University of Technology

Faculty of Mathematics and Natural Sciences

Task of the Master's final degree project

Topic of the project	The impact of the contrast material on dose planning for volumetric arc treatment of head and neck tumours
Requirements and conditions (title can be clarified, if needed)	
Supervisor	Lect. dr. Jurgita Laurikaitienė (position, name, surname, signature of the supervisor) (date)

Simas Jankauskas. The impact of the contrast material on dose planning for volumetric arc treatment of head and neck tumours / supervisor Lect. dr. Jurgita Laurikaitienė; faculty of Mathematics and Natural Sciences, Kaunas University of Technology.

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Summary

Many cancer treatment centres does not use contrast material for radiotherapy planning, because contrast media consists of high atomic number materials like iodine. These materials artificially increases density of soft tissues and blood vessels. In that way it leads to different dose distribution in plans that were computed using contrast-enhanced computed tomography (CT) scans rather than non-enhanced CT scans.

Most of the oncological centres worldwide does not use contrast media for treatment planning, contrast media artificially increases density of tissues, which can influence dose calculation process.

Study shown that the mean increase of radiodensity of jugular vein and soft tissues after administration of intravenous contrast material was 84.43 HU and 23.4 HU respectively. Statistical tests shown that this increase is statistically significant. Meanwhile, the dose for cancer and organs at risk was higher in VMAT plans computed using CT scans made after administration of intravenous contrast material. However, statistical tests have shown that the increase in dose is not statistically significant. Despite the fact that the differences between homogeneity indexes of VMAT plans made using contrast-enhanced and non-enhanced CT scans is very low (on average $2.17 \cdot 10^{-3}$ a.u.), statistical test shown that the increase is statistically significant and plans computed using CT scans acquired after administration of contrast media are more homogenous.

Simas Jankauskas. Kontrastinės medžiagos įtaka dozių planavimui taikant arkinį moduliuoto intensyvumo galvos ir kaklo navikų spindulinį gydymą. Magistro baigiamasis projektas / vadovė Lekt. dr. Jurgita Laurikaitienė; Kauno technologijos universitetas, Matematikos ir gamtos mokslų) fakultetas.

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Kaunas, 2020. p.48.

Santrauka

Radikalus gydymo planavimas galvos-kaklo navikams naudojant radioterapiją yra labai sudėtingas procesas. Šio proceso metu reikalinga suplanuoti taip, kad kuo didesnę jonizuojančios spinduliuotės dozę gautų pats navikas, tačiau šalia esantys gyvybiškai svarbūs organai nepasiektų savo galimos gauti dozės ribų. Kad tai būtų įmanoma, labai svarbus yra tikslus kritinių organų ir taikinių apibrėžimas gautuose kompiuterinės tomografijos vaizduose. Šiam tikslui gali būti pasitelktos papildomos priemonės, tokios kaip kontrastinė medžiaga.

Dauguma onkologinių centrų nenaudoja kontrastinės medžiagos gydymo planavime, nes kontrastinė medžiaga dirbtinai padidina audinių tankį, o tai gali daryti įtaką dozės skaičiavimo procesui.

Tyrimas parodė, kad radiotankis KT vaizduose po kontrastinės medžiagos suleidimo vidutiniškai jungo venai pakilo 84.43 HU, o minkštiesiems audiniams 23.4 HU. Statistiniai testai parodė, kad šis pokytis yra statistiškai reikšmingas. Iš kitos pusės, dozė kritiniams organams ir taikiniams buvo didesnė VMAT planuose suskaičiuotuose naudojant CT vaizdus gautus po kontrastinės medžiagos suleidimo, tačiau šis skirtumas buvo statistiškai nereikšmingas. Neskaitant fakto, kad homogeniškumo indekso skirtumas tarp VMAT planų (sukurtų naudojant KT vaizdus prieš ir po kontrastinės medžiagos pacientui suleidimo) yra labai mažas (vidutiniškai $2.17 \cdot 10^{-3}$ a.u.), tačiau statistiniai testai parodė, kad šis skirtumas yra statistiškai reikšmingas ir, kad VMAT planai sukurti naudojant KT vaizdus po kontrastinės medžiagos pacientui suleidimo yra labiau homogeniški.

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Abbreviations:

Lect. – lecturer;

Prof. – professor;

dr. – doctor;

PTV – planning treatment volume;

CTV – clinical treatment volume;

GTV – gross tumour volume;

VMAT – volumetric modulated arc therapy;

IMRT – intensity-modulated radiation therapy;

3D-CRT – Three-dimensional conformal radiation therapy;

HI – homogeneity index;

a.u. – arbitrary units;

OAR – organs at risk;

MLC - multileaf collimator;

QUANTEC - quantitative analysis of normal tissue effects in the clinic;

RSC – radiation safety centre;

Gy – Gray (unit of ionizing radiation);

H&N – head and neck;

CT – computed tomography.

Introduction

Radical treatment planning for head and neck tumour in radiotherapy is technically very challenging. It requires to deliver as high as possible tumorcidal dose to the target volume, while lowering the dose and sparing adjacent critical organs at risk [1]. In addition these kind of tumours frequently occur as aggressive phenotype and grows very fast due to abundant supply of lymph in the head and neck region, therefore it can be often present in a locally advanced stage [2]. Radiotherapy is a main alternative treatment modality to surgical resection in head and neck cancer treatment, because surgical resection can end in functional impairment or unacceptable cosmetic disfigurement [3-4].

To obtain accurate delivery of x-ray photons, an accurate delineation of the treatment target is prerequisite in order to get as high as possible dose conformity in VMAT [5.]. For this intravenous contrast-enhanced computed tomography (CT) can be used in radiotherapy treatment planning in order to improve the outlining of the organ at risk (OAR) and tumour volume, but this can affect radiation dose calculation in VMAT plans [6-7].

The aim of this work: to evaluate the effect of an intravenous contrast material on dose calculations in volumetric modulated arc therapy (VMAT) for head and neck cancers.

Tasks of the work:

1. To determine and compare the differences in radiodensity of contrast-enhanced and non-enhanced computed tomography scans.
2. To determine and compare the differences of effective doses for tumour and organs at risk in VMAT plans computed using contrast-enhanced and non-enhanced computed tomography scans.
3. To determine and compare the differences in homogeneity indexes of VMAT plans computed using contrast-enhanced and non-enhanced computed tomography scans.

1. Literature Review

1.1. Head and neck tumours

Cancer starts when normal healthy cells starts growing out of control and forming a mass that is called a tumour. A tumour can be two types: cancerous and benign. Cancerous or in other words malignant tumour can grow and spread throughout the body. A benign tumour can only grow, but not spread [9].

Cancers that generally are known as head and neck (H&N) cancers frequently begins in the flat squamous cells where it makes a layer of tissue on mucosal surfaces on the H&N structures (i.e. the throat and nose or inside the mouth) (figure 1) [10]. These mucosal surfaces are made of moist tissue and are located directly beneath squamous cell lining called the epithelium. When cancer is found only in the layer of squamous cells, this cancer is called carcinoma [9]. If the cancer is spread outside this layer of cells and penetrated into the deeper tissues, it is called invasive squamous cell carcinoma. In relatively uncommon cases cancer can begin in the salivary glands [10]. In this case it will be usually classified as an adenoid cystic carcinoma, mucoepidermoid carcinoma or adenocarcinoma [9-11].

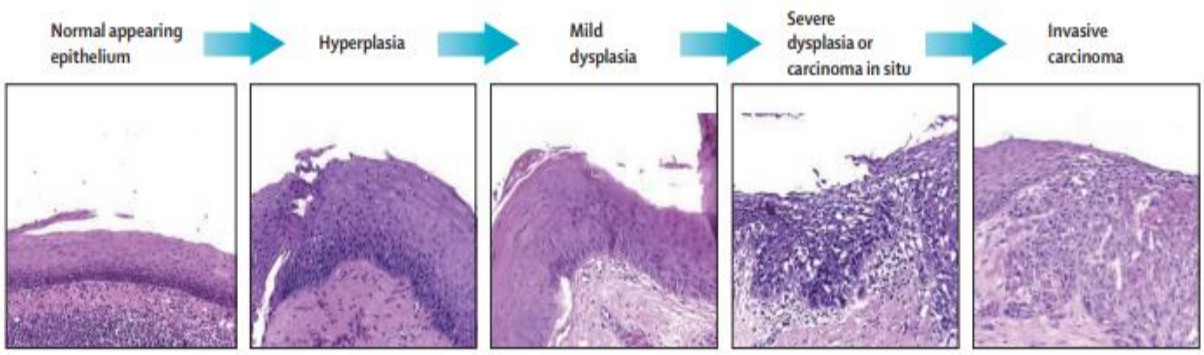


Fig. 1. Phenotypical progression in head and neck carcinogenesis [11]

Head and neck cancers can be categorized by their starting location in the head and neck (figure 2) [12].

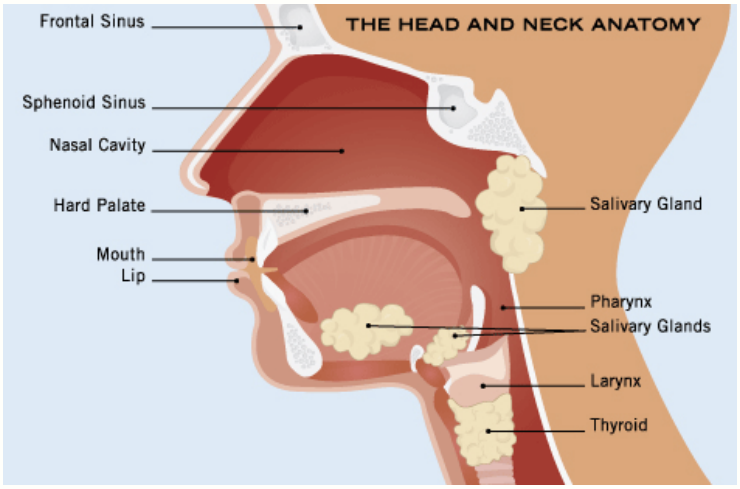


Fig. 2. The head and neck anatomy [12]

There are five main starting locations of H&N cancer [9]:

1. *Oral and oropharyngeal* (3-17 % of cases)*:* Includes the mouth and the tongue, the lips, the gums, the floor of the mouth, the lining inside the cheeks and lips, the hard palate [9-10].

2. *Larynx* (13-26 % of cases)*:* Also called the voice box, is a short tube-shaped organ formed by cartilage in the neck. It plays important role in talking, breathing and swallowing. Larynx is located just below the pharynx. It also has the epiglottis, a small piece of tissue, which prevents from food entering the air passages [9-10].

3. *Pharynx* (2-3 % of cases)*:* is a hollow tube about 13 centimeters long. It begins behind the nose and continues until the esophagus. Pharynx consists of three parts: the first part of pharynx is called the nasopharynx that is behind the nose. The second part is called oropharynx, it includes the soft plate. And the third part is called the hypopharynx that is the lower part of the pharynx [9].

4. *Salivary glands* (5-9 % of cases)*:* They are producing saliva. The major salivary glands are located near the jawbone, in the floor of the mouth [9].

5. *Nasal cavity and paranasal sinuses* (2-4 % of cases)*:* The nasal cavity is the empty, hollow space behind the nose. The paranasal sinuses are the small air-filled hollow areas in the bones that are surrounding the nose [9-10].

The main causes of H&N cancer are: smoking and/or chewing tobacco, alcohol abuse, human papillomavirus – 16 and 18, diet rich in red meat, oral hygiene, carcinogen exposure, chronic irritation to the lining of the mouth, dental plaque formation, low body mass index, family history and exposure to ultraviolet light [14]. Probabilities of some risk factors to cause head and neck cancer are presented in table 1.

Table 1. Probability of risk factor to cause head and neck cancer [13]

Variables	**Parameters**	**Probability ratio (%)**	**P value**
Age group	0-25	1.00	<0.001
	26-50	1.71	
	>50	8.09	
Gender	Male	1.00	0.925
	Female	1.04	
Residence	Rural	6.50	<0.001
	Urban	1.00	
Occupation	Labor	10.13	0.108
	Farmer	5.66	
	Service	1.00	
Diet	Vegetarian	1.00	<0.001
	Mix	4.1.	
Type of habit	Tobacco chewer	8.11	0.018
	Tobacco smoker	4.33	
	Both	4.67	
	None	1.00	
Duration of habit	<10 years	1.00	0.383

The risk factors that has statistically significant probability to cause head and neck cancer are: Age, residence, diet and type of habit. The highest probability to get H&N cancer has person that is over 50 years old that lives in rural environment working physical work and chewing tobacco.

1.2. Aspects of Head and neck tumor treatment planning

Treatment planning usually starts from computer tomography (CT) scanning/simulation and is a complex process. During CT scanning head and neck patient is positioned on CT table and his head is fixated with plastic mask that is made individually for every patient (figure 3). This head fixation prevents from unnecessary patients and treatment targets movement. To ensure that patient is positioned on the linear accelerators table in the same position as he was during simulation various pillows and skin markings are used [16].

Fig. 3. Plastic mask for patients head fixation

CT scans are reconstructed to make a 3D image of target volume and organs and tissues surrounding it, for example, parotids glands, spine and etc. (figure 4). Then radiation oncologist outlines treatment area, organs at risk and prescribes the treatment dose and number of fractions needed for treatment.

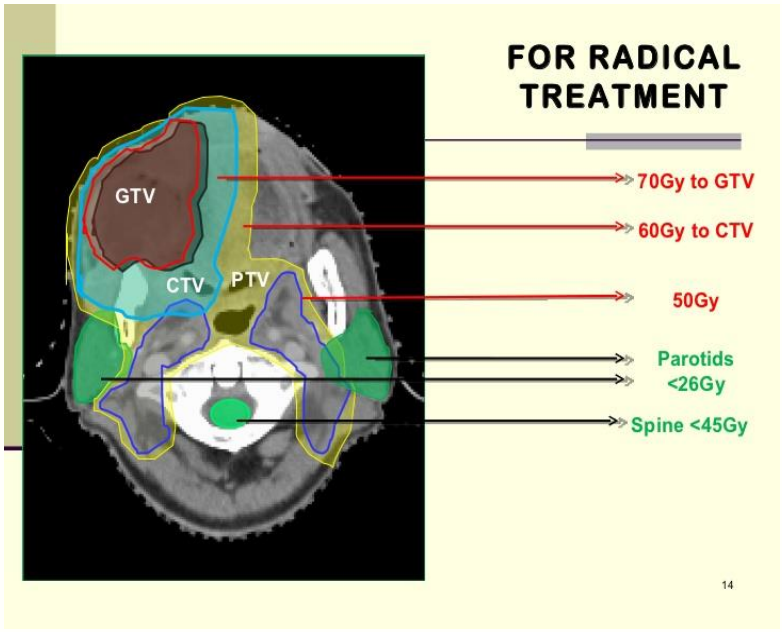


Fig. 4. Target volumes and organs at risk [15.]

Treatment and treatment planning volume consists of the three main volumes (figure 4):

1. The gross tumor volume (GTV) that is defined as a microscopic disease that can be seen on CT scans [17-18].

2. The clinical target volume (CTV). It is the GTV plus a margin for presumable sub-clinical disease spread which cannot be imaged in CT scan [17-18].

3. The planning target volume (PTV). It is the CTV with a margin of about 5-10 mm. PTV allows to ensure that the whole prescribed dose is delivered to the CTV by considering movement of organs and patient and other geometrical inaccuracies [17-18].

After delineation of the target volumes and organs at risk (OAR) treatment planning process starts, creating external beam radiation treatment plan by medical physicist. The main goals of treatment planning is:

1. To achieve that at least 95% of PTV and 99% of CTV receives the prescribed dose [6-19].

2. The maximum dose is not higher than 107% of the prescribed dose using forward planning technique or to be less than 2% of the target volume received more than 107% of the prescribed dose using inverse treatment planning technique [6-19].

3. The dose limits for organs at risk are not exceeded [6-19].

Today the most common treatment planning techniques for head and neck tumors are Intensity-modulated radiation therapy (IMRT) and Volumetric modulated arc therapy (VMAT) [4.]. One of the objectives using innovative radiotherapy techniques is to ensure an accurate prescribed dose delivery to a target/ tumour, at the same time sparing surrounding OARs and healthy tissue. Due to complex anatomy of head and neck (H&N) with OARs located close to the tumour (brain stem, salivary glands, spinal cord) (figure 4) it is paid a special attention to H&N cancer patients. According to the studies [4], IMRT and VMAT treatment planning techniques today allows more accurate and higher dose delivery to the tumour, ensuring a better sparing of OARs, for example in compare in 3D conventional radiotherapy (figure 5) [20-21]. According to this it is seen, that target volume coverage and sparing of OARs, using IMRT and VMAT are comparable, when in VMAT treatment planning is used a single arc. However for more complicated target volumes, such as head and neck cancer, reports are contradictory and claim that two or more arcs must be used [22].

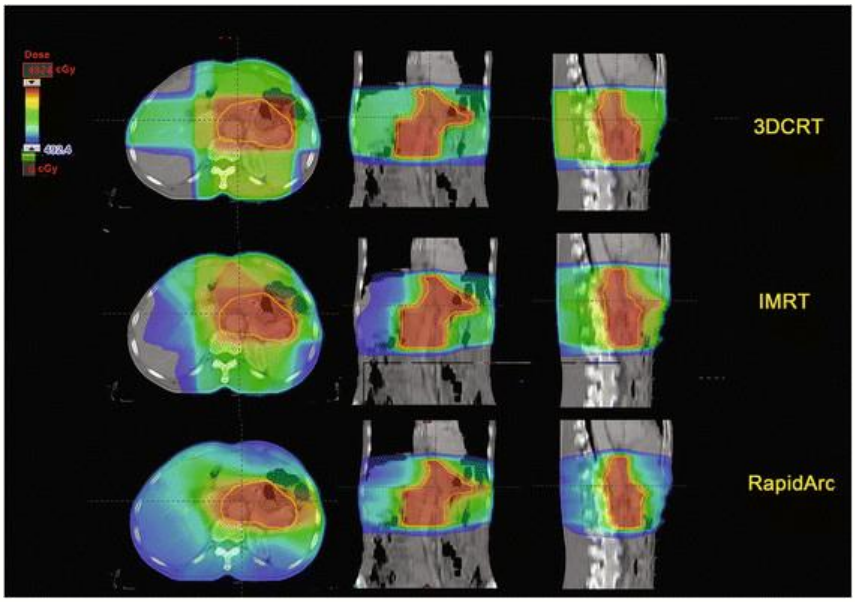


Fig. 5. Dose distribution in VMAT, IMRT and 3D-CRT plans [21]

It is known, that VMAT in compare with IMRT is a faster treatment delivery process, which let to safe irradiation time, at the same time lowering influence of patient's movements, ensuring better treatment outcome [23].Volumetric modulated arc therapy was first introduced in 2007. It was described as a new form of intensity-modulated radiotherapy. Therefore, today using such kind of techniques like VMAT allows to deliver prescribed dose with a high accuracy and efficiency to target volume with simultaneous variation of three different parameters during treatment [4]: The modulation of dose rate, gantry rotation speed and continuous targets shaping using multileaf collimators (MLC) leafs movement. These three parameters allows generate intensity-modulated plans (figure 6). Rotating gantry and simultaneously moving MLC leaves collimates a field regarding to the irregularities of tumour, significantly reducing dose to OARs and the dose delivery time. However high accuracy and efficiency comes with a cost of longer planning time due to longer dose calculation and plan optimization processes [24].

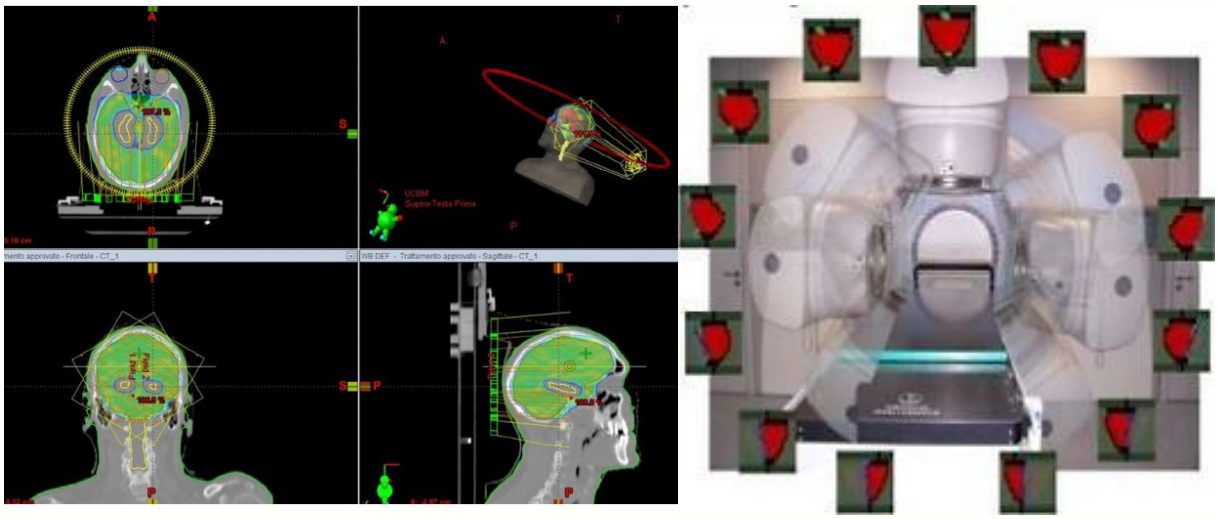


Fig. 6. Gantry rotation and MLC leafs positions [25]

VMAT (like and IMRT) is using inverse treatment planning technique for the planning process.

This technique is usually called as an optimisation problem. The main constrains and objective function of inverse treatment planning process contains of terms which are designed for various practical and clinical considerations, like capability of linear accelerator to deliver a plan and dose volume criteria. This optimization problem can be solved mathematically by determining variables (like fluence map) that are defining a treatment plan (figure 7) [26].

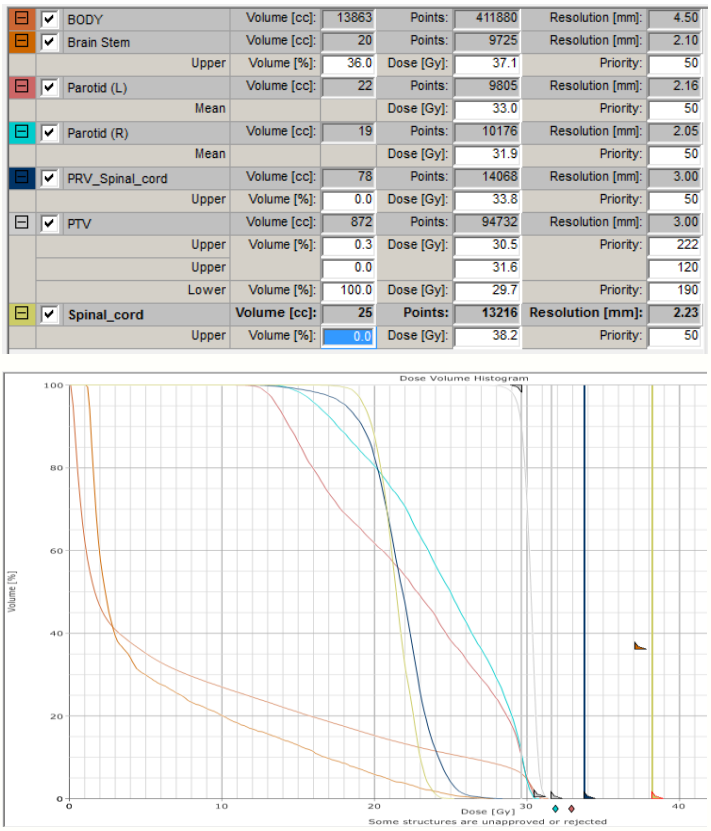


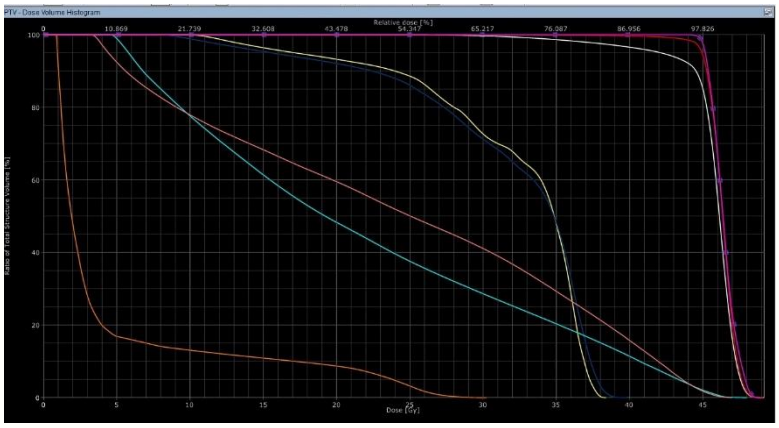
Fig. 7. Objectives of VMAT treatment plan

Organs at risk must be considered during the treatment planning, because ionising radiation can cause damage and pathological changes in organs and tissues. These changes can result in irreversible functional consequences [27]. All OARs can be classified as:

- Serial – it is enough even for a small part of organ to overcome its tolerance limit and whole organ may lose its functionality [27].
- Parallel – larger part of organ needs to be irradiated in order to damage it [27].
- Serial-parallel – the probability for side effects to take place depends on the size of volume affected by irradiation and the maximal dose applied to it [27].

Though the inverse planning process ensures better sparing of healthy tissues and OARs, also it faces to some challenges in achieving consistent and high quality plans. The main challenge is a selection of optimization parameters, like dose constrains for organs at risk and for target itself, in order to the highest quality of plans as possible in a time frame to assure an efficient clinical workflow.

The planned treatment plans are usually evaluated using so called dose-volume histograms (DVH), which that shows dose to volume of treatment target and organs at risk (figure 8).



DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]	Median Dose [Gy]	STD [Gy]
	CTV	Unapproved	PTV_contrast	C2								
	PTV	Unapproved	PTV_contrast	C2	763.7	100.0	100.0	23.215	49.335	45.685	46.134	2.326
	Spinal_cord	Unapproved	PTV_contrast	C2	18.6	100.0	100.1	10.102	38.302	32.247	34.917	6.032
	Parotid (L)	Unapproved	PTV_contrast	C2	18.6	100.0	100.0	3.295	46.996	24.315	25.021	13.220
	BODY	Unapproved	PTV_contrast	C2								
	GTV	Unapproved	PTV_contrast	C2								
	PRV_Spinal_cord	Unapproved	PTV_contrast	C2	65.1	100.0	100.1	7.793	40.193	31.925	34.884	6.684
	Parotid (R)	Unapproved	PTV_contrast	C2	16.8	100.0	100.0	4.544	48.107	22.250	19.706	12.498
	CTV1	Unapproved	PTV_contrast	C2								
	CTV2	Unapproved	PTV_contrast	C2								
	PTV2	Unapproved	PTV_contrast	C2								
	LM_NODES	Unapproved	PTV_contrast	C2								
	Dose 106[%]u	Unapproved	PTV_contrast	C2								
	Brain Stem	Unapproved	PTV_contrast	C2	21.2	100.0	100.0	0.874	30.355	4.612	1.950	6.678

Fig. 8. DVH statistics

Treatment planning results of optimization during VMAT planning process, could be adjusted by medical physicist changing DVH objectives in each optimization "stage", trying to get clinically acceptable plan for the treatment [28]. The results of these optimizations depends on the choice of numerous plan parameters, like the maximum dose delivery time, number of arcs, choice of collimator angle and gantry angle spacing (figure 9) [23].

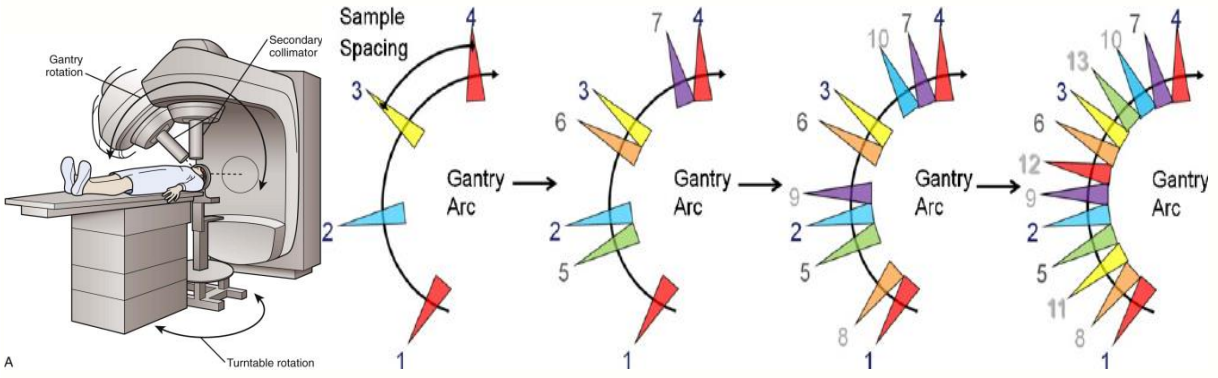


Fig. 9. Movement of linear accelerators parts and sample spacing [29]

VMAT planning is trial-and-error, time-consuming process that is ran by the amount of time that a medical physicist spends and his experience of planning [28]. Therefore medical physicists experience and qualification is very important issue, which allows to ensure the quality of treatment outcome, especially if the dose delivery and dose calculation accuracy is so important like it is in IMRT and VMAT techniques, planning H&N where OARs are in close vicinity of the irradiated area and dose gradients are very high. Therefore, it is known, that dose accuracy in treatment planning depends on motion of internal organs, continuous adjustment of

irradiation beams, uncertainties in delivery and planning processes [30] and on change of organs and tissues HUs that is caused by intravenous contrast agents injected in pre-treatment CT scans.

1.3. The impact of contrast material on treatment dose planning for H&N

It is known, that giving intravenous contrast agents during head and neck computed tomography allows better delineation of targets and OARs, while at the same moment artificially increasing density of some organs and tissues which leads to the increased attenuation of x-rays. The attenuation of x-rays in CT scanning is quantified by Hounsfield units (HU) [31]:

$$HU = \frac{\mu - \mu_w}{\mu_w} \cdot 1000, \quad (1)$$

where μ is linear attenuation coefficient in a matter and μ_w is attenuation coefficient in a water.

The dose calculation during treatment planning, is carried out on the HU conversion related to attenuation coefficients [1]. The linear attenuation coefficient μ is the most important parameter, which characterizes x-ray penetration into an absorbing media. This attenuation coefficient depends on photon energy and atomic number (Z) of the absorbing material. The linear attenuation coefficient (μ) is a constant and is described as the probability of a photon interacting with an absorber per unit path length [32]. Standard law of exponential attenuation for monoenergetic beam of photons is expressed as follows as follows:

$$I = I_0 e^{-\mu x}, \quad (2)$$

where: I – the beam intensity with attenuator; I_0- the initial intensity of photons (without attenuator); μ - the linear attenuation coefficient, x – absorber thickness.

When a photon beam is produced by x-ray device like CT or linear accelerator, photon beam will have a spectrum of energies and the attenuation would not be exponential. Lower energy photons traveling through material attenuates faster than higher energy photons. This effect is called beam hardening. this effect is very useful in practice, because low energy photons increases the surface dose and contributes to scattering processes that lowers image quality in diagnostics [33]. Beam hardening can be achieved by attaching filter (made from material with high Z number) on the device [34]. The Half Value Layer (HVL) describes the thickness of material (filter?) that is required to attenuate a half of the primary intensity of photon beam [34.]:

$$HVL = \frac{0.693}{\mu}, \quad (3)$$

where μ - the linear attenuation coefficient.

Linear attenuation coefficient depends on the density of a material interacting with ionizing radiation. That is why the mass attenuation coefficient $\left(\frac{\mu}{\rho}\right)$ is often used. Mass attenuation coefficient takes out the density as a factor from determining attenuation, instead justifying attenuation off the substances atomic properties [34] (4).

$$I(x) = \frac{I_0}{e^{\frac{\mu}{\rho}\rho x}}, \tag{4}$$

Where: *I(x)* – the intensity of photons transmitted across some distance, I_0- the initial intensity of photons, μ - the linear attenuation coefficient, x – distance that photon traveled, ρ – density of the material, $\frac{\mu}{\rho}$ – mass attenuation coefficient.

Most photons traveling through material will lose some energy by interacting through incoherent scattering. Thus, it is beneficial to weight the amount of photon energy that is transferred through various interactions to electrons of the interacting material (5), because electrons are responsible for the most of the dose deposition in the tissues and organs, furthermore intravenous contrast material increases density of tissues and organs which results in increase of electron density (figure 10) [34].

$$\mu_{tr} = \frac{\bar{E}_{tr}}{hv}\mu, \tag{5}$$

Where: μ_{tr}– the energy transfer coefficient, $\bar{E}_{tr}$- the average energy transferred, *hv* – photon energy, μ - the linear attenuation coefficient.

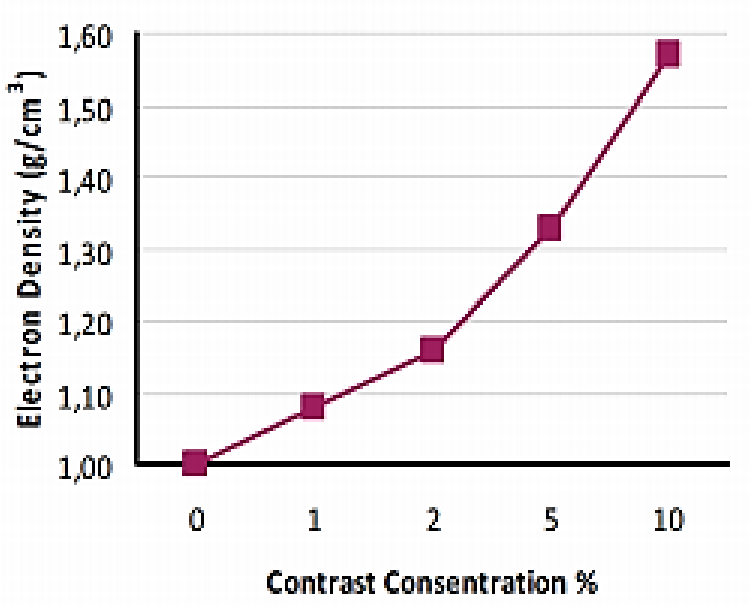


Fig. 10. Relationship between contrast concentration and electron density [35]

Two types of studies have been implemented on the influence of contrast-enhanced CT scans on dose calculations. To the first group belongs mathematical calculations or researches carried out on phantoms. These studies have shown that contrast material does influence dose distribution and computation (figure 11), but it depends on the concentration of contrast material in medium. However the concentrations of the CM in the tissues are smaller in clinical applications [6-8].

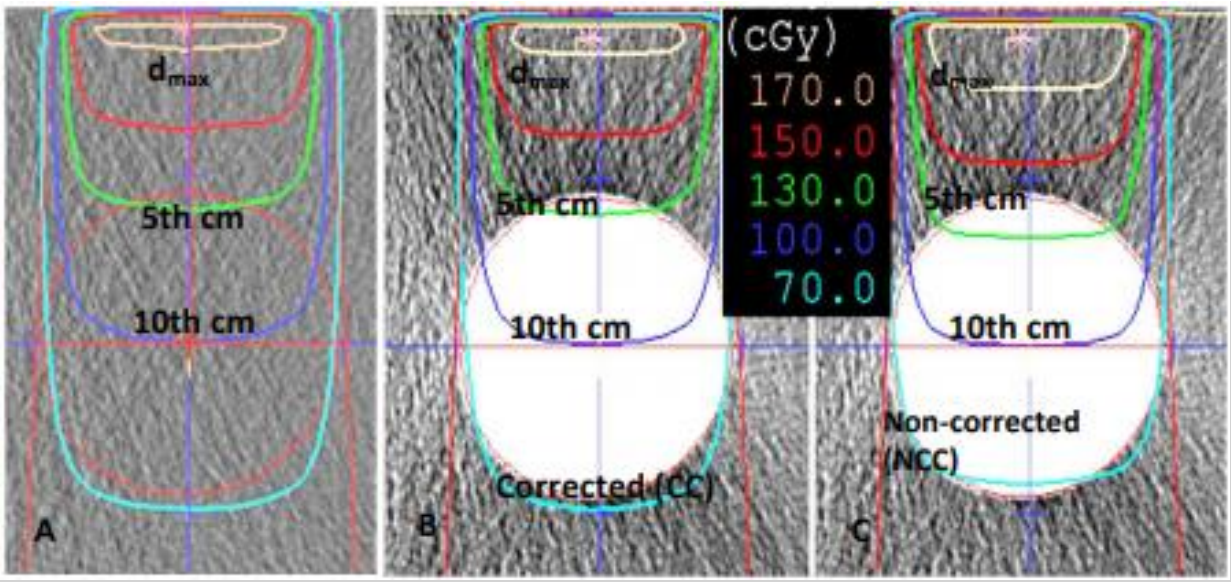


Fig. 11. Dose distribution in depth. A) Dose distribution with 0% of contrast. B) Dose distribution with 5% of contrast, but density adjusted to 1 (density of water). C) Dose distribution with 5% of contrast without any corrections [35.]

The second group investigates the influence of contrast material on the dose computations for tumors at different anatomical regions in patients [36]. The results of the second group researches have shown that the influence of CM on dose computations in treatment planning is insignificant for regions where the contrast material concentration is relatively low. The recent studies have shown that the increase in the monitor units (MUs) if the CM administration is low is considered insignificant for whole-neck irradiation [6].

However, contrast materials (CMs) are normally made of elements that has high atomic number like iodine (Z = 53). Using CMs, will increase HUs in CT scans from decreasing x-ray transmissions. Therefore high HUs areas will always be considered as high-density tissues (figure 12) [31]. Thus, higher absorption for photon beams will be calculated [7-9]. Using CT scans made with CM where some heterogeneities are accounted can negatively influence the dose distribution during treatment planning, since the contrast material is only present during the CT scanning process, but not during treatment. Based on this concern some treatment centers and radiation oncologists have never used contrast materials CT for treatment planning [6-8]. While intravenous contrast material is very helpful in refining the outlining and recognition of tumors from computed tomography images, carrying out full-scale study on the influence of intravenous CM on the CT-based treatment planning of dose distribution is necessary [6].

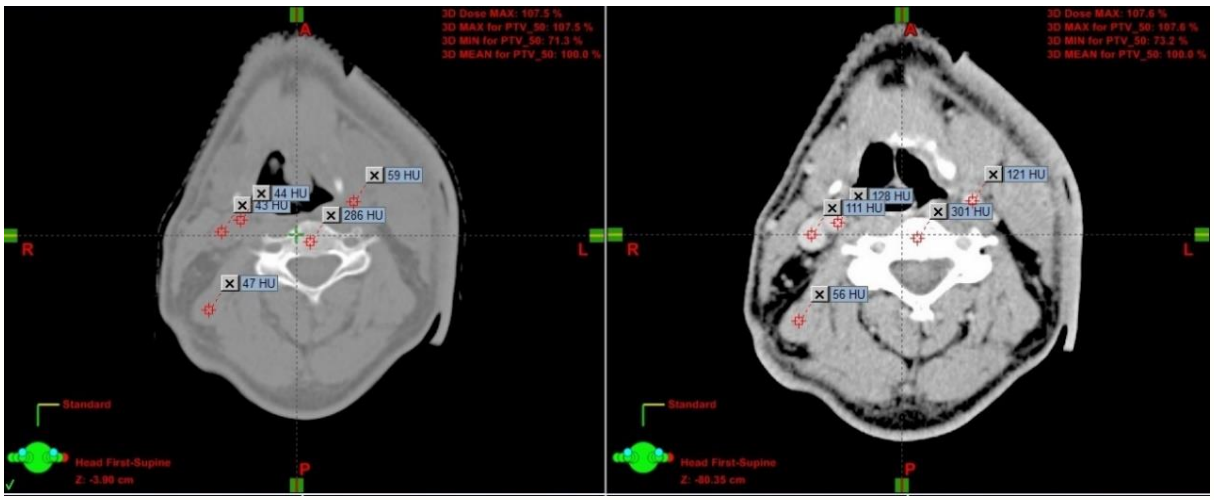


Fig.12. Difference of HUs between non-enchanted (left) and contrast enchanted CT scans

Therefore after treatment planning is done there still is one more very important step left – plan evaluation. During plan evaluation it is crucially important to evaluate early and late reactions of tissues and organs. Evaluating the complexity of head and neck tumours treatment planning and trying to protect OARs that are near or even inside the PTV there is a possibility to check the probability of early and late reactions depending on the dose that tissues and organs received (table 2). In Lithuania, for evaluation of the possibility to develop early and late reactions, quantitative analysis of normal tissue effects in the clinic (QUANTEC) is used. QUANTEC is a set of articles that describes tolerance doses for various organs at risk [37].

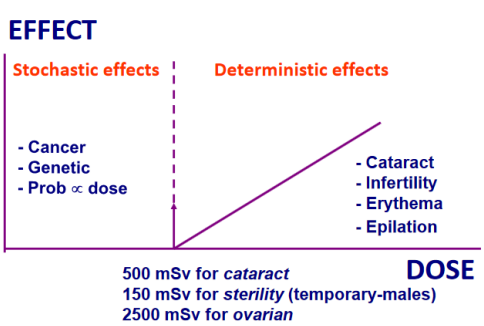
Table 2. QANTEC dose limits for organs at risk [37]

Organ	**Endpoint**	**Dose (Gy) or dose/volume parameters**	**Rate (%)**
Optic nerves	Optic neuropathy	D_{max} < 55	<3
		D_{max} 55-60	3-7
		D_{max} <60	>7-20
Cochlea	Sensory neural hearing loss	D_{mean} < 45	<30
Brainstem	Permanent cranial neuropathy or necrosis	≤ 50	Safe dose
		D_{max} <54	<5
		D_{max} > 60	25-30
		D_{max} <65	50
Pituitary gland		D_{max} <50	
Retina		D_{max} <45	
Lacrimal gland		D_{max} <40 $V_{30\ Gy}$< 50%	
Lens	Cataract	D_{max} <6	Safe dose
		D_{max} <10	60
Spinal cord	Myelopathy	D_{max} <50	0.2
		D_{max} <60	6
Parotid, bilateral	Long term parotid salivary function reduced to <25% of pre-RT level	D_{mean}<25	20
Parotid, bilateral		D_{mean}<39	50
Parotid, unilateral		D_{mean}<20	20
Submandibular gland		D_{mean}<35	
Pharynx	Symptomatic dysphagia and aspiration	D_{mean}<50	<20
Larynx	Vocal dysfunction, aspiration, edema	D_{max} <66	<20
		D_{mean}<50	<30
		D_{mean}<44	<20
		$V_{50\ Gy}$ <27%	<20
Esophagus	Grade ≥ 3 acute esophagitis	D_{mean}<34	5-20

1.4. Health effects of ionizing radiation

The consequences of irradiation with ionizing radiation is divided into two groups: deterministic (due malfunctions or killing large part of cells) and stochastic (in example

heritable effects and cancer involving heritable disease in their descendants or cancer development in exposed organism) [38]. For deterministic effects to take place a certain threshold must be exceeded. However, this threshold can be different for every person. When the threshold is overstepped the severity of the deterministic effects increases with the radiation dose. On the other hand stochastic effects often occurs incidentally. Thus these two kinds of effects develops from direct effect of ionising radiation. Consequently it is very important to evaluate the probability for stochastic effects to occur, since there is no threshold for them (figure 13) [39].



	Deterministic effects	Stochastic effects
onset time	short	long
threshold	yes	no
probability	1 for all individuals above	increasing with dose
severity	increasing with dose	independant of dose
Consequences for nuclear installations	to prevent the occurrence of accidental situations and if any, to limit the consequences	to limit the exposure of workers, to reduce the exposure as low as possible

Fig. 13. Types of effects caused by ionising radiation to tissues and organs

The damage caused by radiation to organs and tissue depends on the absorbed dose which is expressed by a unit so called Gray (Gy), quality of radiation and dose rate [40]. The damage caused by absorbed dose depends on the sensitivity of different organs and tissues and on the type of radiation [14.]. Different organs sensitivity to ionising radiation can be expressed by weighting factor (W_T). The higher the weighting factor is the less sensitive organ is to ionising radiation (table 3) [41].

Table 3. Weighting factors of organs [41]

Organ	**Skin, Bone surface, Salivary glands, Brain**	**Bladder, Liver, Oesophagus, Thyroid**	**Gonads**	**Remainder of body**
W_T	0.01	0.04	0.08	0.12

After reaching certain step radiation can harm the main functions of organs and tissues that can end in acute effects such as radiation burn, hair loss, skin redness or acute radiation syndrome (table 4). The higher the dose or dose rate the more severe effects occur [14, 24, 42].

If the radiation is delivered over a long period of time and/or the dose is low, the risk for tissues and/or organs is lower due to greater probability of tissues and organs repairing the damage [43].

Table 4. Acute effects and their thresholds [42]

Tissue/organ	Effect	Threshold (Gy)	Time to develop the effect
Skin	Skin reddening (erythema)	3-6	1-4 weeks
	Skin burns	5-10	2-3 weeks
	Temporary hair loss	4.0	2-3 weeks
Testes	Temporary sterility	0.1	3-9 weeks
	Permanent sterility	6.0	3 weeks
Ovaries	Permanent sterility	3.0	< 1 weeks
Heart	Cardiovascular disease	0.5	Long-term effect
Bone marrow	Depression of haematopoiesis	0.5	3-7 days
Circulatory system	Stroke	0.5	Long-term effect
Lung	Pneumonitis	6.5	3-6 months
Kidneys	Renal failure	7.0	
Lens of the eye	Visual impairment	0.5	Long-term effect

Different studies [44-45] have shown that deoxyribonucleic acid (DNA) that is in the cells of organs and tissues can repair itself after myriad types of damages via difficult repair mechanisms. However, residual DNA damage and misrepair can still occur. It is known, that the risk of long-term effects like cancer after irradiation with ionising radiation does not disappear and it can appear many years later. [45]. The long-term effects may not even occur, but their probability for them to develop is proportional to the radiation dose. Children and adolescents are more sensitive to radiation than adults, so the risk of long-term effects for them is significantly higher [43].

Epidemiological studies, made on groups of people exposed to radiation, gave a valid results that showed a meaningful increase in risk of getting a cancer at doses higher than 100 mSv. Recent studies on people exposed to medical exposures in young age propose that cancer risk can increase even at low doses (50-100 mSv) [43]. However epidemiological studies alone does not provide final evidence of the non-existence or existence of carcinogenic effects due to low dose-rate or low dose radiation exposure for human body. The lack of epidemiological evidence does not prove that low dose or low dose-rate radiation exposure effects do not exist. Those kind of studies have not detected any hereditary effects of radiation exposure in humans that could be considered as statistically significant [45].

Prenatal exposure to dose over 100 mSv between weeks 8-15 of pregnancy and 200 mSv between weeks 16-25 of pregnancy may cause acute brain damage in foetuses. Human studies have not shown any radiation damage risk to foetus brain development from radiation exposure after week 25 or before week 8 of pregnancy [43].

All requirements for medical exposure to ionising radiation in Lithuania is written in Lithuanian hygiene norm HN 73:2018. This document states that exposure to ionising radiation must give

more benefits than harm and only in that case it is justified. Furthermore, when it comes to radiation therapy it is very important that every treatment plan is made individually for every patient taking into account doses to targets and organs at risk. Dose in radiotherapy must be justified to. The main aim of radiotherapy is to achieve dose as high as possible dose delivery to a tumour, thus at the same time keeping as low as possible dose to adjacent organs [47].

1.5. Radiotoxicity

Ionising radiation can damage human body directly by damaging DNA of the cells or indirectly by changing their chemistry. The same primary event, like damaged chromosome, can have different outcomes: it can lead to cell death, metabolic changes, sterility or even death. But it is not necessary to lead to harmful effects, since the human body has natural repair mechanisms. At high doses acute damage can occur. Effects are deterministic and depend on the ionising radiation dose level above a threshold value [40]. At the low doses of radiation the effects are stochastic. That means that the dose received influences the chance of induction of tumours or other negative health effects occurring. The assumption is that this probability decreases with the dose, but there is no dose that doesn't have any effects on human body. The predicted effects, based on extrapolations from high doses, are very small, so they cannot be disproved or proved directly. The true relationship of dose to effect is a big issue debated in scientific circles. Even more controversial is the functioning of DNA repair mechanisms, whether low doses can cause positive effects (hormosis) on these mechanisms or not [45].

Before starting radiotherapy it is needed to know what are dose constrains for tumour and organs at risk, because after exceeding certain thresholds some unwanted reactions can start that causes potential risk for patients life quality and life itself [46]. Furthermore, even if those thresholds are not exceeded during treatment planning, there is still a chance for them to take place because of some kind of unwanted events like: bad patient positioning, patients tolerance to ionising radiation and equipment failures. All these unwanted events are categorised into grades of toxicity (from 0 to 5) by radiation safety centre (RSC), where events from level 0 is the least dangerous and events that belongs to level 5 are deadly [47].

When we are talking about impacts of ionising radiation acute and late reactions (table 5) should be excluded. acute reactions takes places during treatment, while late reactions occur only after several weeks, months or even years after the end of the treatment [48].

Table 5. Toxicity profile of head and neck radiotherapy suing VMAT [48]

Toxicity	**Acute toxicity**		**Late toxicity**	
	Grade	**Patient (%)**	**Grade**	**Patient (%)**
Mucosal	0	15	0	97
	1	32	1	2
	2	42	2	1
	3	11	3	-
Salivary	0	73	0	63
	1	23	1	19
	2	4	2	18
	3	-	3	1
Taste	0	64	0	80
	1	28	1	13
	2	8	2	7
Swallowing	0	48	0	97
	1	20	1	2
	2	25	2	1
	3	6	3	-
Skin	0	25	0	100
	1	38	1	-
	2	31	2	-
	3	4	3	-

From out of 102 patient treated for head and neck cancer using VMAT the most frequent acute reactions were grade 0 salivary (73%) and taste (64%) toxicities. As for late reactions the most common toxicities were grade 0 mucosal (97%), swallowing (97%) and skin (100%) toxicities. Grade 3 mucosal, swallowing and skin (grade 1-3) toxicities have not developed for any of the patients, however these toxicities were presented as acute [48].

Studies made by other authors [49] showed that there is a connection between head and neck tumours radiation therapy treatment and other diseases and complications. Types of complications and their rate are presented in table 6. Despite all complications and their rates, the overall survival rate of all 3328 treated head and neck cancer patients 8 years after treatment completion was ~70% [49].

Table 6. Late complications [49]

Complication	**Number**	**Rate (%)**
Endocrinopathy	447	13.4
Hearing impairment	235	7.1
Cranial nerve palsy	171	5.1
Dysphagia	100	3
Second primary tumors	63	1.9
Recurrent aspiration pneumonia	64	1.9
Osteoradionecrosis	61	1.8

Table 6 represents that there is about 1.9% chance for secondary tumour development and the biggest probability disorders and complications to develop has Endocrinopathy [49].

2. Materials and Methods

2.1. Patient selection

For this study 12 patients (8 males and 4 females) were selected. Information about the patients is presented in table 7.

Table 7. Patient information

Nr.	Prescribed dose, Gy	PTV volume, cm^3	Sex	Age	Diagnose
1	50	773.0	M	68	Malignant neoplasm of glottis
2	50	872.0	F	62	Overlapping malignant neoplasm of oropharynx
3	50	1714.7	M	62	Overlapping malignant neoplasm of tongue
4	50	80537.0	F	63	Malignant neoplasm of lateral wall of nasopharynx
5	50	725.3	M	87	Overlapping malignant neoplasm of larynx
6	50	763.7	M	81	Overlapping malignant neoplasm of larynx
7	50	764.6	M	66	Overlapping malignant neoplasm of tongue
8	50	864.2	M	74	Malignant neoplasm of glottis
9	50	894.0	F	67	Malignant neoplasm of glottis
10	50	723.0	M	69	Overlapping malignant neoplasm of tongue
11	50	769.4	F	70	Overlapping malignant neoplasm of oropharynx
12	50	857.7	M	73	Overlapping malignant neoplasm of larynx

2.2. Volumetric modulated arc therapy planning process

Casual Volumetric Modulated Arc Therapy (VMAT) treatment process for oncological patients is composite and complex. Usually this process consists of 4 main stages:

1. After patient was diagnosed with oncological disease, patient is positioned on the Computed tomography (CT) table using lasers and fixation measures (5-point masks and pillows) (Figure 14.) and scanned.

Fig. 14. Patient positioning on the CT table (left) [55], pillows (middle) and 5-point mask (right)

2. Preparation for VMAT treatment procedure (delineation of targets (GTV, CTV, PTV) and organs at risk (OARs)) and planning using treatment planning software.
3. VMAT plan simulation and verification.
4. Patients treatment.

2.3. Acquisition of computed tomography

12 patients' simulation were performed using a 40 slice computer tomography (CT) scanner "Siemens Somatom Sensation Open". The scanning parameters used for the scanning head and neck cancer patients are presented in Table 8. Helical studies were performed in a craniocaudal direction (Figure 15), because this direction of scanning reduces streak artefacts that comes from various metal objects in head and neck area, due to beam hardening [50].

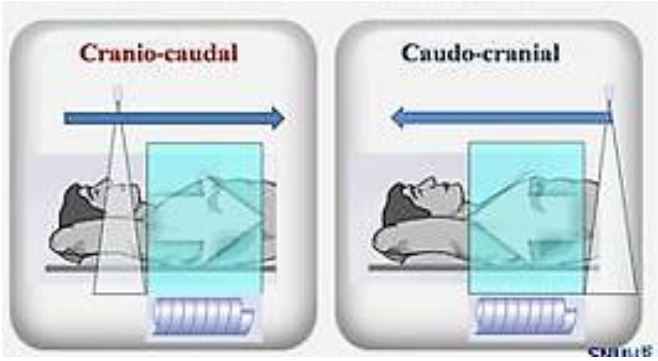


Fig. 15. CT scanning directions

Table 8. The scanning parameters used for head and neck scanning

Parameters	
kV	120
Effective mAs	60
Rotation time	1 second
Slice collimation	1.5 mm
Pitch factor	0.9

Each patient was scanned two times. Both scans (without and with contrast material) were done using the same parameters (Table 2), and patient's positioning. Positioning of the patient is very important step, since it is needed to ensure that patient is laying in the same position on the linear accelerators table every time he is treated as he was laying during CT scanning for treatment planning. For this purpose 5–point individually for every patient made masks and various pillows are used. These masks and pillows (figure 14) prevents unnecessary patient and organ movement and increases accuracy of the treatment [51].

First scan was done without contrast material, the second then patient was injected with contrast material and scanned again. The used contrast agent contained 350 mg/ml of nonionic contrast media (Omnipaqe 350 mg*I*/ml). The total dose of the contrast media was 100 ml. The enhanced scans were started to scan about 100 seconds after a contrast material injection. Contrast materials were injected intravenously manually by licensed radiography technician. Visual difference between the two scans (without and with contrast material) is shown in figure 16.

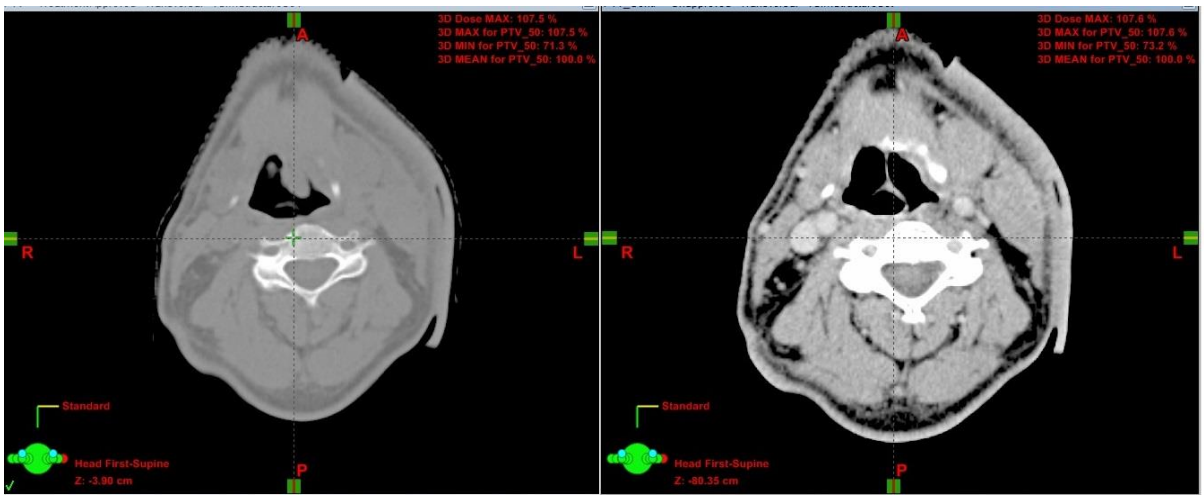


Fig. 16. CT scans made before (left) and after (right) administration of contrast material

The difference of CT number (HU) in jugular vein and soft tissues between two sets of scans were evaluated for comparison of density differences between contrasts enhanced and non-enhanced CT scans. To obtain the arithmetical mean and standard deviation of the CT number in the vessels and tissues of contrast enchanted and non-enhanced CT scans, measurements were made in five points of the each chosen vessel and tissue site. The measurements were done using treatment planning system "Eclipse" (version 10.0.42, Varian Medical System, Palo Alto, CA).

The arithmetical mean is the central value of set of numbers. It is obtained by adding up all values in dataset and dividing the sum of values by the number of values (6).

$$\overline{x} = \frac{1}{n}\left(\sum_{i=1}^{n} x_i\right) = \frac{(x_1 + x_2 + \cdots + x_n)}{n}, \tag{6}$$

where $x_1,\ x_2, \ldots, x_n$ is values of the samples and n is a number of samples.

Standard deviation is a measure of the mean amount of dispersion of a set of values around arithmetical mean. A low standard deviation shows that values are spread closely around the arithmetical mean, while high standard deviation shows that values are spread more widely (7).

$$\mathrm{s} = \sqrt{\frac{\sum_{\mathrm{i}=1}^{\mathrm{n}}(\mathrm{x_i} - \overline{\mathrm{x}})^2}{N-1}}, \tag{7}$$

where x_i – sum of the observed values of the samples, $\bar{x}$ – the mean of values, N – number of observed values.

2.4. Contouring and dose prescription

After the acquisition of the computed tomography scans, images were reconstructed and both of scans were sent to a radiotherapy planning system "Eclipse" using a DICOM RT. Treatment planning system "Eclipse" (version 10.0.42, Varian Medical System, Palo Alto, CA) offers features such as: contouring, image registration, 3D – CRT (3D conformal radiotherapy

treatment), IMRT (Intensity modulated radiation therapy), VMAT (Volumetric modulated arc therapy), brachytherapy and electron planning, plan evaluation, dose calculations.

The non-enchanced CT scan set was fused with the contrast enchanted one using Eclipse software. Then radiology physician delineated the GTV, CTV, PTV and OARs (bilateral parotids, spinal cord, brain stem, mandible, chiasm, brain) (figure 17), and prescribed the dose of 50 Gy for treatment stage one and 20 Gy for treatment stage 2. In both treatment stages the dose of single fractions was 2 Gy. Thus, all plans were generated using non-enchanted CT sets. However, to avoid volume errors of re-delineating targets and OARs all structures were copied from non-enchanted CT sets and pasted on contrast enchanted CT sets. Because of different PTV volumes and locations in head and neck region in treatment stage 2 plans, for statistical comparison between doses only plans for treatment stage one PTVs were taken.

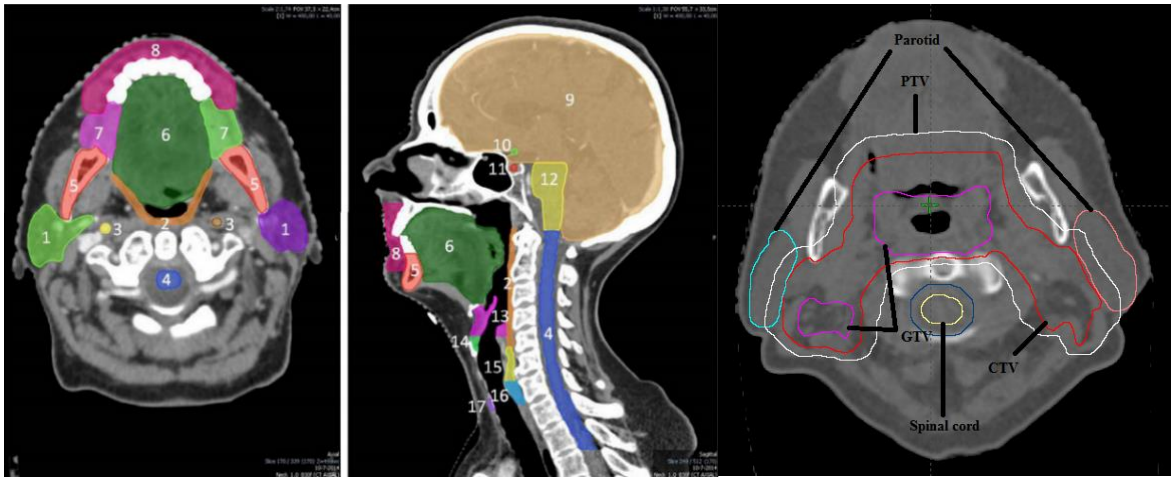


Fig. 17. Targets and organs at risk. Parotid glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), spinal cord (4), mandible (5), extended oral cavity (6), buccal mucosa (7), lips (8), brain (9), chiasm (10), pituitary gland (11), brainstem (12), supraglottic larynx (13), glottic area (14), cricopharyngeal inlet (15), cervical esophagus (16) and thyroid (17) [51]

Due to complexity of head and neck anatomy it is very important to select the best methods for head and neck cancer treatment.

2.5. Treatment planning and dose evaluation

Head and neck patients were planned using volumetric arc therapy tecnique (VMAT) with treatment planning system “Eclipse” (version 10.0.42, Varian Medical System, Palo Alto, CA). All 12 patients’ treatments were planned using inverse treatment planning technique. Inverse treatment planning allows for the user to select dose limits and parameters for targets and OARs. It is very important if the patient’s anatomy is complex, like head and neck patients’ cases. The main parameters of the treatment plans are presented in table 9.

Table 9. The main parameters of VMAT treatment plans for H&N patients

Parameter	
Photon energy	6 MV
Number of arcs	2
Angle of arc	0º -360º
Maximum time of one arc rotation	5 min
Angle of collimator	30º
Maximum dose rate	500 MU/min

The arc characteristics (gantry rotation angle and collimator angle) of the plan made in the non-enchanted CT scan sets were also copied and pasted on the contrast enchanted CT scan sets. Radiation doses and their distributions in the enhanced CT scan sets were obtained by recalculation of each plan using the same parameters of the non-enhanced plans. Dose calculations were made using 6 MV photon beams. The objective of planning was to deliver the prescribed dose to at least 98% of the PTV, with the maximum dose being where less than 2% of the target volume receives more than 107% prescribed dose and not to exceed dose limits for organs at risk. Thus, when plans met all requirements dose homogeneity (3), doses to targets and OARs were compared between plans made on contrast enchanted and non-enchanted CT scan sets.

$$HI = \frac{D_{5\%} - D_{95\%}}{D_{50\%}}, \tag{8}$$

where: $D_{5\%}$, $D_{95\%}$, $D_{50\%}$ is the dose received by 5%, 95% and 50% of volume. *HI* = 1 is the ideal homogeneity.

All doses for organs at risk were taken from dose volume histograms (DVH) (Figure 8) and evaluated by comparing them with recommended doses specified by QUANTEC. Therefore, dose limits for various OARs in head and neck region are presented in table 10.

Table 10. Dose limits for organs at risk in head and neck region

Organ	**Dose limit by QUANTEC**
Spinal cord	D_{max} <50
Brain stem	D_{max} <54
Bilateral parotids	D_{mean}<39
Oesophagus	D_{mean}<34
Larynx	D_{max} <66

After plans were calculated one more step before patient treatment start had to be made. This is step is called plan verification during which the quality of the plan is checked. Plan verification allows to check whether the theoretical dose distribution meets practical dose distribution of our calculated plans. However, it is acceptable that theoretical dose distribution differs from practical dose distribution by less than 5%. This difference may occur because of

various reasons. In example one of them may come from bandwidth of MLC leaves which may influence dose distribution in irradiance volume.

After all plans met all the requirements and were approved by radiation physician as appropriate for treatment additional qualitative analysis were made using program called R project. For this additional qualitative analysis 3 tests were used:

1. Shapiro-Wilk test. This test shows whether data in dataset is distributed by normal or non-normal distributions [52].
2. Mann-Whitney-Wilcoxon test. This test is used to compare difference between two independent groups when data does not follow criteria of normal distribution [53].
3. Student's t test. Test is used to compare difference between two independent groups when data follows criteria of normal distribution [54].

3. Results

3.1. Changes of radiodensity

Descriptive statistics of Jugular veins radiodensity measured in CT scans are presented in figure 18.

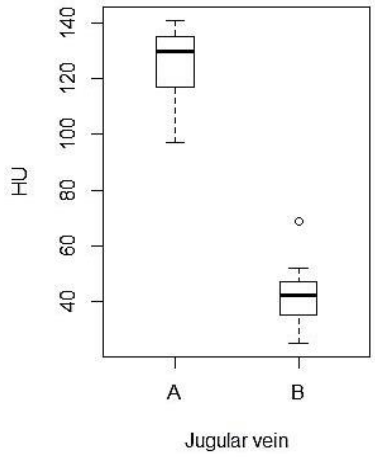


Fig. 18. Hounsfield Units of Jugular vein. A – with contrast media, B – without contrast media

In CT scans without contrast material the lowest radiodensity of Jugular vein was 25 HU, The highest radiodensity was 69 HU. The median and mean of radiodensity measured were 42.5 HU and 41.77 HU respectively. Nevertheless, after injection of contrast media the minimum, maximum, mean and median radiodensity of jugular vein increased up to 97; 141; 126.2 and 130 respectively.

Descriptive statistics of soft tissues radiodensity measured in CT scans are presented in figure 19.

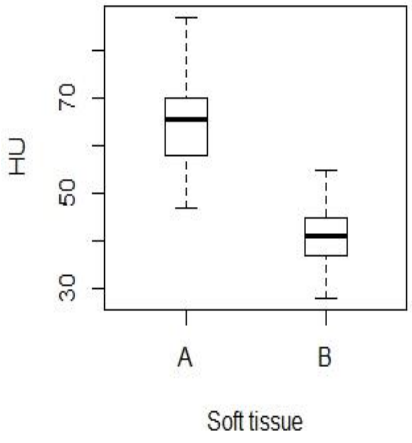


Fig. 19. Hounsfield Units of soft tissue. A – with contrast media, B – without contrast media

In CT scans without contrast material the lowest radiodensity of soft tissue was 28 HU, The highest radiodensity was 55 HU. The median and mean of radiodensity measured were 41 HU

and 40.83 HU respectively. However, after injection of contrast media the minimum, maximum, mean and median radiodensity of jugular vein increased up to 47; 87; 64.23 and 65.5 respectively.

The changes in radiodensity after contrast media administration are presented in table 11.

Table 11. The changes in radiodensity after contrast media administration

Location	**Min** (Gy)	**Max** (Gy)	**Median** (Gy)	**Mean ± SD** (Gy)
Jugular vein	59	112	87.5	84.43 ± 14.44
Soft tissue	2	57	24	23.4 ± 12.422

The mean increase of radiodensity was 84.43 (about 67%) for jugular vein and 23.4 (about 27%) for soft tissue. The mean increase of HUs in this study was lower than in Nasrollah J. et al. [6] study (about 140 HU). This may be because in Nasrollah J. et al. [6] less contrast media dosage was used and scan after injection of contrast media was started earlier.

To determine whether variables in dataset are distributed normally Shapiro-Wilk test was used (table 12).

Table 12. Shapiro-Wilk test results for HUs values in CT scans

	p value
Jugular vein with contrast material	0.231
Jugular vein without contrast material	0.127
Soft tissue with contrast material	0.817
Soft tissue without contrast material	0.98

Shapiro-Wilk test shown that all variables are distributed by normal distribution, because $p > \alpha = 0.05$, however there is still 5% chance to make a mistake.

To determine whether radiodensity of CT scans (with and without contrast media) statistically significantly differs from each other Student's t test was used (table 13).

Table 13. Results of Student's t test for radiodensity

	Soft tissue with contrast material	**Soft tissue without contrast material**	**Jugular vein with contrast material**	**Jugular vein without contrast material**
Soft tissue with contrast material		$3.233 \cdot 10^{-11}$	$2.2 \cdot 10^{-16}$	$7.919 \cdot 10^{-12}$
Soft tissue without contrast material	$3.233 \cdot 10^{-11}$		$2.2 \cdot 10^{-16}$	**0.6839**
Jugular vein with contrast material	$2.2 \cdot 10^{-16}$	$2.2 \cdot 10^{-16}$		$2.2 \cdot 10^{-16}$
Jugular vein without contrast material	$7.919 \cdot 10^{-12}$	**0.6839**	$2.2 \cdot 10^{-16}$	

Student's t test shown that in all cases there is a statistically significant difference between HU measuring points in CT scans except for Jugular vein and soft tissues in CT scans before contrast media administration ($p = 0.6839 > \alpha = 0.05$). This means that radiodensity of jugular vein and soft tissues in CT scans made without using contrast media does not statistically differ from each other. Therefore, this means that contrast media helps radiology physician delineating targets and organs at risk by making blood vessels and different soft tissues more visible (Figure 20).

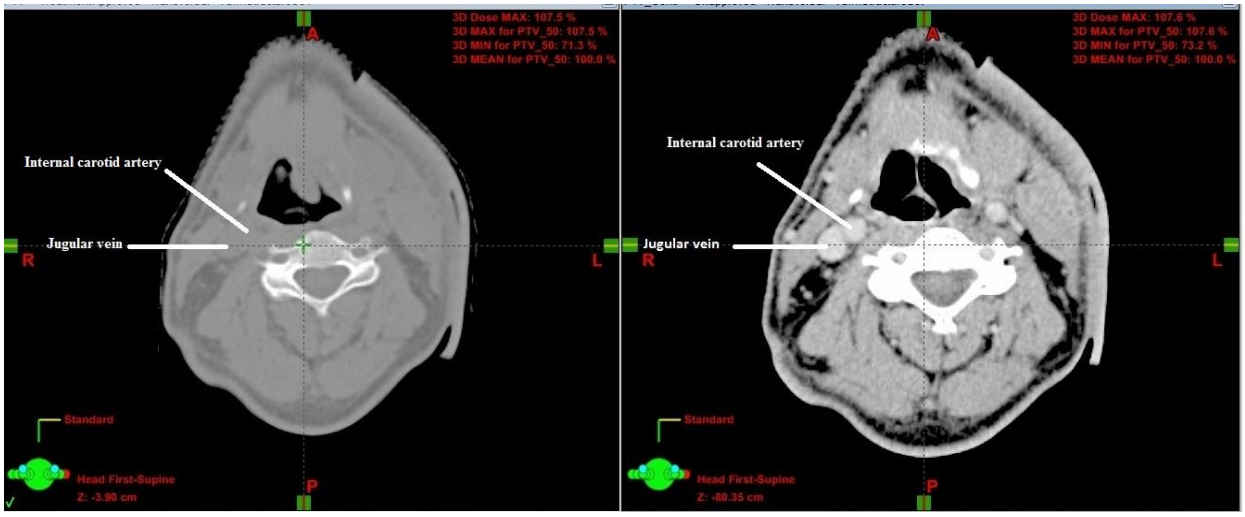


Fig. 20. Blood vessels in CT scans before (left) and after (right) administration of contrast material

In Figure 20 we can see that contrast media helps to separate blood vessels from soft tissues.

3.2. Changes of dose

Descriptive statistics of the doses received by PTV and organs at risk are presented in table 14 and 15.

Table 14. Doses for PTV and organs at risk in VMAT plans made using non-enhanced CT scans

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Mean ± STD**	**Median**
The dose minimum for PTV (Gy)	38.57	37.14	35.70	28.93	23.65	23.21	37.161	36.46	30.16	35.49	23.19	24.94	31.22 ± 38.35	31.22
The maximum dose for PTV (Gy)	51.64	52.96	53.75	52.62	53.09	51.34	52.33	52.48	51.94	53.21	52.64	52.41	52.53 ± 0.46	52.53
The mean dose for PTV (Gy)	49.98	50.15	50.11	50.06	49.81	50.13	50.04	49.99	50.055	50.05	50.06	50.09	50.08 ± 0.007	50.06
The maximum dose for Brain stem (Gy)	31.48	30.28	29.54	41.98	35.19	39.22	31.46	30.94	33.94	36.89	37.49	38.78	34.76 ± 16.78	34.76
The mean dose for bilateral parotids (Gy)	16.82	38.25	36.58	39.63	23.42	23.03	24.98	28.02	33.49	27.89	27.99	31.99	29.34 ± 47.11	28.02
The maximum dose for spinal cord (Gy)	38.06	38.38	37.88	37.84	39.08	37.53	37.95	38.53	38.18	38.67	37.88	38.33	38.19 ± 0.18	38.18

In volumetric modulated made using CT scans made before administration of contrast media the mean of the dose minimum for PTV was 31.2 Gy. The mean of the dose maximum for PTV was 52.57.

Table 15. Doses for PTV and organs at risk in VMAT plans made using contrast-enhanced CT scans

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Mean ± STD**	**Median**
The dose minimum for PTV (Gy)	40.72	36.81	35.52	28.78	22.41	23.21	36.98	36.86	30.24	35.34	23.48	25.03	31.28 ± 42.61	31.28
The maximum dose for PTV (Gy)	51.37	52.99	53.81	52.67	53.41	51.69	52.49	52.76	52.09	53.31	52.76	52.84	52.68 ± 0.49	52.76
The mean dose for PTV (Gy)	50.01	50.14	50.1	50.06	49.8	50.19	49.93	49.98	50.02	50.15	50.08	50.01	50.04 ± 0.01	50.04
The maximum dose for Brain stem (Gy)	31.59	30.54	29.64	40.34	35.56	40.69	31.59	31.22	34.06	37.02	37.38	38.94	34.88 ± 15.75	34.88
The mean dose for bilateral parotids (Gy)	16.91	38.24	36.64	40.19	23.19	23.28	25.76	28.43	33.98	28.32	28.46	32.26	29.63 ± 47.61	28.46
The maximum dose for spinal cord (Gy)	37.9	38.09	39.1	37.39	37.88	38.42	37.76	38.21	38.02	38.51	37.83	38.21	38.11 ± 0.18	38.09

In VMAT plans made using CT scans acquired after administration of the contrast media the mean of the minimum dose for PTV increased by 0.42 Gy, up to 31.247 Gy.

Such low minimal dose for PTV (about 62% of prescribed 50 Gy dose) is because of the air gaps in PTV made by air in oesophagus and pharynx that are located inside of the PTV.

As it is shown in tables 14 and 15 the dose mean of PTV in VMAT plans made using CT scans with and without contrast media differs only by 0.01 Gy, which may be, because all plans were normalised using normalisation function 100% to dose mean. This function makes plan mean dose to be equal to prescribed dose (in this case 50 Gy). As for the organs at risk the doses for VMAT plans made using CT scans with and without contrast media are very similar.

Table 15. The changes in dose after contrast media administration

	Min (Gy)	**Max** (Gy)	**Median** (Gy)	**Mean ± STD** (Gy)
The dose minimum for PTV	0	2.15	0.18	0.43 ± 0.39
The maximum dose for PTV	0.03	0.35	0.15	0.19 ± 0.017
The mean dose for PTV	0	0.11	0.02	0.014 ± 0.001
The maximum dose for Brain stem	0.1	1.64	0.14	0.4 ± 0.29
The mean dose for bilateral parotids	0.01	0.78	0.34	0.33 ± 0.05
The maximum dose for spinal cord	0.05	1.22	0.24	0.43 ± 0.17

Only minimal dose to PTV and maximal dose to spinal cord and brain stem has more than 1 Gy change in dose. Results of increase of dose to targets and organs at risk are similar to results in Shibamoto Y. et. al. studies [8] (increase of dose is <1%).

To determine in what type of distribution all variables are distributed (normally or non-normally) Shapiro-Wilk test was used (table 16).

Table 16. Shapiro-Wilk test results for HUs values in CT scans

	p value with contrast media	**p value without contrast media**
The dose minimum for PTV	0.048	0.015
The maximum dose for PTV	0.071	0.116
The mean dose for PTV	0.031	0.0155
The maximum dose for Brain stem	0.024	0.016
The mean dose for bilateral parotids	0.0147	0.0147
The maximum dose for spinal cord	0.078	0.056

The Shapiro-Wilk test showed that all variables are distributed by non - normal distribution ($p < \alpha = 0.05$), except for maximum dose for PTV and spinal cord, which are distributed by normal distribution ($p > \alpha = 0.05$).

To check is there any statistically significant difference in doses for targets and OARs between VMAT plans made using CT scans with and without contrast media two types of test were used. Mann-Whitney-Wilcoxon test for non-normally distributed variables and Student's t test for variables that follows normal distribution. Results of these test are presented in table 17.

Table 17. Influence of contrast media for doses

	p value
The dose minimum for PTV	0.747
The maximum dose for PTV	0.226
The mean dose for PTV	0.772
The maximum dose for Brain stem	0.869
The mean dose for bilateral parotids	0.974
The maximum dose for spinal cord	0.53

While study made by Ramm U. et. al. [5] shown that the dose increase linearly with the increase of HU value, tests made in this study shown that there is no statistically significant differences in doses for targets and OARs between VMAT plans made using contrast-enhanced and non-enhanced CT scans ($p > \alpha = 0.05$), but there is still a 5% chance to make a mistake. This meets results that were made in study made by Shibamoto Y. et. al. [8].

3.3. Changes of homogeneity index

Descriptive statistics of the dose homogeneity index are presented in table 18.

Table 18. Homogeneity index

	With contrast media	**Without contrast media**	**Difference**
Min	0.0478	0.0486	$1.87 \cdot 10^{-4}$
Max	0.164	0.1734	$8.53 \cdot 10^{-3}$
Median	0.0173	0.0932	$8.65 \cdot 10^{-4}$
Mean ± STD	0.0961 ± 0.0428	0.0981 ± 0.0453	$2.17 \cdot 10^{-3} \pm 8.46 \cdot 10^{-6}$

The difference of homogeneity indexes of VMAT plans made using CT scans with and without contrast media is very low.

Shapiro-Wilk test shown that homogeneity indexes of both types VMAT plans are following normal distribution ($p > \alpha = 0.05$). To check is there any statistically significant difference between homogeneity indexes of VMAT plans made using CT scans with and without contrast media Student's t test was used. Results are presented in table 19.

Table 19. Shapiro-Wilk and Student's t tests results for homogeneity index

	Shapiro-Wilk test p value without contrast media	**Shapiro-Wilk test p value with contrast media**	**Student's t test p value**
Homogeneity index	0.12	0.1	0.048

Student's t test shown that there is statistically significant difference between homogeneity indexes of VMAT plans made using CT scans with and without contrast media. Plans made on CT scans that were made using contrast media are more homogeneous. This may be because

contrast-enhanced plans has higher increase in minimum dose for PTV than maximum dose for PTV.

Conclusions

1. The mean increase of radiodensity after administration of intravenous contrast material was 84.43 HU for jugular vein and 23.4 HU for soft tissues. Statistical tests shown that there is a statistically significant difference between radiodensities of jugular vein and soft tissues measured in contrast-enhanced and non-enhanced computed tomography scans.
2. The dose for cancer and organs at risk was higher in VMAT plans computed using CT scans made after administration of intravenous contrast material. The highest mean increase of dose was for the maximum dose for brain stem (by 0.673 Gy) and the lowest mean increase of dose was for the mean dose for PTV (by 0.018 Gy). However, statistical tests have shown that the increase in dose is not statistically significant.
3. Despite the fact that the differences between homogeneity indexes of VMAT plans made using contrast-enhanced and non-enhanced CT scans is very low (mean increase $2.17 \cdot 10^{-3}$), statistical test shown that the increase is statistically significant.

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