



## Relationship analysis of radiation dosage with nasopharynx cancer stadium classification using intensity-modulated radiotherapy technique

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### Abstract

Nasopharyngeal cancer is caused by abnormal development of body cells in the throat area. Radiotherapy is a standard therapy for treating nasopharyngeal tumors or cancer using the Intensity Modulated Radiation Therapy radiation technique. This study aims to determine the amount of radiation dose patients receive at different stages of nasopharyngeal cancer. Analysis was carried out on 25 nasopharyngeal cancer patients using the IMRT radiation technique to obtain the relationship between the radiation dose received by Planning Target Volume (PTV) and Organ at Risk (OAR). Patient dose data is obtained through Dose Volume Histogram graph simulation using the Treatment Planning System. Data analysis was carried out on PTV according to the International Commission on Radiation Units and Measurements Report 62 of 1999 and ICRU Report 83 of 2010, dose achievement at OAR with Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines and for stage classification using the TNM system under the classification according to the American Joint Committee on Cancer in 2018. The research analyzed the OAR in the patient's brainstem, optic chiasm, spinal cord, parotid gland, oral cavity, and eye lens. In general, PTV receives an average received radiation dose of 68.78 Gy. In OARs, the highest radiation dose is found in the brainstem, followed by the optic chiasm, spinal cord, oral cavity, parotid gland, and eye lens. The results of the analysis showed that there was no significant difference between radiation dose and Nasopharyngeal cancer stage classification. However, analysis of individual patient doses showed that some patients received radiation doses to the OAR exceeding the QUANTEC regimen.

**Keywords:** Nasopharyngeal cancer, intensity modulated radiation therapy, planning target volume, organ at risk, quantitative analysis of normal tissue effects in the clinic

### Introduction

Currently, cancer is one of the leading causes of death in the world. Cancer is a disease caused by body cells that grow and develop abnormally, beyond normal limits, and wildly. Cancer occurs when normal cells change and multiply so the body cannot control them. In women, the most frequent case is breast cancer, while in men, the most frequent case is nasopharyngeal cancer because most of the causative agents are tobacco and alcohol (Long, 2017) [8].

Cases of nasopharyngeal cancer are pretty rare. According to the World Health Organization (WHO), nasopharyngeal cancer accounts for only 0.7% of all cancers. Nasopharyngeal cancer (NPC) is a type of malignant tumor that is common, especially in Southeast Asia. Nasopharyngeal cancer has the highest incidence rate, with Indonesia as the country with the second highest incidence after Malaysia (Adham, 2012) [1]. NPC is a cancer that appears above the throat and behind the nose. Nasopharyngeal cancer is the most common malignant tumor among other malignant ears, nose, and throat (ENT) tumors in Indonesia. NPC is mainly found in men of productive age and is the 4th most common cancer in Indonesia after cervical cancer, breast cancer, and lung cancer (Adham, 2012) [1].

Delays often occur in diagnosing NPC; therefore, many are found to have metastases in the form of lumps in the neck. As a result, nasopharyngeal cancer that has metastasized forms a lump in the neck that gets bigger and presses on the esophagus and can cause difficulty swallowing (dysphagia), thus affecting oral food intake to a deficit, which can indirectly affect nutritional status. If patients do not receive

proper treatment and if left untreated, this can result in death (Zhang, 2020) [13].

The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) use the Tumor, Node, Metastasis (TNM) classification method to diagnose NPC. The TNM classification is the most accurate reference tool for classifying patients in determining treatment and evaluating treatment results. This system is purely based on the following three anatomical criteria: local extent of cancer within the site of origin (T), degree of regional lymph node metastatic involvement (N), and the presence or absence of distant metastatic disease (M) (Amin, 2017) [2].

Radiotherapy is a cancer treatment that uses high-energy radiation beams that target cancer tissue to destroy or stop cell division. One of the modalities that can be used for radiotherapy treatment is a Linear accelerator (LINAC). LINAC is a device that uses high-frequency electromagnetic waves in the microwave range (<3000 megacycles/second) to accelerate charged particles, such as electrons, to high levels of energy through a linear tube (Tseng, 2020) [11].

Patients who receive radiotherapy modalities must undergo a series of processes to determine the radiation dose to be given. Radiation dose is the amount of radiation in a radiation field or the amount of energy received by a material passed through in the radiotherapy process. The amount of radiation dose to be determined is influenced by several factors, such as the tumor stage. According to research by Willner, 2002, the higher the stage, the more complicated the tumor shape, affecting the dose. In other words, the higher the stage level, the greater the dose that will be provided.

In NPC treatment, a LINAC modality can use two radiation techniques: Three Dimension Conformal Radiation Therapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT). The 3D-CRT method uses an uneven radiation field according to the shape of the cancer and a uniform radiation intensity in each field direction, while the IMRT method uses an uneven intensity in each direction of the radiation field. The IMRT technique is more efficient in treating cancer because the radiation dose received by organs at risk is minimal compared to the 3D-CRT technique. IMRT technology is believed to be able to maximize success in computer treatment procedures by generating a radiation field with high precision according to the shape of the tumor, which is read from the computed tomography (CT)-Simulator examination results and shows non-uniform radiation intensity according to the needs of each part of the target in each direction of radiation (Lee, 2014) [6].

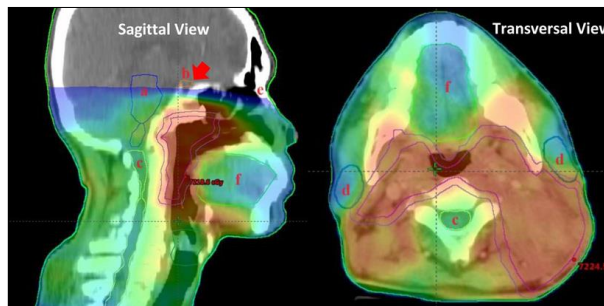
Based on research by Ibrahim (2019) [3], X-ray irradiation using the 3D-CRT technique causes complications in healthy tissue around the cancer or the radiation target. Radiotherapy is effective in treating cancer, but it can also cause changes to the surrounding normal tissue, such as Nasopharyngeal cancer. Therefore, it is necessary to know whether there is damage to other soft tissues around the cancer area and analyze the images obtained from radiation therapy. The dose received by healthy organs must refer to the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) rules. QUANTEC is a publication

regarding the toxicity of radiation to healthy organs that are at risk of radiation exposure (Lee, 2019) [7].

Several organs at risk have high sensitivity to radiation in cases of nasopharyngeal cancer radiotherapy, namely the brainstem, optic chiasm, spinal cord, eye lens, parotid gland, and oral cavity. These organs are close to the nasopharynx, so they risk exposure to high radiation doses. Good protection is needed when planning radiotherapy (Lee, 2019) [7]. It is known that the location of cancer can be determined and processed using the Treatment Planning System (TPS) algorithm to form a Dose Volume Histogram (DVH) graph, which shows the coordinates of the radiation dose distribution on the Planning Target Volume (PTV) and Organs at risk (OAR). As a result, the PTV receives the maximum radiation dose, and the OAR receives the minimum radiation dose. Therefore, this study aims to analyze the relationship between radiation dose from the IMRT technique on PTV and OAR with cancer stage classification to provide an overview of the distribution of radiation doses according to QUANTEC.

**Materials and Methods**

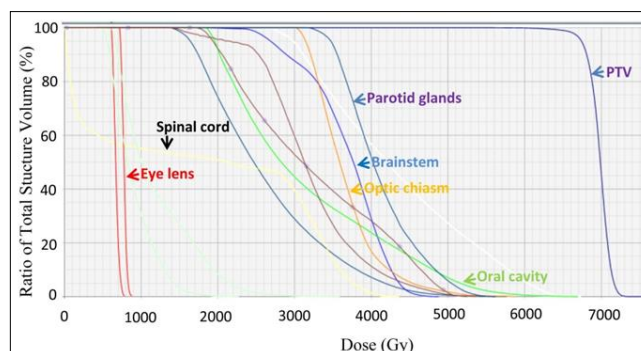
Retrospective digital image data from stage III nasopharyngeal cancer patients (9 patients) and stage IV patients (16 patients) were used in this study via head CT examination. Fifteen patients were over 50 years old, and 20 patients were men. In this study, the OARs analyzed were the brainstem, optic chiasm, spinal cord, parotid gland, oral cavity, and eye lens, which can be seen in Figure 1.



**Fig 1:** The Organs at risk position of Nasopharyngeal cancer: a) Brainstem, b) optic chiasm (shown by arrowhead), c) spinal cord, d) parotid gland, e) eye lens, f) oral cavity

The DVH graph, as shown in Figure 2, is created from the patient's digital image using Monaco TPS software. All patients' radiation doses at the PTV and OAR were tested for data normality. Then, the average value of each stage was compared using the One-Way ANOVA test for normally distributed data and the Kruskal-Wallis test for data that was not normally distributed. A significance value

of  $P < 0.05$  indicates that the radiation dose significantly differs from other values. Therapy planning was evaluated in PTV using ICRU Report 62 in 1999 and ICRU Report 83 in 2010. Meanwhile, the evaluation of radiation planning in OAR used QUANTEC for OAR doses (Lee, 2019) [7]. The limits of the average and maximum radiation dose of each OAR according to QUANTEC are presented in Table 1.



**Fig 2:** Example of the Dose Volume Histogram graph of the Planning Target Volume and Organs at Risk of Nasopharyngeal Cancer

**Table 1:** QUANTEC dose limits for Organs at risk of Nasopharyngeal Cancer (Lee, 2019) [7]

Organ at Risk	Average radiation dose	Maximum radiation dose
Brainstem		64 Gy
Optic chiasm		60 Gy
Eye lens		10 Gy
spinal cord		50 Gy
parotid gland	≤ 39 Gy	
Oral cavity	< 35 Gy	

**Results**

The PTV and OARs dose profile of each patient for different tumor stages is shown in Table 2. In general, the average received radiation dose at the PTV for all patients was 68.78 Gy. In OARs, the highest radiation dose is found

in the brainstem (50.56 Gy), followed by the optic chiasm (47.03 Gy), spinal cord (43.31 Gy), oral cavity (33.19 Gy), parotid gland (30.28 Gy), and eye lens (6.3 Gy). One-way ANOVA test showed no significant radiation dose difference in the three cancer stage groups ( $P > 0.05$ ) at the PTV, spinal cord, right eye, and left eye lens. The same condition was also seen in the brainstem, optic chiasm, parotid gland, and oral cavity, where the Kruskal-Wallis H test showed no significant radiation dose difference in the three cancer stage groups ( $P > 0.05$ ). However, analysis in each patient revealed that two patients received doses higher than the QUANTEC limit in the optic chiasm and one patient in the parotid gland. In the oral cavity, five patients received radiation doses more significantly than the QUANTEC limit.

**Table 2:** Dose Measurement of Nasopharyngeal Cancer at Planning Target Volume and Organs at Risk

	PTV Dose (Gy)	Brainstem Dose (Gy)	Optic chiasm Dose (Gy)	Spinal cord Dose (Gy)	Parotid gland Dose (Gy)	Right lens Dose (Gy)	Left lens Dose (Gy)	Oral cavity Dose (Gy)
Stage III (n = 9)	68.10	52.20	56.03	42.05	30.21	7.40	7.35	33.29
	68.14	50.47	48.93	45.05	34.46	5.53	5.40	38.16*
	68.28	49.6	56.86	40.6	32.48	4.62	5.25	33.13
	68.39	50.61	48.45	42.66	31.70	4.29	3.69	31.59
	69.30	49.84	52.75	41.65	25.85	6.86	6.84	30.14
	69.32	50.36	61.53*	42.03	27.37	8.73	8.16	32.13
	69.48	48.86	48.32	41.32	28.71	7.38	7.86	32
	69.70	48.86	58.73	43.65	26.31	7.77	6.72	31.58
	69.76	53.30	54.78	44.81	25.48	8.17	7.81	33.27
<i>Average</i>	68.94	50.46	54.04	42.65	29.17	6.75	6.56	32.81
Stage IVA (n = 12)	67.59	50.47	56.90	41.99	31.30	5.29	5.37	33.53
	67.75	51.61	52.83	43.01	30.65	4.68	4.79	35.88*
	68.01	49.77	56.56	42.61	35.60*	5.39	5.90	33.77
	68.67	53.80	54.95	45.27	27.20	7.42	7.08	34.07
	68.68	52.69	58.96	44.19	28.35	7.06	7.39	33.31
	68.93	52.55	11.13	43.77	28.41	4.77	5.56	33.59
	69.05	44.97	7.05	47.46	35.26	4.29	5.02	33.18
	69.06	51.72	55.44	44.63	26.98	7.68	7.88	31.78
	69.09	50.55	43.22	42.12	31.61	5.15	5.20	34.58
	69.15	50.53	6.50	43.17	28.82	4.50	4.36	35.46*
	69.31	51.11	47.94	38.89	27.78	7.39	7.66	29.29
	69.58	50.45	54.71	43.85	27.71	6.73	7.12	32.24
<i>Average</i>	68.74	50.85	42.18	43.41	29.97	5.86	6.11	33.39
Stage IVB (n = 4)	67.59	51.70	62.66*	41.43	38.81	6.41	6.26	37.50*
	68.42	53.05	57.95	44.62	34.34	7.78	7.76	33.85
	68.65	41.05	55.67	46.68	30.90	7.80	7.05	35.72*
	69.40	53.87	6.92	45.13	30.72	4.34	4.14	26.72
<i>Average</i>	68.52	49.92	45.80	44.47	33.69	6.58	6.30	33.45

\*The dose value exceeds the QUANTEC average or maximum dose limit for the specific OAR.

**Discussion**

This study shows that the amount of radiation dose received by PTV and OARs is generally below the dose threshold required by QUANTEC, so it is still safe from radiation hazards. However, individual analysis of some patients showed that in certain OARs, patients received radiation doses higher than the QUANTEC limits to the optic chiasm of the parotid gland and oral cavity.

Based on the QUANTEC review, whole organ optic chiasm doses < 5000 cGy were associated with < 1 % risk of blindness. Blindness is quite rare, up to a dose of 5000 cGy. Between 5500-6000 cGy, the risk of blindness increases to 3-7 %. At doses > 6000 cGy, the risk of damage even

reaches 7-20 %. This risk damage shows that when the optic chiasm receives a specific radiation dose, it will still experience stochastic effects, namely, side effects that can only be reduced and not eliminated. From the analysis of the data obtained, it turned out that there were 2 cases of patients who were at risk of experiencing radiation side effects with a toxicity rate of > 7 % because they received radiation exposure doses exceeding 6000 cGy.

Although the study results show that the radiation dose received by the spinal cord is below the QUANTEC limit of 50 Gy, spinal cord doses < 4500 cGy are associated with a 0.03 % risk of Myelopathy. In fact, at doses > 4500 cGy, the risk of damage dramatically increases to 0.2 %. This risk

damage shows that when the spinal cord receives a specific radiation dose, it will still have a stochastic effect. From the analysis of the data obtained, there were 4 cases of patients who were at risk of experiencing radiation side effects with a toxicity rate of 0.2% because they received radiation exposure doses exceeding 4500 cGy.

Research by Nguyen in 2019 showed that eye lens doses below 700 cGy can reduce the risk of cataracts by up to 25 %. This value indicates that when the eye lens receives a specific radiation dose, it will still experience stochastic effects. From the analysis of the data obtained, there were 13 cases of patients who were at risk of experiencing radiation side effects with a toxicity rate of > 25 % because they received radiation exposure doses exceeding 700 cGy.

The QUANTEC rule shows that the parotid gland that receives a dose of radiation will have a risk of damage to salivary function in the long term, also known as the stochastic effect. Furthermore, research by Sunaga in 2020, shows that doses in the 20-30 Gy range can worsen mucositis, and doses in the 51-62 Gy range can cause swallowing dysfunction, reducing the patient's quality of life. In this study, five patients with oral cavities received doses exceeding the prescribed dose limit. QUANTEC is set at 35 Gy, so there is potential for organ function disorders, as has been reported by Sunaga.

In this study, obtaining a relationship between radiation dose and cancer stage was challenging. The challenge occurs because of the limited number of patients and the rarity of patients coming for therapy in the early stages (stages 1 and 2). The number of patients in each cancer stage in this study is also limited, providing only early indication of dose similarity at different cancer stages. Hence, further research is needed with more patients at all stages to improve the quality of research results.

### Conclusions

In conclusion, the analysis showed no significant relationship between the classification of Nasopharyngeal cancer stage and the dose received by PTV and OARs. Furthermore, even though the radiation doses received by PTV and OARs in the patient group followed the QUANTEC rules, an analysis of each patient shows that some patients still received OAR doses exceeding the QUANTEC limits.

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