Research

Correlation of nodule with body mass index and Karnofsky status in nasopharyngeal carcinoma chemotherapy

Bagus Harning Efranto, Soehartono, Edi Handoko
Department of Otorhinolaryngology Head and Neck Surgery
Faculty of Medicine, Brawijaya University / Dr. Saiful Anwar General Hospital, Malang

ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharyngeal epithelium, usually present in the Rosenmüller fossa. NPC is a cancer of the head and neck that is most common in Indonesia. The main therapeutic for NPC is radiotherapy. Neoadjuvant chemotherapy reduces the local spread of advanced NPC, optimizing the eradication of micrometastases, and improved local control. Neoadjuvant chemotherapy's effectiveness can be assessed by changes in the patient's neck nodule size (N), Body Mass Index (BMI), and Karnofsky's status. **Purpose:** To determine the correlation between N with BMI and Karnofsky status on neoadjuvant chemotherapy with Cisplatin and 5-Fu in WHO type 3 of NPC patients. **Method:** Analytical observational study using medical record data. An assessment of N, BMI and Karnofsky status of NPC WHO type 3 of 23 patients who had undergone neoadjuvant chemotherapy using Cisplatin and 5-Fu for three cycles. **Result:** The N value decreased, p = 0.001. BMI value decreased, p = 0.615. Karnofsky's status value, p = 0.564. The correlation between N and BMI before and after three cycles of neoadjuvant chemotherapy: r = -0.201 and p = 0.358 ; r = -0.070 and p = 0.751. Correlation of N with Karnofsky status: r = 0.155 and p = 0.480; r = 0.571 and p = 0.004. **Conclusion:** Neoadjuvant chemotherapy with Cisplatin and 5-Fu was effective towards reducing the N and also in correlation between N and BMI but less effective in the correlation between N and Karnofsky status.

Keywords: nasopharyngeal carcinoma, neoadjuvant chemotherapy, nodule, body mass index, Karnofsky's status

ABSTRAK

Latar belakang: *Karsinoma nasofaring (KNF) adalah keganasan yang berasal dari epitel nasofaring yang biasanya timbul di fossa Rosenmüller. KNF merupakan kanker di kepala dan leher yang paling umum terjadi di Indonesia. Terapi utama pada KNF adalah radioterapi. Kemoterapi neoajuvan dapat menurunkan penyebaran lokal KNF stadium lanjut, mengoptimalkan eradikasi mikrometastasis, dan meningkatkan kontrol lokal. Efektivitas kemoterapi neoajuvan dapat dinilai dengan perubahan ukuran nodul leher (N) pasien, indeks massa tubuh (IMT) dan status Karnofsky pasien.* ***Tujuan:*** *Mengetahui korelasi antara N dengan IMT dan status Karnofsky pada pemberian kemoterapi neoajuvan Cisplatin dan 5-Fu pada pasien KNF WHO tipe 3.* ***Metode:*** *Penelitian observasional analitik dengan menggunakan data rekam medis. Penilaian dilakukan terhadap N, IMT dan status Karnofsky pada 23 pasien KNF WHO tipe 3 yang telah menjalani kemoterapi neoajuvan dengan menggunakan Cisplatin dan 5-Fu sebanyak tiga siklus.* ***Hasil:*** *Nilai N menurun, p=0,001. Nilai IMT menurun, p=0,615. Nilai status Karnofsky, p=0,564. Korelasi antara N dengan IMT sebelum dan setelah tiga siklus kemoterapi neoajuvan: r= -0,201 dan p= 0,358; r= -0,070 dan p=0,751. Korelasi N dengan status Karnofsky: r=0,155 dan p=0,480; r=0,571 dan p=0,004.* ***Kesimpulan:*** *Kemoterapi neoajuvan dengan Cisplatin dan 5-Fu efektif terhadap penurunan N serta korelasi antara N dengan IMT, namun kurang efektif menilai korelasi antara N dengan Status Karnofsky.*

Kata kunci: *karsinoma nasofaring, kemoterapi neoajuvan,nodul, indeks massa tubuh, status Karnofsky*

Correspondence address: Bagus Harning Efranto. Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Brawijaya University / Dr. Saiful Anwar General Hospital, Malang. Email: bagushe16@gmail.com.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharyngeal epithelium, which is usually present in the Rosenmüller fossa and can infiltrate adjacent anatomical spaces or organs.[1] NPC is rare worldwide; about 86.691 cases of NPC were reported in 2012 (0-6% of all cancers diagnosed). In endemic areas such as southern China, Hong Kong, and several countries in Southeast Asia, including Indonesia, the number of NPC incidents can reach 30 cases per 100.000 populations. In 2018 and 2019, there were around 70 new cases in the Oncology polyclinic, Department of Otorhinolaryngology - Head and Neck Surgery (ORL-HNS) Faculty of Medicine, Universitas Brawijaya / Dr. Saiful Anwar General Hospital Malang. The diagnosis of NPC is through histopathological examination of biopsy tissue. *World Health Organization* (WHO) categorized NPC in 1978. There are three NPC categories which consist of keratinizing *squamous cell carcinoma* (SCC), *non-keratinizing SCC*, and *undifferentiated carcinoma*.[1-3]

The pathogenesis of NPC and other malignancies is not known with certainty. It is thought to be multifactorial. Chronic inflammation and *Epstein Barr Virus* (EBV) infection are thought to trigger the appearance of NPC.[4] Diagnostic modalities have been developed such as serologic immunoglobulin A (IgA) anti-viral capsid antigen (VCA), serum EBV DNA and Positron Emission Tomography (PET) scan and other investigations for NPC.[1,4] The main therapeutic modality for stage I NPC is radiation therapy (RT), and for NPC stage II-IV is concurrent chemoradiotherapy with or without adjuvant chemotherapy.[5]

Chemotherapy functionally can be neoadjuvant, adjuvant and concurrent. The combination of chemotherapy with radiotherapy is a good choice for advanced NPC.[1] Neoadjuvant chemotherapy is used to reduce the local spread of advanced NPC that cannot be achieved with radiation without posing a significant risk to adjacent normal tissue.[5] The advantages of neoadjuvant chemotherapy are tolerance and good adherence of patients against chemotherapy; higher micrometastasis eradication, and chemosensitivity testing can be performed, and local tumor control compared to radiation alone.[6]

This research analyzed neoadjuvant chemotherapy Cisplatin and 5-Fu cycles I to III in NPC WHO type 3 patients at Dr. Saiful Anwar General Hospital Malang in 2018-2019. In a meta-analysis study comparing the effectiveness of neoadjuvant chemotherapy with adjuvant chemotherapy for NPC patients based on Randomized Controlled Trials (RCT) by OuYang et al.[7], it showed hazard ratio (HR) of death for neoadjuvant chemotherapy was relatively low, accompanied by a high absolute survival after 3 years. Yang et al.[8] study evaluated the prognostic value of the tumor volume reduction rate (TVRR) of neoadjuvant chemotherapy in patients with advanced NPC. Their study concluded that TVRR with neoadjuvant chemotherapy was an independent prognostic factor for NPC patients who were going to receive radiotherapy. Chen et al.[9] evaluated tumor volume after neoadjuvant chemotherapy for prognostication in advanced NPC. In-

conclusion, the primary gross tumor volume (GTV-P) and gross tumor volume lymph node (GTVnd) were indicators of effective evaluation of NPC patients' response after neoadjuvant chemotherapy.

Head and neck cancer patients including NPC often experience malnutrition. Takenaka et al.[10] examined the nutritional status and its relationship with chemotherapy or radiotherapy via BMI. BMI classification: BMI underweight <18.5 kg/m^2, normal : 18.5-22.9 kg / m^2, overweight: 23-27.5 kg /m^2 and obesity : ≥ 27.5 kg/m^2. The results showed the 5-year survival rates for the underweight, normal, and overweight groups were 32.2%, 62.7%, and 73.5%, respectively. BMI HR in the surgery, chemoradiation, and radiation groups were 0.95, 0.91, and 0.79. The type of cancer treatment determines the impact of BMI.

Several studies were conducted to determine the relationship between nutritional status through Body Mass Index (BMI) and NPC patients' survival rate, but the results were still inconsistent. Wulandari et al.[11] suggest that patients with a higher BMI have a better survival rate, and increasing BMI in underweight NPC patients can improve the survival of NPC.

Karnofsky performance status (KPS) is a value of functional status of patients measured from a value of 0-100 percent. A scale of 80-100% is in category A, a scale of 50-70% is in category B and a scale of 0-40% is in category C. The advantage of Karnofsky status is the ability to reproducibly quantify the impairment.[12] The Health-related quality of life (HR-QOL) assessment on NPC patients are essential to assess the success of NPC treatment and identify the effects on certain functional disorders.[13]

Wei et al.[14] study evaluated the impact of neoadjuvant chemotherapy (NACT) of various NACT cycles before radiotherapy on distant metastases and survival of patients with N2-3. The study results showed overall survival (OS), disease-free survival (DFS), local-relapse-free survival (LRFS) and distant-metastasis-free survival (DMFS) of the four-cycle NACT group was better than the two-cycle NACT group and the two-cycle NACT group patients without NACT. In conclusion, in NPC patients with N2-3, the number of NACT cycles was an independent factor associated with increased survival. NPC stage was determined based on the TNM classification of patients according to NCCN Guidelines Version 1.2020 Head and Neck Cancers.[15]

METHOD

In this study, we conducted an assessment of changes in N, BMI, and Karnofsky status of NPC WHO type 3 patients who had undergone neoadjuvant chemotherapy using the Cisplatin and 5-Fu regimens for three cycles in the period 1 January 2018-31 December 2019. This study was conducted from September to November 2020.

The population of this study was NPC patients according to WHO type III who had undergone chemotherapy I-III at Dr. Saiful Anwar General Hospital, Malang. The research subject was a population that met the inclusion and exclusion criteria.

Inclusion criteria: (1) Patients with NPC WHO type 3 who had not received radiotherapy and / or chemotherapy. (2) WHO type 3 NPC patients with a minimum BMI of 18.5 kg/m2 before Cisplatin neoadjuvant chemotherapy and 5-Fu cycle I. (3) WHO type 3 NPC patients with Karnofsky status at least 70 before neoadjuvant Cisplatin chemotherapy and 5-Fu cycle I. (4) NPC WHO type 3 patients with minimal N1 before neoadjuvant Cisplatin chemotherapy and 5-Fu cycle I (5) NPC WHO type 3 patients who had completed medical record data according to research variables. Exclusion criteria: Patients who dropped out during the cycle of neoadjuvant chemotherapy cycle I-III.

The effectiveness of neoadjuvant chemotherapy with Cisplatin and 5-Fu in NPC patients who had undergone chemotherapy I-III to changes in N, BMI, and Karnofsky status of patients using the Paired T-Test for normal distribution, and abnormal distribution using the Wilcoxon test for parametric tests, while non-parametric tests used Pearson's test for normal distribution and abnormal distribution using the Spearman test. Note: using the confidence level of 95%, $\alpha = 0.05$, statistically significant as $p < 0.05$.

RESULT

Data were collected from medical records of NPC WHO type 3 patients who underwent neoadjuvant chemotherapy with Cisplatin and 5-Fu cycles I-III from 2018 to 2019. The number of NPC patients who underwent chemotherapy in 2018-2019 was 71 people. The prevalence of NPC sufferers was 46 male and 25 female. Out of these 71 patients, only 23 subjects met the inclusion criteria as the sample.

The general characteristics of research subjects, including gender and age group, are listed in table 1. In this study, there were more male subjects than female with a ratio of 1.55:1.

Table 1. General Characteristics of Research Subjects Based on Gender and Age Group

General Characteristics	n	%
Gender		
Men	14	60,9
Women	9	39,1
Age group		
16-25 years	2	8,7
26-35 years	2	8,7
36-45 years	2	8,7
46-55 years	11	47,8
56-65 years	5	21,7
>65 years	1	4,3
Mean age ± SD (years)	48,35±12,61	

SD: standard deviation

Evaluation of N Before and After Neoadjuvant Chemotherapy Three Cycles of Cisplatin and 5-Fluorouracil

The results obtained of neck nodule size before cycle I neoadjuvant chemotherapy with a minimum value of N1 and a maximum of N3. After three cycles of neoadjuvant chemotherapy, a minimum value of N0 and a maximum of N3 were obtained.

The N value before cycle I neoadjuvant chemotherapy in this study had a mean and SD of 2.17 ± 0.834 (Table 2). T and M values varied from T1-4 and M0-M1, but the values T and M were not the subject of the study.

Table 2. Neck Lymphnode Size Changes Before Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle I and After Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle III

N	Before Neoadjuvant Chemotherapy Cycle I (Patients)	After Neoadjuvant Chemotherapy Cycle III (Patients)
N0	0	5
N1	6	10
N2	7	4
N3	10	4
Mean age ± SD (years)	2,17±0,834	1,3±1,02

SD: standard deviation

Evaluation of Body Mass Index Before and After Neoadjuvant Chemotherapy Three Cycles of Cisplatin and 5-Fluorouracil

BMI before cycle I neoadjuvant chemotherapy with a minimum value of 18.6 and a maximum of 31.9. After receiving neoadjuvant chemotherapy for up to three cycles, the minimum value was 14.6 and the maximum was 28.6 (Table 3). BMI values were normally distributed, with $p = 0.615$.

Evaluation of Karnofsky's Status Before and After Neoadjuvant Chemotherapy Three Cycles of Cisplatin and 5-Fluorouracil

The value of Karnofsky status before cycle I neoadjuvant chemotherapy in this study had a mean and SD of 89.57 ± 8.78 and after cycle III, neoadjuvant chemotherapy had a mean and SD of 88.26 ± 7.78 (Table 4)

Table 3. BMI Changes in NPC Patients Before Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle I and After Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle III

BMI	Before Neoadjuvant Chemotherapy Cycle I (Patients)	After Neoadjuvant Chemotherapy Cycle III (Patients)
Underweight	0	2
Normal	17	14
Overweight	3	6
Obesity	3	1
Mean age ± SD (years)	22,1±3,52	21,87±3,56

SD: standard deviation

Table 4. Karnofsky Status of NPC Patients Before Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle I and After Cisplatin and 5-Fu Neoadjuvant Chemotherapy Cycle III

Karnofsky Status	Before Neoadjuvant Chemotherapy Cycle I (Patients)	After Neoadjuvant Chemotherapy Cycle III (Patients)
A	21	20
B	2	3
C	0	0
Mean age ± SD (years)	89,57±8,78	88,26±7,78

Correlation between N and BMI Before and After Neoadjuvant Chemotherapy Three Cycles of Cisplatin and 5-Fluorouracil

This study also observed the correlation between N with BMI before and after neoadjuvant chemotherapy three cycles of Cisplatin and 5-Fluorouracil. The data variable N with BMI before cycle I neoadjuvant chemotherapy and after cycle III neoadjuvant chemotherapy were not normally distributed with values of r = -0.070 and p = 0.358, respectively; r = -0.070 and p = 0.751 (Figures 1.1 and 1.2 Correlation of neck nodule size with body mass index (Scatter Plot).

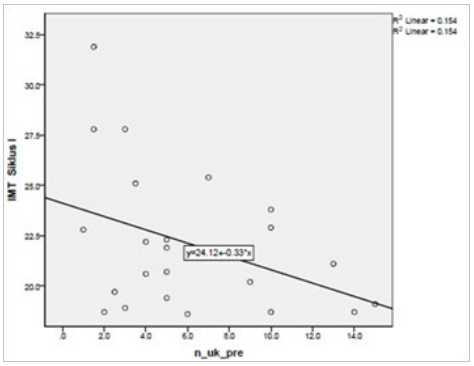

Figure 1.1 Correlation between N and BMI Before Neoadjuvant Chemotherapy of Cisplatin and 5-Fluorouracil Cycle I (Scatter Plot).

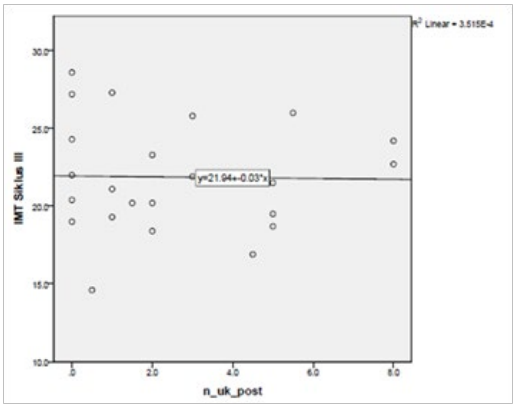

Figure 1.2 Correlation between N and BMI after Neoadjuvant Chemotherapy of Cisplatin and 5-Fluorouracil Cycle III

Correlation between N and Karnofsky status before and after Neoadjuvant Chemotherapy Three Cycle of Cisplatin and 5-Fluorouracil

This study also observed the correlation between N with Karnofsky's status before and after neoadjuvant chemotherapy three cycles of Cisplatin and 5-Fluorouracil. The data variable N with Karnofsky status before cycle I neoadjuvant chemotherapy and after cycle III neoadjuvant chemotherapy was not normally distributed with r = 0.155 and p = 0.480, respectively; r = 0.571 and p = 0.004.

DISCUSSION

In this research, the number of samples collected was 23 people with NPC WHO type 3 to undergo neoadjuvant chemotherapy that met the inclusion and exclusion criteria. The mean age was 48.35 ± 12.61 years with an age range between 16 and 70 years, and male patients (60.9%) was more than female (36.1%), with a ratio of 1.55: 1. Patients' dominance was in the age group 46-55 years, as many as 11 patients (47.8%) and aged 56-65 years, five patients (21.7%).

This study and several other studies, presented similar findings. One hundred twenty-nine thousand new NPC cases based on data from the International Agency for Research on Cancer in 2018 had a higher incidence of NPC in men than women with a ratio of 5:2, with an age distribution of 45-54 years.[1,4] Environmental factors such as formaldehyde, wood dust, smoke, chemicals and smoking habits are thought to be the etiology of the incidence of NPC in men, and the habit of consuming certain foods (salted fish).[4]

Xie et al.[16] stated that the male predominance in NPC might have an endogenous estrogen effect.

Interestingly, NPC occurs in young ages patients, between 16-35 years (17.4%). In Adham et al.[17] study, forty-nine NPC patients under the age of 31 years, between July 2004 and January 2007 in Jakarta, Indonesia, 46 patients were at advanced stage NPC (WHO type 3) (94%), and only three patients (6%) were in WHO type 1. The percentage of NPC of undifferentiated carcinoma in young patients was higher and strongly correlated with the EBV virus. It is maybe due to an undifferentiated tumor, which tends to progress to distant metastases. Another hypothesis is the delay in diagnosing NPC.

Evaluation of N before and after neoadjuvant chemotherapy (three cycles of Cisplatin and 5-Fluorouracil)

Al-Amro et al.[18] assessed the effectiveness of the neoadjuvant chemotherapy Cisplatin and Epirubicin followed by Cisplatin chemotherapy and radiotherapy in advanced NPC patients, conducted in 110 studied patients, showing that total remission and partial remission were achieved, respectively in 87 people (79%) and 23 people (21%). In conclusion, neoadjuvant chemotherapy followed by concurrent chemoradiotherapy was safe and effective for advanced NPC.

Cao et.al.[19] had analyzed the impact of neoadjuvant chemotherapy in NPC patients on locoregional treatment in advanced NPC, divided into treatment with neoadjuvant chemotherapy (NACT) followed by concurrent chemoradiotherapy (CCRT), compared with CCRT only.

Gosh[20] outlined the effectiveness of Cisplatin which induces oxidative stress by forming reactive oxygen species (ROS) which is responsible for lipid peroxidation, depletion of sulfhydryl groups, changing different signal transduction pathways, Ca-homolysis and so on which can cause DNA damage and consequently cell apoptosis.

Evaluation of BMI before and after neoadjuvant chemotherapy (three cycles of Cisplatin and 5-Fluorouracil)

Cisplatin typically distributes to tissues by rapidly proliferating cells. 5-HT has 14 receptors. The study of Hattori T et al.[21] stated that the 5-HT1b, 5-HT2b, and 5-HT2c receptors were shown to play a more important role in suppressing feeding behavior in trials with cisplatin-induced mice and guinea pigs than 5-HT3 or 5- receptors HT4.

Cisplatin accumulates in the mitochondria and causes overproduction of mROS, which causes mitochondrial break down, TCA cycles, and interferes with MMP, resulting in the electron-transport chain (ETC) collapse. In parallel, the resulting mROS induces up-regulation of p53 inhibiting glycolysis, leading to glucose accumulation and pyruvate

depletion. Finally, the continuous depletion of ATP leads to cell cycle cessation and cell death.[22]

Nadal-Serrano et al.[23] explained that leptin reduces ROS levels in treated breast cancer patients with Cisplatin. Leptin does not produce any changes in the mitochondrial oxidative phosphorylation (OXPHOS) complex, except for a decrease (24%) in Complex I (NADH: ubiquinone oxidoreductase). They are uncoupling protein 2 (UCP2), a membrane protein capable of releasing respiration from ATP synthesis and preventing ROS production. UCP2 protein levels decreased by 26% in cells exposed to leptin. Leptin does not affect antioxidant enzymes.

In our study, BMI values were normally distributed, so using the Paired T-test, which had a value of $p = 0.615$, meant that there was no significant difference between the mean BMI before cycle I neoadjuvant chemotherapy and after cycle III neoadjuvant chemotherapy. The results of this study indicated that there was a decrease in BMI from before cycle I neoadjuvant chemotherapy to post three cycles of neoadjuvant chemotherapy. This result supported by the study of Takenaka et al.[10]

NPC patients with underweight BMI

In this study, none of the patients in the sample fell into the underweight BMI category. Based on the study, more than 50% of HNSCC patients experienced significant weight loss at the time of diagnosis and before starting treatment. Weight loss negatively affects patient survival.[24]

The risk of cachexia and patient deterioration depends on several factors such as the type and stage of cancer, the degree of systemic inflammation, and the rate of response to anticancer therapy. There is a consistent association between symptoms, the presence of inflammatory markers, and enhanced immune response. Poor cancer outcome is predicted by the systemic inflammatory response by acute-phase proteins (increased C-reactive protein (CRP), hypoalbuminemia, and the combination as a Glasgow Prognostic Score and changes in white blood cells, namely high NLR (neutrophil-lymphocyte ratio).

Much evidence supports cytokines' role (interleukin 1 (IL-1), IL-6, and TNF-α). Cytokines can affect neuroendocrine control of appetite that causes anorexia. Circulating cytokines can alter the production of acute-phase proteins by the liver, which can suppress drug clearance pathways and pose a risk of toxicity to anticancer regimens. Tumor hypoxia occurs when tumor cells lose oxygen. A rapidly growing tumor can exceed its blood supply, resulting in areas of the tumor with a lower oxygen partial pressure than those in healthy tissue. It is related to increased tumor growth, development of malignancy, and resistance to anticancer therapy. Poor dietary intake is often the result of cancer treatment side effects, or local tumor-related effects.[25]

The rapid increase in systemic inflammatory factors such as tumor necrosis factor-a (TNF-α) and interleukin-6 (IL-6) can facilitate proliferation, tumor cell development and promote malignant processes. Malnutrition status in underweight patients can decrease chemotherapy response and increase chemotherapy toxicity.[24,26]

The tumor stage is known to be related to the nutritional status before treatment. The underweight group's survival was significantly worse than the normal weight group (five-year survival rates 32.2% and 62.7%, $p < 0.001$, respectively). Survival was worse in the normal weight group than in the overweight group (62.7% vs. 73.5%), although this difference was not significant.[10]

NPC patients with normal BMI

In our study, 17 patients (73.91%) NPC were included in the normal BMI category, which dominated the number of patients in the sample, with the proportion of male:

women was 10:7. Patients in this category who experienced an increase in BMI after three neoadjuvant chemotherapy cycles were 8 patients (47.06%), with 2 patients (25%) increasing to BMI overweight. In comparison, 6 patients (75%) experienced an increase in BMI but still in normal category. Nine patients (52.94%) experienced a decrease in BMI, with the proportion of 6 patients (66.7%) still in the normal category and 3 patients to the underweight category (33.3%).

These data indicated that there was a fairly balanced proportion of the increase and decrease in BMI up to three cycles of neoadjuvant chemotherapy Cisplatin and 5-Fu, as many as 8 patients (47.06%) increased, and 9 patients (52.94%) decreased. The reduced patient's weight or BMI was not a statistically significant effect of neoadjuvant chemotherapy. Various theories suggest a decrease in BMI or body weight (BW) of patients after chemotherapy. The increase in BMI after chemotherapy is still unexplainable.

NPC patients with BMI overweight and obese

An interesting matter in this study included NPC patients who were overweight and obese. A person is categorized as overweight when the BMI is ≥ 25 - 29.9 kg/ m^2, and as obese when the BMI is ≥ 30 kg/ m^2.[10]

Table 5. Overweight and obese NPC patients

Patient	Age	BMI before CT	BMI after 3 cycles CT
Overweight			
Mr. S	48 years	23.8 kg/m^2	26.0 kg/m^2
Mr. K	61 years	25.1 kg/m^2	25.8 kg/ m^2
Mr. S	19 years	25.4 kg/m^2	24.3 kg/m^2
Obese			
Mrs. T	59 years	31.9 kg/m^2	27.2 kg/m^2
Mrs. A	47 years	27.8 kg/m^2	28.6 kg/m^2
Mrs. R	40 years	27.8 kg/m^2	27.3 kg/m^2

The study of Hollander et al.[27] explained that a large BMI is associated with an increased incidence and mortality of several cancers, such as esophageal adenocarcinoma, breast cancer and colon cancer, and causing problems related to diagnosis and treatment of HNSCC. Several studies have shown a stronger association between obesity and death in smokers. Smoking is known to trigger NPC development, increasing the risk of treatment failure and death in NPC patients. Adipocytes can accelerate tumor growth and progression through insulin resistance, hyperinsulinemia, hyperglycemia, and low-grade chronic inflammation.[24,26] There is a hypothesis that overweight or obese patients have high nutrition to compensate for the decline body weight during treatment compared to patients with normal body weight, although overweight or obese conditions did not show a protective effect in NPC patients.[24]

Huang et al.[26] investigated the relationship between patient's BMI and clinical outcomes in advanced locoregional NPC patients treated with a combination of chemotherapy and radiotherapy. The results of this study stated that the five-year cancer-free survival rates for underweight, normal weight, overweight and obesity groups were 44%, 61%, 68% and 73%, respectively ($p = 0.014$). The overall five-year survival was 51%, 68%, 80% and 72% ($p = 0.001$). BMI is a powerful prognostic factor of overall survival and cancer-free survival.

Evaluation of Karnofsky's status before and after neoadjuvant chemotherapy three cycles of Cisplatin and 5-Fluorouracil

In our study, Karnofsky status values had an abnormal distribution, so using the

Wilcoxon test had a value of p = 0.564, which means there was no significant difference between the mean values of Karnofsky status before cycle I neoadjuvant chemotherapy and after cycle III neoadjuvant chemotherapy. It is most likely because the Karnofsky status assessment has high subjectivity depending on different residents' assumptions and examinations.

The patient assessment of Karnofsky's status is a key factor in the choice of treatment in patients with head and neck cancer, given the high impact of tumors on nutritional status and the potential for treatment toxicity, according to a 2013 West study suggesting that treatment outcomes in patients with poor performance status before treatment will also provide bad results.[28]

Correlation be tween N and BMI before and after neoadjuvant chemotherapy three cycles of Cisplatin and 5-Fluorouracil

The correlation between N and BMI before a cycle I neoadjuvant chemotherapy and after three neoadjuvant chemotherapy cycles was found as negative, which was not significant. This result means that the smaller the N value, the BMI in the patient will increase. Hattori et al.[21] proved that the 5-HT1b, 5-HT2b, and 5-HT2c receptors were shown to play a more important role in suppressing feeding behavior in trials with Cisplatin-induced mice and guinea pigs than 5-HT3 or 5-HT4 receptors, and without affecting leptin levels.

The study of Nadal-Serrano et al.[23] explained that leptin reduces ROS levels in breast cancer patients treated with Cisplatin. Leptin does not produce any changes in the mitochondrial oxidative phosphorylation (OXPHOS) complex. Leptin does not affect antioxidant enzymes, so UCP2 can release respiration from ATP synthesis and prevent ROS production. SIRT1 protein levels increased by 60% in chronically leptin-treated cells so that intracellular regulation could occur with mono-ADP-ribosyltransferase activity. SIRT1 also increases insulin sensitivity, deacetylate and influences both members of the PGC1-alpha / ERR-alpha complex. It was an important metabolic regulatory transcription factor, deactivating acetate and then inactivating the p53 protein. SIRT1 also plays a role in activating helper T cells 17, which contribute to autoimmune diseases.

Based on this mechanism, it can be assumed that there is a competitive reaction between the Cisplatin stimulus and 5-HT2b and 5HT2c in triggering anorexia by suppressing ghrelin with the mechanism of action of cisplatin in triggering leptin activation. It can suppress ROS, p53 and increase insulin sensitivity and the body's metabolic genes (SIRT1, OXPHOS, and UCP2). Although according to theory, the difference is not significant. It can occur due to various comorbid factors in the patient, the level of depression, the patient's family and spiritual support, and perhaps because of the subjectivity in patient's N assessment.[21,23]

Correlation between N and Karnofsky status before and after neoadjuvant chemotherapy three cycles of Cisplatin and 5-Fluorouracil

Both tests showed a positive relationship between N and Karnofsky's status before a cycle I neoadjuvant chemotherapy, but the difference was not significant. It means that the higher the N value, the Karnofsky's status will also increase. Meanwhile, there was a strong positive relationship between N and Karnofsky's status after cycle III neoadjuvant chemotherapy, with a significant difference. These results indicated that the higher the N value, the Karnofsky's status in the patient also increased. In the test between N and Karnofsky's status before a cycle I neoadjuvant chemotherapy, the difference was not significant, which means it was not theoretical.

If N increased, it indicates that the patient's malignancy process is still high and will trigger cytokines' secretion (interleukin 1 (IL-1), IL-6, and TNF-α), which causes anorexia, cachexia, fatigue, and physical activity disturbances, resulting in a decrease in Karnofksy value.[24,26] There were similar reasons for the strong positive correlation between N and Karnofsky's status after cycle III neoadjuvant chemotherapy, with a significant difference. These are most likely due to the subjectivity of the examiner's assessment of N and Karnofsky's status and require practical support or guidelines such as using the WHO PS.

This study showed that the administration of neoadjuvant chemotherapy Cisplatin and 5-Fu to NPC WHO type 3 patients effectively reduces the size of the patient's neck nodule and influences the increase in BMI in patients. There was a significant decrease between the mean N of WHO type 3 NPC patients before neoadjuvant chemotherapy Cisplatin and 5-Fu cycle I and after cycle III neoadjuvant chemotherapy. There was a strong positive correlation between N and Karnofsky status after three neoadjuvant Cisplatin and 5-Fu chemotherapy cycles.

Further research is needed to evaluate the effectiveness of neoadjuvant chemotherapy in NPC WHO type 3 patients so that it can be used as therapy guidelines for patients with advanced NPC and to assess the factors that influence the success of neoadjuvant chemotherapy in NPC WHO type 3 patients.

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