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Vitamin D3 enhances chemotherapy efficacy in advanced nasopharyngeal carcinoma patients

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Abstract
Introduction: Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from epithelial cells of the nasopharynx. Cisplatin is the first-line drug for chemotherapy in NPC patients. Chemoresistance is a major cause of oral cancer progression and mortality. Research has revealed the anticancer properties of vitamin D, suggesting that it can impede the development of cancer. This study is to determine the effect of vitamin D3 administration on chemotherapy response in advanced NPC patients who were receiving Cisplatin-based chemotherapy.
Methods: This research is an analytic observational study with a pretest-posttest sectional design. The research sample was NPC Stage III and IV patients in Sub-Oncology of Otorhinolaryngology-Head and Neck Surgery clinic undergoing neoadjuvant chemotherapy, whose chemotherapy response was assessed based on two groups, namely the neoadjuvant chemotherapy group and neoadjuvant chemotherapy with 1000 IU Vitamin D3 premedication.
Results: This study involved 32 patients with NPC stage III and IV, with 75% male and 25% female. The average age was 49 years. Most of the patients were in stage IV, which was 87.5%, while stage III was 12.5%. The neoadjuvant chemotherapy group had 56.3% with positive chemotherapy responses and 43.8% negative responses, while the neoadjuvant chemotherapy group with Vit D3 premedication had 93.8% with positive responses, and 6.3% negative responses. The statistical test results obtained $p = 0.037$, which means that there was a significant effect of vitamin D3 administration on chemotherapy response in advanced NPC patients who were receiving Cisplatin-based chemotherapy.
Conclusion: Administration of Cisplatin-based Neoadjuvant chemotherapy with 1000 IU vitamin D3 premedication has an effect 2.33 times more effective in increasing chemotherapy response compared to neoadjuvant therapy alone.

Keywords: Nasopharyngeal carcinoma, chemotherapy, cisplatin, vitamin D

Introduction
Nasopharyngeal carcinoma (NPC) is a cancerous tumor that develops from the epithelial cells of the nasopharynx. It is prevalent in various regions of Asia, with Indonesia reporting NPC as the fourth most prevalent cancer, following cervical, breast, and skin cancer [1]. A preliminary study conducted by researchers found 119 cases of nasopharyngeal carcinoma at Kalinga Institute of Medical Science. Based on the data, the incidence of NPC at Kalinga Institute of Medical Science is 18% of the total number of cancer patients. The origins of nasopharyngeal carcinoma (NPC) are primarily linked to Epstein Barr virus (EBV) infection. However, various other risk factors, such as age, gender, genetics, occupation, geographic location, intake of grilled food, consumption of canned goods, salted fish, and smoking, can also contribute to the development of nasopharyngeal carcinoma [2]. Treatment modalities for NPC include radiotherapy, chemotherapy, and surgery. Radiotherapy given alone at an advanced stage becomes less effective, with a 5-year survival rate of less than 50%. Patients with advanced NPC are better off using a combination of chemotherapy and radiation with a 5-year survival rate of more than 70%. The drug that is often used in chemotherapy for NPC patients is the platinum group, one of which is cisplatin. Cisplatin has the ability to decrease tumor size, enhance tumor sensitivity to radiation, and diminish the likelihood of micro-metastases. As a systemic agent, cisplatin impacts both cancerous and normal cells.

The utilization of cisplatin in chemotherapy medications demonstrates a response rate ranging from 15% to 47% [3]. Vitamin D is a type of fat-soluble secosteroid (also known as 1, 25-dihydroxy-vitamin D3 (1, 25 (OH) 2D3)). This vitamin plays a role in diverse physiological functions, including the regulation of calcium and phosphorus metabolism, the maintenance of stable plasma levels of calcium and phosphorus, and involvement in the development of teeth and bones. Clinically, it is often used for the treatment of rickets and osteoporosis [4]. In the case of head and neck cancer, research indicated that a majority of patients exhibited a greater prevalence of vitamin D deficiency when compared to a healthy control group adjusted for age and sex. Additionally, lower levels of vitamin D are linked to an increased occurrence of tumors [5]. Recently, findings from both pre-clinical and clinical investigations have suggested that supplementing with vitamin D could lower the likelihood of developing cancer. Urashima suggested that the higher the serum vitamin D level, the better the cancer prognosis [6]. Huang conducted a previous study, which investigated the effect of vitamin D on cisplatin-based chemosensitivity in 65 patients diagnosed with NPC. It was found that vitamin D could increase cisplatin chemotherapy and suggested that vitamin D should be given during chemotherapy.

Based on these studies, the authors sought to conduct a study to evaluate the effect of administering vitamin D3 on the chemotherapy response in advanced nasopharyngeal carcinoma (NPC) patients undergoing Cisplatin-based chemotherapy.

Methods

This research used experimental with pretest-posttest design. This research was conducted at Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha for 3 months. The target population of this study were patients at the Sub-Oncology of Otorhinolaryngology-Head and Neck Surgery clinic with a diagnosis of NPC stage IV undergoing chemotherapy with a cisplatin-based regimen at Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha. The inclusion criteria used were NPC patients with undifferentiated cell carcinoma histopathology; advanced stage NPC patients; patients receiving cisplatin, mesna, and ifosfamide chemotherapy regimens; patients with an age range of 18 - 60 years; Ecog scale $\leq$ 2 and Karnofsky $\geq$ 70%; willing to participate marked with informed consent. Patients excluded were with the following criteria: hepatic and renal impairment; history of radiotherapy; diabetes mellitus; and immunocompromised patients. The sampling method used is the consecutive sampling method. Samples were divided into 2 groups: the intervention group received additional oral vitamin D3 at a dose of 1000 IU for 3 days before chemotherapy was carried out in one series (Intervention group) and the control group received tablets containing saccharin (Control group). Chemotherapy response was assessed based on MSCT-scan examination before and after chemotherapy.The data collected earlier underwent analysis through the application of the Kolmogorov-Smirnov test to assess its normality. If the test results show a p value > 0.05, the data has a normal distribution and vice versa. Then, the data will be analyzed using Chi-square test.

Results

Characteristics of Advanced Stage NPC Patients Receiving Cisplatin-Based Chemotherapy

This study involved thirty-two advanced NPC patients receiving cisplatin-based chemotherapy. In this study, the sample was divided into 2 treatment groups with each group had 16 subjects. In this study, there were 24 cases (75.0%) of male patients, and 8 cases of women (25.0%). The average age of NPC patients was 49.28 with a standard deviation of 8.15 (49.28±8.15). Most of the patients were in stage IV with 28 cases (87.5%), while the remaining 4 (12.5%) were in stage III. Table 1 presents an overview of the characteristics of the research subjects.

Table 1: Description of Characteristics of Advanced Stages of NPC Patients Receiving Cisplatin-based Chemotherapy

Basic Characteristics	Total N=32	Chemotherapy Group		p-values
		Neoadjuvant (n=16)	Neoadjuvant + Vitamin D3 (n=16)	
Gender[a]				1000
Male	24 (75.0%)	12 (75.0%)	12 (75.0%)	
Female	8 (25.0%)	4 (25.0%)	4 (25.0%)	
Age[b]	49.28±8.15	50.25±7.57	48.31±8.83	0.510
Tumor Size				
Pre-test[c]				0.137
T1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
T2	11 (34.4%)	4 (25.0%)	7 (43.8%)	
T3	16 (50.0%)	8 (50.0%)	8 (50.0%)	
T4	5 (15.6%)	4 (25.0%)	1 (6.3%)	
Post-test[c]				0.011*
T0	2 (6.3%)	0 (0.0%)	2 (12.5%)	
T1	22 (68.8%)	9 (56.3%)	13 (81.3%)	
T2	1 (3.1%)	1 (6.3%)	0 (0.0%)	
T3	2 (6.3%)	2 (12.5%)	0 (0.0%)	
T4	5 (15.6%)	4 (25.0%)	1 (6.3%)	

Categorical data results were presented through a frequency distribution (%), while numerical data findings were expressed as the mean ± SD. [a]For nominal categorical data used the chi square/fisher exact test. [b]For numerical data passed the normality requirements (independent t-test). [c]For ordinal categorical data used the Mann-Whitney test. *Significant at $p<0.05$.

The average age of patients in the control group was 50.25±7.57 years, and in the intervention group the average was 48.31±8.83 years (p = 0.510). There was no significant difference based on age between the control group and the

intervention group.

The NPC stage of patients in the control group and the intervention group had similar proportion of patients with the highest being stage IV. There were 15 patients (93.8%) in the control group and there were 13 patients (81.3%) in the intervention group (p = 0.600; p>0.05). There was no significant difference based on NPC stage between the control group and intervention group.

Prior to therapy, the highest proportion of tumor size of the patients in the control group and the intervention group was similar, which was T_3, with 8 patients (50.0%) in each group (p = 0.137). There was no significant difference in tumor size between the control group and the intervention group before treatment.

After therapy, the highest proportion of the tumor size in the control group and intervention group was the same, which was T_1, with 9 patients (56.3%) and 13 patients (81.3%), respectively (p = 0.011). We found a significant difference in tumor size between the control group and the intervention group after therapy.

Effect of Vitamin D3 Administration on Chemotherapy Response in Advanced NPC Patients Receiving Cisplatin-Based Chemotherapy

The resulting data were analyzed using chi square/fisher exact test to know the effect of vitamin D3 administration on chemotherapy response in advanced NPC patients receiving cisplatin-based chemotherapy. The results were shown in table 2.

Based on table 2, the results of the response to chemotherapy for most patients, 24 patients (75.0%), were in the positive category or there were improvements, while 8 patients (25.0%) had negative results (p = 0.037). The number of patients in control group and the intervention group with positive response were 9 (56.3%) and 15 (93.8%), respectively. Therefore, treatment of neoadjuvant with additional vitamin D3 was more effective in increasing chemotherapy response. The results of this study also obtained a RR value = 2.33 (95% CI = 1.31-4.16), which means that the treatment of neoadjuvant with additional vitamin D3 had an effect 2.33 times more effective in increasing chemotherapy response compared to neoadjuvant treatment alone. There was a significant effect of vitamin D3 administration on chemotherapy response in advanced NPC patients who were receiving Cisplatin-based chemotherapy.

Based on table 3, some patients in control group and intervention group experienced a change in their tumor status (Based on pretest-posttest). In the control group, 4 patients (25.0%) experienced a status change from T2 to T1, 5 patients (31.3%) from T_3 to T_1, 1 patient (6.3%) from T_3 to T_2, while 2 patients (12.5%) remained at T_3 and 4 patients (25.0%) remained at T_4 without changes (p = 0.004; p<0.05). Meanwhile, in the intervention group, 5 patients (31.3%) exhibited a status change from T_2 to T_1, 2 patients (12.5%) from T_2 to T0, 8 patients (50.0%) from T_3 to T_1, and 1 patient (6.3%) remained at T_4 without changes (p = <0.001; p<0.05). The change of tumor status in both control and intervention group were statistically significant. This shows additional therapy of vitamin D can lower tumor status of NPC patients receiving cisplatin-based chemotherapy.

Table 2: Effect of vitamin D3 administration on chemotherapy response in advanced stage NPC patients receiving cisplatin-based chemotherapy

Variable	Total N=32	Chemotherapy groups		p-value
		Neoadjuvant	Neoadjuvant + Vit D3	
Chemotherapy response				0.037*
Negative	8 (25.0%)	7 (43.8%)	1 (6.3%)	
Positive	24 (75.0%)	9 (56.3%)	15 (93.8%)	

The categorical data were described with the frequency distribution (%), for categorical data used the chi square/fisher exact test. *Significant at p<0.05.

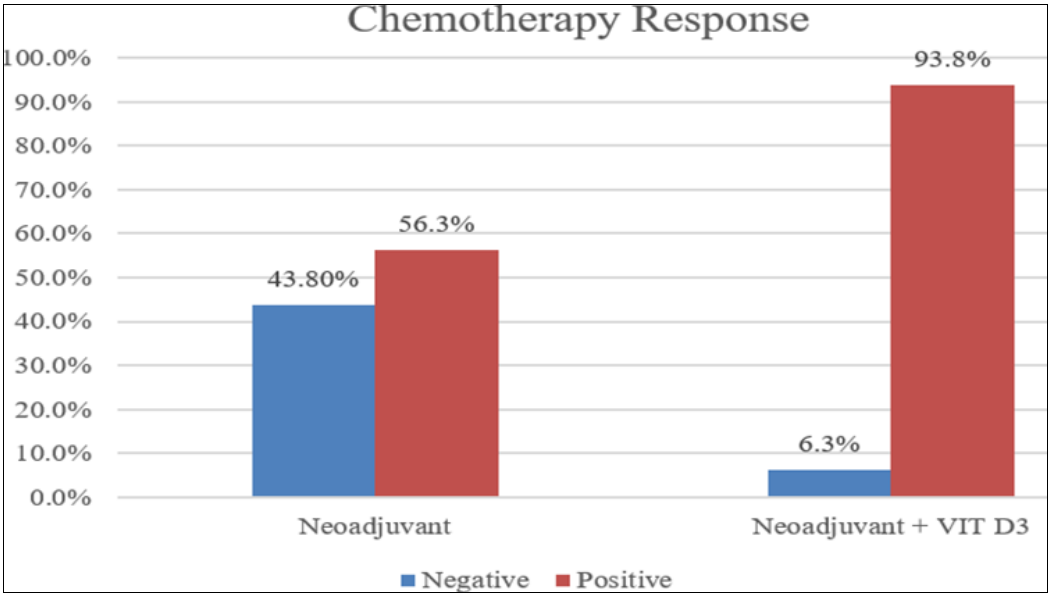

Fig 1: Bar chart depicting chemotherapy response between the neoadjuvant control group and the neoadjuvant + vitamin D3 group.

Table 3: Effect of Vitamin D3 Administration on Changes in Tumor Status in NPC Patients Receiving Cisplatin-based Chemotherapy

Perubahan Status Tumor (pre-post)	Neoadjuvant		Neoadjuvant + Vit D3	
	F	%	F	%
$T_2 \rightarrow T_1$	4	25.0%	5	31.3%
$T_2 \rightarrow T_0$	0	0.0%	2	12.5%
$T_3 \rightarrow T_1$	5	31.3%	8	50.0%
$T_3 \rightarrow T_2$	1	6.3%	0	0.0%
$T_3 \rightarrow T_3$	2	12.5%	0	0.0%
$T_4 \rightarrow T_4$	4	25.0%	1	6.3%
P-value	0.004*		<0.001*	

Wilcoxon Rank Test, *Significant at $p<0.05$

Nasopharyngeal carcinoma (NPC) is a cancerous tumor that originates from the epithelial cells of the nasopharynx[1]. Nasopharyngeal carcinoma (NPC) is a malignancy predominantly prevalent in the Asian region, and its global incidence is relatively low, with fewer than 1 case per 100, 000 population. The highest occurrence of NPC worldwide is observed in Guangdong Province, South China, where the incidence ranges from 20 to 40 cases per 100, 000 population. In Indonesia, NPC ranks fourth as the most common cancer after cervical cancer, breast cancer and skin cancer. In studies focused on the head and neck region, nasopharyngeal carcinoma (NPC) holds the leading position, constituting approximately 60% of cases [3]. This study aims to determine the effect of vitamin D3 administration on chemotherapy response in advanced stage NPC patients who are receiving cisplatin-based chemotherapy.

Nasopharyngeal carcinoma (NPC) occurs more frequently in males than females and typically manifests in individuals aged 40-50 years, accompanied by a high mortality rate. The high incidence of NPC, associated with infection with Epstein Barr virus, the environment and eating habits. Furthermore, a past pattern of regular exposure to carcinogenic substances like benzopyrene, benzoathracene (A hydrocarbon present in coal charcoal), industrial fumes, chemical gases, wood smoke, and certain plant extracts is thought to potentially elevate the risk of nasopharyngeal carcinoma occurrences [7].

Based on the Indonesian Ministry of Health, the highest number of people with NPC was identified in the productive age (15-64 years). Our findings align with a study conducted by Shofi Faiza at Dr. M. Djamil Padang Hospital, revealing that the majority of individuals with NPC fell within the productive age bracket of 41-65 years, accounting for 68.18% of cases with 30 individuals. Wulan Melani's research at Adam Malik Hospital in Medan also showed similar results, with 50 people (33.1%) in their productive age (41-50 years) [7]. Comparable results were noted in a 2018 study carried out by Trimonika at Dr. Kariadi Semarang Hospital, revealing that the average age of NPC patients was 45 years. The youngest patient was 18 years old, while the oldest was 67 years old. Negative environmental factors, coupled with pollution stemming from technological influences, can contribute to genetic mutations that may increase the likelihood of cancer development among younger individuals [3]. According to the results of Melvern's research at Kariadi General Hospital in Semarang in 2022, the highest incidence of nasopharyngeal carcinoma was found in the 50-60 year age group [8]. These results are very close to the results obtained in the current study which the average age of the patients was 49 years, with the youngest being 33 years and the oldest being 60 years.

Based on gender, in this study the male sex was more dominantly affected by NPC. This is similar to the research conducted by Shofi Faiza at Dr. M. Djamil Padang Hospital which showed that men were more likely affected by NPC, with 23 people (52.27%). This study is also in accordance with Vito F Jayali which was conducted at Cipto Mangunkusumo General Hospital, which had a higher incidence of males, with 114 people (681.2). Research conducted by Eka Savitri is also in line with this research where it is stated that there is a male to female ratio of 3.2:1 [7]. These results are almost similar to other studies which found the ratio of men compared to women is 2.24:1 [8]. The disparity in incidence rates between men and women is notably substantial, consistent with findings from previous studies. In our study, we observed a ratio of 3:1, with 24 male patients (75%) and 8 female patients (25%). This gender distribution aligns with earlier research indicating a higher prevalence of nasopharyngeal carcinoma (NPC) in males, although the difference is not deemed statistically significant. Dawolo suggests that this pattern may be attributed to distinct lifestyles between men and women, such as higher smoking rates among men. Additionally, occupational exposures to chemicals in certain male-dominated professions are believed to contribute to the occurrence of NPC [9]. Drawing from prior research, various risk factors for nasopharyngeal carcinoma, including age, gender, and histopathological type, share common explanations for their influence on the incidence of this cancer. Environmental exposures, such as smoking, alcohol consumption, and occupational history, have been identified as contributing factors [10]. This establishes a correlation between age and sex with the histopathological type of nasopharyngeal carcinoma. However, based on the analysis that has been done, this study failed to prove the hypothesis. This may be due to the limited number of certain sample groups so that the results provided by the analysis do not follow the hypothesis. Earlier studies have similarly indicated an absence of a noteworthy correlation between gender and the histopathological type of nasopharyngeal carcinoma, although the reasons for this remain unclear [11]. Currently no studies providing evidence against the existence of a correlation between age and the histopathological type of nasopharyngeal carcinoma.

In this study, most patients diagnosed with advanced stage NPC. According to study carried out in Palembang, the initial clinical symptom reported by patients is ear ringing. Nevertheless, a considerable number of patients sought treatment only when the condition had progressed to an advanced stage. Consequently, the symptoms at that point were no longer confined to ear ringing but included a neck lump, nasal congestion, and nosebleeds [9]. The large number of patients found at advanced stage indicates a delay in the early detection of a tumor in the nasopharynx. This situation may arise due to unusual initial symptoms and a lack of public awareness prompting individuals to seek medical attention only when their complaints worsen. Moreover, there remains a substantial portion of the population unfamiliar with cancer, particularly nasopharyngeal carcinoma (NPC). Additionally, there is a deficiency in the knowledge of doctors and frontline health workers regarding the initial symptoms and signs of NPC.

The results of response to chemotherapy in this study were that the control group had a positive response of 56.3% (CR

0% and PR 56.3%) and the intervention group of 93.8% (CR 12.5% and PR 81.3%). The negative response in the control group was 43.8% (25% NC and 18.8% PD) and the intervention group was 6.3% (6.3% NC and PD 0%) (Complete Response [CR]; Partial Response [PR]; Progressive Disease [PD]; No Change [NC]).

In this study, it was found that premedication of 1000 IU of vitamin D3 before chemotherapy was significantly associated with response to therapy (p = 0.037). This indicates that administering an additional premedication of 1000 IU of vitamin D3 before neoadjuvant chemotherapy is 2.33 times more effective than undergoing neoadjuvant chemotherapy without premedication [12].

The percentage of negative responses in this study was greater in the neoadjuvant chemotherapy group. Molecularly, apoptosis is accomplished through the activation of caspases. Caspases are a category of intracellular cysteine proteases that cleave substrates at aspartic acid residues. Following their activation, caspases selectively target and assail both nuclear and cytoplasmic factors involved in maintaining cell architecture and participating in DNA repair, replication, and transcription. This process is further facilitated by the observation that the regulation of the apoptotic pathway is heightened in the presence of both anti-apoptotic and apoptotic proteins. Nevertheless, as highlighted by Bagnobianchi, certain cancer cells often exhibit varying degrees of resistance to cisplatin treatment. This resistance is attributed in part to the failure of apoptosis and the caspase pathway. Inhibitors of apoptosis proteins (IAPs) constitute a group of intracellular proteins responsible for impeding cell death by inhibiting downstream caspase activation. Broadly, IAPs serve as primary inhibitors of cancer drugs such as cisplatin, shielding cancer cells from the diverse extrinsic and intrinsic pathways triggered by these drugs [13].

Another possible cause is the existence of resistance to platinum-based chemotherapy. Initially, over 30% of patients show insensitivity to chemotherapy based on platinum, and with subsequent rounds of chemotherapy, the remaining patients progressively develop resistance to previously effective drugs. Both intrinsic and acquired chemoresistance stand as significant contributors to cancer progression and mortality. Various approaches, including combinations of chemotherapy, radiotherapy, and diverse types of chemotherapy drugs, have been implemented in patient treatments. Owing to shared underlying mechanisms, individuals resistant to chemotherapy typically exhibit insensitivity to alternative therapeutic strategies [13].

The responsiveness to chemotherapy may stem from alterations in gene expression triggered by epigenetic changes, such as DNA methylation in promoters, following treatment. Methylation at the promoter site has been identified as a key factor in controlling LCN2 expression. Cisplatin treatment has been observed to decrease methylation, while vitamin D treatment has the opposite effect, increasing methylation of the LCN2 promoter. Furthermore, vitamin D has been found to reverse cisplatin-induced abnormal methylation, ultimately diminishing LCN2 expression. The regulation of LCN2 expression by both vitamin D and cisplatin is mediated through the control of LCN2 promoter methylation. Importantly, LCN2 expression is linked to cisplatin insensitivity in SCC-type cancer cells [12].

The investigation into the antitumor properties of vitamin D is a widely explored area of research. Epidemiological studies have examined the correlation between serum vitamin D levels and the prognosis of patients with breast and rectal cancer, revealing a positive association-higher serum vitamin D levels are linked to improved patient outcomes. Vitamin D gains entry into cells through two pathways: the steroid receptor pathway and the direct entry pathway. The vitamin D receptor (VDR) serves as a membrane receptor for vitamin D [14, 15]. VDR signaling to genes that have the effect of converting back 1,25(OH)2D3 to a stable form is associated with the finding that in some studies VDR is overexpressed in cancer cells compared to normal cells. This can be used as the origin of the use of vitamin D as an anticancer agent or as a window therapy agent in initiating cancer therapy [12].

The active metabolite of vitamin D's antitumor effect is found in VDRE binding to target genes that function as gene transcription regulators. This binding results in the binding of co-activators and co-repressors, which contribute to the anticancer effects of calcitriol. The key to apoptosis is also activated through suppression of anti-apoptotic genes such as B-cell Lymphoma 2 (BCl2) and BCl2-Associated X Protein (BAX). Calcitriol also has the ability to prevent tumor cell migration. Migration plays a significant role in invasion and metastasis [16].

Vitamin D, in addition to being involved in anti- proliferative and migratory mechanisms, enhances the effects of chemotherapeutic agents. Numerous studies have identified that calcitriol heightens the sensitivity of cancer cells to DNA-damaging agents by impeding the expression and activity of the cytoplasmic antioxidant enzyme Cu/Zn superoxide dismutase. *In vitro*, calcitriol augments the cytotoxicity of the Michigan Cancer Foundation 7 (MCF7) breast cancer cell line by reducing Bcl2 protein levels, thereby intensifying the oxidative damage directly induced by chemotherapy. Calcitriol also increases cell sensitivity to therapy through calcium sensitive receptors [17].

Conclusion

Administration of cisplatin-based neoadjuvant chemotherapy with premedication of 1000 IU of vitamin D3 provides an effect 2.33 times more effective in increasing chemotherapy response compared to neoadjuvant therapy alone. As for age, gender and staging, there was no significant effect on chemotherapy response. It is recommended to incorporate 1000 IU vitamin D3 supplements as premedication for three days before chemotherapy in NPC patients to enhance the chemotherapy response. Additional research is essential, involving varying doses and administration methods of vitamin D3 supplements in NPC patients undergoing chemotherapy, to determine the optimal dose and method for improved outcomes.

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