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Article

The Primary Tumor and Regional Lymph Node Clinical Status of Distant Metastasis in Nasopharyngeal Carcinoma

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Abstract: Background: Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma derived from nasopharyngeal epithelium. NPC characteristic is highly invasive and can metastasize rapidly. The presence of distant metastasis is a major factor in determining the patient's management and prognosis. The magnitude of radiologic and molecular costs encouraging the need to know the clinical variables associated with distant metastasis of NPC. **Methods:** Cross-sectional analytical retrospective studies of undifferentiated NPC (WHO type III) patients at initial diagnosis in the ORL-HNS Department of Dr. Sardjito Hospital Yogyakarta from January 2014 to December 2016. **Results:** At 276 NPC patients with the ratio of 197 men (71.4%) and 79 women (28.6%) was 2.5:1, mean age 48.5 years, distant metastasis was found in 37 patients (13.4%). There was no significant difference in the frequency of sex (p = 0.346), age (p = 0.784), and primary tumor clinical status (p = 0.297) between NPC with distant metastasis and without distant metastasis. There was significant difference in the frequency of regional lymph node clinical status between NPC with distant metastasis and without distant metastasis (p = 0.004; PR = 3.866). **Conclusions:** There is no statistically significant difference of primary tumor clinical status between NPC with and without distant metastasis. There is statistically significant difference of lymph node clinical status between NPC with and without distant metastasis.

Keywords: primary tumor clinical status; regional lymph node clinical status; distant metastasis; nasopharyngeal carcinoma

1. Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma derived from nasopharyngeal epithelium. This tumor is derived from the Rosenmuller fossa, which is a transitional region in which the columnar epithelium turns into a squamous epithelium [1]. In Indonesia, NPC is the fourth most common cancer, with an incidence of 6.2/100,000 populations per year and ranks first in the head and neck region malignancy [2]. In Yogyakarta, NPC ranks first in malignancy at male and ranks third in malignancy at female [3].

The characteristics of NPC is different from other head and neck malignancies, because NPC is highly invasive and can metastasize rapidly [4]. NPC has tendency to spread to regional lymph node by 80%, whereas distant metastasis by 30% [5]. If there is a distant metastasis, 85% of NPC patients will die in the first year [4].

Precautions of distant metastasis at initial diagnosis is very important. Clinical symptoms of distant metastasis to target organ are difficult to identify. On the other side, the magnitude of

radiologic and molecular costs encouraging the need to know the clinical variables associated with distant metastasis. There are several retrospective cohort studies that examine the clinical variables associated with distant metastasis, including the primary tumor (T) and regional lymph node (N) clinical status. The distant metastasis of NPC is most common in T3-4 or N2-3 [6,7]. The previous studies analyzed the distant metastasis that occurred in patients who had received treatment for NPC according to the staging at the time of diagnosis, whereas the distant metastasis examined in this study was at initial diagnosis of NPC.

The relationship between the primary tumor and regional lymph node clinical status with distant metastasis at NPC patients in Indonesia, especially in Yogyakarta has not been studied previously. Because of the importance of determining clinical variables associated with distant metastasis, it is necessary to research the difference of primary tumor and regional lymph node clinical status between NPC with and without distant metastasis.

This study aims to determine the difference of primary tumor and regional lymph node clinical status between NPC with distant metastasis and without distant metastasis.

2. Materials and Methods

This is a retrospective analytic study with cross sectional design. The data of sample study were taken from the medical record, specifically undifferentiated NPC patients (WHO type III) at initial diagnosis in ORL-HNS Department of Dr. Sardjito Hospital Yogyakarta from January 2014 to December 2016.

The clinical status of NPC was determined by using TNM classification according to AJCC 1997. The clinical status of primary tumor was determined from CT scan of nasopharynx, whereas regional lymph node involvement was determined based on neck palpation examination, FNAB mass of the neck, and CT scan of nasopharynx extended cervical. Distant metastasis is determined by the results of chest X-ray, upper-lower abdominal ultrasound, and bone survey.

3. Results and Discussion

The subjects that met the inclusion and exclusion criteria were 276 patients. The gender characteristics of the study consisted of 197 (71.4%) male and 79 (28.6%) female, with male and female ratio 2.5:1 (Table 1). This value corresponds to the epidemiology ratio of male and female NPC patients, i.e., 2 - 3:1 [2]. This may be due to the lifestyles of men who are more vulnerable exposed by the carcinogenic substances, such as tobacco. In addition, there are studies showing that men with VEGF-2578 C alleles have a higher risk of developing NPC than women. Androgens can induce proliferative changes in cancer cell lines and promote tumorigenesis in animal models by androgen [8]. In contrast, estrogen can inhibit inflammatory responses that play a role in carcinogenesis and activate estrogen receptors that act as negative regulators of NPC cell growth [9].

The result of the x^2 test showed there was no significant difference between male and female NPC patients with distant metastasis compared with no distant metastasis ($p = 0.346$) (Table 1). The result of this study was similar to Cheng et al. (2001) that showed no difference of distant metastasis NPC at men and women ($p = 0.39$) [10]. However, the result was different from Xiao et al. (2013) that showed the men are at greater risk of distant metastasis than women ($p = 0.004$) [8].

The age characteristics of the study consisted of minimum 15 years, maximum 75 years, median 49 years, and mean 48.5 years. This age corresponds to the literature that mentions the peak age of NPC occurring at the age of 40–50 years [1]. The x^2 test result showed there was no significant difference between the two age groups of NPC patients with distant metastasis compared with no distant metastasis ($p = 0.784$) (Table 1). The result of this study was similar to Li et al. (2015) that showed no difference in the occurrence of distant metastasis from NPC at age $\leq$43 years and age >43 years ($p = 0.85$) [7]. The result was different from Xiao et al. (2013), which states a younger age i.e., <45 years is a risk factor for distant metastasis [8].

Table 1. Subject Characteristics.

Variable		Distant Metastasis (+)		Distant Metastasis (−)		Total	%	*p* Value
		n	%	*n*	%			
Gender	Male	24	8.7%	173	62.7%	197	71.4%	0.346
	Female	13	4.7%	66	23.9%	79	28.6%	
Age (year)	<45	12	4.3%	83	30.1%	95	34.4%	0.784
	≥45	25	9.1%	156	56.5%	181	65.6%	
T	1	7	2.6%	47	17%	54	19.6%	0.297
(Primary Tumor Clinical Status)	2a	2	0.7%	13	4.7%	15	5.4%	
	2b	11	4%	38	13.8%	49	17.8%	
	3	5	1.8%	55	19.9%	60	21.7%	
	4	12	4.3%	86	31.2%	98	35.5%	
N	0	2	0.7%	48	17.4%	50	18.1%	0.001
(Regional Lymph Node Clinical Status)	1	3	1.1%	42	15.2%	45	16.3%	
	2	7	2.5%	48	17.4%	55	19.9%	
	3a	14	5.1%	88	31.9%	102	37%	
	3b	11	4%	13	4.7%	24	8.7%	

x^2 test, p value significancy < 0.05.

In 276 NPC subjects, distant metastasis was found at 37 patients (13.4%). This value was higher than previous studies that showed the distant metastasis in initial diagnosis of NPC were 4.4–7% [6,11]. The location of distant metastasis of NPC in this study was most prevalent in bone, experienced by 19 patients (44.2%), followed by liver as many as 14 patients (32.6%), lung as many as 9 patients (20.9%), and spleen in 1 patient (2.3%) (Table 2). This result was similar to the previous studies that showed the location of distant metastasis of NPC was most common in bone (70–80%), followed by liver (30%) and lung (18%) [6]. The distant metastasis of NPC to the lien occurs only at 1.19% of all distant metastasis NPC [12].

Table 2. Distant Metastasis Location of NPC.

No.	Metastasis Location	*n*	%
1	Bone	15	40.54%
2	Liver	9	24.32%
3	Lung	6	16.22%
4	Spleen	1	2.70%
5	Bone + liver	3	8.11%
6	Bone + lung	1	2.70%
7	Liver + lung	2	5.41%
	Total	37	100%

The distant metastasis of NPC to the bone (Table 3) occurred most frequently in calvaria in 11 patients (40.8%), followed by femur as many as 5 patients (18.5%), vertebrae of 3 patients (11.1%), humerus of 3 patients (11.1%), mandibles 2 patients (7.4%), radius of 1 patient (3.7%), metacarpal 1 patient (3.7%), and tibia 1 patient (3.7%).

Table 3. Distant Metastasis Location of Bone.

No.	Metastasis Location	*n*	%
1	Calvaria	6	31.58%
2	Femur	2	10.54%
3	Vertebra	2	10.54%
4	Humerus	1	5.26%
5	Mandibula	1	5.26%
6	Calvaria + vertebra	1	5.26%
7	Calvaria + humerus	1	5.26%
8	Calvaria + mandibula	1	5.26%
9	Calvaria + radius	1	5.26%
10	Femur + humerus	1	5.26%
11	Femur + metacarpal	1	5.26%
12	Calvaria + femur + tibia	1	5.26%
	Total	19	100%

Chong et al. (2011) reported the most frequent distant metastasis location of NPC is to vertebra (59.6%), followed by pelvis (16.3%), femur (9.9%), rib and sternum (7.8%), and humerus (5%) [13]. On the other hand, distant metastasis of NPC to calvaria (1.4%), mandibles (0.9%), radius (0.9%), metacarpal (2.3%), and tibia (0.9%) are less common [14].

In this study, the result of the x^2 test showed there was no significant difference between the frequency of primary tumor clinical status of NPC patients with distant metastasis compared with no distant metastasis (p = 0.297) (Table 1). This result was different from some previous studies. Cheng et al. (2001) indicates that T4 classification is an independent predictive factor of distant metastasis (p = 0.02) [10]. Bensouda et al. (2011) and Li et al. (2015) showed that there was a 5-year difference in metastasis between T1-2 and T3-4 (p = 0.001) [6,7]. The previous studies analyzed the distant metastasis that occurred in patients who had received treatment for NPC according to the staging at the time of diagnosis, whereas the distant metastasis examined in this study was at initial diagnosis of NPC.

No significant difference in primary tumor clinical status among NPC patients with distant metastasis compared with no distant metastasis suggests that distant metastasis of NPC is unlikely to be dependent to local extension of tumor cells based on primary tumor clinical status. However, this study could not exclude the involvement of tumor volume, because the primary tumor clinical status was defined based on the extension of local structure invasion (AJCC), but had not considered the tumor volume. Li et al. (2015) states that in addition to primary tumor clinical status (T), tumor volume is a predictive factor of distant metastasis of NPC. Larger tumor volume indicates an increase of clonogenic power, which then causes hypoxia and distant metastasis [7].

The spread of regional lymph node in 276 NPC subjects occurred in 226 patients (81.9%). This value corresponds to the NPC tendency to spread to the regional lymph node by 80% [5]. In this study, the x^2 test result showed a significant difference between regional lymph node clinical status of NPC patients with distant metastasis compared with no distant metastasis (p = 0.001) (Table 1). After the regional lymph node clinical status of N0 and N1 were grouped into the initial regional lymph node status, whereas the regional lymph node clinical status of N2 and N3 were grouped into advanced regional lymph node status [6], the x^2 test result showed a significant difference in initial and advanced regional lymph node clinical status between NPC patients with distant metastasis compared with no distant metastasis (p = 0.004) (Table 4). The prevalence ratio (PR) of statistical analysis showed 3.866, means that NPC patients with advanced regional lymph node clinical status (N2 and N3) were 3.866 times more likely to have distant metastasis compared with NPC patients of initial regional lymph node clinical status (N0 and N1).

Table 4. Analysis of Regional Lymph Node Clinical Status and Distant Metastasis.

Regional Lymph Node Clinical Status	Distant Metastasis (+)		Distant Metastasis (−)		Total	%	*p* Value
	n	%	*n*	%			
Advanced	32	11.6%	149	54%	181	65.6%	0.004
Initial	5	1.8%	90	32.6%	95	34.4%	
Total	37	13.4%	239	86.6%	276	100%	

x^2 test, *p* value significancy < 0.05.

The result of this study was in accordance with the research of Cheng et al. (2001), which showed the multivariate analysis of regional lymph node clinical status (RR = 3.39; $p = 0.01$) was the independent predictive factor of distant metastasis [10]. Li et al. (2015) showed that there was a difference of distant metastasis within 5 years between N0-1 and N2-3 ($p < 0.001$), N2-3 was an independent predictive factor of distant metastasis (HR = 1.79; $p = 0.01$) [7]. The presence of bilateral lymph node, lymph nodes larger than 6 cm, and low jugular lymph node involvement are associated with distant metastasis [15].

The malignancy occurs due to uncontrolled cell proliferation, caused by gene mutation that alters the cellular metabolic system of the tumor. Increased proliferation of the tumor cells will stimulate an increase number of blood vessels needed to meet nutrients and oxygen [16]. Tumors can not expand more than 2 mm without vascularization [17]. Hypoxia will stimulate the production of proangiogenic cytokines, such as vascular endothelial growth factor (VEGF), through activation of hypoxia-induced factor-1α (HIF-1α) [17]. In addition to angiogenesis (VEGF-A,B,C,E), VEGF production also plays role in lymphangiogenesis (VEGF-C,D) [18]. Angiogenesis and lymphangiogenesis can be the route for tumor cells to escape from primary site into the blood circulation, then metastasize to distant organs [17].

The lymphatic capillaries are 10–60 μm in diameter which are larger than blood capillaries (5–20 μm), lymphatic vessels are relatively leaky compared to blood vessels, provide a better route for the cancer cell dissemination. The hematogenous spread begins with primary tumor vascularization, whereas lymphogenous spread through the lymph vessels begins via regional lymph nodes, then to the distant lymph nodes to the thoracic duct, subclavian vein, and into the blood circulation to the distant organ [19]. There is a close relationship between the lymph nodes spread and the occurrence of distant metastasis NPC, hematogenous dissemination occurs most often through drainage of the inferior jugular chain into the blood vessels [20]. Chen et al. (2013) suggest that the regional lymph node clinical stastus can reflect the behavior of cancer metastasis [11].

This study shows the need to increase awareness of distant metastasis in NPC patients with bilateral lymph node involvement, regional lymph node size more than 6 cm, and the extension to supraclavicula fossa.

The limition of this study was taken from medical record of NPC patients that was established the clinical stage at initial diagnosis which the primary tumor clinical status was defined based on the extension of local structure invasion (AJCC), but had not considered the tumor volume which can complement the role of primary tumor clinical status in relation to distant metastases in NPC.

4. Conclusions

There is no statistically significant difference of primary tumor clinical status between NPC with distant metastasis and without distant metastasis ($p = 0.297$). There is statistically significant difference of lymph node clinical status between NPC with distant metastasis and without distant metastasis ($p = 0.004$).

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