

Sensitivity and specificity of narrow-band imaging nasoendoscopy compared to histopathology results in patients with suspected nasopharyngeal carcinoma

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Abstract. Nasopharyngeal carcinoma (NPC) is a disease which is prevalent in developing countries like Indonesia. There were 164 new cases of nasopharyngeal carcinoma in the ear, nose, and throat (ENT) oncology outpatient clinic of the Cipto Mangunkusumo hospital in 2014, and 142 cases in 2015. Unfortunately, almost all of these cases presented at an advanced stage. The success of nasopharyngeal carcinoma treatment is largely determined by the stage when patients are diagnosed; it is critical to diagnose NPC as early as possible. Narrow-band imaging (NBI) is an endoscopic instrument with a light system that can improve the visualization of blood vessels of mucosal epithelial malignant tumors. NBI is expected to help clinicians to assess whether a lesion is malignant or not; to do so, it is important to know the value of sensitivity and specificity. This study is a cross-sectional form of a diagnostic test which was performed in the outpatient clinic of the ENT Head and Neck Surgery Department for the Cipto Mangunkusumo Hospital, from January to June 2016, and involved 56 subjects. Patients with a nasopharyngeal mass discovered by physical examination or imaging, and a suspected nasopharyngeal carcinoma were included as a subject. An NBI examination and biopsy was performed locally. Based on this research, NBI could be used as a screening tool for nasopharyngeal carcinoma with high sensitivity (100%), but with a low specificity result (6.7%).

1. Introduction

Nasopharyngeal carcinoma is a malignancy that occurs in nasopharyngeal mucosal epithelial cells. It can occur anywhere along the nasopharyngeal epithelium, but it more often begins in the Rosenmuller fossa because it is an epithelial transition area. According to data from Global Cancer Statistics in 2011, the total number of nasopharyngeal carcinoma incidents rank 22nd in developing countries, or a total of 0.7% of all malignancies in the world. There were, however, 84,400 new nasopharyngeal carcinoma case incidents resulting in 51,600 deaths in 2008. The number of new cases of nasopharyngeal carcinoma in the Oncology Division of Cipto Mangunkusumo hospital recorded 64 cases in 2013, 159 cases in 2014, and 71 new cases by mid-2015 [1,2]. Cases of stage I nasopharyngeal carcinoma showed remarkable results with radiation, including a 98% chance for a survival rate of 10 years and 94% recurrence-free, with a local control of 96%. In stage II, survival decreased to 60% [1-3].



Nasopharyngeal carcinoma patients have one or more of the four symptom groups associated with the location of the primary mass, infiltration of the mass into the surrounding structures, or due to mass metastases to the lymph nodes of the neck. Symptoms of the nose and ear complaints in nasopharyngeal carcinoma are less specific than that of enlarged lymph nodes without accompanying pain, which resulted in frequent treatment of patients in an advanced stage. Early diagnosis of nasopharyngeal carcinoma is important because although the five-year average survival rate of nasopharyngeal carcinoma sufferers is high, 90% of patients with metastatic nasopharyngeal carcinoma are predicted to die within one year of diagnosis. The exact diagnosis of nasopharyngeal carcinoma with histopathologic examination of suspected mass tissue, however, becomes difficult when the lesions resemble inflammatory forms or hidden mass locations that cannot be detected by conventional white light imaging, so it is difficult to determine whether malignancy is suspected [4,5].

New methods of using nasoendoscopy have been introduced by scientists in recent years. Narrow-band imaging (NBI), a proven diagnostic aid for screening in the field of gastroenterology, is being used in the field of malignancy of the head and the neck. Superficial mucosal lesions in the neck and head region (undetectable with conventional nasoendoscopy) can be identified by NBI because of its advantages in distinguishing neovascularization patterns of mucosal lesions. NBI utilizes short waves of blue light (415 nm) and green (540 nm) that can be absorbed by hemoglobin so that the mucosal and submucosal vascular patterns can be clearly visualized [5].

Research conducted by Fujii *et al.* [6] suggests a relationship between the thickness of the mass and the infiltration of blood vessels in malignant squamous cell carcinoma of the pharyngeal region due to the higher blood supply required for the proliferation of mass cells. Wang *et al.* [7] gained 97.1% NBI sensitivity and 93.3% specificity using certain vascular patterns to detect nasopharyngeal carcinoma. NBI is useful as a tool for early diagnosis of suspected malignant lesions because it can improve accuracy in diagnosing, thus preventing a false diagnosis [6-11]. Unlike conventional nasoendoscopy devices, NBI enhances visualization of epithelial vascular patterns and subepithelial lesions at the time of examination, suggesting that NBI may provide more value in routine use than the use of traditional methods. This study attempted to determine the sensitivity and specificity of NBI in assessing changes in nasopharyngeal mucosal patterns in patients with suspicion of nasopharyngeal carcinoma.

2. Materials and Methods

This research is a diagnostic study with cross-sectional design aimed at determining the accuracy value of the NBI diagnostic tool. The study was conducted for six months in the Integrated Outpatient Unit of THT-KL FKUI / RSCM Oncology Division after obtaining FKUI's ethics commission license. The subjects who entered the study were all patients with complaints resulting from a nasopharyngeal mass. The mass of each subject was found in the nasopharynx through a white light nasoendoscopy examination or computed tomography (CT). There was no nasopharyngeal biopsy at the outer hospital and no nasopharyngeal biopsy with local anesthesia. All subjects, after signing the research approval form, will have the NBI nasoendoscopy examination and subsequent nasopharyngeal biopsy with NBI guidance.

3. Results and Discussion

3.1 Results

The non-nasopharyngeal carcinoma group contained 11 subjects with Type 1 patterns, including three malignant lymphomas, one with atypical cells, and one hemangioma, with the remaining subjects having chronic nasopharyngitis. Type 2 patterns were demonstrated in this group by 12 subjects: three subjects with lymphoma, one each with hemangioma, polyp, or atypical cell, and six cases of chronic nasopharyngitis. The Type 3 pattern was found in 13 subjects, with the distribution of three lymphoma subjects, subjects with polyps and atypical cells, and the rest with chronic nasopharyngitis.

Table 1. Distribution of subject characteristics by sex, age group, family history of malignancy, history of smoking habits and consumption of salted fish (n=56)

Subject Characteristic	Amounts	Percentage
Gender		
Male	38	67.9%
Female	18	32.1%
Age group		
≤17 year	3	5.4%
18-40 year	19	33.9%
41-60 year	30	53.6%
> 60 year	4	7.1%
Nasopharyngeal carcinoma history or family malignancy		
Present	8	14.3%
Absent	48	85.7%
Smoking history		
Present	30	53.6%
Absent	26	46.7%
History of salted fish consumption		
Present	22	39.3%
Absent	34	60.7%

Table 2. Propagation of nasopharyngeal mucosa patterns in patients with suspicion of nasopharyngeal carcinoma based on narrow-band imaging (NBI).

Pattern of nasopharyngeal mucosal smear based on NBI	Nasopharyngeal carcinoma (n=41)	Non- nasopharyngeal carcinoma (n=15)
Type 1		
Clear brown spots are concentrated in one area of the nasopharyngeal mucosa	41	11
Type 2		
Loss of polygonal follicular pattern with regular arrangement	41	12
Type 3		
Large mucous capillary blood vessels with irregular arrangement	41	13

Table 3. Changes in nasopharyngeal mucosal patterns based on narrow-band imaging (NBI) were compared with histopathologic results.

Shift changes	Histopathology		Total	p*
Narrow-Band Imaging	Positive	Negative		
+	41	14	55	0.000
-	0	1	1	
Total	41	15	56	

*McNemar test

Sensitivity NBI	= 41/41	= 100%
Specificity NBI	= 1/15	= 6.7%
Positive Accident Value	= 41/55	= 74.5%
Negative Accident Value	= 1/1	= 100%
Positive Possible Ratio	= 41/41:14/15	= 1.93
Negative Possible Ratio	= 0/41:1/15	= 0.03

3.2 Discussion

The male subjects in this study contributed to 67.9% of the total subject group, with a male/female ratio of 2.1:1, respectively. Zhang *et al.* [12] found that the comparison of incidence of nasopharyngeal carcinoma in Guangdong province between men and women was 2.3:1. The same was also described by Bray *et al.* [13], who states that the proportion of nasopharyngeal carcinoma incidences in both men and women varied considerably, but the incidence of nasopharyngeal carcinoma is higher in men. The male is larger than the female and is thus often found with a ratio greater than 2:1 [12,13]. The most prevalent (53.6%) age group among these subjects is the age group of 41-60 years of age, with the mean age being 43.5 years old. The youngest age in the subject group is 10 years old, and the oldest age is 74 years old. Others studying nasopharyngeal carcinoma have found similar results regarding age. Ng *et al.* [14], in her study, found that the age group suffering the most from nasopharyngeal carcinoma was those aged 30-60 years. Chang *et al.* [15] found increased incidences of nasopharyngeal carcinoma at ages 50-59 in areas with high risk population (thought to be due to exposure to carcinogenic substances during young age). Previous studies stated that the incidence of nasopharyngeal carcinoma in Indonesia resembles a direct uphill pattern that starts in children ages 4 to 5 years old [14-16].

In this study, a family history of nasopharyngeal carcinoma or other malignancies in occurred in 14.3% of the subjects. The risk of developing nasopharyngeal carcinoma increased by four- to eight-fold in the first generation of offspring from the parent with nasopharyngeal carcinoma, as quoted from Ng *et al.* [14]. Vice versa, it was stated that no less than 10% of nasopharyngeal carcinoma patients had a family history of malignancy: nasopharyngeal carcinoma, or other malignancies such as malignant breast. In the Multidisciplinary Management of Nasopharyngeal Carcinoma, Loh [17] states that although cohort studies have rated the average family history of malignancy to vary between 2-15%, the figure is not sufficient enough to strongly suggest the role of genetic factors in nasopharyngeal carcinoma incidents. This correlation could also be the result of group exposure to environmental factors such as the same type of food in a family [14,17,18].

Just over fifty-three percent (53.6%) of subjects are known to have a smoking habit, with an average duration of 30 years of smoking. The shortest length of smoking habit is at least two years, with 50 years being the highest. This subject group averaged 12 cigarettes per day, with a minimum of two cigarettes per day up to 50 cigarettes per day at most. Observing the effect of tobacco on the incidence of nasopharyngeal carcinoma, Fachiroh *et al.* [19], noted that smoking for at least one year doubles the subject's chance of NPC compared to those who never smoked. Also in comparison to those who had never smoked, subjects who smoked for at least two years saw a 60% chance increase for NPC, and those who had smoked for at least 10 years had two times the risk for NPC. In 1999, Cheng *et al.* [20] found that the risk of nasopharyngeal carcinoma was particularly determined by a smoking duration of at least 25 years, but was not influenced by the number of cigarettes smoker per day. This is likely due to the location of the nasopharynx and its direct exposure by cigarette smoke; continuous and lengthy exposure to cigarettes is more determinate of the incidence of nasopharyngeal carcinoma [19,20].

Jia *et al.* [21] concluded that the consumption of fish that has been preserved through marinating has a strong relationship with the incidence of nasopharyngeal carcinoma. Jia *et al.* [21] mentions that, when compared with individuals who rarely consume this fish, the risk increases 1.8-7.5 times if consumed regularly every day, whereas in individuals who consume each week the risk is reduced to 1.4-3.2 times. This is due to the presence of carcinogenic nitrosamines in salted fish which can cause genetic mutations and oncogenic activation [21]. Out of 56 subjects suspected of nasopharyngeal carcinoma, 41 were found with histopathologic results of nasopharyngeal carcinoma and had all the patterns of mucosal shell based on NBI (i.e., pattern Type 1, Type 2, and Type 3). In another study, Madana *et al.* [22] found brown spot patterns concentrated in one mucosal area of 93% of the NPC group; it was not found in the normal nasopharyngeal group. This pattern is characteristic of suspicion of nasopharyngeal carcinoma. Madana *et al.* [22], stated that brown spots collected in one area are indicative of a tumor angiogenesis process that describes a newly formed microvascular dilatation.

Kumagai *et al.* quoted from Thong J F *et al.* [23] in his research, which states that the brownish spots present in the lesions illustrate the occurrence of a microvascular proliferation process, which is a marker characteristic of the occurrence of neoplasm and pre-neoplasm processes. Similarly, Madana [22] says that brownish spots concentrated in a mucosal area indicate an increased process of angiogenesis in tumors that can only be detected with NBI [22,23].

Type 2 traits, loss of regularly arranged polygonal follicular patterns were obtained in 100% of the nasopharyngeal carcinoma group and in 95% of post-radiotherapy nasopharyngeal carcinoma groups in Madana *et al.* Type 2 does not become a marker of the occurrence of malignant processes in individuals with a history of radiation. Vlantis *et al.* [1] observed that the nasopharynx mucosa had a regularly arranged polygonal follicular pattern and a pale color in the center of the follicle larger than the periphery. The polygonal follicular pattern of nasopharyngeal mucosa is formed by the grouping of lymphoid follicles, measuring +1 millimeters in lamina propria, separated by fibroelastic tissue and capillary plexus which nourish each mucosal layer [24]. The loss of this polygonal form or the changing ratio of the dark part becoming wider than the middle pale color is one of the signs of mucosal changes becoming malignant. JF Thong *et al.* [23] observed that 88% of nasopharyngeal carcinoma subjects in his study did not have polygonal follicular patterns, while the rest were found to have irregular follicular patterns [22-24].

Type 3 shapes are formed due to microvascular branches that are irregularly arranged in the mucosa. Capillary blood vessel deformities include dilation, grooving, and incremental diameter and shape uniformity with the development of malignancy in the mucosa. Fujii *et al.* [6] compares the picture of microvascular histology with NBI patterns and found the irregularity of blood vessels in the mucosa of the pharyngeal region detectable by the NBI from dysplasia. Pharynx mucosal epithelium begins. The further along the malignancy process is, the more extensive the microvascular will be regarding the diameter of the blood vessels and branching of blood vessels that also multiply [6,25,26]. This study conducted a diagnostic test between NBI nasoendoscopy and histopathology, with histopathology being considered the gold standard. The McNemar test found a significant difference ($p < 0.001$) between NBI and histopathologic results: high sensitivity values (100%) with low specificity (6.7%), and a positive predictive value of 74.5% with a negative predictive value of 100%. The NBI's sensitivity rating allows NBI to be used as an individual screening for suspicion of nasopharyngeal carcinoma. In his study, Yoshimura *et al.* quoted from Guang [25] that his study found 100% NBI sensitivity value with $p < 0.001$, the specificity value in Yoshimura's study (78.6%) being higher than this research.

The difference in outcomes is likely due to the different selection of study subjects. Suspicion of nasopharyngeal carcinoma in Yoshimura's research is based on clinical symptoms and serological examination of Epstein-Barr virus (EBV), whereas in our study nasopharyngeal masses in subjects were found through ordinary nasoendoscopy or from CT/MRI. The majority of the current research subjects came with large tumor sizes that adequately affected the subjectivity when assessing NBI patterns. Malignant tumors in general have a neo-angiogenetic ability to grow well. This form of neovascularization can actually be evaluated by the NBI. This type of malignancy in the nasopharynx is not only the primary malignancy of the nasopharyngeal epithelium but may also be derived from the adnexa present in the nasopharynx, e.g., a malignant lymph node in the nasopharynx which formally resembles a nasopharyngeal carcinoma. A notable weakness of this study which also plays a role in reducing the specificity of the research value is that there are four subjects with NBI pattern changes due to lymphoma biopsy and malignant atypical cells rather than nasopharyngeal carcinoma, which are included in the subject group. Thong *et al.* [23], explicitly clarifies both nasopharyngeal carcinoma and non-neoplasm groups so as to exclude subjects when malignancies other than nasopharyngeal carcinoma are found. It is intended to recall the NBI function of differentiating nasopharyngeal carcinoma (epithelial neoplasm) from non-neoplastic masses [23,25].

Non-nasopharyngeal carcinoma groups have nine subjects with chronic nasopharyngitis results where there is a possibility of tissue sampling errors. These are less representative and are unlikely to describe the actual state of mucosal pathology. Watanabe *et al.* [27] obtained a 99.8% NBI specificity

value by performing a general anesthetic biopsy to mucosal resection after Lugol's iodine staining on a suspected malignant pharyngeal mucosa based on NBI. Biopsy with local anesthesia in this study also did not allow researchers to take tissue from multiple sites because it would cause severe pain in the subject. The possibility of insufficient representative tissue for histopathologic assessment resulted in low specificity values [27].

The false-positive values in this study are caused mainly by chronic inflammation. Nonaka and Saito, citing from Yang [28], suggest microvascular inflammation is also modified slightly in the absence of irregularity. The difficulty of obtaining the number of subjects with suspicion of nasopharyngeal carcinoma who entered the inclusion criteria and did not meet the exclusion criteria was a major obstacle. The number of nasopharyngeal carcinoma suspect patients has declined significantly since January 2016 with an average of nine new patients with nasopharyngeal carcinoma per month compared to 2014 and 2015, which averaged 18 people per month. This resulted in a subject group that contained only 56 people for a period of six months. The second obstacle is that the NBI nasoendoscopy device cannot be taken out of URJT, and thus subjects cannot be studied at network hospitals. Both obstacles resulted in the researcher only finding subjects at the Cipto Mangunkusumo hospital or by contacting the ENT doctor who volunteered to send subjects to Cipto Mangunkusumo hospital. The third obstacle is the difficulty of getting a subject with very early lesions, so that the evaluated profile is not specific for nasopharyngeal carcinoma but for all types of malignancy involving the nasopharyngeal mucosa.

4. Conclusion

Nasoendoscopy NBI can be used as a nasopharyngeal carcinoma screening tool because of its high sensitivity (100%), although its specificity is low (6.7%). NBI achieved a 74.5% positive predictive value and a negative predictive value of 100%. NBI indicates excellent NBI probability to exclude nasopharyngeal carcinoma possibilities based on the evaluation of changes in nasopharyngeal mucosal features.

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