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Clinicopathological Profile of Laryngeal Carcinoma at Dr Soetomo General Academic Hospital, Surabaya 2018-2021

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ABSTRACT

Introduction
Laryngeal carcinoma is the second most common malignancy of the respiratory tract. Based on 2020 Global Cancer Observatory data, the incidence rate of laryngeal carcinoma is 184,615 cases with a mortality rate >50%. There are some prognostic factors that predict the prognosis and 5 years survival rate of the patients. Study of this factor is very important because it will affect the patient's management. The clinicopathological profile is very important in laryngeal carcinoma because the majority of specimen are received in the small biopsies.

Methods
This research is observational descriptive study with a retrospective approach. Population of this study are paraffin blocks obtained from biopsy and surgical that had been diagnosed histopathologically as laryngeal carcinoma in the Dr. Soetomo General Academic Hospital from January 2018-December 2021. Demographic, radiologic and histopathology data were taken from the patient's medical records.

Results
The majority patients were males (93%). The average age of patients was 59 years old (±5.91), with age range is 27-84 years old, peak incidence were in 61-70 years old (34.1%). The tumor located mostly in glottic (60.2%). Based on the T and N staging, most patient came at T4 and N2 stage. All the tumor were conventional squamous cell carcinoma.

Conclusion
Clinicopathology profile is very important in determine the prognostic factor in laryngeal carcinoma. Most of patient were males, in age group 61-70 years old, located in glottis. Most patient came at advanced stadium. Most tumor were conventional squamous cell carcinoma, and the majority was well differentiated grade.

Keywords: laryngeal carcinoma, clinicopathology, prognostic, stage, squamous cell carcinoma

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INTRODUCTION

Laryngeal carcinoma is the second most common malignancy of the respiratory tract (after lung carcinoma).[1] Based on 2020 Global Cancer Observatory data, the incidence rate of laryngeal carcinoma is 184,615 cases with a mortality rate of 99,840 cases (> 50%). This carcinoma is more common in males than females with a ratio of 7:1[1,2] and the peak incidence occurs in the fifth decade[3] to the seventh decade.[1] Smoking is the main risk factor for laryngeal carcinoma, and around 70-95% of laryngeal carcinomas are related to smoking[4]. Consumption of alcohol and using marijuana at young age in large quantities also increases the risk of developing this carcinoma. The role of the Human Papillomavirus (HPV) is unclear in laryngeal carcinoma.[1,4] The presence of HPV involvement is only found in 25% of cases of laryngeal carcinoma and the most commonly found is HPV-16. Other factors that are also thought to have a role in laryngeal carcinoma are age, gastroesophageal reflux, diet, nutritional status.[3]

Clinical staging and location are important and related prognostic factors that must be evaluated simultaneously. The 5 years survival rate depends on the location of the tumor and how far its invasion into the surrounding tissue.[1,3] Laryngeal carcinoma location is divided into glottis, supraglottis, subglottis, and transglottis if it involves supraglotis and glottis, with or without subglottis. Location is greatly influences the clinical features and tumor invasion pattern.[5]

The histopathological feature of laryngeal carcinoma is mainly conventional squamous cell carcinoma (90%).[1,3] The main characteristics of this type of carcinoma are squamous differentiation and invasion. Squamous differentiation is characterized by the presence of keratinization (which can be keratin pearls) and/or intercellular bridging. Tumor invasion is characterized by the presence of non-intact basement membranes and the growth of tumor into underlying stromal tissue. The presence of invasion usually be accompanied by a desmoplastic stromal reaction.[1]

The clinicopathological profile is very important in laryngeal carcinoma because the majority of specimen are received in the form of small biopsies. The aims of this study is to identify the clinicopathological profile of laryngeal carcinoma at Dr. Soetomo General Academic Hospital from January 2018-December 2021.

METHODS

This research is an observational descriptive study with a retrospective approach. The population of this study were all paraffin blocks from biopsy and surgical materials that had been diagnosed by histopathology as laryngeal carcinoma in the Anatomical Pathology Unit of the Central Laboratory Installation of Dr. Soetomo General Academic Hospital from January 2018-December 2021. Demographic data including age, sex, when diagnosis is made. Radiological data is assessed from CT scan head and neck, including tumor (T) and nodes (N) staging, and location of the tumor. Histopathology data are tumor type and grading of the tumor. All the data were taken from the patient's medical records The TNM stage was assessed radiologically based on the WHO Classification of Tumors of the Head and Neck 2017 criteria and the 7th American Joint Committee on Cancer (AJCC) 2020. This system includes information consists of: category T (tumor), N (nodes) and M (metastases).[1]

This retrospective study is part of a study entitled "Correlation between N-Cadherin and MMP-9 Expression to Various Radiological N Stages in Laryngeal Squamous Cell Carcinoma". This research has obtained ethical approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital with number 1196/LOE/301.4.2/2023.

RESULTS

The total number of cases obtained in this study were 202 cases of laryngeal carcinoma diagnosed histopathologically from 1 January 2018-31 December 2021. Out of a total of 202 patients, only 152 patients had radiological examinations by CT scans of the head/neck and of these only 146 which has TNM staging information. Clinical and radiological data of patients are shown in Table 1.

Clinical and radiological characteristics

The number of laryngeal carcinoma patients in this study who were male was 188 people (93%) and 14 female (7%) with an incidence ratio of male and female was 13.4:1. The age range of the research subjects was 27-84 years old, with mean age 59.12 years old (±5.9). Peak incidence is in the group 61-70 years old (34.1%) followed by 51-60 years old (31.2%).

Determination of the location and staging of TNM was assessed from head/neck CT scans, and only 152 patients had

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radiological examinaton. Most laryngeal carcinomas are located in the glottis (48%), followed by the transglottis (34%), supraglottis (9%), subglottis (8%) and hypopharynx (2%). Radiological data on TNM staging were only found in 146 patients. Stage T was determined based on location and invasion of surrounding tissue, where the majority were stages T4 (58.9%) and T3 (23.3%) at the time of diagnosis. Stage N is determined based on the size of the regional lymph nodes. The majority patients were in stage N2 (67.1%), which are size >3 but ≤6 cm.

Table 1. Patient demographics and radiological characteristics in patient with laryngeal carcinoma.

Variable	N
Sex (n=202)	
Male	188 (93%)
Female	14 (7%)
Age (n=202)	
≤20 years old	0
21-30 years old	3 (1.5%)
31-40 years old	9 (4.5%)
41-50 years old	29 (14.3%)
51-60 years old	63 (31.2%)
61-70 years old	69 (34.1%)
71-80 years old	27 (13.3%)
>80 years old	2 (0.9%)
Mean	59 years old (±5.9)
Median	60 years old (27-84)
Location (n=152)	
Glottis	75 (49%)
Supraglottis	14 (9%)
Subglottis	12 (8%)
Transglottis	51 (34%)
Stadium T (n=146)	
T1	11 (7.5%)
T2	10 (6.8%)
T3	34 (23.3%)
T4	86 (58.9%)
Stadium N (n=146)	
N0	8 (5.5%)
N1	34 (23.3%)
N2	98 (67.1%)
N3	1 (0.6%)

Histopathological characteristics

The diagnosis of laryngeal carcinoma was made histopathologically from both biopsy and laryngectomy materials and is presented in Table 2. Based on the histopathological type, all laryngeal carcinomas in this study were conventional squamous cell carcinomas (100%). Conventional squamous cell carcinoma (n=202) was divided based on its differentiation, namely well differentiated (48.4%), moderate (42.8%), and poorly differentiated (8.8%) tumors. The remaining cannot be graded because the specimen were too small. An overview of laryngeal squamous cell carcinoma differentiation is shown in Figure 1.

Tabel 2. Histopathology feature of laryngeal carcinoma.

Histopathological feature	n
Type of tumor (n=202)	
Conventional Squamous cell carcinoma	202(100%)
Differentiation degree (n=186)	
Well differentiated	89 (44,1%)
Moderately differentiated	78 (38,6%)

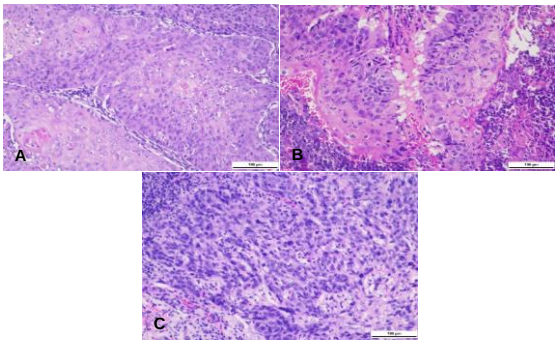

Figure 1. Grading in laryngeal squamous cell carcinoma (HE, 200 times). A. Well differentiated. B. moderately differentiated. C. poorly differentiated.

DISCUSSION

In laryngeal carcinoma, there are some prognostic factors that predict the prognosis and 5 years survival rate of the patients. Calculation of this prognostic factor is very important because it will affect the patient's management. These prognostic factors are divided based on clinical, histopathological and molecular. The clinicopathological profile is very important in laryngeal carcinoma because the majority of specimen are received in the form of small biopsies. Clinical staging and location are very important prognostic factors that must be evaluated simultaneously

Gender

The data obtained in this study showed that the gender distribution of laryngeal squamous cell carcinoma patients was dominated by males (93%), with a male to female ratio of 13.4:1. This figure is almost the same as a study conducted by Ciolofan et al (2017) where the percentage of male subjects was 97%.[6] Data from WHO also shows that in general, the incidence of laryngeal carcinoma is 1.6-2% of all malignancies in men and 0.2-0.4% in women.[1,3] A study in Indonesia obtained almost the same results, where men have a 6-fold risk of developing laryngeal carcinoma compared to women. According to this study, this difference in risk is most likely the result of lifestyle (smoking) and lack of awareness of this

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disease[7]. Active smokers have a 15-fold risk of developing laryngeal carcinoma, while patients with a history of smoking have a 5-fold risk.[8] According to Wang et al (2020), hormonal factors and sex chromosomes also played a role in influencing the immunity and survival rate of the two groups. The X sex chromosome contains many genes related to immunity. In addition, some X-linked microRNAs can stimulate the production of sex-specific modulation of immune responses by targeting immune-related genes[8]. Hormonal factors are also known to be associated with susceptibility to cancer. Research conducted by Nainani et al (2014) showed that estrogen has a protective effect on head and neck malignancies, so that men are more likely to suffer from this malignancy. Damage to liver function due to alcohol causes metabolic disorders of sex-related hormones (estrogen and testosterone).[9]

Age

This study showed that the peak incidence of laryngeal carcinoma patients were in the age group of 61-70 years old (34.1%), followed by the age group of 51-60 years old (31.2%), with mean age of 59 years old. The age range of the research subjects was 27-84 years old. These results are in accordance with WHO data which states that laryngeal carcinoma is most common in the sixth and seventh decades.[1] According to the American Cancer Society (2023), the majority of patients are diagnosed at age >55 years old, with an average age of 66 years old.[10] Laryngeal carcinoma that occurs in young patients and non-smokers is often associated with the HPV virus (8-54%).[3]

Research conducted in Indonesia also shows that the majority of subjects are aged 50-79 years old (82.5%). This high incidence rate in elderly patients can be caused by an accumulation of mutations in the body, so that the DNA repair process becomes less efficient, or a decrease in the function of the immune system so that the body's protection against cancer cells is reduced. Another theory that is being developed is the possibility that the process of malignancy is caused by a cellular senescence process that accumulates in old age.[7]

Location

Based on its location, laryngeal carcinoma is divided into four, namely carcinomas located in the supraglottis, glottis and subglottis, and transglottis when it involves the glottis and supraglottis, with or without subglottis involvement.[11] Supraglottic carcinoma is a carcinoma of the larynx that involves the epiglottis area, false cord, laryngeal ventricle or arytenoid region. Supraglottic carcinoma often invades the low pre-epiglottic space and, through the anterior commissure, extends into the glottis and subglottis to form a transglottic tumor. Carcinoma located in the supraglottis often causes metastases in the neck regional lymph nodes level 2 or 3.[3] Glottic carcinoma usually arises from the anterior part of the vocal cord and causes vocal cord obstruction. Tumors located in the glottis tend to stay for a long time due to the presence of a cartilaginous wall and the small number of lymphatic vessels in the area.[3] Small tumors (T1) rarely metastases to the ipsilateral lymph nodes.[3] Glottis carcinoma can metastases if it has extended to the transglottis, both towards the supraglottis and subglottis. Subglottic carcinoma is usually asymptomatic, that patients come in an advanced state and worsen the prognosis.[11] Involvement of the subglottic area in laryngeal carcinoma is more likely to result from supraglottic and inferior glottic spread of tumors compared to primary tumors originating from the subglottis. Primary tumors of the subglottis are very rare and tend to invade the trachea, thyroid, or esophagus. Subglottic carcinoma is more likely to cause regional lymph node metastases than glottic carcinoma. This is due to the presence of lymphatic drainage towards the lower jugular and upper mediastinal lymph nodes.[3]

There are slight differences in location depending on the geographic distribution of patients. The most common location for laryngeal carcinoma in several countries such as France, Spain, Italy, Finland and the Netherlands is the supraglottis, while in America, England, Canada and Sweden, tumors are more often located in the glottis.[1]

Most of the laryngeal carcinomas in this study were located in the glottis (48%), followed by the transglottis (34%), supraglottis (14%) and subglottis (12%). This is concordance with McHugh (2018) where most laryngeal carcinomas are found in the glottis (60-65%), especially from the true vocal cords, in the anterior 1/3 of the glottis. Carcinoma located in the glottis often causes vocal cord disorders so that patients tend to seek treatment.[3] The large number of transglottic carcinomas in this study is probably due to the fact that the location of the data collection was a tertiary referral hospital, so patients have arrived at an advanced stage, so the tumor has spread

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transglottis and the location of origin of the primary tumor is difficult to determine.

T and N staging

T staging in this study was divided into 4 groups, namely T1, T2, T3, and T4. The largest group in this study was T4 (58.9%) followed by T3 (23.3%). This situation is different from other studies conducted in Cairo 12 and in India 13, where the most T group was T3, namely 66.1%, followed by T2 (12.8%).[12,13]

The distribution of nodal metastatic status in the subjects of this study was divided into 4, namely N0, N1, N2, N3. The largest group in this study was group N2, namely patients with metastases in one/multiple ipsilateral/contralateral lymph nodes with the largest dimensions >3 but ≤6 cm, totaling 98 samples (67.1%), while the least was group N3 which only has 1 sample (0.6%). This situation is slightly different from the study conducted by Xu et al (2020), where pathologically the majority of patients had nodal metastatic status N0 of 40.3%, followed by N2 of 38.8%, N1 of 20.4%, and the least was N3 is 0.5%.[14]

This difference could be due to Dr. Soetomo General Academic Hospital, where the sample was taken, is a tertiary referral hospital, so the majority of patients who come are patients with advanced disease. Patients usually come when they have palpable nodules. As stated before, the most common location for laryngeal carcinoma in this study is the glottis. Carcinoma located in the glottis rarely metastasizes, unless it has spread to the supra/subglottis. Subglottic carcinoma rarely produces symptoms unless it is in an advanced stage.[1,3] Few subjects were included in the T4 and N3 groups because patients generally came when a lump was felt and the higher the stage, the worse the prognosis.

Histopathological characteristics

All cases of laryngeal carcinoma in this study were conventional types of squamous cell carcinoma. These results are the same as research conducted by Shariff (2018).[13] Although very rare, there are several variants of squamous cell carcinoma that can be found, namely verrucous squamous cell carcinoma, basaloid squamous cell carcinoma, papillary squamous cell carcinoma, spindle cell squamous cell carcinoma, adenosquamous carcinoma, and lymphoepithelial carcinoma.[1,3]

The main features of this type of carcinoma are the presence of squamous differentiation and invasion. Squamous differentiation is characterized by the presence of keratinization (which can be keratin pearls) and/or intercellular bridging. Tumor invasion is characterized by the presence of a non-intact basement membrane and the presence of tumor growth that enters between the underlying stromal tissue[1]. Squamous cell carcinoma is divided into three grades. This division is based on differentiation, tumor cell pleomorphism and mitotic activity. Tumors with lower differentiation have greater risk for perineural invasion, recurrence and metastasis, poorer prognosis. In this study, the majority of tumors were well differentiated (44.1%), followed by moderately differentiated (38.6%). Not all the tumors could graded because the size of tumors were very small. The results are consistent with study in Padang, Indonesia.[15]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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