

RISK FACTORS FOR REGIONAL LYMPH NODE METASTASIS IN PAPILARY THYROID CARCINOMA**Viator Nadeak¹, Raden Yohana², Kiki Rizki³**¹Departement of Surgery, Raja Ahmad Tabib Hospital, Tanjungpinang, Indonesia²Departement of Surgery, Oncology Division, Hasan Sadikin Hospital, Bandung, Indonesia³Departement of Surgery, Oncology Division, Hasan Sadikin Hospital, Bandung, Indonesia**Corresponding Author:** vnadeak@gmail.com**ABSTRACT**

Thyroid cancer is a common malignancy of the endocrine system. One of the current challenges is to control the loco-regional recurrence. Until today, clinical characteristics and histopathological result as predictive factors that can be used to identify patients for prophylactic radical neck dissection are still unclear. Therefore this study aimed to assess the relationship between clinical characteristics and histopathological result to regional neck lymph node metastases. This was a cross-sectional study, to explain the relationship between clinical characteristic and histopathological result in the incidence of regional neck lymph node metastases. During the study period January 2017 to January 2018, there were 74 patients included in the analysis. The mean age of the patient was $45.31 \pm 13,433$ years. There were 47 (63.3%) patients with the age categories of <20 and > 40 years old and 27 (36.5%) with age category 20-40 years old. Male patients was accounted for 15 (20.3%) and women 59 (79.7%). The size categories of the tumor were ≤ 5 cm 67 (90.5%) and > 5 cm 7 (9.5%). There were 57 (77.0%) patients with papillary thyroid carcinoma (PTC) and 17 (23.0%) with follicular thyroid carcinoma (FTC). There were 30 (40.5%) positive and 44 (59.5%) negative for Lymphovascular Invasion, For Capsular invasion there were positive 27 (36.5%) and negative 47 (63.5%). There were 45 (60.8%) and 29 (39.2%) patients with positive and negative regional neck lymph node metastases. The factors that influence the occurrence of lymph metastasis were sex, lymphovascular invasion, capsular invasion and histopathology of papillary thyroid carcinoma.

Keywords : Local Recurrence, Lymph Node Metastases, Papillary Thyroid, Risk Factors Carcinoma, Thyroid Carcinoma.

INTRODUCTION

Thyroid cancer is a malignancy that commonly occurs in the endocrine system. The data from United States revealed that the incidence increased by more than 300% within 30 years.¹ The mortality rate of all deaths due to thyroid cancer is less than 0.5%. Dharmais Cancer Hospital Jakarta, found an increased incidence of thyroid malignancy, 87 patients in 2010 to 147 patients in 2013.² In Dr. Hasan Sadikin Hospital, there were 913 patients treated

with thyroid malignancy and the mortality rate were 45 (4.9%) patients death over the last 5 years.¹ Papillary thyroid cancer (PTC) is one of the well-differentiated thyroid malignancies, the other malignancy is follicular thyroid cancer (FTC). One characteristic of PTC in general is having a slow growth properties with a low mortality rate that has a good prognosis, but one of the current challenges is to control locoregional recurrence.^{1,3} In addition to having a slow growth characteristics PTC

rarely metastasize, but in the course of the disease, it was found that 70% is metastasized to regional lymph nodes (RLN) while the FTC is only metastasized in 20-30% cases to RLN.^{2,4} Patients with RLN metastasis with the diagnosis of thyroid cancer has the incidence of loco-regional recurrence as much as 10 times more than patient without RLN metastasis. The surgical treatment of PTC is total thyroidectomy. Ernest, et al. (2015) conducted a study on 1,355 patients over 30 years, they found the recurrence rate was about 30%, with a mortality rate of 8% in patients with thyroid cancer. Therefore consideration for prophylactic radical neck dissection is still controversial.^{1,3}

The controversy of the need for prophylactic radical neck dissection can not be separated from the high morbidity as a result of nerve damage and physiological functions of the neck, the length of operating time and increase the risk for spreading the tumor cell, but all that reason can be reduced if they are operated by experience surgeons and the patients hardly need to have another surgery because the recurrence will be very low. Generally, surgeons still using age, metastasis, extension, size (AMES) score as a consideration for the selection of operative procedure in patients with PTC.^{1,3} High risk patients are male, age above 40 or below 20 years old, presence of metastases, tumor size is more than 5 cm. The selection of therapy in patients with high risk is more radical than patients with low risk. However, the research Nobuyuki. et al. (2014) found that loco-regional recurrence did not differ between groups with prophylactic and therapeutic lymphadenectomy and tumor size did not affect the rate of recurrence. They only suggest the therapeutic lymphadenectomy for patients with lymphadenopathy.^{1,3} As Amirsina, et al. (2016) found that patients with prophylactic radical neck dissection has a better prognosis results, thus reducing the occurrence of subsequent operations due to the loco-regional recurrence.³ Seo

Kim Kim, et al. (2015) also found in male patients, the tumor size of more than 1 cm, multifocality, extra capsular invasion are the factors that influence the prevalence of RLN metastasis in thyroid cancer.⁵

Until today, the clinical characteristics and histopathological examination result as predictive factors used for prophylactic RND are still unclear. Therefore, this study aimed to assess the relationship of clinical characteristics and histopathological examination result to RLN metastasis.

METHODS

The subject of research were patients treated at the Department of Head and Neck Surgical Oncology Dr. Hasan Sadikin Hospital from January 2017 to January 2018. This is a retrospective analytic study with cross-sectional design. The protocol were approved by the Ethics Committee of Dr. Hasan Sadikin Hospital. Patients with papillary and follicular thyroid carcinoma specimen that have been examined by the Anatomical Pathologist at Dr. Hasan Sadikin Hospital were included in this study. The exclusion criteria were other pathological types of thyroid cancer. Based on the inclusion and exclusion criteria, there were 74 patients to be reviewed, including age, tumor size, histopathological type of tumor, capsular and lymphovascular invasion.

There were 2 divided groups, 45 patients with positive RLN metastasis and 29 patients with negative RLN metastasis. There were dependent variables as age, tumor size, histopathology, capsular invasion and lymphovascular invasion, that we are going to compare with independent variable positive and negative RLN metastasis. We retrospectively collected the clinical and histopathological characteristics from these 2 groups. All of data were collected and statistically analysis with SPSS version 22.0 for categorical data were tested using the chi-square test and Fisher's Exact test. We were perform the univariate analysis of correlation between

clinical and histopathological characteristics with RLN metastasis. Variables with $P < 0.25$ on the univariate analyses were included in the multivariate analyses with logistic regression. The 95% confidence intervals (Cis) were calculated to show significant differences, significant when $P < 0.05$.

The variables that pass selection with p value $< 0,25$, entered the regression model. Variables that pass the selection are sex, histopathology of the tumor, lymphovascular invasion and capsular invasion. A multivariate analysis was performed for these four significant factors that were identified. We used the values of *Nagelkerke R Square* to see the ability of independent variables to explain the dependent variable. *Nagelkerke R Square* values are 0.523, which indicates that the ability of the independent variables to explain the dependent variable is 0.523 or 52.3% and there are $100\% - 52.3\% = 47.7\%$ other factors outside a model that explains the dependent variable. It showed the value of $\exp(B)$ or odds ratio from lymphovascular invasion is very large with p value 0.999 and the capsular invasions odds ratio value is the opposite as 0,000 with p value 0.999. Partial test results is invalid because there is a multicollinear problem caused by strong correlation between two independent variables. In this case it is between lymphovascular invasion

and capsular invasion with correlation coefficient is -1, it means both are perfectly correlated. Then the next step is to issue one of the two variables then we are going re-analysis.

RESULTS

Table 1, represents the patients characteristics. The mean age of the patients was 45.31 years old and the median age was 46 years old. There were 47 (63.5%) patients classified in the group of <20 years and > 40 years old and 27 (36.5%) in the group between 20 until 40 years old. Male was accounted in 15 (20.3%) and female in 59 (79.7%) patients. We identified tumors on the right thyroid in 31 (41.9%), left thyroid in 33 (44.6%) and bilateral thyroid in 10 (13.5%) cases. The mean tumor size was 2.85 (2.07) cm. As many as 67 (90.5%) patients were classified in less than 5 cm and 7 (9.5%) patients in more than 5 cm tumor size. The most common histopathology types were PTC and FTC in 55 (77%) and 17 (23%) patients, respectively. Lymphovascular invasion was found positive in 30 (40.5%) and negative in 44 (59.5%) cases. Capsular invasion was found positive in 27 (36.5%) and negative in 47 (63.5%) cases. We found 45 (60.8%) patients had RLN metastasis and 29 (39.2%) was negative for RLN metastasis.

Table 1 Characteristics of Data

Variables	N = 74
Category Age	
<20 years> 40 years	47 (63.5%)
Median	46
20-40 years	27 (36.5%)
Sex	
Male	15 (20.3%)
Female	59 (79.7%)
Location of tumors	
Right	31 (41.9%)

Left	33 (44.6%)
Bilateral	10 (13.5%)
Category Size	
<= 5 cm	67 (90.5%)
Median cm	2.45
> 5 cm	7 (9.5%)
Histopathological type of tumor	
papillary carcinoma	57 (77.0%)
follicular carcinoma	17 (23.0%)
Lymphovascular invasion	
Positive	30 (40.5%)
Negative	44 (59.5%)
Capsular invasion	
Positive	27 (36.5%)
Negative	47 (63.5%)
Metastatic RLN	
Positive	45 (60.8%)
Negative	29 (39.2%)

We found that in high risk age category (< 20years and > 40 years old) there were 30 (66.7%) patients with RLN metastasis. However there were statistically no significant relationship (P=.483) between the age category and RLN metastasis. From the tumor features, we found statistically no significant (P=.697) relationship between tumor size and RLN metastasis. In patients with PTC we found there were 38 (84.4%) with RLN metastasis and it showed significant relationship between PTC and RLN metastasis (P<0.05). We also found that in group with RLN metastasis cases with capsular invasion were 26 from 27 patients and lymphovascular invasion were 29 from 30 patients. Statistically there were significant relationship (P=.000) between tumor

characteristics (capsular invasion and lymphovascular invasion) and RLN metastasis. We concluded there were four factors sex, histopathological type of tumor, capsular invasion and lymphovascular invasion that could be associated with RLN metastasis.

As shown in table 2, we found the most dominant independent variable affecting RLN metastasis is lymphovascular invasion or capsular invasion (lymphovascular invasion and capsular invasion are identical) with p value 0,000. It shows odds ratio value is 52.231 and has a positive relationship with RLN metastasis. Sex and histopathology show it odds ratio 3.786 and 1.251 respectively but statistically no significant relationship with RLN metastasis

Table 2. Multivariate analysis of relationship between sex, lymphovascular or capsular invasion and histopathology to metastatic RLN

variables	Metastatic RLN			Sig.
	B	Exp (B)	CI for Exp (B)	
Sex	1.331	3.786	0.767 – 18.682	0.102
Lymphovascular or capsular invasion *	3.956	52.231	6.264 – 435.514	0.000
Histopathology	0.224	1.251	0.316 – 4.949	0.749

***lymphovascular and capsular invasion are identical**

DISCUSSION

In general, thyroid malignancies have a good prognosis, but the incidence of local recurrence after surgery has always been one of the important issues that need to be known.^{1,3} In our centre, we do prophylactic neck dissection to remove of lymph nodes that have been deemed to be normal on pre – and intraoperative assessment by palpation or imaging, therefore the lack of clinical factors in predicting loco-regional recurrence, the issue of doing prophylactic radical neck dissection is still controversy.^{1,3,8} From data that we have been collected, patients with age category <20 years and > 40 years has no significant relation with RLN metastasis, although it has 63.8% positive RLN metastasis. While the study by Amirsina, et al. (2016) patients with age > 45 years had a risk factor for the local recurrence and have a significantly related.³ Interestingly, the study by Yasuhiro ito, et al. (2014) from observation of 1235 patients with papillary thyroid carcinoma, the progression of carcinoma was lowest in old (> 60 years) patients but highest in young patients (<40 years).⁶ They demonstrated the incidence rates of

size enlargement, novel appearance lymph node metastasis, and progression clinical disease were 8.0%, 3.8%, and 6.8% respectively from 10 years observation, and they do prophylactic node dissection after observation.⁶

For the tumor size, from our study its statistically no significant relationship $P > 0.05$ between tumor size and RLN metastasis, but from the study by Andreas Machens, et al. (2005) they found from 366 PTC patients, the tumor size (mean 20.6 mm) have significant lymph node metastasis ($p < 0.001$).⁷ They suggest that earlier intervention is warranted to keep suspicious thyroid nodules from growing more than 20 mm (or greater than T1).⁷ For histopathological type of tumor, our study showed statistically marginal significant association with $P < 0.05$. along with other study, they found lymph node metastasis were higher in patients with papillary thyroid carcinoma than in patients with follicular thyroid carcinoma.⁷ Also some studies have found that patients with papillary thyroid carcinoma have a high incidence of recurrence after initial surgery.^{3,5}

The data suggested that lymphovascular invasion and capsular invasion were an independent predictor of RLN metastasis. In line with our study, lymphovascular invasion and capsular invasion in some studies are considered as one of the recurrence factors.^{1,3,5} Seo Kim Kim, et al. (2015) found that the greater the extension of the tumor the greater the incidence of local recurrence^{1,5}. Today several oncogenes are being assessed histologically in thyroid carcinoma especially in papillary thyroid carcinoma including p53, VEGF and BRAF.^{4,8} BRAF positivity predicts for poor prognosis as well as a higher probability of lymph node metastasis.^{5,8}

From this study, we found the factors that influence statistically the incidence of RLN metastasis were sex, histopathological type of tumor, lymphovascular invasion and capsular invasion, with the most dominant influence on the incidence of RLN metastasis is lymphovascular invasion or capsular invasion. As shown in table 2, a multivariate analysis for these significant factors that were identified, which showed that lymphovascular invasion or capsular invasion statistically have a significant association with RLN metastasis. But making recommendation for the management of thyroid carcinoma is difficult for several reasons, first our study had several limitations, we found there was a wide interval estimation on multivariate analysis, it means our data have higher probability but our sample have a small information for representing the entire population, second this study was conducted retrospectively and the data might have been incomplete so in future we need a randomized prospective trial study, so we can find the other factors that can affect the incidence of RLN metastasis such as multifocality of the tumor, location of tumor and extra thyroidal extension, oncogenes factors like p53, VEGF, BRAF and there were 47,7% factors outside the model need to be found. third, due to limited time for research we are still lacking

the size of the sample. We still need more and balanced data between the two groups of RLN metastasis. The majority of reports are retrospective cohorts at best or case series, because the disease is by and large slow growing and indolent so that detection of differences in outcome requires large number of cases and followed for many years.

In summary, clinical and histopathological factors in thyroid carcinoma has been increasingly recognized to be important in predicting prognosis as well as directing appropriate surgical therapy. Aggressive, a good management of demonstrated a RLN metastasis in thyroid carcinoma provides a therapeutic benefit in respect to local recurrence and possible overall survival as well.

CONCLUSIONS

From our study showed patients with capsular invasion or lymphovascular invasion in histopathological findings considered as patients with a high risk of metastatic RLN, surgical options with prophylactic radical neck dissection is recommended.

DECLARATIONS

Ethics approval and consent to participate

The study comes with Ethics Approval Letter No. LB.04.01 / A05 / EC / 308 / X / 2017 by Komitee of Ethics Hasan Sadikin Hospital

Competing interest

The authors declare no competing interest in this study

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