Predictive Factors For The Recurrence Of Papillary Thyroid Cancer Following Resection At Dr. Soetomo General Hospital Indonesia

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ABSTRACT

BACKGROUND
Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for 80%–90% of cases, with generally favorable prognosis. However, recurrence occurs in a significant subset of patients and is associated with reduced long-term survival. Predictive factors such as tumor size, multifocality, lymph node metastasis, aggressive histology, and extrathyroidal extension have been identified, though their relevance may vary across populations. Given regional variations in clinical presentation and treatment outcomes, identifying locally relevant predictors is essential to optimize risk stratification and management. This study evaluates predictive factors for PTC recurrence following surgical resection at Dr. Soetomo General Hospital.
OBJECTIVES
This study aims to evaluate and analyze predictive factors associated with the recurrence of papillary thyroid carcinoma following surgical resection at Dr. Soetomo General Hospital.
METHODS
A retrospective cohort study was conducted using an analytical observational approach based on medical record data. The study analyzed potential predictors of recurrence in patients who underwent surgical resection for PTC between 2019 and 2024.
RESULTS
Multivariate logistic regression analysis identified several significant predictive factors for papillary thyroid carcinoma recurrence. Tumor size >5 cm was significantly associated with increased recurrence risk ($p = 0.030$; OR = 18.52). Extrathyroidal extension was also a strong predictor ($p = 0.017$; OR = 16.95), indicating that local invasion contributes to recurrence. Multifocal tumors significantly raised the likelihood of recurrence ($p = 0.048$; OR = 17.42), as did aggressive histological variants ($p = 0.015$; OR = 45.70). Lymph node metastasis showed a significant correlation with recurrence ($p = 0.014$; OR = 27.39), and the presence of lymphovascular invasion was also associated with higher risk ($p = 0.026$; OR = 13.56).
CONCLUSION
Tumor size >5 cm, extrathyroidal extension, multifocality, aggressive histological subtypes, lymph node metastasis, and lymphovascular invasion were found to be significant predictive factors for recurrence of papillary thyroid carcinoma. These findings highlight the importance of comprehensive risk stratification to guide surveillance and postoperative management strategies.

Introduction

Papillary thyroid carcinoma (PTC) is a malignancy arising from the epithelial cells of the thyroid gland. It is the most common type of thyroid cancer, accounting for 80%–90% of cases and predominantly affects women (Huang, Wang, and Jia, 2021). PTC is often associated with prior exposure to ionizing radiation (Limaiem et al., 2022). The standard treatment involves total thyroidectomy or lobectomy, with neck dissection in advanced tumors to assess lymph node involvement (Hunsaker and Hoffman, 2022). Radioactive iodine (RAI) ablation is typically administered postoperatively to eliminate residual thyroid tissue, followed by lifelong levothyroxine (LT4) therapy (Limaiem et al., 2022).

Although PTC generally carries a favorable prognosis with 10-year survival rates of up to 90% (Huang, Wang, and Jia, 2021), recurrence significantly reduces this survival rate to 49%–68%, and to 25%–42% in cases with distant metastasis (Galuppini et al., 2022). Therefore, identifying high-risk patients is critical to determining the need for more aggressive surgical or follow-up strategies.

Several predictive factors for recurrence have been reported, including lymph node metastasis, tumor size, multifocality, extrathyroidal and extranodal extension, aggressive histological variants, male sex, and age over 45 (Bates et al., 2018). Additional contributors include incomplete surgery, patient noncompliance, and aggressive tumor subtypes (Grant et al., 2018). Clinicopathological features like lymphovascular invasion and elevated postoperative thyroglobulin also correlate with recurrence risk (Wang et al., 2019; Chatchomchuan et al., 2021; Ywata de Carvalho et al., 2021). Given regional variation, this study aims to evaluate predictive factors for PTC recurrence following resection at a top referral hospital in eastern Indonesia, Dr. Soetomo General Hospital Surabaya.

Method

This study used an analytical observational design with a retrospective cohort model based on patient medical records. The study population included all patients diagnosed with papillary thyroid carcinoma (PTC) and treated at Dr. Soetomo General Hospital, Surabaya, between 2019 and 2024. Inclusion criteria were complete medical records of patients diagnosed with PTC within the study period. Exclusion criteria included incomplete data, patient death, or loss to follow-up. Sample size was calculated using a categorical cohort formula, requiring a minimum of 40 patients in both the recurrence and non-recurrence groups. Patients were selected consecutively based on the inclusion and exclusion criteria until the sample size was met. The dependent variable was PTC recurrence. Independent variables included nine predictive factors covering patient demographics, pathological features, and surgical characteristics, as detailed in the corresponding table. Data were analyzed descriptively and statistically using SPSS software, with results presented in the form of tables, charts, and cross-tabulations.

Results

A total of 127 patients diagnosed with papillary thyroid carcinoma who had undergone resection procedures were included in this study. The distribution of subject characteristics by sex showed that the majority were female, accounting for 94 patients (74%), while males numbered 33 patients (26%). In terms of age groups, most patients were in the 51–80 years range, comprising 63 patients (49.6%). Regarding recurrence, 58 patients (45.7%) experienced recurrence after resection. The results are summarized in Table 1.

Table 1. General Characteristics of Study Subjects

Characteristic	Number	Percentage
Sex		
Male	33	26%
Female	94	74%
Age (years)		
≤40	40	31,5%
>40-50	20	15,7%
>50-80	63	49,6%
>80	4	3,1%

Recurrence		
Yes	58	45,7%
No	69	54,3%

The pathological characteristics of the study subjects showed significant variation. Regarding tumor size, the majority of patients had tumors ≤5 cm (88 patients, 69.3%), while 39 patients (30.7%) had tumors >5 cm. Analysis of extrathyroidal extension revealed a nearly even distribution between minor and gross extension; 67 patients (52.8%) had a minor extension, and 60 patients (47.2%) had a gross extension. Multifocal tumors were found in 59 patients (46.5%) and aggressive histology was present in 59 patients (46.5%). Lymph node metastasis (LNM) was observed in 54 patients (42.5%) and lymphovascular invasion (LVI) was found in 58 patients (45.7%). These findings are presented in Table 2.

Table 1. Pathological Characteristics of Subjects

Characteristic	**Number**	**Percentage**
Tumor Size (cm)		
≤ 5	88	69,3%
> 5	39	30,7%
Extrathyroidal Extension		
Minor	67	52,8%
Gross	60	47,2%
Multifocality		
Yes	59	46,5%
No	68	53,5%
Aggressive Histology		
Yes	59	46,5%
No	68	53,5%
Lymph Node Metastasis		
Yes	54	42,5%
No	73	57,5%
Lymphovascular Invasion		
Yes	58	45,7%
No	69	54,3%

The comparison of general characteristics between the recurrence and non-recurrence groups revealed distribution differences in several parameters. In the recurrence group, most patients were female (48 patients, 37.8%), while only 10 males (7.9%) experienced recurrence. In the non-recurrence group, 36.2% were females and 18.1% were males, indicating that recurrence was more common in female patients. In terms of age, the majority of patients in the recurrence group were aged 51–80 years (34 patients, 26.8%), similar to the non-recurrence group (29 patients, 22.8%). Patients aged ≤40 years were more prevalent in the non-recurrence group (27 patients, 21.3%) compared to 13 patients (10.2%) in the recurrence group. These comparisons are detailed in Table 3.

Table 2. General Characteristics by Recurrence Status

Characteristic	**Recurrence (N=58)**	**No Recurrence (N=69)**
Sex		
Male	10 (7,9%)	23 (18,1%)
Female	48 (37,8%)	46 (36,2%)
Age (years)		
≤40	13 (10,2%)	27 (21,3)
>40-50	9 (7,1%)	11 (8,7%)
>50-80	34 (26,8%)	29 (22,8%)
>80	2 (1,6%)	2 (1,6%)

The analysis of pathological characteristics in the recurrence and non-recurrence groups revealed significant differences across various parameters associated with tumor aggressiveness. Tumor size analysis showed that the proportion of patients with tumors larger than 5 cm was higher in the recurrence group, with 26 patients (20.5%), compared to 13 patients (10.2%) in the non-recurrence group. Conversely, tumors measuring ≤5 cm were more frequently observed in the non-recurrence group, with 56 patients (44.1%) versus 32 patients (25.2%) in the recurrence group. The extrathyroidal extension also showed a marked difference. In the recurrence group, 57 patients (44.9%) exhibited gross extrathyroidal extension, while only one patient (0.8%) had minor extension. In contrast, the majority of patients in the non-recurrence group presented with minor extension, totaling 66 patients (52%), while only three patients (2.4%) had gross extension. Multifocality was more frequently observed in the recurrence group, with 57 patients (44.9%) having multifocal tumors, compared to only two patients (1.6%) in the non-recurrence group. In contrast, 67 patients (52.8%) in the non-recurrence group did not exhibit multifocality, whereas only one patient (0.8%) in the recurrence group was free of this feature. Aggressive histology was identified in nearly all patients in the recurrence group (57 patients, 44.9%), while only two patients (1.6%) in the non-recurrence group showed such characteristics. The majority of patients in the non-recurrence group (67 patients, 52.8%) did not display aggressive histological features. Lymph node metastasis was more common in the recurrence group, with 43 patients (33.9%) affected, compared to 11 patients (8.7%) in the non-recurrence group. Conversely, 58 patients (45.7%) in the non-recurrence group had no lymph node metastasis, compared to only 15 patients (11.8%) in the recurrence group. Lymphovascular invasion was also more frequently observed in the recurrence group, affecting 47 patients (37%), in contrast to 11 patients (8.7%) in the non-recurrence group. On the other hand, 58 patients (45.7%) in the non-recurrence group showed no signs of lymphovascular invasion, compared to only 11 patients (8.7%) in the recurrence group who lacked this feature. The results of the study are presented in Table 4.

Table 3. Pathological Characteristics by Recurrence Status

Characteristic	**Recurrence (N=58)**	**No Recurrence (N=69)**
Tumor Size (cm)		
≤ 5	32 (25,2%)	56 (44,1%)
> 5	26 (20,5%)	13 (10,2%)
Extrathyroidal Extension		
Minor	1 (0,8%)	66 (52%)
Gross	57 (44,9%)	3 (2,4%)
Multifocality		
Yes	57 (44,9%)	2 (1,6%)
No	1 (0,8%)	67 (52,8%)
Aggressive Histology		
Yes	57 (44,9%)	2 (1,6%)
No	1 (0,8%)	67 (52,8%)
Lymph Node Metastasis		
Yes	43 (33,9%)	11 (8,7%)
No	15 (11,8%)	58 (45,7%)
Lymphovascular Invasion		
Yes	47 (37%)	11 (8,7%)
No	11 (8,7%)	58 (45,7%)

Based on the results of the multivariate logistic regression analysis, several predictive factors demonstrated a significant association with the risk of papillary thyroid cancer recurrence. Larger tumor size showed a significant influence (p-value = 0.030; OR = 18.52), indicating that in our population, larger tumor size is associated with an decreased risk of recurrence. Extrathyroidal extension showed significant association (p-value = 0.017; OR = 16.95), suggesting that extrathyroidal involvement contributes to recurrence risk. Furthermore, multifocality (p-value = 0.048; OR = 17.417) had a significant effect, where patients with multifocal tumors had a higher risk of recurrence compared to

those without multifocality. Aggressive histology was a significant factor as well (p-value = 0.015; OR = 45.697), showing a strong influence on recurrence risk. For lymph node metastasis, the test results showed a p-value of 0.014 and an OR of 27.389, confirming that lymph node involvement increases the likelihood of recurrence. Lymphovascular invasion was also statistically significant (p-value = 0.026; OR = 13.562), indicating that the presence of vascular invasion is strongly associated with the risk of recurrence.

Table 6. Multivariate Logistic Regression Analysis

Predictive Factors	p-value	OR
Male sex	0,983	0,619
Age	0,486	1,030
Tumor size	0,030	18,520
Extrathyroidal extension	0,017	16,950
Multifocality	0,048	17,417
Aggressive Histology	0,015	45,697
Lymph Node Metastasis	0,014	27,389
Lymphovascular Invasion	0,026	13,562

Discussions

This study included 127 patients diagnosed with papillary thyroid carcinoma (PTC) who had undergone resection procedures. The distribution of subject characteristics based on sex revealed that the majority were female (74%). Within the recurrence group, most patients were female (37.8%), whereas male patients constituted only 7.9%, indicating that recurrence was more frequently observed among female patients. Sex plays an important role in the prognosis of PTC. A study by Sun et al. (2022) demonstrated that male sex was more commonly found among patients with advanced-stage recurrence compared to the non-recurrent group. Furthermore, Woo et al. (2021) reported that in patients with multifocal PTC—more commonly observed in women—recurrence was more frequent than in those with unifocal tumors. Nevertheless, male remains a significant factor associated with increased recurrence risk, particularly in advanced stages (Woo et al., 2021). Contrary to previous studies, in our hospital, the majority of recurrency occurred in female patients.

Based on age group distribution in this study, the majority of patients were between >50–80 years old, comprising 63 individuals (49.6%). We found no difference in age distribution between patients in recurrent or non-recurrent cancer; most patients were in the 50–80 years age group. Age is also closely associated with prognosis in PTC patients. Research by Sun et al. (2022) showed that patients with early-stage PTC tended to be younger (median age 36 years) compared to those with advanced-stage disease (median age 58 years). Additionally, a study by Chereau et al. (2016) found that patients over 75 years of age had nearly twice the risk of recurrence compared to those under 65 years. More recent findings by Kauffmann et al. (2018) also indicated that older age is associated with a higher mortality rate. The recurrence analysis in this study revealed that 58 patients (45.7%) experienced post-resection recurrence, while 69 patients (54.3%) did not. Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, generally associated with a favorable prognosis. However, postoperative recurrence remains a major challenge in managing PTC patients, with reported recurrence rates ranging from 8% to 23% (Sun et al., 2022; Wang et al., 2017).

Tumor size is a very important factor in predicting the risk of recurrence. Based on the findings in this study, the majority of patients with tumors measuring ≤5 cm (69.3%) did not experience recurrence, whereas patients with tumors >5 cm had a higher likelihood of experiencing recurrence (30.7%). This is consistent with previous findings showing that larger tumors have a greater potential to spread more extensively, both locally and metastatically, thereby increasing the likelihood of recurrence after resection. A study conducted by Sun et al. (2022) also showed that larger tumor size (>2 cm) is significantly associated with an increased risk of recurrence, with an odds ratio (OR) of 2.69 (95% CI 2.06–3.50). This indicates that an increase in tumor size may worsen the prognosis and heighten the need for closer postoperative monitoring (Sun et al., 2022). The extrathyroidal extension also demonstrates a clear distinction**.** In the recurrent group, 57 patients (44.9%) experienced gross

extrathyroidal extension, while only one patient (0.8%) had minor extension. A study by Hung Sun et al. (2022) showed that advanced-stage extrathyroidal extension is associated with an increased recurrence rate, where the recurrence rate reached 28.2% in patients with extrathyroidal extension. Thus, early detection of extrathyroidal extension is crucial for appropriate management and reducing the risk of recurrence (Sun et al., 2022).

Multifocality and aggressive histological types have also been shown to be associated with an increased risk of recurrence**.** In this study, multifocality was found in 44.9% of patients with recurrence, indicating that PTC occurring in multiple locations within the thyroid gland is more likely to recur. A study by Woo et al. (2021) revealed that multifocal PTC has a higher recurrence rate, with a lower recurrence-free survival (RFS) compared to unifocal tumors (93.3% vs. 97.1%) (Woo et al., 2021). Lymph node metastasis and lymphovascular invasion are pathological factors that significantly influence the risk of recurrence in PTC**.** Patients with lymph node metastasis have a higher risk of recurrence, with a prevalence of 42.5% among all study subjects. Additionally, lymphovascular invasion, which occurred more frequently in patients with recurrence (45.7%), suggests that tumor cells can spread through lymphatic and vascular channels, thereby increasing the likelihood of both local and distant metastasis and contributing to recurrence. This supports findings from a previous study by Wang et al. (2017), which showed that lymph node metastasis (N1b) and lymphovascular invasion significantly increase the risk of recurrence, with a hazard ratio (HR) of 3.24 (95% CI 2.61–4.02) for lymph node metastasis and 2.31 (95% CI 1.48–3.60) for lymphovascular invasion (Wang et al., 2017).

Several variables were found to have a statistically significant association with the recurrence of papillary thyroid carcinoma (PTC) in our study. Tumor size larger than 5 cm was found to have a significant association, with a p-value of 0.030 and an odds ratio (OR) of 18.520. In the study by Sun et al. (2022), patients with larger tumor sizes tended to have higher recurrence rates, suggesting that a tumor size greater than 2 cm serves as a significant risk factor for recurrence (Sun et al., 2022). A meta-analysis by Wang et al. (2017) also demonstrated that a tumor size greater than 2 cm had a significant odds ratio for increasing the likelihood of recurrence (Wang et al., 2017). Further studies are needed to confirm whether this findings are unique of those in the Indonesian population.

The extrathyroidal extension was also found to be a significant factor ($p = 0.017$; OR = 16.950), indicating that the presence of invasion beyond the thyroid significantly decreases the likelihood of recurrence-free survival. Extrathyroidal extension, defined as tumor invasion into the tissues surrounding the thyroid gland, is an important factor in predicting the risk of recurrence. A study by Woo et al. (2021) found that patients with more extensive extrathyroidal extension tend to experience recurrence more frequently, particularly in those with multifocal tumors (Woo et al., 2021). This is related to the tumor's aggressiveness and its ability to spread to adjacent tissues, thereby increasing the potential for metastasis.

Multifocality was proven to be a strong predictor with $p = 0.048$ and an odds ratio (OR) of 17.417. This indicates that patients with multifocal tumors are approximately 17 times more likely to experience recurrence compared to those with unifocal tumors, after adjusting for other variables. Woo et al. (2021) demonstrated that multifocal tumors have a higher prevalence among patients with extrathyroidal extension and lymph node metastasis, which in turn contributes to the elevated risk of recurrence (Woo et al., 2021). Aggressive histological subtypes, such as tall cell variant or oncocytic variant, were also found to be associated with higher recurrence rates (Guo and Wang, 2014). Aggressive histology contributed significantly to the model, with $p = 0.015$ and OR = 45.697. This suggests that patients with aggressive histological subtypes have nearly 46 times higher likelihood of recurrence compared to those with non-aggressive histological types. This finding aligns with the results of Woo et al. (2021), who stated that aggressive histological variants such as tall cell, columnar cell, and hobnail types exhibit more invasive biological behavior, thereby contributing to an increased risk of recurrence and metastatic spread (Woo et al., 2021). In addition, lymph node metastasis was also statistically proven to be a significant risk factor for recurrence ($p = 0.014$; OR = 27.389). Lymph node involvement, particularly in the lateral neck region, is often associated with a high burden of microscopic tumor cells that may escape early detection and lead to recurrence later on. Galuppini et al. (2022) emphasized that the involvement of both central and lateral lymph nodes is one of the key indicators in risk stratification for PTC patients. This is also supported by Bates et al. (2018), who showed that the presence of lymph node metastasis significantly increases the likelihood of both local

and regional recurrence, and negatively affects long-term prognosis (Galuppini et al., 2022; Bates et al., 2018).

Another significant factor was lymphovascular invasion, with a p-value of 0.026 and an odds ratio (OR) of 13.562. This condition indicates a higher biological aggressiveness of the tumor, which has been associated with an increased risk of metastasis and local recurrence. Although lymphovascular invasion is not a standalone factor in the TNM staging system, its presence has been recognized as an important predictor in various clinical guidelines and contemporary thyroid oncology literature (Galuppini et al., 2022). Overall, the most robust predictive variables for recurrence in this analysis were aggressive histology, lymph node metastasis, multifocality, and lymphovascular invasion, each presenting with high OR values and p-values < 0.05. This highlights the need for particular attention to these factors when formulating follow-up monitoring strategies and adjuvant therapy plans for patients after PTC surgery.

Conclusion

This study found that 45.7% of patients with papillary thyroid carcinoma (PTC) who underwent surgical resection at Dr. Soetomo General Hospital experienced postoperative recurrence. The recurrence was significantly associated with several clinicopathological factors. Tumor size >5 cm, extrathyroidal extension, multifocality, aggressive histological subtypes, lymph node metastasis, and lymphovascular invasion were all identified as independent predictive factors for recurrence. Among these, aggressive histology and lymph node metastasis showed the strongest association, highlighting their importance in postoperative risk stratification.

Contrary to some previous literature, recurrence in our population was more frequently observed among female patients, suggesting the need for localized data in guiding clinical decisions. Although age was not found to be a statistically significant factor in this study, older patients remain a group of interest based on international findings. These results emphasize the need for individualized follow-up strategies and potentially intensified surveillance and adjuvant therapies for patients exhibiting high-risk features. The findings support the integration of these predictive factors into clinical decision-making protocols and underscore the importance of early identification of aggressive disease to improve long-term outcomes. Future multicenter studies with longer follow-up and inclusion of molecular markers are recommended to enhance the predictive accuracy and generalizability of recurrence risk in PTC.

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