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Recurrence Analysis of Pediatric Thyroid Carcinoma in Dr. Cipto Mangunkusumo General Hospital and its Associated Factors

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Abstract

Introduction. Thyroid cancer is the most common endocrine malignancy in children aged 0-14 years, frequently occurring in adolescents and young adults. The global incidence rate stands at 0.54 cases per 100,000 individuals. Pediatric patients exhibit higher recurrence rates compared to adults, although their mortality rates are low. Research exclusively for the pediatric population is still sparse in Indonesia. Thus, This study aimed to provide essential data on recurrence and mortality rates of pediatric thyroid cancer, along with an analysis of contributing factors.
Method. This study is a retrospective cohort focusing on survival analysis. The research sample was drawn from the medical records registry of Cipto Mangunkusumo General Hospital (CMGH) from 2014 to 2020. Inclusion criteria encompassed all pediatric patients (0-18 years) diagnosed with thyroid cancer since January 1, 2014, and with confirmed thyroid cancer pathology results. Bivariate and multivariate analyses and recurrence event analyses proceeded. Results were considered significant at $p < 0.05$.
Results. Out of 35 pediatric subjects with thyroid cancer, complete data for analysis were available for 29 patients. The overall median age was 16 (5-18) years. No reported mortality was observed among the subjects. The median overall survival was 60.0 months (32.5-60.0). The overall recurrence rate was 25.0%. None of the factors studied age, sex, histopathology, therapy, and types of surgery affect recurrency ($p > 0.05$).
Conclusion. The recurrence rate among pediatric patients with thyroid cancer at CMGH is 25.0%, with a median disease-free survival of 96.0 months. No significant factors contributing to the increased risk of recurrence.

Keywords: thyroid carcinoma, pediatric, survival, recurrence, management

Introduction

Thyroid cancer is the most common endocrine cancer in children, although cases are relatively rare. The standardized incidence worldwide is 0.54 cases per 100,000 people for thyroid cancer. The most common type is differentiated thyroid cancer, particularly the papillary type, with a prevalence rate of around 91%. Thyroid cancer ranks as the fifth most common cancer in children aged 0 to 14 years and is the most frequently occurring cancer in teenagers and young adults. There is limited data on the epidemiology, management, and prognosis of pediatric patients with this disease despite a rising incidence. Patients are often diagnosed at advanced stages. However, the prognosis for thyroid cancer is generally better in children compared to adults.[1] In this context, management plays a crucial role but remains controversial. Recommendations for management have changed over the past few decades and may change again. This includes the choice of surgical techniques, the use of radioactive iodine therapy, ^{123}I administration strategies, residual management, residual ablation, and hormonal therapy usage.[2]
In Indonesia, two centers have researched thyroid cancer characteristics and prognosis in children and young adults: Hasan Sadikin Hospital in Bandung and Dr. Cipto Mangunkusumo General Hospital (CMGH) in Jakarta. However, these studies have involved young adults rather than specifically children.[1,3] Study by Harahap et al. (2011) and Rivkees et al. (2022) stated that the recurrence risk is higher in children than adults, but the mortality rate is lower in adults.[1–3] This forms the basis for the classification of stages of differentiated thyroid cancer in children and young adults into only two stages, stage I and stage II, distinguished by the presence or absence of metastasis about mortality. Clinically, these stage classifications are considered impractical because they assess the risk of recurrence and the management of the disease, as well as the morbidity-related therapies experienced by the patients, particularly in children. Although thyroid cancer is rare in children, it is a disease that can be treated with a good prognosis.[1–3]

As a national referral center, Dr. Cipto Mangunkusumo General Hospital (CMGH) receives thyroid cancer cases referred from various regions in Indonesia. Building on a previous study by Harahap et al. (2022) at CMGH, there have been no cases of thyroid cancer-related deaths among pediatric patients. However, recurrence was observed in this group.[3] Therefore, there is a need for data that can serve as a reference to depict the recurrence event analysis and mortality rates of thyroid cancer in children, along with an analysis of the factors influencing its recurrence.

Method

This study is a retrospective cohort with secondary data from medical records conducted at Dr. Cipto Mangunkusumo General Hospital (CMGH) from September 2022 to May 2023. The subjects were derived from all pediatric patients diagnosed with thyroid cancer and undergoing treatment at CMGH from 2014 to 2020. Inclusion criteria consisted of all pediatric patients (ages 0-18 years) diagnosed with thyroid cancer since January 1, 2014, with histopathological results confirming thyroid cancer. Exclusion criteria were subjects with incomplete medical records and those unreachable for confirmation, as well as subjects who had already experienced metastasis before treatment, making it impossible to calculate disease-free survival (DFS). Subjects who did not meet the follow-up duration of 3 years (loss to follow-up) and whose outcomes (events) were unknown were considered censored. Right censoring was not performed in this study as it aimed to observe the most extended survival experienced by pediatric thyroid cancer patients until the study was conducted. This study employed a total sampling method due to its low prevalence.
The independent variables in this study included clinicopathological factors such as age, gender, therapy, type of surgical procedure, and histopathological type. The patients receive surgical therapy, ablative procedures, hormonal therapy, and chemotherapy. Broadly, surgical

procedures were categorized into two groups for bivariate analysis: the total thyroidectomy/completion group, encompassing subjects undergoing total thyroidectomy and completion thyroidectomy, and the non-total/hemithyroidectomy group, including lobectomy, isthmolobectomy, and subtotal thyroidectomy. After the surgery, the histopathological type can be divided into papillary, follicular, medullary, and anaplastic types. The dependent variables were overall survival (OS) and disease-free survival (DFS)/recurrence.

All data were collected and cleaned. Subsequently, the analysis was carried out using IBM® SPSS® Statistics version 20.0. Overall survival and disease-free survival were calculated from the time of the primary intervention until the occurrence of events. Factors influencing recurrence were analyzed using bivariate analysis with the Chi-square test. Survival analysis was conducted using Kaplan-Meier curves and log-rank tests. We also performed Cox regression analysis to obtain unadjusted hazard ratios. Moreover, multivariate Cox regression analysis, which is time-independent, was conducted to obtain adjusted hazard ratios. Prognostic factors significantly affecting overall or disease-free survival were those with a p-value <0.05.

The Health Research Ethics Commitee Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital (HREC-FMUI/CMGH) approved the study (No. KET-832/UN2.F1/ETIK/PPM.00.02/2023).

Results

Subject's characteristics

A total of 35 pediatric subjects diagnosed with thyroid cancer between 2014 and 2020 were included in this study. Among them, 29 subjects had sufficient overall survival (OS) assessment data. Disease-free survival (DFS)/recurrence analysis could be performed for only 28 subjects, as one subject was diagnosed with metastasis before treatment initiation. The subject selection process is depicted in Figure 1.

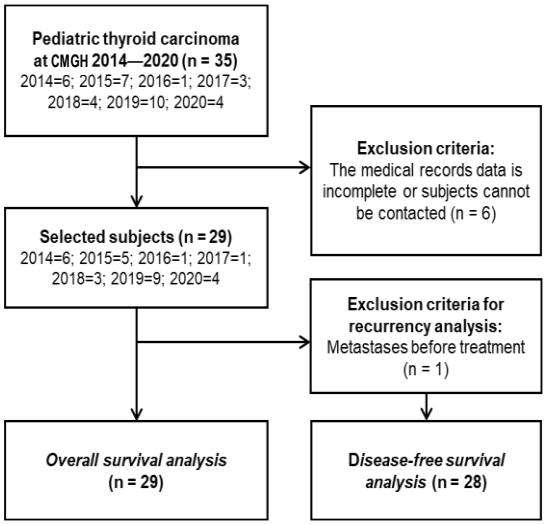

Figure 1. Subject selection flowchart

The median age was 16 years (5–18 years). Most (n=20, 69%) subjects were females, and 24 subjects (82.8%) had no metastasis. The papillary histopathological type was predominant (n = 25, 86.2%), with 11 subjects (37.9%) being papillary carcinoma variants of the follicular type. The follicular histopathological type was found in only four subjects (13.8%), with one having oncocytic variant follicular carcinoma. All subjects (100%) received primary treatment through surgery. Surgical procedures performed consisted of total thyroidectomy (n = 17), subtotal thyroidectomy (n = 1), lobectomy (n = 4), isthmolobectomy (n = 5), and completion thyroidectomy (n = 2). Subject characteristics are detailed in Table 1.

Table 1. Subject characteristics of pediatric thyroid carcinoma

Variables	All subjects (n = 29)	Percentage (%)
Age, year	16 (5 – 18)	
Gender		
– Male	9	31.0%
– Female	20	69.0%
Metastases status		
– No metastases	24	82.8%
– Distant metastases	5	17.2%
Histopathological results		
– Papillary	25	86.2%
– Follicular	4	13.8%
Variant		
– Papillary, follicular variant	11	37.9%
– Follicular, oncocytic variant	1	3.4%
– Papillary, follicular variant with tall cell	2	6.9%
Treatment		
– Surgery	29	100.0%
– Ablation	6	20.7%
– Hormonal	15	51.7%
– Chemotherapy	0	-
Type of surgery		
– Total (total thyroidectomy, completion)	17	58.6%
– Non-total (lobectomy, isthmolobectomy, subtotal)	12	41.4%

Recurrency occurred in seven subjects (24.1%). Distant metastasis was observed in 5 subjects, all involving lung metastasis. Four metastatic events occurred postoperatively and were detected during recurrence events. One metastasis was present at the initial diagnosis, leading to exclusion from recurrence analysis. Recurrence in the thyroid bed was observed in one case, while two subjects experienced recurrence in neck lymph nodes. All our subjects had either papillary or follicular type of thyroid carcinoma based on histopathological results, with papillary being the most prevalent. Neither medullary nor anaplastic type were observed. No mortality events were reported among the subjects. Therefore, median survival could not be computed; only maximum follow-up duration can be reported. The maximum follow-up duration was 60.0 months (32.5–60.0).

Survival analysis

Survival analysis could only be performed on the variable of disease-free survival for 28 subjects. However, Kaplan-Meier curve analysis and Cox regression analysis for overall survival variables could not be conducted (SPSS results could not be generated) due to all subjects experiencing censoring, as no mortality events were reported. This means all subjects had survivor status (survival rate = 100%).

The overall recurrence rates are presented in Table 2. Successively, the recurrence rates at 12 months, 24 months, 36 months, 72 months, 84 months, and >96 months were 3.6%, 10.7%, 14.3%, 17.9%, 21.4%, and 25.0%. The results of the Kaplan-Meier curve analysis for disease-free survival are depicted in Figure 2. Until the end of follow-up (96 months), 75% of subjects did not experience recurrence; therefore, in this study, median disease-free survival cannot be computed.

Table 2. The recurrence rate in each period

Recurrence (month)	12	24	36—60	72	84	>96
%	3.6	10.7	14.3	17.9	21.4	25.0
Yes	1	3	4	5	6	7
No	27	25	24	23	22	21

Associated factors of recurrence

Several characteristics, such as age, gender, metastasis status, histopathological type, and therapy, were analyzed using bivariate tests to determine their impact on recurrence events. No variable was significantly associated with recurrence incidents (**Table 3)**.

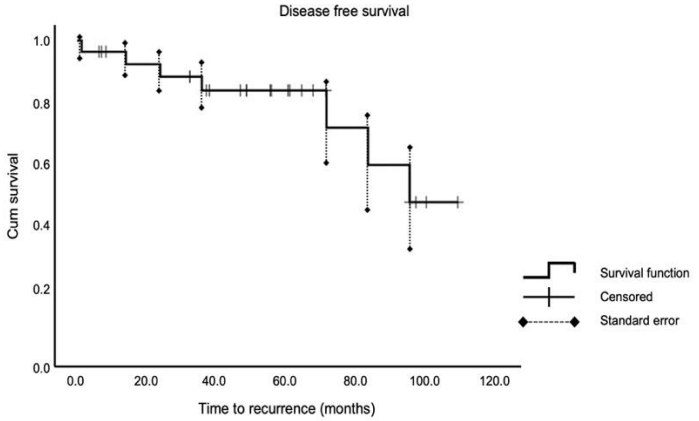

Figure 2. Kaplan-Meier curve of disease-free survival (Median survival: 96.0 months; 95%CI: 71.6–100.7)

Table 3. Bivariate analysis and Cox regression analysis of factors influencing recurrence.

Variables	All subjects (n = 28)	Recurrence		p value*	Unadjusted HR (95%CI)	p value	Adjusted HR (95% CI)	p value
		Yes (n = 7)	No (n = 21)					
Age								
– <15 years	8	2	6	1.000	1	-	1	-
– 15 – 18 years	20	5	15		1.21 (0.23-6.29)	0.817	1.03 (0.15-6.91)	0.980
Gender								
– Male	4	1	3	1.000	1	-	1	-
– Female	24	6	18		0.96 (0.11 -8.05)	0.969	0.14 (0.04-4.44)	0.263
Histopathology								
– Papillary	24	5	19	0.253	1	-	1	-
– Follicular	4	2	2		3.89 (0.65-23.33)	0.137	5.34(0.69 – 41.38)	0.109
Treatment								
– Adequate	23	7	16	0.290	1	-	1	-
– Inadequate	5	0	5		28.45 (0.01 – 90.87)	0.416	$4.57x10^4$	0.980
Type of surgery								
– Total thyroidectomy	17	6	11	0.191	1	-	1	-
– Non-Total	11	1	10		4.1 (0.49-34.35)	0.194	10.77 (0.29-390.34)	0.194

* p value computed using Fisher-exact test; HR: hazard ratio; CI: confidence interval.

Multivariate analysis was also conducted to calculate the hazard ratio (HR) of factors influencing recurrence events. The unadjusted HR results showed a tendency that age between 15 and 18 years, male gender, follicular histopathological type, adequate therapy, and total thyroidectomy surgery type could increase the risk of recurrence. Similar trends were observed after calculating the adjusted HR. None of the HR values were statistically significant.

Discussion

This study evaluated the factors influencing recurrence-free survival in children with thyroid cancer in our center. Out of our 29 subjects, 25% experienced recurrence. Overall, there is no statistically significant difference in factors influencing recurrence between those who had experienced and those who had not experienced recurrence. No mortality was observed during the follow-up period. This result could be attributed to our small sample size. Therefore, our results might be challenging to be extrapolated or corroborated with other studies. This smaller percentage is due to the low prevalence of thyroid cancer in the young age group. Epidemiological studies in the United States by the Surveillance, Epidemiology, and End Results Program (SEER) showed that the pediatric population accounted for only 1.8% of the total thyroid cancer patients.[4]

The demographic data in this study indicated that the median age of the children with thyroid cancer included in the study was 16 years, with the majority being female (69.0%). This median value above ten years aligns with the SEER epidemiological study, showing an increased prevalence of thyroid cancer in the second decade of a child's life.[4] This finding also corresponds with a study by Harahap et al. (2022) conducted at CMGH and a cohort by Banik et al. (2021) with larger sample sizes. Both studies reported a mean age of 14 years for children with thyroid cancer.[3,5] The predominance of females in the population also aligns with previous research.[3–5] Epidemiological data from SEER indicate an increased prevalence of thyroid cancer in females above the age of 10.[4]

In this study, 17.2% of pediatric thyroid cancer patients had distant metastasis. Distant metastasis in pediatric thyroid cancer is rarely encountered, and there is limited research on this topic. The incidence rate found in this study is similar to that of Harahap et al. (2022), who reported a rate of 17.2%. This similarity might be due to both studies being conducted at the same research center. However, this rate is lower than in previous studies.[3] Cohort studies focused on metastasis reported by Nies et al. (2021) indicated a distant metastasis incidence of 24.6%. Nies et al. reported that despite many children undergoing radioactive iodine therapy, the metastasis rate remains relatively high, with unknown specific metastasis-related mortality rates due to potential occurrences in adulthood requiring longer follow-up periods.[6] this study did not report mortality rates due to thyroid disease or metastasis, possibly due to the relatively short follow-up period.

Papillary was the most common histopathological type of cancer (86.2%) in this study. This aligns with cohort studies with large populations reported by Hogan et al. (2009), indicating that papillary histopathological type is the most common thyroid cancer type in children, with an incidence of 0.32 cases per 100,000 population. Papillary thyroid cancer variants of the follicular type ranked second

with an incidence rate of 0.12 cases per 100,000 population. The medullary histopathological type was the least common, with an incidence of only 0.03 cases per 100,000 population.[7] However, in this study, several variant types were found, with follicular variant thyroid carcinoma (37.9%) being the most dominant, followed by papillary variant follicular with tall cell features (6.9%), and only one patient with oncocytic variant follicular carcinoma (3.4%).

All subjects in this study underwent surgical procedures. The most common treatment approach in this sample was total thyroid tissue removal surgery, including both total thyroidectomy and completion thyroidectomy, involving 58.6% of the total subjects. Total thyroidectomy surgery is the primary choice in managing thyroid cancer in children, especially papillary and follicular types, due to the increased prevalence of bilateral and multifocal thyroid cancer.[8] Among those who underwent total thyroidectomy, 20.7% of subjects received additional postoperative ablation therapy using radioactive iodine I-131. This therapy is indicated in children as residual therapy to reduce recurrence rates, although long-term follow-up results still show insignificant outcomes.[8,9]

This study focused on recurrence rates in pediatric thyroid cancer patients and identified influencing factors. The study revealed an overall thyroid cancer recurrence rate of 25.0% in observations spanning more than 96 months. Recurrence rates during the follow-up were 3.6% at 12 months, 10.7% at 24 months, 14.3% at 36 – 60 months, 17.9% at 72 months, and 21.4% at 84 months. These recurrence rates occurred with a median recurrence-free survival of 96.0 months. A previous retrospective cohort study by Azhar et al. (2021) demonstrated that despite lower mortality rates in children compared to adults, this age group has a higher risk of recurrence. Cox regression analysis comparing children under 18 with young adults indicated an increased recurrence hazard in the pediatric group (HR: 3.88)[1] The recurrence rates reported in this study are like those of previous cohort studies. Wang et al. (2020), a cohort study involving 150 subjects, reported recurrence rates of 13.6%, 18.7%, and 28.6% at 3, 5, and 10 years, respectively.[10] Rubinstein et al. (2020) reported a recurrence rate of 23.6% with a median survival of 24.6 months.[11]

This study examined the significant factors influencing recurrence in pediatric thyroid cancer patients. The study employed a cutoff age of 15 years to assess differences in recurrence rates between children under 15 and those above this age. This age threshold was based on a literature review by Paulson et al., who reported that studies on thyroid cancer in children commonly use age limits of 14 or 15 years. This choice was influenced by the higher incidence of thyroid cancer cases in children aged 15 to 18.[12] This study found that age did not impact the recurrence rate in children with thyroid cancer, both in proportion difference analysis with chi-square and Cox regression analysis. However, this might be influenced by our very small sample size. These findings contradict previous studies. Kaplan-Meier survival analysis conducted by Wang et al. indicated significantly lower recurrence-free survival in the 13–16 age group compared to children aged 16–18 and 6–12 years.[10] Nevertheless, Rubinstein et al. (2020) reported nonsignificant findings, showing no significant differences in the median age of patients with recurrence (17.0 years) and those without recurrence (17.0 years).[11] This simple comparison indicates that the influence of age on thyroid cancer recurrence in children still yields varied results.

Gender was assessed as a risk factor in this study. While it increases the risk of thyroid cancer in children, the female gender did not significantly affect recurrence rates compared to males. Cox regression analysis in this study showed a nonsignificant hazard ratio (HR) for recurrence risk in females compared to males (unadjusted HR 0.96; 95% CI 0.11– 8.05; p = 0.969). Similar findings were reported by Wang et al., with a chi-square test value of 0.45.[10]. Another cohort study by Chen et al. conducted in 2022 also showed nonsignificant differences in the percentage of females between the recurrence and non-recurrence groups (53.3% vs. 66.7%; p = 0.56).[13] These concurrent findings support that gender does not have a significant impact on thyroid cancer recurrence in children.

This study identified seven recurrences. Distant metastasis was observed in some study subjects, with lung metastasis found in 4 cases, while local recurrence occurred once in the thyroid bed and twice in cervical lymph nodes. As a national referral center, CMGH receives patients referred from other health centers. Consequently, some subjects' data on surgical incision margins, the number of positive lymph nodes during initial surgery at other hospitals, or initial data from previous hospital visits were not entirely available. However, it is known that tumor cell invasion into surrounding thyroid tissue is a recurrence risk factor. A previous cohort study by Dinauer et al. indicated that the presence of both local and distant metastasis (odds ratio [OR] 2.8) significantly reduces recurrence-free survival in children, adolescents, and young adults with thyroid cancer. Additionally, other parameters indicating high tumor proliferation and tissue spread, such as multifocal tumors (OR 7.5; 95% CI 2.5–22.8), palpable cervical nodules at diagnosis (OR 3.0; 95% CI 1.0–9.3), and tumors larger than 2 cm (OR 4.1; 95% CI 1.1–15.5), increase both local and distant recurrence rates.[14] Wang et al. also indicated reduced recurrence-free survival in pediatric patients with tumor extrathyroidal extension, cervical lymph node metastasis, and tumor invasion into the trachea and esophagus.[10] However, some nonsignificant findings were reported in newer studies, such as by Chen et al., who found no significant effects of local invasion, cervical lymph node metastasis, and lung metastasis on recurrence rates. Thyroid cancer management in children with metastasis typically involves radioactive iodine therapy (I-131) based on guideline recommendations. This is because children with distant metastasis, especially in the lungs, often have micro-nodular thyroid cancer, which responds well to radioactive iodine therapy. During iodine radiation therapy, pediatric thyroid cancer patients with metastasis are regularly monitored for suppressed thyroglobulin levels and thyroid stimulating hormone (TSH) and undergo whole-body scans.[8] This aligns with the practices at CMGH, where patients with distant and locoregional recurrence receive iodine radiation therapy, leading to an excellent overall survival rate in this study (100%).

Histopathological variations in pediatric thyroid cancer can affect patient prognosis. This study revealed a higher proportion of follicular histopathological thyroid cancer and a lower proportion of papillary cancer in children with recurrence compared to those without recurrence, although this difference was not significant. However, Cox regression analysis did not indicate a significant effect on recurrence hazard for papillary and follicular thyroid cancer relative to their variant types, despite tall cell variants being associated with higher aggressiveness.[3] This finding was reinforced by previous research supporting the impact of histopathological type on recurrence in pediatric patients. Unlike adults, papillary thyroid cancer in children tends to be multifocal and aggressive, increasing the incidence of distant metastasis and recurrence.[15] National-scale studies by van de Berg et al. (2022) showed that stage pN1b tumors dominated the papillary subtype of thyroid cancer with tumor cell invasion into lymphatic tissue.[16] A retrospective analysis using SEER data conducted by Zeng et al. (2021) indicated that the papillary subtype of thyroid cancer is a risk factor for increasing distant metastasis rates in the 2–16-year-old age group.[17]

Adequate and inadequate therapies did not show statistical significance on outcomes in this study. The research indicated a nonsignificant

increase in the hazard of recurrence in the group receiving adequate therapy, with an adjusted hazard ratio of $4.57x10^4$ (95% CI 0.00–∞; p = 0.980). Mean and median survival values could not be calculated due to the absence of recurrence in the inadequate therapy group. This statement contradicts the findings of a study conducted by Francis et al., which stated that adequate management is a critical factor in improving the prognosis of recurrence in pediatric thyroid cancer patients. Total thyroidectomy with neck lymph node dissection in children showing evidence of lymphatic tissue involvement in the central or lateral neck is recommended as the primary modality in most cases of pediatric thyroid cancer.[8] A study by Chen et al. (2022) demonstrated a proportion of patients with total thyroidectomy accompanied by zone VI dissection in the group of children without recurrence. Total and adequate thyroid removal might be one of the factors reducing recurrence rates.[13] A cohort study by Handkiewicz-Junak et al. (2007) indicated that one of the risks of increasing thyroid cancer recurrence rates in children, adolescents, and young adults is incomplete thyroid removal and the absence of postoperative radioactive iodine therapy.[18] However, in this study, distant metastasis was found even in subjects who received adequate therapy, namely total thyroidectomy with radical neck lymph node dissection, as well as hormonal and radioactive iodine therapy. This possibility arises because these subjects had papillary thyroid carcinoma with a follicular variant, and evidence of level II lymph node involvement was detected at the initial diagnosis.

In this study, no statistically significant results were obtained ($p<0.05$). The youngest age at initial diagnosis was five years, with a tall cell variant, and after completion and hormonal therapy, no recurrence was recorded either locoregionally or distantly. Meanwhile, there were also patients aged 15-18 years with recurrence in the form of local and distant metastasis despite receiving adequate therapy and total thyroidectomy with papillary histopathology. Further investigation into the differences in recurrence among cases is needed due to the small sample size, making it challenging to conclude the observed variations. However, this study recommends that appropriate patient-indicated management and strict surveillance according to guidelines can help detect and address recurrence incidents in pediatric thyroid cancer patients.

Some limitations in this study could be taken as points for evaluation in future research. The main limitation is the limited sample size due to the scarcity of pediatric thyroid cancer cases treated at CMGH. The small sample size can limit the interpretation of the results presented in this study, primarily due to high Type II errors and failure to reject the null hypothesis in statistical analysis.[19] The minimal sample size needs to be achieved despite including all patients within a 6-year range, which indicates the need for a broader recruitment period, perhaps spanning the last 10-20 years. Additionally, the insufficient sample size could be addressed by conducting a multicenter study involving more than one tertiary healthcare center in Indonesia. In addition to increasing the sample size, a multicenter study can yield research outcomes that can be interpreted more broadly as it encompasses a wider reachable population than a single-center study. The second limitation of this study is its retrospective nature, which prevents the control of confounding variables during the follow-up process. One variable that might have an impact is genetic factors. Besides genetics, several other uninvestigated confounding variables include a family history of malignancy, medications taken outside thyroid cancer management during the study, and surgical incision margins. A prospective cohort study can provide research outcomes with more substantial evidence of quality.

Conclusion

All subjects in this study survived (overall survival rate 100%). During the 96-month follow-up duration, the recurrence rate for pediatric thyroid cancer at CMGH was 25%. Survival analysis revealed a median disease-free survival (DFS) of 96.0 months. Statistically, no significant factors influencing recurrence were identified in this study, including age, gender, histopathological type, therapy, or type of surgery received by the patients. However, a small sample size could influence this result.

Disclosure

The authors declare no conflict of interest.

Role of authors

Conceptualization MMPP EDY, Data curation MMPP EDY, Formal analysis MMPP, Funding acquisition MMPP, Investigation MMPP, Methodology MMPP EDY, Project administration MMPP, Resources MMPP EDY, Software MMPP, Supervision EDY, Validation MMPP EDY, Visualization MMPP, Writing original draft preparation MMPP, Writing review and editing MMPP EDY.

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