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# Pediatric with differentiated thyroid cancer have higher recurrence rates than young adult patients: A retrospective cohort analysis for over 60 months



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## ABSTRACT

**Background:** Pediatrics thyroid cancers tend to be at more advanced stages at the time of diagnosis and have a higher frequency of recurrences than adulthood thyroid cancers. The aim of the study was to evaluate clinical characteristics, and outcome between children and young adults patients with Differentiated Thyroid Cancer (DTC) treated in our hospital.

**Material and Methods:** The medical records of 144 patient with DTC who underwent thyroid surgery followed by radioiodine and thyroid hormone suppression were retrospectively reviewed. Subjects consisted of 43 patients who were younger than 21 years old, and 101 young adult patients (older than 21 years old but younger or equal to 40 years). The clinical characteristics and outcomes were analyzed and compared, then Recurrence Free Survival (RFS) was evaluated using Kaplan-Meier Methods.

**Results:** Female has higher tendency to have thyroid cancer than male ( $p = 0.006$ ). Based on histopathology report, classic papillary thyroid cancer is the most common cancer type in children than young adult. However, there was no significant difference between two groups regarding thyroid cancer size and multifocality ( $p=0.815$  and  $p=0.370$ ). The risk of the recurrent ratio of children to young adults is 3.88 (95% CI 1.38; 10.91). Similar result trend is shown for sex type, histopathology type, the number of nodules, surgical technique and metastasis parameters. (adjusted HR = 7.91, 95% CI 2.11; 29.67).

**Conclusions:** Differentiated Thyroid Cancers in children show more aggressive behavior compared to young adult patients.

**Keywords:** Differentiated Thyroid Cancer, Pediatrics, Recurrence-Free Survival

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## INTRODUCTION

Although thyroid cancer is less common in pediatrics than adult patients, the incidence of pediatrics thyroid cancer has increased gradually in Indonesia as well as throughout the world. Thyroid cancer has become the fifth most common cancer in children age of 0-14 years and the most common cancer in adolescents and young adults. Cancer screening tests for early detection of thyroid cancer have been implicated as the impact of its rise in adult thyroid cancer. However, because children and adolescents generally do not undergo such test, genetic or environmental factors have been suggested as possible causes of the increased incidence of pediatrics thyroid cancer.<sup>1-2</sup>

The clinicopathological characteristics and outcomes of thyroid cancers in adults were recently published. Pediatrics thyroid cancers tend to be at more advanced stages at the time of diagnosis and have higher frequency of recurrences than adulthood thyroid cancers. However, it remains unclear whether the pathology diagnosis and long-term outcomes differ between children and adolescents thyroid cancer patients.<sup>3</sup>

Furthermore, despite their advanced pathological presentations, pediatrics patients have better prognosis and significantly lower mortality rates than adult patients. This finding reveals that, even in similarly advanced stage at the time of diagnosis, long-term outcome and prognosis may differ between pediatrics and adult patients. As the prognostic implications of the pathology according to age at diagnosis are unknown, no age-related optimal clinical practice guidelines for treatment and monitoring of thyroid cancer in pediatrics patients are available. The comparison between pediatrics and adult patients with thyroid cancer in this study may help to develop age-related optimal management and follow-up guidelines in the future.<sup>4</sup>

We investigated changes in the clinical and pathological presentation and long-term outcomes of pediatrics thyroid cancer according to age at diagnosis during the year of 2009-2011, and compare the clinicopathological predictors of Recurrence-Free Survival (RFS) between pediatrics and adult patients with differentiated thyroid cancer.

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## MATERIALS AND METHODS

### Materials

The medical records of 144 children and young adults patients (< 40 years of age) with thyroid cancer diagnosed during January 2007 and December 2011 at Hasan Sadikin Hospital were retrospectively reviewed. We also obtained data from cancer registry, hospital charts, operation reports, and records from other cancer-related division, such as nuclear and external radiation department using a standardized form. The data contained entries of demographic and staging data, treatment, complications, Radio Active Iodine (RAI) treatment and patient medical records.

From those, forty-three of subjects were below 21 years of age and categorized as pediatrics patients. The pediatric age should be limited to 21 years as from pragmatic point of view, our centers may transfer pediatrics patients between 18 and 21 years of age to adult care and manage those children under pediatrics guidelines until transition period has been completed.<sup>5</sup> One hundred one young adult patients with thyroid cancer were recorded. Eight patients with intermediate histopathology such as tall cell and insular carcinoma were excluded from the analysis. Clinicopathological characteristics including age, sex, primary tumor size, multimodality therapy, extra thyroidal extension (ETE), lymph node (LN) and/or distant metastasis at diagnosis were investigated. The long-term outcomes of 43 pediatric patients data were assessed and compared to those of 101 of young adults. All patients had been followed up for 60 months after multimodality treatment. The analysis of patients from the Oncology, Head, and Neck Surgery Department in Hasan Sadikin General Hospital was obtained from an individual review of hospital archives, registry, and databases. Data base was limited in patients that was diagnosed from January 1<sup>st</sup>, 2007 until December 31<sup>st</sup>, 2011.

In addition, specific categories were included to specify disease progression. A clinical measurement was taken before or at the time of surgery if the pathologic measurement was not available. Distant metastases were identified most commonly by plain chest X-ray or Whole-Body Scan. All patient should at least, had one-year follow-up from initial treatment.

### Methods

Disease progression was chosen as the endpoint of analysis because many patients already had metastatic disease at diagnosis. We would consider disease progression if there were local recurrence recognized within thyroid bed or regional lymph nodes after a complete removal, progression in

the thyroid bed or regional nodes after incomplete surgical resection and the development or progression of distant metastatic disease (lung, bone). Age, an extrathyroidal extension of primary tumor into surrounding tissue, primary tumor size, number of nodules, regional lymph nodes involvement, presence of distant metastases, the technique of initial surgery, the use of RAI and histopathology type were assessed as independent variables for their influence on disease progression.

Initial thyroid surgery was divided into three groups: 1) lobectomy and isthmectomy. 2) Total thyroidectomy. 4) Total thyroidectomy + comprehensive Neck Dissection.

Morbidity during treatment was assessed by determining the association of significant wound complications, permanent recurrent nerve paralysis, permanent hypocalcemia with the extent of thyroid surgery or nodal dissection. Wound complication included serous hemorrhage or hematoma (requiring exploration), infection, pneumothorax, and requirement for tracheostomy. Permanent hypoparathyroidism was presumed if there was a postoperative need for calcium supplements and/or vitamin D replacement for more than 6 months after surgery and continued until the last follow-up. Permanent recurrent nerve paralysis was defined by change in voice and/or indirect laryngoscope evidence of vocal cord paralysis that lasted, at least 6 months after the primary thyroid surgery. This included cases of operations that sacrificed the recurrent nerve. Temporary recurrent nerve injury or hypoparathyroidism resolved within 6 months of surgery. The pediatrics patient data were then compared to those of 101 young adult patients with Differentiated Thyroid Carcinoma.

## RESULTS

The average age at diagnosis of thyroid cancer was 18 years old (IQR 8,8). The pathological finding Papillary Thyroid Carcinoma (PTC) were 91% in pediatrics versus 66% in young adult. The average rate of size was 4,65 cm (IQR 1,10) and multifocality was found in 9 patients (21%). Metastasis in children was found in 5 patients (12%) while there were 10 patients (10%) in young adults. Total thyroidectomy was the most common procedure to treat differentiated thyroid cancer in both groups (n= 37, 86% and n=88, 87%). The report of operative injury to laryngeal nerve revealed in one pediatric patient (2%) and none in young adult patient. Hypocalcemia was common after surgery, and was the most common complication in pediatrics group (n=9,18%), presumably due to more fragile anatomy structure in children's laryngeal nerves than ones in adult (Table 1). Some traction caused

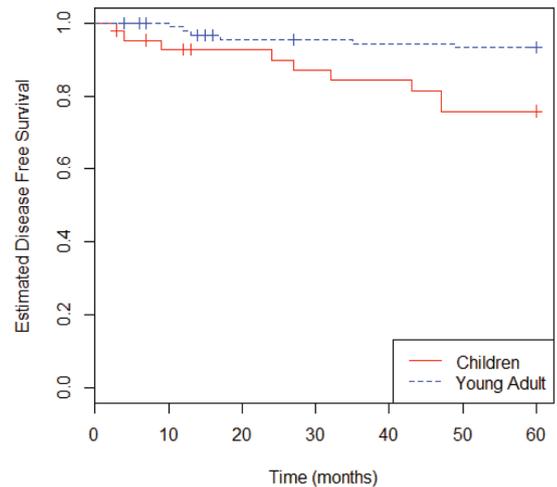
**Table 1 Comparison of clinicopathological and treatment characteristics of children and young adults with differentiated thyroid carcinoma**

Characteristic	Children	Young adult	Total	p-value
	n = 43	n = 101	n = 144	
Gender, frequency (%)				
Female	29 (67)	88 (87)	117 (81)	0.006 <sup>§</sup>
Male	14 (33)	13 (13)	27 (19)	
Histopathology type, frequency (%)				
FTC	0 (0)	7 (7)	7 (5)	0.012 <sup>#</sup>
FTCV	0 (0)	1 (1)	1 (1)	
PTC	39 (91)	67 (66)	106 (74)	
PTCV	4 (9)	26 (26)	30 (21)	
Nodule				
Number, frequency (%)				
Single	34 (79)	86 (85)	120 (83)	0.370 <sup>§</sup>
Multiple	9 (21)	15 (15)	24 (17)	
Size (cm)				
For single, median (IQR)	4.65 (1.10)	4.30 (1.48)	4.30 (1.23)	0.815 <sup>§</sup>
For multiple, mean (SD)				
First	4.64 (1.22)	5.33 (2.24)	5.08 (1.92)	0.407 <sup>*</sup>
Second	4.13 (0.71)	4.75 (1.49)	4.52 (1.27)	0.189 <sup>*</sup>
Metastasis, frequency (%)				
Yes	5 (12)	10 (10)	15 (10)	0.770 <sup>#</sup>
No	38 (88)	91 (90)	129 (90)	
Surgical procedure, frequency (%)				
Isthmo-lobectomy	3 (7)	5 (5)	8 (5)	0.919 <sup>#</sup>
Total thyroidectomy	37 (86)	88 (87)	125 (87)	
Total thyroidectomy with RND	3 (7)	8 (8)	11 (8)	
Injury of n. Laryngeus, frequency (%)				
Yes	1 (2)	0 (0)	1 (1)	0.299 <sup>#</sup>
No	42 (98)	101 (100)	143 (99)	
Hypocalcaemia after surgery, frequency (%)				
Yes	8 (19)	1 (1)	9 (6)	< 0.001 <sup>*</sup>
No	35 (81)	100 (99)	135 (94)	
RAI treatment, frequency (%)				
Yes	39 (91)	88 (87)	127 (88)	0.544 <sup>§</sup>
No	4 (9)	13 (13)	17 (12)	

Note: FTC = Follicular Thyroid Carcinoma PTC = Papillary Thyroid Carcinoma, FTCV = Follicular Thyroid Carcinoma Variant, PTCV = Papillary Thyroid Carcinoma Variant. RND = Radical Neck Dissection

spasm to anterior thyroid artery and temporary hypocalcemia due to parathyroid gland failure. The Addition of RAI treatment seemed to have no correlation with recurrence for both groups.

Bivariate analysis found that gender, histopathology type, surgical procedure, and metastasis have a correlation with RFS. (Table 2) Histopathological feature and laryngeal nerve



**Figure 1** Disease free survival according to age group

injury were not included in the multivariable analysis with Cox - proportional hazard models because of zero number cell. The Kaplan-Meier curve (Figure 1) and Hazard Ratio only used in 136 subjects, excluded 8 young adult subjects (Eight patients with intermediate histopathology such as tall cell and insular carcinoma were excluded from the analysis. Compared histopathology features were only PTC and PTCV)

**DISCUSSION**

Previous guidelines for management of thyroid cancers were mostly for adults. Compared to thyroid neoplasm in adults, those in the pediatric population exhibit differences in pathophysiology, clinical presentation, and long-term outcomes.<sup>6-7</sup> Furthermore, therapy that may be recommended for an adult may not be appropriate for children who are at low risk for death but at higher risk for long-term harm caused by overly aggressive treatment. For these reasons, specific guidelines for children and adolescent with thyroid tumors are needed. Several studies have compared the clinical presentation and outcomes for children diagnosed with DTC < 10-15 years of age with that patient of 10-18 years old. The data are unclear as to whether younger age indicates a greater risk for extensive disease of recurrence. All studies are retrospective, and most include only small numbers of children of the above age. Overall studies in which 25% to 30% of the cohort are of younger age have shown that young age is associated with persistence disease or recurrence, although studies with fewer young children have not confirmed this.<sup>8</sup>

In this study, there was a significant difference between children group and young adults. Recurrence risk in thyroid cancer for pediatric

**Table 2** Cox model prediction of recurrence in pediatric age groups and young adults groups.

Variable	Crude HR (95% CI)	p value	Adjusted HR (95%CI)			
			Model 1	p value	Model 2	p value
Age group	3.88 (1.38, 10.91)	0.010	7.91 (2.11, 29.67)	0.002	7.11 (2.10, 24.04)	0.002
Gender	0.71 (0.20, 2.51)	0.594	1.14 (0.28, 4.65)	0.858	-	-
Histopathology type	2.13 (0.48, 9.42)	0.321	0.70 (0.13, 3.64)	0.668	-	-
Number of nodule	1.18 (0.33, 4.17)	0.802	0.98 (0.24, 4.05)	0.978	-	-
Isthmo-lobectomy	22.62 (6.88, 74.36)	< 0.001	98.25 (17.40, 554.77)	< 0.001	87.56 (18.34, 418.13)	< 0.001
Metastasis	4.63 (1.58, 13.55)	0.005	8.69 (2.42, 31.18)	0.001	8.08 (2.45, 26.71)	0.001
Hypocalcaemia	7.81 (2.47, 24.69)	< 0.001	-	-	-	-
RAI treatment	0.18 (0.06, 0.56)	0.003	-	-	-	-

patients was higher in the young adult group compared to children with HR 3.88 at a confidence interval of 95%. This study is consistent with the research of Young Ah Lee *et al.* (2015).<sup>8</sup>

Additionally, there was a specific characteristic in pediatric thyroid cancer in children for the presence of multiple nodules. Young Ah Lee *et al.* (2015) study revealed a close relationship between multiple nodules with the recurrence risk. In our study, multiple nodules were dominantly found in children group patient, rather than in adult case, accounted for 21% and 15% respectively. However, this was not statistically proven as significant factors to regulate the recurrence in the future.<sup>8</sup>

Another important role, apart from the age of the patient, the presence of metastasis in lymph nodes is important to be observed. If the neck lymph node is present, the possibility of loco-regional recurrence will be more prevalent. This is confirmed by study by Nobuyuki *et al.* in 2009.<sup>9</sup>

Furthermore, treatment regimens vary which may impact outcomes. For example, surgeons may be less aggressive in lymph node dissection in younger children and this factor, rather than age, may impact recurrence rates. In our studies, we found that younger age was associated with an increased risk of recurrent nodal disease and lung metastases after adjustment for other risk factors.

There are uncertain factors to clinically predict the recurrence. Many practitioners tend to avoid conducting radical operation on children's thyroid carcinomas. However, operation of only one side of thyroid (lobectomy with or without isthmus) that contains relatively small size tumor, will be against by the group of surgeons who apply radical operation of thyroidectomy in thyroid cancer, even conducting prophylaxis central lymph node dissection for tumor which size extend 1 cm as discussed by Qiang Chen *et al.*<sup>10</sup>

This is understandable as in our research, lymph node metastasis is an accurate predictor factor to

expect recurrence. Clinical research also agrees to importantly pursue the aggressiveness predictor factor on children's thyroid cancers. Studies by Conzo *et al.* support this assumption.<sup>11</sup>

Nixon and Barczynski recommended routine central node dissection to prevent long-term recurrence and decrease postoperative thyroglobulin levels, citing the high risk of cervical lymph node metastasis.<sup>12-13</sup> In contrast, Giordano D and Chisholm E.J summarized that this procedure increases the risk of postoperative complications such as hypothyroidism or recurrent laryngeal nerves injury, without any demonstrable long-term survival benefits.<sup>14-15</sup>

The result from our research also shows that the neck lymph node metastasis presentation is the strong predictor factor to indicate recurrence. Therefore, we support the aggressive therapy. However, we feel that this should be supported by molecular biology study to seek predictor that can be used as reference for the aggressive therapy application.

Compared to adults, differentiated thyroid cancer in childhood is characterized by higher prevalence of gene rearrangements and lower frequency of point mutations in proto-oncogenes. Recent molecular studies have shown that BRAF mutation is the most common molecular abnormality in adults (36%-83% of cases), while this is rare in children.<sup>16</sup>

In contrast to the adults' PTC, PTC on children's molecular pathogenesis occur sporadically in which 80% of them related to RET gene mutation, following the process of realignment with other genes, i.e., H4 and Elei that formed oncogenes RET / PTC. These genes encode proteins that play a role in the kinase tyrosine pathway in cells of the thyroid gland that is the path of Mitogen-Activated Protein Kinase (MAPK). Until now the RET / PTC oncogenes family have been found to be 11, but the most commonly associated with the incidence of

PTC in children and young adults are RET / PTC1 and RET / PTC3 oncogenes. PTC that is caused by mutations in RET / PTC1 is more common in the age group above 20 years with sub-type classic PTC, with tumors grow relatively slowly and occurs sporadically, whereas mutations in RET / PTC3 are more common in the age group under 20 years old and have aggressive biological characteristic usually as tall cell variant PTC and a history of radiation exposure associated with head and neck area as happened in Chernobyl and Nagasaki-Hirosima.<sup>17</sup>

In general, the aggressiveness of a tumor is characterized by increasing proliferation and the ability of tumor cells to migrate out of the primary tumor to the other organs. This process is known as metastasis. Children and young adults with PTC have increased proliferation allegedly because of gene mutations and realignment of RET / PTC that will activate the MAPK pathway. RET / PTC, respectively phosphorylate proteins that work in the MAPK pathway, ranging from Ras, Raf, MEK and ERK. The active ERK proteins undergo translocation into the cell nucleus to activate the transcription factor that will stimulate the transcription process by promoters of genes that play a role in the proliferation.<sup>18</sup>

The ability of tumor cells to migrate begins with the unchain of bonds with neighboring cells and change in the cell skeleton or framework. Change in the framework of the cell causes the cell to penetrate the extracellular matrix and induce the transcription factors that alter epithelial cells into mesenchymal cells. This process is key to the progression of all the cancer cells derived from epithelial. Integrity between epithelial structures with each other and between epithelial and basement membrane is the barrier to prevent the occurrence of epithelial-mesenchymal transition (EMT). Integrity between cells is maintained by E-Cadherin and E-Cadherin strong bond relating to the actin framework of the cell. E-Cadherin bonding loose between these cells that will cause disruption of desmosomes that maintain ties inner filaments order that prevents the cells to penetrate the extracellular matrix. Epithelial cells are transformed into mesenchymal cells have the ability to transcribe the factors that can degrade extracellular matrices such as matrix metalloproteinase (MMP). Formed mesenchymal cells also have the ability to stimulate synergy of protein signal that stimulates the formation of cancers' epithelial cell such as Epidermal Growth Factor (EGF), Hepatocyte Growth Factor (HGF) and fibroblast growth factor family (FGF), such as transforming growth factor  $\beta$  (TGF $\beta$ ).<sup>18-19</sup>

On children and young adults with PTC, TGF $\beta$  RII role is suspected in reducing the expression

of E-Cadherin. Excessive expression of TGF $\beta$  RII can be activated by TGF  $\beta$  produced by the thyroid tumor cells themselves or as a product of other cells. The subsequent activity of SMAD pathway that leads to activation of transcription factors, such as SNAIL will stimulate E-Cadherin gene promoter. The process that occurs is a co-repressor to the transcription so that the expression of E-Cadherin decreased.<sup>20</sup>

It can be concluded that fundamental protein in the beginning of process is E-Cadherin given proof this protein expression changes will affect the expression of other proteins. In other words, E-Cadherin acts as a conductor of an orchestra, and the orchestra is an EMT so that the expression of E-Cadherin can represent EMT. If EMT occurs, then tumor cells will be able to move to other organs, showing those tumor cells are more aggressive. Hence the aggressiveness of children and young adults PTC can be represented by EMT.

This theory needs further research. However, if this is relevant, then molecular biology can be considered to determine therapy management on Papillary Thyroid Cancer in children.

## CONCLUSION

To conclude, the recurrent ratio of children compared to young adults with DTC is 3.88 (95% CI 1:38 10,91), which means that children are more likely to have recurrence compared to young adults. Similarly, after sex type, histopathology type, number of nodules, surgical technique, and metastasis (model 2) controlling, the conclusion remains the same (adjusted - HR = 7.91, 95% CI 2.11, 29.67). Differentiated thyroid cancer in children presents more aggressive behavior than in young adult patients.

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