

Radioactive iodine therapy of juvenile differentiated thyroid carcinoma

Abstract

Introduction: Thyroid cancer in children and adolescents is usually a major concern for physicians, patients, and parents. Controversies regarding the aggressiveness of the clinical presentation and the ideal therapeutic approach remain among the scientific community. The current recommendations and staging systems are based on data generated by studies in adults, and this might lead to overtreatment in some cases as well as undertreatment in others. Our objective was to evaluate the presentation, the contribution of therapy by iodine 131 and long-term outcome in patients with pediatric DTC and to analyze factors that can influence the success of post ablation by iodine 131.

Patients and methods: In this retrospective study, presentation, therapy with iodine 131 and outcome of patients with pediatric DTC (age at diagnosis ≤ 21 y) treated in the nuclear medicine department of king Fahd medical city, between 2006 and 2018 were assessed using medical records.

Results: We identified 53 patients. Overall survival was 100% after a median follow-up of 8 years (range 0.6–13y). Median age at diagnosis was 17.5years (range 7–21y). At initial diagnosis, 43.3% of the patients had cervical lymph node metastases; 16.9% had distant metastases. All patients underwent total thyroidectomy. Radioiodine was administered to 100%, with a median cumulative activity of 5.7GBq (range 0.81–13.5GBq). At last known follow-up, 18.8% of the patients had persistent disease and no patient experienced a recurrence.

Conclusions: Lymph nodal and distant metastases are important predictors of the persistence of disease after initial therapy in children and adolescents with differentiated thyroid cancer.

Keywords: thyroid cancer, differentiated thyroid cancer, clinical outcome, radioiodine, children and adolescents

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Introduction

Thyroid cancer is a rare pathology in childhood and adolescence being responsible for 1.5–3% of all carcinomas in this age group in the USA and Europe.¹ Such as the adults, the differentiated thyroid carcinoma is the most commonly found, especially the papillary thyroid carcinoma (PTC), followed by its follicular variant.² The prognosis in children has been reported to be excellent with 15-year survival rates greater than 95%.³ Due to sparse pediatric data, however, thyroid cancer care for pediatric patients is based predominantly on evidence from adult series. In 2016, the American Thyroid Association (ATA) published their first guidelines for children with DTC, thereby providing a thorough overview of the available literature.⁴

The initial treatment for children with DTC generally consists of a (near) total thyroidectomy with or without lymph node dissection, although for patients with minimally invasive follicular thyroid carcinoma (FTC) of 4 cm or less and lacking other adverse risk factors, a less aggressive treatment has recently been recommended.^{4,5} In the vast majority of patients, surgery is followed by ablation therapy with radioactive iodine (¹³¹I) to destroy residual tumor foci and to facilitate disease monitoring by follow-up scans and measurement of serum thyroglobulin (Tg). However, currently ¹³¹I administration often depends on risk stratification.^{4–6} Pediatric patients with residual tumor and/or metastases are generally treated by cyclic ¹³¹I administrations, with the activity of ¹³¹I being

a matter of discussion.⁷ To decrease the risk of recurrent disease, TSH suppressive therapy with thyroid hormone has for decades been considered necessary during follow-up, but its use is currently tempered in patients showing no evidence of disease.^{4,8–10} The objective of this study was to evaluate the presentation and long-term outcome in patients with pediatric DTC treated with iodine 131 and to analyze factors that can influence the success of initial post radioiodine ablation.

Patients and methods

Study design and population

In this unicentric retrospective cohort study, children 21 years old or younger diagnosed with PTC or FTC between January 2006 and June 2018 and treated in the nuclear medicine department of king Fahd medical city in Riyadh were eligible for inclusion. Patients with medullary thyroid carcinoma or anaplastic thyroid carcinoma were excluded. Medical history, diagnosis, and treatment details were obtained from patients' medical files. Histopathological data were obtained from the original pathology reports. Because the tumor node metastasis (TNM) classification of malignant tumors was changed several times within the period covered by this study, tumor stage was (re)classified according to the seventh edition of the TNM classification to facilitate comparison of the tumors.¹¹ Data regarding ¹³¹I administrations (number and activities of ¹³¹I and results of

scans, both therapeutic and imaging) were collected from our reports. Date of diagnosis was defined as the date of histological confirmation of thyroid carcinoma. Follow-up time was calculated from the date of diagnosis until the date of the patient's last known assessment. Age at diagnosis was classified into three groups: age 0–10, 11–14, and 15–21 years.

Patient follow-up was performed every 6–12 months after initial treatment with surgery and radioiodine therapy. Remission was defined as the absence of clinical, scintigraphical, or radiological evidence of disease and undetectable serum Tg under TSH-suppressive therapy for at least 1 year after the last 131-I therapy. Persistent disease was defined as the absence of remission. Recurrent disease was defined as histological, cytological, radiological, or biochemical evidence of disease after remission. Patients were classified according to risk of recurrence: low (T1–T2, N0, M0), intermediate (any T3 or N1 tumor), or high (any T4 or M1 tumor).

Statistical analysis

Groups were compared using χ^2 or Fisher's exact tests (if conditions for χ^2 test were not met) in the case of categorical variables. Mann–Whitney U and Kruskal–Wallis tests were performed for non-normally distributed continuous variables. Missing or unknown values were excluded from statistical testing. A value of $P < 0.05$ was considered significant. IBM SPSS Statistics version 22 was used for statistical analyses.

Results

Data regarding baseline characteristics are provided in Table 1. 45 patients with pediatric DTC were identified. The female to

male ratio was 4.3:1. Median age at diagnosis was 17.5 years (range 7–21 y). PTC was diagnosed in 85% of the patients; the remaining 15% had FTC. At initial diagnosis, histologically confirmed cervical lymph node metastases were found in 23/53 patients (43.3%) and distant metastases in 9/53 patients (16.9%). Of these, 8 patients had lung metastases, and 1 patient had both lung and bone metastases. Pathological features and TNM stage did not differ between the three age groups. Total thyroidectomy was performed in all patients. In 33/53 patients (62.2%), the total thyroidectomy was performed as a single procedure. In the remaining 20 patients (37.7%), a diagnostic hemithyroidectomy was performed, followed by a completion thyroidectomy. Overall survival was 100% after a median follow-up of 8 years (range 0.6–13 y).

131-I administrations and TSH-suppressive therapy

Data regarding 131-I administrations are provided in Table 2. All 53 patients (100%) were treated with 131-I, with a median cumulative activity administered during initial treatment and follow-up of 5.7 GBq (range 0.74–13.5 GBq). The median number of 131-I administrations was 1 (range 1–5). All 53 patients (100%) underwent 131-I ablation therapy within 6 months after initial surgical treatment. Higher tumor stage (T3–T4), lymph node involvement, and distant metastases were independently associated with a higher administered cumulative 131-I activity ($P < 0.001$) and with an increase in the number of 131-I administrations ($P < 0.001$). The cumulative 131-I activity and the number of 131-I administrations during initial treatment and follow-up did not differ between age groups at diagnosis (P not significant, data not shown). No patients were treated with external beam radiotherapy, chemotherapy, or tyrosine kinase inhibitors for DTC.

Table 1 Baseline characteristics

Variable	All patients (n=53)	0–10y (n=4)	11–14y (n=14)	15–21y (n=35)
Sex, n(%)				
Male	10 (18.8%)	2	3	5
Female	43 (84.4%)	2	11	30
Age at diagnosis, y				
Median (range)	17.5 (7–21%)	7	13	19
Histology, n(%)				
Papillary	45 (85%)	4	12	29
Follicular	8 (15%)	0	2	6
TNM stage, n(%)				
T				
T1-T2	37 (69.8%)	3	11	23
T3-T4	16 (30.1%)	1	3	12
N				
N0	30 (55.5%)	2	10	18
N1a-N1b	23 (43.3%)	2	4	17
M				
M0	44 (83%)	3	12	29
M1	9 (16.9%)	1	2	6
Lung	8	1	2	5
Bone	0	0	0	0
Lung and bone	1	0	0	1
Surgery, n(%)				
Total thyroidectomy	53 (100)	4	14	35

Table 2 131-I Administrations

Group	Cumulative 131-I Activity, GBq	PValue ^a	131-I Administrations, n	PValue ^a
All patients (n=53)	5.7 (0.81–13.5)		1 (1–5)	
T1-T2 (n=37)	2.5 (0.81–5.4)	<.001	2 (1–5)	<.001
T3-T4 (n=16)	4.5 (1.7–13.5)		4 (1–5)	
N0 (n=30)	2.1 (0.81–5.4)	<.001	1 (1–5)	<.001
NIa-NIb (n=23)	3.1 (0.74–9)		3 (1–6)	
M0 (n=44)	2.5 (0.74–5.6)	<.001	2 (1–6)	<.001
M1 (n=9)	5.55 (2.1–13.5)		5 (1–5)	

At last known follow-up, 10 patients (18.8%) had persistent disease. No patient experienced a recurrence. T3–T4 stage, lymph node involvement, and the presence of distant metastases were associated with persistent disease ($P=0.040$, $P=0.010$, and $P=0.020$, respectively). Outcome did not differ between patients with PTC and FTC or between the three age groups ($P=0.512$ and $P=0.791$, respectively). Outcome could not be assessed for five patients, for three patients because of follow-up less than 1 year. For two patients, information to evaluate outcome was not available.

Discussion

DTC is rare in children and it represents less than 1% of childhood cancers, as mentioned by travagli.² It is a well-differentiated papillary carcinoma in 90% of cases, according to Busnardo.¹² Pediatric thyroid cancer is aggressive, has a higher prevalence of lymph node metastasis and pulmonary metastasis at the time of initial diagnosis and occurs more frequently after surgery.^{13–16} The prevalence of cervical lymph node metastases at initial diagnosis in our cohort (43.3%) is in the lower range of prevalence as reported in other pediatric series (39%–90%).^{17–21} However, the prognosis is excellent. The reason for this discrepancy is unclear, but some hypotheses for pediatric thyroid cancer have been suggested. Zimmerman et al. reported that nondiploid DNA amount was 10% in pediatric thyroid cancer and 20% in adult thyroid cancer. The authors suggested that a low incidence of nondiploid DNA was related to the good prognosis in pediatric thyroid cancer.¹³ The other possibility is that the thyroid gland during infancy and childhood is more susceptible to carcinogenic stimuli.

In our study, the incidence of thyroid carcinoma increased with age (<5yr, n=4; 5–15yr, n=14; 15–21yr, n=35), with female predominance. The female to male ratio was 4.3:1. Our results were comparable with those of Harrach.²² In his study, he noted a female predominance with a marked increase in incidence after 10 years.²² This study of pediatric patients with well-differentiated thyroid cancer confirms an excellent overall survival. All patients underwent total thyroidectomy with nodal dissection, followed in all patients by high-dose 131-I ablation therapy. A significant number of patients had persistent disease. Therefore, the need for further centralization of care for pediatric patients with DTC is essential, as has been recommended by the ATA.⁴ The cumulative therapeutic 131-I activity during initial treatment and follow-up in our study was relatively high. Given the good survival rate, it can be questioned whether children could just as well be treated with lower therapeutic activities, as suggested by recent guidelines.^{4,5} The dosage of 131-I is of importance, given that

pulmonary fibrosis was observed as a side effect in 7.2% of patients with lung metastases in a high-risk Chernobyl-related pediatric cohort.²² In our cohort we did not observe pulmonary fibrosis. Because the presence of pulmonary fibrosis was assessed from medical records in our study, we may have missed subclinical cases. Nevertheless, it is our opinion that the administration of 131-I should be considered very carefully in pediatric patients to prevent possible early and late adverse effects.^{23–25} This is especially the case in children with low-risk DTC because no benefit of 131-I ablation therapy has been shown in adults with low-risk disease.²⁶ High 131-I activities should be reserved for children with metastatic disease, as advocated earlier by Verburg et al.⁷

The prevalence of distant metastases in our study is comparable with that from other pediatric cohorts.^{20, 21} The findings of the study demonstrated that a large number of children are not free of disease after initial therapy (even when considered “low risk” by conventional staging systems) and that clinical factor such as extent of initial disease presentation, especially lymph node metastasis, seemed to be important to predict outcomes after initial therapy in this population. In addition, most of the patients either are free of disease in some point in the follow up or they had persistent stable disease in this present study. Persistent disease was more often found in patients with higher T stage, cervical lymph node involvement, and distant metastases at diagnosis. We did not report any recurrence in our study. Our study definitions of recurrent disease may have contributed to the zero recurrence rate because we did not interpret disease activity within 1 year after initial treatment as recurrent disease. The overall survival was very good as previously shown in other studies.

Conclusion

According to the literature data and the results of our study, we conclude that the life expectancy for young patients with DTC is excellent; however, there is more aggressive clinical presentation with more frequent lymph node and distant metastasis comparing to what is usually seen in adults. Those seem to be the most important prognostic factors for the good response to initial therapy in these patients. Unfortunately, most of the risk stratification systems do not give enough emphasis to the presence of lymph node metastasis in this population which might decrease the ability to identify “real low-risk patients”. Evidence shows that, in well selected cases, total thyroidectomy and 131I therapy is an effective and safe treatment for the young patients with DTC.

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None.

Conflicts of interest

The authors declares that there are no conflicts of interest

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