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ORIGINAL ARTICLE

Efficacy of ^{131}I therapy and its influencing factors in children and adolescents with differentiated thyroid carcinoma

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Summary

Purpose: *We aimed to explore the efficacy and safety of iodine-131 (^{131}I) therapy in children and adolescents with differentiated thyroid carcinoma (DTC), and to analyze the possible factors affecting the efficacy.*

Methods: *A retrospective analysis was performed on the clinical data of 94 children and adolescent DTC patients aged ≤21 years old, who received ^{131}I therapy. The efficacy was assessed, and the levels of serum thyroglobulin (Tg) and Tg antibody (TGAb), and adverse reactions were observed. Besides, the possible influencing factors for the efficacy were explored.*

Results: *There were 79 cases of overall response (84.0%) and 15 cases of no response (16.0%). Besides, the initial ^{131}I ablation of thyroid remnants was efficacious in 61 (64.9%) patients, but not in 33 (35.1%) patients who continued to receive the subsequent ^{131}I therapy. As of June 2019, 18 (54.5%) patients reached remission, whereas the other 15 (45.5%) patients failed to reach remission. Of 23 patients with distant metastases in the lungs, there were 8 cases of lesion elimination, 12 cases of improvement or stable disease and 3 cases of no response or progressive disease after ^{131}I therapy. Among 44 patients with only lymph node metastasis, 28 patients were negative for the whole-body ^{18}F-FDG tumor imaging. Moreover, the whole-body ^{18}F-FDG tumor imaging was positive in 16 patients. Furthermore, the clinical tumor stage and pre-treatment Tg and RAIU were found to be the independent influencing factors for the efficacy of ^{131}I therapy.*

Conclusion: *^{131}I therapy is exactly effective in treating DTC in children and adolescents, and the clinical tumor stage and pre-treatment Tg and RAIU are the major factors affecting the efficacy.*

Key words: *thyroid carcinoma, children, adolescents, ^{131}I, efficacy*

Introduction

Thyroid carcinoma is a less common malignancy in children and adolescents aged ≤18 years old and represents 0.5-3.0% of the total malignant cases in children and adolescents, but its morbidity rate has been increasing in recent years [1]. Differentiated thyroid carcinoma (DTC) accounts for 90-95% of the total [2]. Thyroid carcinoma has become the 8th most common malignant tumor in the adolescents aged 15-19 years. Its morbidity rate in females is obviously higher than that in males, with a ratio of 3/1. With elusive causes, thyroid carcinoma is mainly associated with the history of head/neck radiation, and the thyroid gland in children younger than 5 years is the most sensitive to radiation [3-5].

A complete standard mode of therapy for DTC in adults has been formed: total or near-total thyroidectomy (+different degrees of lymph node resection) + iodine-131 (^{131}I) ablation of thyroid remnants (+^{131}I ablation for metastases) + endocrine suppression therapy [6,7]. The combination of surgery and ^{131}I therapy enables the survival rate of DTC patients to reach 86-100% [8]. ^{131}I has been gradually recognized and accepted in treating DTC in children and adolescents [9]. The present study

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explored the efficacy through a retrospective analysis on the clinical information of 94 children and adolescent DTC patients aged ≤21 years, who underwent ^{131}I therapy in our hospital. Besides, based on the pathological features after thyroid carcinoma surgery, univariate and multivariate analyses were conducted on the factors affecting the efficacy of ^{131}I therapy in DTC in children and adolescents, so as to provide evidence for formulating clinical strategies for such patients.

Methods

General information

Clinical information was collected from 94 children and adolescent DTC patients aged ≤21 years. Among them, there were 25 boys and 69 girls, aged 8-21 years (mean 17.57±3.9). Moreover, 77 patients underwent bilateral total thyroidectomy, while 17 patients received bilateral near-total thyroidectomy, and the postoperative pathological diagnosis results confirmed papillary thyroid carcinoma (PTC) in 91 cases, and follicular thyroid carcinoma (FTC) in 3 cases. Prior to ^{131}I therapy, there were 71 cases of stage I thyroid carcinoma, consisting of 27 cases of no metastasis, and 44 cases of only lymph node metastasis. The remaining 23 patients had stage II thyroid carcinoma, with distant metastasis only in the lungs, which were definitely diagnosed through single-photon emission computed tomography/CT (SPECT/CT) and ^{131}I whole-body scan. After surgery, all the patients received ^{131}I therapy for anywhere between one and 5 times, during which ^{131}I was administered orally once. Based on the disease conditions of patients, ^{131}I therapy was performed only once in 51 cases, and for 2-5 times in 43 cases. The initial ^{131}I therapy mainly ablated thyroid remnants, while the subsequent ^{131}I therapy removed metastases and residual neck lesions. Table 1 lists the clinical baseline information of patients. All the subjects followed the Declaration of Helsinki, were informed of the present study, and signed the informed consent. This study was approved by the Ethics Committee of our hospital.

Surgical procedures

Before ^{131}I therapy, the patients discontinued taking levothyroxine sodium tablets for 3-4 weeks, during which they were not allowed to eat food with high levels of iodine, such as kelp, nori and seafood, take iodine-containing drugs and subjected to an enhanced CT scan. Additionally, the following routine examination and assessments were conducted: radioimmunoassay (RIA) for total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxin (FT4), thyroid stimulating hormone (TSH) and thyroglobulin antibody (TGAb), chemiluminescence immunoassay (CLIA) for Tg, radioactive iodine uptake (RAIU) measurement, SPECT/CT through technetium-99m (99m Tc) thyroid scan before the initial therapy, and a 99m Tc-MIBI scan before the subsequent therapies, color Doppler ultrasonography of thyroid and regional lymph nodes, and a chest CT scan. Based on the age, disease conditions and thyroid remnant size of patients, the dose was determined as 1.48-7.03 GBq in the initial ^{131}I therapy and 3.70-9.62 GBq in the 2nd-5th treatment. Before ^{131}I therapy, the patients were informed of precautions after and before taking ^{131}I, and signed the informed consent, and they took ^{131}I orally once on an empty stomach. After administration of ^{131}I, some supportive treatments were carried out to prevent early neck swelling, nausea and vomiting. At 72 h after treatments, levothyroxine replacement and inhibition therapy was started. Moreover, the patients taking ^{131}I were isolated for 5-7 days in the hospital, and at 3-5 days after administration of ^{131}I, ^{131}I whole-body scan was performed to observe the RAIU in the thyroid remnants and lesions, thereby providing bases for the subsequent follow-up and treatments. The therapy was performed at an interval of 6-12 months, and was discontinued in the cases of complete remission and no response.

Observation indicators

The efficacy was evaluated as follows: Every 6 months after taking ^{131}I, the patients discontinued using levothyroxine for at least 14 days to raise the TSH level, and received ^{131}I whole-body scan at a diagnostic dose of 5 mCi. The Tg level and ^{131}I whole-body scan results in the last therapy were taken as the data for assessment. Complete remission, partial remission and stable disease were defined as response, while progressive disease as no response. Complete remission: 1) Stimulated Tg <1.0 ng/mL or inhibited Tg <0.2 ng/mL, and TGAb <30% or positive-to-negative TGAb conversion; 2) no aberrant radioactive focal lesions seen in the ^{131}I whole-body scan; and 3) no abnormalities in other imaging examinations. Partial remission: 1) Lessening of lesions and/or decline in uptake, or decrease in lesion number indicated by ^{131}I whole-body scan; and 2) an obvious decrease in Tg by >50% and TGAb <30%. Stable disease: 1) No obvious changes in lesions according to ^{131}I whole-body scan; 2) no changes in lesions as indicated in other imaging examinations; and 3) a lower level of Tg with no obvious increase. Progressive disease: 1) An increase in or progressive enlarging of lesions as indicated in ^{131}I whole-body scan; 2) increased RAIU in DTC lesions; 3)

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*Cases (n=94)*
Age, years	17.57±3.9
Gender (Male/Female)	25/69
Surgical method, n (%)	
Bilateral total thyroidectomy	77 (81.9)
Bilateral subtotal thyroidectomy	17 (18.1)
Pathological type, n (%)	
Papillary thyroid carcinoma	91 (96.8)
Follicular thyroid carcinoma	3 (3.2)
Clinical staging, n (%)	
I	71 (75.5)
II	23 (24.5)

long-standing increase in or high level of Tg; or 4) a persistent increase in TGAb.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data conforming to normal distribution were subjected to t-test or t'-test, while those not fulfilling normal distribution to rank sum test. x^2 test or Fisher's exact test were conducted for enumeration data. Besides, the influencing factors for the efficacy of ^{131}I therapy screened through univariate analysis were analyzed using multivariate logistic regression analysis. P<0.05 suggested statistically significant differences.

Results

Comparison of clinical efficacy in the two groups of patients

A total of 94 children and adolescent DTC patients underwent ^{131}I therapy at a median interval of 6.75 months (6-12 months) for 3.25 times as a median (1-5 times) using the median cumulative dose of 20.68 GBq (10.06-110.7 GBq). Among them, there were 79 cases of overall response (84.0%) and 15 cases of no response (16.0%). Besides, the initial ^{131}I ablation of thyroid remnants was effictive in 61 (64.9%) patients, but not in 33 (35.1%) patients. The 33 patients with no response to the initial thyroid remnant ablation underwent subsequent ^{131}I therapy. As of June 2019, 18 (54.5%) patients reached remission, among whom 1 patient underwent cervical lymphadenectomy for persistent enlargement of lymph nodes taking in ^{131}I as indicated in the ultrasonography, whereas the other 15 (45.5%) patients failed to reach remission (Table 2).

Among the 23 patients with distant metastasis in the lungs, 16 patients had multiple millet-like nodules in both lungs according to the chest CT findings, with ^{131}I (+) and fluorodeoxyglucose F18 (^{18}F-FDG) (-) functional imaging manifestations. After ^{131}I therapy, there were 8 cases of lesion elimination, 12 cases of improvement or stable disease, and 3 cases of no response or progressive disease, who had multiple differently sized nodules in both lungs as indicated by the chest CT findings and ^{131}I (-) and ^{18}F-FDG (+) functional imaging manifestations. Among 44 patients with lymph node metastasis, 28 were negative for whole-body ^{18}F-FDG tumor imaging, of whom there were 22 cases of lesion elimination or stable disease and 6 cases of no response after ^{131}I therapy. Moreover, whole-body ^{18}F-FDG tumor imaging was positive in 16 patients, and after the ^{131}I therapy, 11 patients experienced improvement or stable disease, while 5 patients had no response, namely no ^{131}I was taken in by lesions.

Table 2. Clinical effective rates of the studied patients

	Cases (n=94) *n (%)*
CR	21 (22.3)
PR	31 (33.0)
SD	27 (28.7)
PD	15 (16.0)
ORR	79 (84.0)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Adverse reactions after treatment in the two groups of patients

On the day of taking ^{131}I, 3 patients suffered from nausea and vomiting, which were relieved after symptomatic treatments and never occurred in the subsequent therapies. Two days after the initial therapy, there were 6 cases of neck swelling and pain. The 94 patients were followed up for a median of 49.7 months (9-60) and had a survival rate of 100%. During the follow-up, no new metastases, pulmonary fibrosis, and hematopoietic suppression were detected, and the patients had normal growth and development of intelligence as well.

Analysis on the factors for efficacy in children and adolescent DTC patients

The onset age, gender, course of disease, surgical procedures, pathological type, number and size of tumors, and pre-treatment TSH level, TGAb, Tg and RAIU (%) were included into univariate analysis, and the results revealed no statistically significant differences in the course of disease, gender, surgical method, pathological type, and pre-treatment TSH and TGAb between response group and no response group (p>0.05). Moreover, there were statistically significant differences in the age at the first diagnosis, tumor stage, number and size of tumors, and Tg and RAIU (%) before treatment between the two groups (p<0.05) (Table 3).

Multivariate logistic regression analyses were then performed and included the onset age, tumor stage, number and size of tumors, and pre-treatment Tg and RAIU, the statistically significant factors in the univariate analysis, and according to the results, the clinical tumor stage and pre-treatment Tg and RAIU were independent influencing factors for the efficacy of ^{131}I therapy [odds ratio (OR)=0.067, 95% confidence interval (CI)=0.019-0.503, p=0.016, OR=0.897, 95% CI=0.763-0.974, p=0.008, OR=0.742, 95% CI=0.581-0.843, p=0.029]. The onset age and number and size of tumors may be the important factors for improving the efficacy (Table 4).

Table 3. Univariate analysis of predictors for efficacy after treatment in the studied patients

Predictors	*Effective (n=75)* *n (%)*	*Ineffective (n=15)* *n (%)*	*p value*
Age, years			0.001
>15	13 (16.5)	9 (60.0)	
≤15	66 (83.5)	6 (40.0)	
Gender			0.111
Male	18 (22.8)	7 (46.7)	
Female	61 (77.2)	8 (53.3)	
Course of the disease, months			0.767
>6	44 (55.7)	8 (53.3)	
≤6	35 (44.3)	7 (46.7)	
Pathological type			1.000
Papillary thyroid carcinoma	76 (96.2)	15 (100)	
Follicular thyroid carcinoma	3 (3.8)	0 (0)	
Surgical method			0.196
Bilateral total thyroidectomy	72 (91.1)	12 (80.0)	
Bilateral subtotal thyroidectomy	7 (8.9)	3 (20.0)	
Clinical staging			0.001
I	69 (87.3)	2 (13.3)	
II	10 (12.7)	13 (86.7)	
Number of tumors			0.003
1	55 (69.6)	4 (26.7)	
2 or more	24 (30.4)	11 (73.3)	
Tumor largest diameter (cm)			0.045
>2	50 (63.3)	5 (33.3)	
≤2	29 (36.7)	10 (66.7)	
Pretreatment TSH level (mIU/L)			0.250
>30	11 (13.9)	4 (26.7)	
≤30	68 (86.1)	11 (73.3)	
Pretreatment TGAb			0.383
<30, %	57 (72.2)	10 (66.7)	
≥30, %	22 (27.8)	5 (33.3)	
Pretreatment Tg	24.97±18.56	87.07±33.41	0.001
Pretreatment RAIU (%)	4.29±6.59	14.74±10.87	0.001

TSH: thyroid stimulating hormone; TGAb: anti-thyroglobulin antibody; Tg: thyroglobulin; RAIU: radioactive iodine uptake.

Table 4. Multivariate logistic regression analysis of predictors for efficacy of children and adolescents with differentiated thyroid carcinoma

Parameters	*OR value*	*95% CI*	*p value*
Age	1.071	0.916-1.630	0.256
Clinical staging	0.067	0.019-0.503	0.016
Number of tumors	0.192	0.155-2.716	0.211
Tumor largest diameter (cm)	0.695	0.019-3.614	0.369
Pretreatment Tg	0.897	0.763-0.974	0.008
Pretreatment RAIU (%)	0.742	0.581-0.843	0.029

OR: odds ratio; CI: confidence interval; Tg: thyroglobulin; RAIU: radioactive iodine uptake.

Discussion

DTC metastasis in children and adolescents differs greatly from that in adults in terms of features and manifestations and tends to be cervical lymph node metastasis and distant metastasis when definitely diagnosed. The possible causes include more obvious gene rearrangements than point mutations, more invasive tumor growth and being more likely to decrease local immunity in children and adolescent with thyroid carcinoma, but the ^{131}I therapy still has favorable efficacy [10-12]. In the present study, the incidence rates of lymph node metastasis and lung metastasis were 71.3% (67/94) and 24.5% (23/94), respectively. There were 33 cases of lesion elimination or stable disease among the 44 patients with only lymph node metastasis, and 20 cases of lesion elimination or stable disease among the 23 patients with lung metastasis. It can be inferred that ^{131}I therapy has preferable efficacy in DTC accompanied by lymph node or lung metastasis. According to severed reports, children and adolescent DTC patients have a higher expression of sodium-iodide symporter gene than adult patients, so the responses to ^{131}I and the final efficacy in children and adolescents are better than those in adults [12,13]. Therefore, most authors believed that ^{131}I therapy can improve the survival quality and cure rate and decrease the mortality rate in the children and adolescents DTC patients after surgery.

The efficacy of ^{131}I therapy varies in different DTC patients, and it is associated not only with the individual patient physical conditions, but also with other disease characteristics. Hence, it is vital to identify the influencing factors for the efficacy of ^{131}I therapy for guiding clinical practices, and analysis of these factors can help determine the dose for the clinical ^{131}I therapy, raise the cure rate and reduce adverse reactions. In the present study, univariate and multivariate logistic regression analyses were conducted on the age, gender, pathological type and stage of tumors, surgical method and pre-treatment TSH level, TGAb and RAIU (%) in 94 children and adolescents DTC patients receiving ^{131}I therapy. Based on the results, the clinical tumor stage and pre-treatment Tg and RAIU were independent influencing factors for the efficacy of ^{131}I therapy.

It is controversial whether pathological types affect the remission rate of DTC after ^{131}I therapy. Lymph node metastasis tends to develop in PTC, while distant metastasis often occurs in FTC due to the main hematogeneous metastasis, and it is generally held that thyroid remnant ablation in PTC is more efficactive than in FTC [14]. According to another report, the success rate of the initial ^{131}I ablation of thyroid remnants was not associated with pathological types that will affect the remission rate after ^{131}I therapy for several times, and FTC had a lower remission rate and high recurrence and mortality rates [15]. However, FTC in children and adolescents may be less invasive, and less likely to metastasize and recur than PTC, so FTC patients may have longer survival [16]. Based on the results of this study, the efficacy was not associated with pathological types ($p>0.05$), but the efficacy of ^{131}I therapy remains to be analyzed in more children and adolescents FTC patients ^{131}I in the future, since the sample size (3 out of 94) was too small in this study.

It is proposed in the ATA guidelines for the diagnosis and treatment of DTC that lesions >2 cm, involvement in the peripheral tissues and multifoci heighten the risk of recurrence and metastasis of thyroid carcinoma [17]. In this study, the tumor stage, lesions with a diameter >2 cm and large numbers of tumors were the crucial factors affecting the prognosis. Postoperative routine ^{131}I therapy is advised for the child and adolescent DTC patients with the above high-risk factors for recurrence to lower the recurrence rate.

Tg, a kind of globulin synthesized and secreted in thyroid tissues, serves as an important marker for monitoring tumor recurrence and metastasis in the postoperative follow-up of DTC patients, and its detection is more sensitive than other imaging examinations [7]. According to the results of this study, the low level of Tg before ^{131}I therapy was an important factor for improving the response rate in the children and adolescent DTC patients and also an independent influencing factor for the efficacy. RAIU represents the ability of thyroid tissues and metastases to specifically take in RAI, and the higher RAIU generally indicates more remnants [18]. In the present study, the univariate and multivariate analyses results manifested that low RAIU was a critical factor for improving efficacy, suggesting that a low level of RAIU can potentiate the efficacy. However, surgical procedures were not statistically significant ($p>0.05$). A total or near-total thyroidectomy was performed for 94 DTC patients. During the total thyroidectomy, a macro relative concept, thyroid remnants are preserved to protect the recurrent laryngeal nerve, parathyroid glands and other tissues in child and adolescent patients who particularly have relatively more preserved thyroid remnants to ensure the forthcoming growth, development and quality of life. The near-total thyroidectomy refers to the operation after which there are less than 1-2% residual thyroid tissues. Therefore, the efficacy is not correlated with the surgical procedures probably due to the overlap of the definition of the two surgical procedures. Since

radical surgery reduces the risk of disease recurrence, and low RAIU improves the efficacy, thyroid tissues should be removed surgically as completely as possible, without affecting the growth, development and quality of life of patients [19].

The present study has some shortcomings, such as a limited sample size, less comprehensive follow-up contents and no statistical analysis on the long-term survival of patients. At present, there has been neither consensus on the standard therapy for DTC in children and adolescents or definite specifications for ^{131}I dose formulation. Therefore, prospective clinical studies featuring strict design, high reliability and large sample size are required to provide supportive data for the conclusion in this study in the future.

Conclusions

^{131}I therapy has exact efficacy in DTC in children and adolescents, and the clinical tumor stage and pre-treatment Tg and RAIU are the major factors affecting the efficacy.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Catelinois O, Verger P, Colonna M, Rogel A, Hemon D, Tirmarche M. Projecting the time trend of thyroid cancers: its impact on assessment of radiation-induced cancer risks. Health Phys 2004;87:606-14.
2. Bashir K, Sarwar R, Fatima S, Saeed S, Mahjabeen I, Akhtar KM. Haplotype analysis of XRCC1 gene polymorphisms and the risk of thyroid carcinoma. J BUON 2018;23:234-43.
3. Wei Q, Wu D, Luo H, Wang X, Zhang R, Liu Y. Features of lymph node metastasis of papillary thyroid carcinoma in ultrasonography and CT and the significance of their combination in the diagnosis and prognosis of lymph node metastasis. J BUON 2018;23:1041-8.
4. Deligiorgi MV, Mahaira H, Eftychiadis C et al. RANKL, OPG, TRAIL, KRas, and c-Fos expression in relation to central lymph node metastases in papillary thyroid carcinoma. J BUON 2018;23:1029-40.
5. Miccoli P, Minuto MN, Ugolini C et al. Papillary thyroid cancer: pathological parameters as prognostic factors in different classes of age. Otolaryngol Head Neck Surg 2008;138:200-3.
6. Mitsutake N, Knauf JA, Mitsutake S, Mesa CJ, Zhang L, Fagin JA. Conditional BRAFV600E expression induces DNA synthesis, apoptosis, dedifferentiation, and chromosomal instability in thyroid PCCL3 cells. Cancer Res 2005;65:2465-73.
7. Durante C, Costante G, Filetti S. Differentiated thyroid carcinoma: defining new paradigms for postoperative management. Endocr Relat Cancer 2013;20:R141-54.
8. Demidchik YE, Demidchik EP, Reiners C et al. Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. Ann Surg 2006;243:525-32.
9. Hanscheid H, Verburg FA, Biko J et al. Success of the postoperative 131I therapy in young Belarusian patients with differentiated thyroid cancer after Chernobyl depends on the radiation absorbed dose to the blood and the thyroglobulin level. Eur J Nucl Med Mol Imaging 2011;38:1296-302.
10. Parisi MT, Mankoff D. Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. Semin Nucl Med 2007;37:340-56.
11. Kuo SF, Chao TC, Chang HY et al. The role of radioactive iodine therapy in young patients with papillary thyroid cancer. Clin Nucl Med 2009;34:4-6.
12. Yamashita S, Saenko V. Mechanisms of Disease: molecular genetics of childhood thyroid cancers. Nat Clin Pract Endocrinol Metab 2007;3:422-9.
13. Faggiano A, Coulot J, Bellon N et al. Age-dependent variation of follicular size and expression of iodine transporters in human thyroid tissue. J Nucl Med 2004;45:232-7.
14. Roy R, Kouniavsky G, Schneider E et al. Predictive factors of malignancy in pediatric thyroid nodules. Surgery 2011;150:1228-33.
15. McHenry CR, Phitayakorn R. Follicular adenoma and carcinoma of the thyroid gland. Oncologist 2011;16:585-93.
16. Raval MV, Bentrem DJ, Stewart AK, Ko CY, Reynolds M. Utilization of total thyroidectomy for differentiated thyroid cancer in children. Ann Surg Oncol 2010;17:2545-53.
17. Francis GL, Waguespack SG, Bauer AJ et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015;25:716-59.
18. Jin Y, Ruan M, Cheng L et al. Radioiodine Uptake and Thyroglobulin-Guided Radioiodine Remnant Ablation in Patients with Differentiated Thyroid Cancer: A Prospective, Randomized, Open-Label, Controlled Trial. Thyroid 2019;29:101-10.
19. Bongers PJ, Greenberg CA, Hsiao R et al. Differences in long-term quality of life between hemithyroidectomy and total thyroidectomy in patients treated for low-risk differentiated thyroid carcinoma. Surgery 2020;167:94-101.