Childhood differentiated thyroid carcinoma: clinical course and late effects of treatment

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CHAPTER 1

General introduction

The thyroid gland

The thyroid is an endocrine gland, located ventrally from the trachea. The gland consists of two lobes that are connected through the isthmus. The thyroid is composed of follicles, follicular cells, and parafollicular cells (also called C cells) (1). The follicular cells produce thyroxin (T4, thyroid hormone) and triiodothyronine (T3), which are composed of iodine and thyroglobulin (Tg, a precursor protein from the thyroid). T4 is the sole product of the thyroid gland, whereas T3 is produced in the thyroid and peripheral organs by deiodination of T4. Thyroid hormones are involved in a wide range of mechanisms within the body, and affect basal metabolic activity, growth, and neural development (2). Calcitonin, a hormone produced by the C cells and this hormone decreases the blood calcium concentration (3). The hypothalamic-pituitary-thyroid axis regulates the synthesis of the thyroid hormones. The hypothalamus releases thyrotropin-releasing hormone (TRH), causing the anterior pituitary gland to secrete thyroid-stimulating hormone (TSH). This results in thyroid hormone synthesis and secretion. T3 and T4 subsequently provide negative feedback to the hypothalamus and the pituitary gland (2).

Thyroid cancer and differentiated thyroid cancer

Thyroid cancer ensues when cells of the thyroid gland reproduce uncontrollably and develop the potential to spread (metastasize). Histologically, the most common subtype of thyroid cancer is (well-)differentiated thyroid cancer (DTC, which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)). DTC accounts for 90% of all thyroid cancers (4, 5). Differentiated cancers derive from the follicular cells. DTC can occur at all ages, but its peak incidence is from the 3rd to 5th life decades (4). Poorly differentiated thyroid cancers, such as medullary thyroid cancer (MTC, arising from C cells) and anaplastic thyroid cancer (ATC, arising from the follicular epithelium) are less common (5, 6).

Differentiated thyroid cancer in children

DTC in children (diagnosed before the age of 19 years) is rare, but incidence rates are increasing (7). Age-adjusted incidence rates of childhood DTC are 0.6 to 11.0 per 100,000, varying between age group and country of origin (7-9). Most children diagnosed with DTC are post-pubertal. Up to puberty, the incidence of DTC in boys and girls is similar, but from puberty onwards most patients are female (6), making female sex the most important risk factor for DTC. The explanation for this sex-dependent diagnosis probably lies within the proliferative effect of estrogen on thyroid cells, but the exact mechanism is not completely understood (10-12). The emergence of thyroid cancer cannot always be explained, but known risk factors for developing childhood thyroid cancer are exposure to radiation, iodine deficiency, a positive family history for DTC, gene rearrangements, or a thyroid cancer syndrome (13-15).

Symptoms of childhood differentiated thyroid cancer

Children most often present with an asymptomatic solitary thyroid nodule or neck mass. Compressive symptoms, such as hoarseness, dysphagia, dyspnea, or experiencing a choking sensation are less common (16-18).

Diagnosis and treatment of childhood differentiated thyroid cancer

Up to now, three official guidelines for the management of DTC in children have been published (19-21). Clinical evaluation, ultrasonography (US), and fine needle aspiration (FNA) are used to determine the origin of the thyroid nodule or neck mass (19). FNA can be makes it possible to obtain cells of the thyroid nodule and/or suspicious lymph node. The FNA of the thyroid nodule can then be evaluated according to the pathologic Bethesda System for Reporting Thyroid Cytopathology (22). Six different Bethesda diagnostic categories determine the follow-up measures, which range from clinical follow-up to surgical intervention (19, 22). When FNA indicates a strong possibility of malignant cells, treatment in children generally consists of a total thyroidectomy. Depending on the presence and the site of metastases, a central or (bi)lateral lymph node dissection can be performed (19). Children are postoperatively staged by means of the tumor-node-metastasis (TNM) classification (23, 24) and corresponding risk level of the disease (19), which determine the consecutive (intensity of the) treatment. After surgery, radioactive iodine (^{131}I) can be administered. When administered in a high dose, the beta radiation of this radioisotope of iodine destroys thyroid cells (25), and may decrease the risk of recurrence of the disease (17, 26, 27). Although the precise role of ^{131}I during treatment of low risk DTC has not yet been defined, the additional value of its administration in children with advanced disease is more established (27, 28). Subsequently, thyroid hormone supplementation with levothyroxine compensates the lack of thyroid hormone resulting from the thyroidectomy, but is also used to induce a certain level of TSH suppression (TSH suppression therapy). The aim of TSH suppression therapy is to suppress the growth-promoting effect of TSH on the thyroid cells, thereby preventing the (re)growth of malignant cells (29, 30). In high risk patients, a more intensive TSH suppression is advised. Recommendations are based on findings in adults, since no studies have as yet focused solely on evaluating children (19). Follow-up of the disease consists of clinical evaluation and neck palpation, US, and measuring of Tg during the thyroid hormone suppletion. Tg serves as a marker for residual or recurrent disease (19).

Outcome after treatment of childhood differentiated thyroid cancer

Subsequent to treatment, survival rates of childhood DTC are up to 99% after 30 years of follow-up (6, 31). Although survival in children is excellent, a relatively high percentage (10 to 30%) of the children develops *recurrent disease*, occurring even decades after diagnosis (30, 32-34). Moreover, after treatment some patients still have

evidence of disease, which is called *persistent disease*. Recurrent or persistent disease occurs more frequently in patients with advanced disease upon diagnosis (35, 36).

Differentiated thyroid cancer in children and adults

In the past, DTC was presumed to be similar in children and adults. However, more advanced knowledge indicates great differences between DTC in children and adults.

Upon diagnosis, children present with more advanced and aggressive disease than do adults. Paradoxically, children have better overall survival rates in children than adults, but also more frequent persistent disease and recurrences (16-18, 31, 32, 34, 37-43). In childhood, the mutational landscape of DTC differs from that of adults (44-54). Table 1 presents an overview an overview of differences between DTC diagnosed during childhood and adulthood.

To date, however, no clear explanation can account for these differences between adult and childhood DTC. Although genetic alterations may play a role, studies are not conclusive. A higher expression of the sodium iodine symporter (NIS, essential in the uptake of iodine) in children may also help to explain their better responsiveness to ^{131}I administrations, but ultimately the origin of the difference between adult and childhood DTC is probably multifactorial.

Adverse effects after childhood cancer

Unfortunately, *survivors* of (childhood) cancer experience unwanted effects of the (treatment of the) cancer. These side effects are being increasingly recognized, as recent decades have seen an increase in the overall survival rate of childhood cancer (60). Side effects can occur during treatment, but may sometimes become manifest only years later. These *late effects* can be physical, mental, and/or psychosocial, such as cognitive impairment, fertility problems, diagnosis of a secondary malignancy,

Table 1. Differences between DTC diagnosed during childhood and adulthood

	Childhood DTC	Adult DTC
Malignant origin of thyroid nodules [16, 18, 39, 40]	19 to 26%	12 to 14%
Incidence of lymph node metastases [17, 31, 34, 41-43, 55]	40 to 90%	15 to 50%
Incidence of distant metastases [17, 56, 57]	20 to 30%	2 to 20%
Most prevalent mutational alteration [44-54]	RET fusion	BRAF V600E mutation
Recurrence rate [32, 34, 58]	Up to 32%	5%
Rate of persistent disease [32, 36, 58, 59]	5 to 33%	2 to 3%
10-year survival rate [17, 32, 37, 38]	95 to 100%	85 to 91%

Abbreviations: DTC, differentiated thyroid carcinoma; RET, rearranged during transfection; BRAF, v-raf murine sarcoma viral oncogene homolog B.

and fatigue (61). Depending on the type of late effect, treatment or support can be offered, but not all effects can be prevented or resolved.

Adverse and late effects after childhood differentiated thyroid cancer

Because the majority of childhood DTC patients will survive their disease, it is important to evaluate late effects in these survivors. However, in contrast to the knowledge of late effects in many other childhood malignancies, little is known about possible adverse effects of childhood DTC.

During treatment of DTC, surgical complications like surgical site infection, parathyroid damage (causing hypocalcaemia) and recurrent laryngeal nerve injury (causing hoarseness or loss of voice) can occur (62, 63). In addition, short-term side effects of ^{131}I administration are radiation thyroiditis, nausea, vomiting, sialadenitis, gastro-intestinal symptoms, and bone-marrow suppression. In the long-term, administration of ^{131}I for adult DTC is associated with salivary dysfunction or sialadenitis, pulmonary fibrosis, secondary malignancies, and gonadal damage in both men and women (causing fertility problems) (32, 64-69). Other long-term effects possibly induced by TSH suppression therapy are cardiovascular deterioration and loss of bone mineral density (also influenced by hypoparathyroidism) (29, 70-74). Moreover, general well-being or quality of life (QoL) can be affected by the diagnosis and the treatment of DTC (75-78).

Some studies have been performed in survivors of childhood DTC, but current knowledge is based mainly on late effects of DTC on adults. Because of the differences between childhood and adult DTC, as shown above, late effects may also differ. However, specific knowledge of the late effects of treatment for DTC during childhood is limited because of the scarcity of studies, the small number of patients evaluated, the lack of clear study definitions, or the poor quality of study designs.

Aims and outline of this thesis

The aim of the current thesis is to evaluate the clinical course and late effects of childhood DTC. The results will ultimately benefit newly diagnosed patients, patients previously treated for DTC, caregivers, and treating physicians.

A multicenter, cross-sectional study was conducted in the Netherlands. Patients diagnosed with DTC before the age of 19 years between 1970 and 2013 were included. **Chapter 2** consists of an overview of the disease, treatment, outcomes, and follow-up characteristics of these patients. A minority of patients had distant metastases (DM). **Chapter 3** specifically evaluates the clinical course of DTC in a large cohort of childhood DTC patients diagnosed with DM. This study was performed at the University of Texas MD Anderson Cancer Center in the United States.

Long-term treatment effects of ^{131}I after childhood DTC in the Netherlands are evaluated in the subsequent chapters. Female fertility after treatment is studied in

Chapter 4, where we evaluate reproductive characteristics in female survivors of childhood DTC, combined with levels of Anti-Müllerian hormone (AMH, a marker of ovarian reserve). Because the minority of childhood DTC patients is male, to attain a substantial and representative group of survivors, **Chapter 5** includes a study of male fertility after treatment in survivors of *adult* DTC. Male fertility was evaluated by performing semen analyses, and assessing reproductive hormones and reproductive characteristics. Adverse effects of long-term TSH suppression therapy are evaluated in **Chapter 6**, including effects on cardiac function in survivors of childhood DTC. The first evaluation of these patients, performed five years after their childhood DTC diagnosis, showed that 21% of the survivors had asymptomatic diastolic dysfunction (79). **Chapter 6** includes a re-evaluated of patients after a total follow-up period of 10 years to assess the course of their cardiac function. In **Chapter 7**, long-term thyroid cancer-specific QoL, health-related QoL, fatigue, and anxiety and depression are evaluated in survivors who were at least 5 years in follow-up after diagnosis. Because childhood cancer has been known to disrupt the course of life, **Chapter 8** evaluates psychosocial developmental milestones in childhood DTC survivors. **Chapter 9** contains the summary and general discussion of this thesis, and suggests it implications.

I

REFERENCES

1. Schünke M, Schulte E, Schumacher U. Prometheus anatomische atlas 2 - Hoofd, hals en neuroanatomie. 2 ed. Houten: Bohn Stafleu van Loghum; 2010. 200-203 p.
2. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012;122(9):3035-3043.
3. Morton DA, Foreman KB, Albertine KH. Viscera of the Neck. The Big Picture: Gross Anatomy, 2e. New York, NY: McGraw-Hill Education; 2019.
4. NKR Cijfers [Internet]. Integraal Kankercentrum Nederland. 2020 [cited April 2020]. Available from: https://www.iknl.nl/nkr-cijfers.
5. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006;295(18):2164-2167.
6. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res. 2009;156(1):167-172.
7. Schmidt Jensen J, Gronhoj C, Mirian C, Jensen DH, Friborg J, Hahn CH, Agander TK, Hjuler T. Incidence and survival of thyroid cancer in children, adolescents, and young adults in Denmark: a nationwide study from 1980 to 2014. Thyroid. 2018;28(9):1128-1133.
8. Dermody S, Walls A, Harley EH, Jr. Pediatric thyroid cancer: an update from the SEER database 2007-2012. Int J Pediatr Otorhinolaryngol. 2016;89:121-126.
9. Steliarova-Foucher E, Stiller CA, Pukkala E, Lacour B, Plesko I, Parkin DM. Thyroid cancer incidence and survival among European children and adolescents (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006;42(13):2150-2169.
10. Manole D, Schildknecht B, Gosnell B, Adams E, Derwahl M. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. J Clin Endocrinol Metab. 2001;86(3):1072-1077.
11. Juvenal G, Christophe D, Roger P, Pisarev M. Thyroid function and growth regulation under normal and abnormal conditions. J Thyroid Res. 2011;2011:805036-805036.
12. Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocr Relat Cancer. 2014;21(5):T273-283.
13. Liu Y, Su L, Xiao H. Review of factors related to the thyroid cancer epidemic. Int J Endocrinol. 2017;2017:5308635-5308635.
14. Tucker MA, Jones PHM, Boice JD, Robison LL, Stone BJ, Stovall M, Jenkin RDT, Lubin JH, Baum ES, Siegel SE, Meadows AT, Hoover RN, Fraumeni JF, the Late Effects Study G. Therapeutic radiation at a young age is linked to secondary thyroid cancer. Cancer Res. 1991;51(11):2885.
15. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res. 2015;8(1):8.
16. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer. 2006;13(2):427-453.
17. Rivkees SA, Mazzaferri EL, Verburg FA, Reiners C, Luster M, Breuer CK, Dinauer CA, Udelsman R. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. Endocr Rev. 2011;32(6):798-826.
18. Bessey LJ, Lai NBK, Coorough NE, Chen H, Sippel RS. The incidence of thyroid cancer by fine needle aspiration varies by age and gender. J Surg Res. 2013;184(2):761-765.
19. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S, American Thyroid Association Guidelines Task Force. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015;25(7):716-759.
20. Jarzab B, Dedecjus M, Slowinska-Klencka D, Lewinski A, Adamczewski Z, Anielski R, Baglaj M, Baldys-Waligorska A, Barczynski M, Bednarczuk T, Bossowski A, Buziak-Bereza M, Chmielik E, Cichocki A, Czarniecka A, Czepczynski R, Dzieciol J, Gawlik T, Handkiewicz-Junak D, Hasse-Lazar K, Hubalewska-Dydejczyk A, Jazdzewski K, Jurecka-Lubieniecka B, Kalemba M, Kaminski G, Karbownik-Lewinska M, Klencki M, Kos-Kudla B, Kotecka-Blicharz A, Kowalska A, Krajewska J, Kropinska A, Kukulska A, Kulik E, Kulakowski A, Kuzdak K, Lange D, Ledwon A, Lewandowska-Jablonska E, Lacka K, Michalik B, Nasierowska-Guttmejer A, Nauman J, Niedziela M, Malecka-Tendera E, Oczko-Wojciechowska M, Olczyk T, Paliczka-Cieslik E, Pomorski L, Puch Z, Roskosz J, Ruchala M, Rusinek D, Sporny S, Stanek-Widera A, Stojcev Z, Sygula A, Syrenicz A, Szpak-Ulczok S, Tomkalski T, Wygoda

Z, Wloch J, Zembala-Nozynska E. Guidelines of Polish National Societies diagnostics and treatment of thyroid carcinoma. 2018 Update. Endokrynol Pol. 2018;69(1):34-74.
21. Lebbink CA, Dekker BL, Bocca G, Braat AJ, Derikx JP, Dierselhuis MP, de Keizer B, Kruijff S, Kwast AB, van Nederveen FH, Nieveen van Dijkum E, Nievelstein RA, Peeters RP, Terwisscha van Scheltinga CE, Tissing WJ, van der Tuin K, Vriens MR, Zsiros J, van Trotsenburg AS, Links TP, van Santen HM. New national recommendations for the treatment of pediatric differentiated thyroid carcinoma in the Netherlands. Eur J Endocrinol. 2020;183(4):P11-P18.
22. Cibas ES, Ali SZ. The 2017 Bethesda System for reporting thyroid cytopathology. Thyroid. 2017;27(11):1341-1346.
23. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours: John Wiley & Sons; 2009.
24. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours: Wiley; 2017.
25. Preedy VR, Burrow GN, Watson RR. Comprehensive handbook of iodine: nutritional, biochemical, pathological and therapeutic aspects: Academic Press; 2009.
26. Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Kropinska A, Pomorski L, Kukulska A, Prokurat A, Wygoda Z, Jarzab B. Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. J Nucl Med. 2007;48(6):879-888.
27. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer. 2005;12(4):773-803.
28. Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Mang O, Lau WH. Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. Pediatr Blood Cancer. 2004;42(2):176-183.
29. Brabant G. Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? J Clin Endocrinol Metab. 2008;93(4):1167-1169.
30. Landau D, Vini L, A'Hern R, Harmer C. Thyroid cancer in children: the Royal Marsden Hospital experience. Eur J Cancer. 2000;36(2):214-220.
31. Hay ID, Johnson TR, Kaggal S, Reinalda MS, Iniguez-Ariza NM, Grant CS, Pittock ST, Thompson GB. Papillary thyroid carcinoma (PTC) in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936-2015). World J Surg. 2018;42(2):329-342.
32. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010;34(6):1192-1202.
33. Grigsby PW, Gal-or A, Michalski JM, Doherty GM. Childhood and adolescent thyroid carcinoma. Cancer. 2002;95(4):724-729.
34. Welch Dinauer CA, Tuttle RM, Robie DK, McClellan DR, Svec RL, Adair C, Francis GL. Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. Clin Endocrinol (Oxf). 1998;49(5):619-628.
35. Russo M, Malandrino P, Moleti M, Vermiglio F, D'Angelo A, La Rosa G, Sapuppo G, Calaciura F, Regalbuto C, Belfiore A, Vigneri R, Pellegriti G. Differentiated thyroid cancer in children: heterogeneity of predictive risk factors. Pediatr Blood Cancer. 2018;65(9):e27226.
36. Verburg FA, de Keizer B, Lam MGEH, de Klerk JMH, Lips CJM, Borel-Rinkes IHM, van Isselt JW. Persistent disease in patients with papillary thyroid carcinoma and lymph node metastases after surgery and Iodine-131 ablation. World J Surg. 2007;31(12):2309-2314.
37. Eustatia-Rutten CFA, Corssmit EPM, Biermasz NR, Pereira AM, Romijn JA, Smit JW. Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2006;91(1):313-319.
38. Links TP, van Tol KM, Jager PL, Plukker JT, Piers DA, Boezen HM, Dullaart RP, de Vries EG, Sluiter WJ. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. Endocr Relat Cancer. 2005;12(2):273-280.
39. Cherella CE, Angell TE, Richman DM, Frates MC, Benson CB, Moore FD, Barletta JA, Hollowell M, Smith JR, Alexander EK, Cibas ES, Wassner AJ. Differences in thyroid nodule cytology and malignancy risk between children and adults. Thyroid. 2019;29(8):1097-1104.
40. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, Wassner AJ, Smith JR, Marqusee E, Alexander EK, Barletta J, Doubilet PM, Peters HE, Webb S, Modi BP, Paltiel HJ, Kozakewich H, Cibas ES, Moore FD, Jr., Shamberger RC, Larsen PR, Huang SA. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab. 2013;98(8):3238-3245.
41. Jarzab B, Handkiewicz-Junak D. Differentiated thyroid cancer in children and adults: same or distinct disease? Hormones (Athens, Greece). 2007;6(3):200-209.

42. LaFranchi SH. Inaugural management guidelines for children with thyroid nodules and differentiated thyroid cancer: children are not small adults. Thyroid. 2015;25(7):713-715.
43. Vaisman F, Corbo R, Vaisman M. Thyroid carcinoma in children and adolescents-systematic review of the literature. J Thyroid Res. 2011;2011:845362.
44. Yamashita S, Saenko V. Mechanisms of disease: molecular genetics of childhood thyroid cancers. Nat Clin Pract Endocrinol Metab. 2007;3(5):422-429.
45. Fenton C, Anderson J, Lukes Y, Dinauer CA, Tuttle RM, Francis GL. Ras mutations are uncommon in sporadic thyroid cancer in children and young adults. J Endocrinol Invest. 1999;22(10):781-789.
46. Fenton CL, Lukes Y, Nicholson D, Dinauer CA, Francis GL, Tuttle RM. The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. J Clin Endocrinol Metab. 2000;85(3):1170-1175.
47. Cordioli MI, Moraes L, Bastos AU, Besson P, Alves MT, Delcelo R, Monte O, Longui C, Cury AN, Cerutti JM. Fusion oncogenes are the main genetic events found in sporadic papillary thyroid carcinomas from children. Thyroid. 2017;27(2):182-188.
48. Diesen DL, Skinner MA. Pediatric thyroid cancer. Semin Pediatr Surg. 2012;21(1):44-50.
49. Sisdelli L, Cordioli M, Vaisman F, Moraes L, Colozza-Gama GA, Alves PAG, Jr., Araujo ML, Jr., Alves MTS, Monte O, Longui CA, Cury AN, Carvalheira G, Cerutti JM. AGK-BRAF is associated with distant metastasis and younger age in pediatric papillary thyroid carcinoma. Pediatr Blood Cancer. 2019;66(7):e27707.
50. Galuppini F, Vianello F, Censi S, Barollo S, Bertazza L, Carducci S, Colato C, Manso J, Rugge M, Iacobone M, Watutantrige Fernando S, Pennelli G, Mian C. Differentiated thyroid carcinoma in pediatric age: genetic and clinical scenario. Front Endocrinol (Lausanne). 2019;10:552.
51. Faggiano A, Coulot J, Bellon N, Talbot M, Caillou B, Ricard M, Bidart JM, Schlumberger M. Age-dependent variation of follicular size and expression of iodine transporters in human thyroid tissue. J Nucl Med. 2004;45(2):232-237.
52. Pekova B, Dvorakova S, Sykorova V, Vacinova G, Vaclavikova E, Moravcova J, Katra R, Vlcek P, Sykorova P, Kodetova D, Vcelak J, Bendlova B. Somatic genetic alterations in a large cohort of pediatric thyroid nodules. Endocr Connect. 2019;8(6):796-805
53. Alzahrani AS, Murugan AK, Qasem E, Alswailem M, Al-Hindi H, Shi Y. Single point mutations in pediatric differentiated thyroid cancer. Thyroid. 2017;27(2):189-196.
54. Mostoufi-Moab S, Labourier E, Sullivan L, LiVolsi V, Li Y, Xiao R, Beaudenon-Huibregtse S, Kazahaya K, Adzick NS, Baloch Z, Bauer AJ. Molecular testing for oncogenic gene alterations in pediatric thyroid lesions. Thyroid. 2018;28(1):60-67.
55. Wang TS, Dubner S, Sznyter LA, Heller KS. Incidence of metastatic well-differentiated thyroid cancer in cervical lymph nodes. Arch Otolaryngol Head Neck Surg. 2004;130(1):110-113.
56. Farahati J, Bucsky P, Parlowsky T, Mader U, Reiners C. Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology. Cancer. 1997;80(11):2156-2162.
57. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schlumberger M. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-2899.
58. Medas F, Canu GL, Boi F, Lai ML, Erdas E, Calò PG. Predictive factors of recurrence in patients with differentiated thyroid carcinoma: a retrospective analysis on 579 patients. Cancers (Basel). 2019;11(9):1230.
59. Nascimento C, Borget I, Ghuzlan AA, Deandreis D, Chami L, Travagli JP, Hartl D, Lumbroso J, Chougnet C, Lacroix L, Baudin E, Schlumberger M, Leboulleux S. Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. Endocrin Relat Cancer. 2011;18(2):R29.
60. Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M, EUROCARE Working Group. Childhood cancer survival trends in Europe: a EUROCARE working group study. J Clin Oncol. 2005;23(16):3742-3751.
61. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board, Hewitt M WS, Simone JV. Childhood Cancer Survivorship: Improving Care and Quality of Life. Washington (DC): National Academies Press (US); 2003. p. 49-89.
62. van Santen HM, Aronson DC, Vulsma T, Tummers RF, Geenen MM, de Vijlder JJ, van den Bos C. Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. Eur J Cancer. 2004;40(11):1743-1751.
63. Elfenbein DM, Schneider DF, Chen H, Sippel RS. Surgical site infection after thyroidectomy: a rare but significant complication. J Surg Res. 2014;190(1):170-176.
64. Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer. 2017;64(11):e26595.

65. Sarkar SD, Beierwaltes WH, Gill SP, Cowley BJ. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. J Nucl Med. 1976;17(6):460-464.
66. Marti JL, Jain KS, Morris LGT. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. Thyroid. 2015;25(6):681-687.
67. Chen L, Shen Y, Luo Q, Yu Y, Lu H, Zhu R. Pulmonary fibrosis following radioiodine therapy of pulmonary metastases from differentiated thyroid carcinoma. Thyroid. 2010;20(3):337-340.
68. Esfahani AF, Eftekhari M, Zenooz N, Saghari M. Gonadal function in patients with differentiated thyroid cancer treated with (131)I. Hell J Nucl Med. 2004;7(1):52-55.
69. Bourcigaux N, Rubino C, Berthaud I, Toubert ME, Donadille B, Leenhardt L, Petrot-Keller I, Brailly-Tabard S, Fromigue J, de Vathaire F, Simon T, Siffroi JP, Schlumberger M, Bouchard P, Christin-Maitre S. Impact on testicular function of a single ablative activity of 3.7 GBq radioactive iodine for differentiated thyroid carcinoma. Hum Reprod. 2018;33(8):1408-1416.
70. Leonova TA, Drozd VM, Saenko VA, Mine M, Biko J, Rogounovitch TI, Takamura N, Reiners C, Yamashita S. Bone mineral density in treated at a young age for differentiated thyroid cancer after Chernobyl female patients on TSH-suppressive therapy receiving or not Calcium-D3 supplementation. Endocr J. 2015;62(2):173-182.
71. Mendonca Monteiro de Barros G, Madeira M, Vieira Neto L, de Paula Paranhos Neto F, Carvalho Mendonca LM, Correa Barbosa Lima I, Corbo R, Fleiuss Farias ML. Bone mineral density and bone microarchitecture after long-term suppressive levothyroxine treatment of differentiated thyroid carcinoma in young adult patients. J Bone Miner Metab. 2016;34(4):417-421.
72. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredeveld EJ, van der Horst-Schrivers AN, van der Horst IC, Kamphuisen PW, Plukker JT, Links TP, Lefrandt JD. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. J Clin Oncol. 2013;31(32):4046-4053.
73. Parker WA, Edafe O, Balasubramanian SP. Long-term treatment-related morbidity in differentiated thyroid cancer: a systematic review of the literature. Pragmatic and observational research. 2017;8:57-67.
74. Cooper DS. TSH suppressive therapy: an overview of long-term clinical consequences. Hormones (Athens). 2010;9(1):57-59.
75. Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJ, van Rijn RR, van der Pal HJ, Neggers SJ, Kremer LC, van Eck-Smit BL, van Santen HM. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma-a systematic review. Cancer Treat Rev. 2015;41(10):925-934.
76. Oren A, Benoit MA, Murphy A, Schulte F, Hamilton J. Quality of life and anxiety in adolescents with differentiated thyroid cancer. J Clin Endocrinol Metab. 2012;97(10):1933.
77. Metallo M, Groza L, Brunaud L, Klein M, Weryha G, Feigerlova E. Long-term quality of life and pregnancy outcomes of differentiated thyroid cancer survivors treated by total thyroidectomy and I(131) during adolescence and young adulthood. Int J Endocrinol. 2016;2016:7586482.
78. de Oliveira Chachamovitz DS, dos Santos Vigario P, Nogueira Cordeiro MF, de Castro CL, Vaisman M, dos Santos Teixeira Pde F. Quality of life, muscle strength, and fatigue perception in patients on suppressive therapy with levothyroxine for differentiated thyroid carcinoma. Am J Clin Oncol. 2013;36(4):354-361.
79. Klein Hesselink MS, Bocca G, Hummel YM, Brouwers AH, Burgerhof JGM, van Dam EWCM, Gietema JA, Havekes B, van den Heuvel-Eibrink MM, Corssmit EPM, Kremer LCM, Netea-Maier RT, van der Pal HJH, Peeters RP, Plukker JTM, Ronckers CM, van Santen HM, van der Meer P, Links TP, Tissing WJE. Diastolic dysfunction is common in survivors of pediatric differentiated thyroid carcinoma. Thyroid. 2017;27(12):1481-1489.