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André Borsatto Zanella

Avanços no Manejo do Carcinoma Diferenciado da Tireoide em Crianças e Adolescentes

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2018

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Esta Tese de Doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, sendo apresentada na forma de manuscritos sobre o tema da Tese:

- **Artigo de revisão:** Avanços no Manejo do Câncer Diferenciado de Tireoide em Crianças e Adolescentes.

- **Artigo original:** Role of Postoperative Stimulated Thyroglobulin as Prognostic Factor for Differentiated Thyroid Carcinoma in Children and Adolescents. Thyroid 2017;27(6):787-792.

- **Artigo original:** Dynamic Risk Stratification in the Follow-up of Children and Adolescents with Differentiated Thyroid Cancer. Thyroid 2018;28(10):1285-1292.

Além dos artigos já citados, ao longo do período do doutorado foram desenvolvidos os seguintes manuscritos relacionados:

- Scheffel RS, Zanella AB, Antunes D, Dora JM, Maia AL. Low Recurrence Rates in Differentiated Thyroid Carcinoma: A Single Institution Experience. Thyroid, v. 25, p. 883-889, 2015.
- Scheffel RS, Zanella AB, Dora JM, Maia AL. Timing of Radioactive Iodine Administration Does Not Influence Outcomes in Patients with Differentiated Thyroid Cancer. Thyroid, v. 26, p. 1623-1629, 2016.
- Duval MADS, Zanella AB, Cristo AP, Faccin CS, Graudenz MS, Maia AL. Impact of Serum TSH and Anti-Thyroglobulin Antibody Levels on Lymph Node Fine-Needle Aspiration Thyroglobulin Measuremnts in Differentiated Thyroid Carcinoma Patients. European Thyroid Journal, v. 6, p. 292-297, 2017.
- Weber Pasa M, Scheffel RS, Zanella AB, Maia AL, Dora JM. Consumptive Hypothyroidism: Case Report of Hepatic Hemangioendotheliomas Successfully Treated Wth Vincristine and Systematic Review of the Syndrome. European Thyroid Journal, v. 6, p. 321-327, 2017.

LISTA DE ABREVIATURAS E SIGLAS

ATA – Associação Americana de Tireoide; American Thyroid Association

BRAF – Serine/threonine-protein kinase B-Raf

CDT – Carcinoma Diferenciado da Tireoide

CFT – Carcinoma Folicular de Tireoide

CI – Confidence interval

CPT – Carcinoma Papilar de Tireoide

CT – Computed Tomography

DTC – Differentiated Thyroid Carcinoma

EVT6 - translocação-Ets-leucemia virus

DRS - Estratificação dinâmica de risco; dynamic risk stratification

FTC – Follicular Thyroid Carcinoma

HCPA – Hospital de Clínicas de Porto Alegre

HR – Hazard ratio

MACIS – Metastasis, Age, Completeness of resection, Invasion and Size

MAPK – Mitogen-activated protein kinase

NTKR – receptor neurotrófico tirosina kinase

POTg - Tireoglobulina pós-operatória; post-operative thyroglobulin

PTC – Papillary Thyroid Carcinoma

RAI – Iodo radioativo; Radioactive Iodine

RAS – Rat sarcoma virus

RCT – Rastreamento Corporal Total

RET – RE arrangement during transfection

RET/PTC - RET tyrosine kinase domain rearrangement with different partners

ROC – Receiver Operator Characteristics

SD – Standard Deviation

SEER - Surveillance, Epidemiology, and End Results

sPOTg – tireoglobulina estimulada pós-operatória; stimulated post-operative thyroglobulin

SPSS – Statistical Package for Social Science Professional Software

sTg – Tireoglobulina estimulada; Stimulated Thyroglobulin

Tg – Tireoglobulina; Thyroglobulin

TgAb – Antithyroglobulin Antibodies

Tg-Ac – anticorpos anti-tireoglobulina

TGCA - Cancer Genome Atlas Research

Tg-T4 – Tireoglobulina em uso de levotiroxina; Thyroglobulin Levels Under TSH Supression

TNM/AJCC – American Joint Committee on Cancer staging system of tumor size, nodal metastases and distant metastases

TSH – hormônio estimulante da tireoide; thyroid stimulating hormone, thyrotropin

US – Ultrasound

WBS – Whole Body Scan

SUMÁRIO

Parte I

Avanços no Manejo do Carcinoma Diferenciado da Tireoide em Crianças e Adolescentes

Avanços no Manejo do Carcinoma Diferenciado da Tireoide em Crianças e Adolescentes

André B. Zanella, MD, Rafael Selbach Scheffel, MD,
José Miguel Dora, MD, PhD and Ana Luiza Maia, MD, PhD

Unidade de Tireoide, Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre e Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil.

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RESUMO

O carcinoma diferenciado de tireoide (CDT) constitui a neoplasia maligna mais comum do sistema endocrinológico na infância. O CDT em crianças e adolescentes costuma se apresentar como uma doença mais extensa e agressiva em relação a população adulta, porém apresenta um prognóstico excelente, mesmo em casos de doença avançada. No entanto, alguns pacientes apresentam doença persistente e/ou recorrente que leva a aumento da morbidade. De fato, um grande desafio no manejo do CDT é a identificação desta parcela de pacientes, com maior risco de desfechos desfavoráveis. Desse modo, um passo fundamental na avaliação dos pacientes com CDT consiste na determinação do prognóstico individual. Para tanto, devem ser analisados os fatores prognósticos conhecidos relacionados ao paciente e ao tumor e os sistemas de estratificação existentes (TNM/AJCCN, classificação de risco da American Thyroid Association e estratificação dinâmica de risco). No artigo de revisão abordamos criticamente o CDT em crianças e adolescentes, com especial ênfase na apresentação clínica, tratamento cirúrgico, avaliação de risco, acompanhamento e perspectivas futuras da doença. Salientamos quatro aspectos importantes: 1) as diversas diferenças existentes entre o CDT pediátrico e adultos na patofisiologia, apresentação clínica e desfechos em longo prazo da doença; 2) existem grandes divergências em relação ao papel dos fatores prognósticos e sua associação com doença persistente/recorrente; 3) os sistemas de estadiamento e classificações de risco provém, na sua maioria, de estudos realizados em adultos, o que dificulta a sua aplicação para a população pediátrica; 4) embora ainda sejam necessários mais estudos, os marcadores moleculares parecem ser um importante fator prognóstico nas crianças e adolescentes com CDT, além de permitirem, futuramente, o uso de terapias-alvo para tratamento individualizado.

No nosso estudo que avaliou o papel da tireoglobulina estimulada pós-operatória (sPOTg) como fator prognóstico do CDT em crianças e adolescentes, demonstramos que esse exame possui alta acurácia para predizer o risco de doença persistente nessa população.

No nosso estudo que avaliou o papel da estratificação dinâmica de risco em crianças e adolescentes com CDT, encontramos que ela é um forte preditor de desfecho da doença, podendo ser útil na definição de estratégias de acompanhamento da doença. Além disso, reforçamos o papel da sPOTg e sua associação com doença persistente, sendo que o valor de ponto de corte com maior sensibilidade e especificidade foi de 37,8 ng/mL.

OBJETIVOS

Objetivo geral

O objetivo dessa tese de doutorado é avaliar aspectos relacionados ao câncer diferenciado de tireoide em crianças e adolescentes que possam auxilar no manejo desses pacientes.

Objetivos específicos

Revisar criticamente o carcinoma diferenciado de tireoide em crianças e adolescentes, com ênfase nos tópicos de apresentação da doença, tratamento cirúrgico, avaliação de risco, acompanhamento e perspectivas futuras.

Avaliar os fatores prognósticos associados com doença persistente, com interesse particular na análise da tireglobulina estimulada pós-operatória em uma coorte contemporânea de crianças e adolescentes em acompanhamento em um centro de referência do sul do Brasil.

Avaliar o papel da estratificação dinâmica de risco como ferramenta prognóstica para estratificação de risco de doença em uma coorte contemporânea de crianças e adolescentes em acompanhamento em quatro diferentes centros de referência no sul do Brasil.

INTRODUÇÃO

O câncer de tireoide é raro na infância, porém constitui a neoplasia maligna mais comum do sistema endocrinológico nessa faixa etária, sendo responsável por 1,5 a 3% dos carcinomas em crianças e adolescentes nos Estados Unidos e Europa (1,2). No mundo, a incidência anual da doença em crianças varia entre 0,54 casos por 100.000 (3) a 1 caso por milhão (1, 4). No Brasil, a incidência pode alcançar 2% de todas as neoplasias pediátricas (5). Dados recentes do National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) demostraram aumento na sua incidência em pacientes com menos de 20 anos (6). Em uma base populacional americana que incluiu 2504 pacientes pediátricos com carcinoma papilar de tireoide (CPT), avaliados entre 1973 e 2011, a taxa de aumento da incidência foi da ordem de 2% ao ano (figura 1) (7). O mesmo estudo (7) também demonstrou que esse aumento ocorre especialmente na faixa de idade de 10-19 anos. O câncer de tireoide é mais comum no sexo feminino (8-11), sendo que dados recentes de um estudo italiano (9) demonstraram que a faixa de idade de 15-19 anos é onde existe a maior diferença na razão mulher/homem na incidência da doença, chegando a uma proporção maior do que 5:1.

Os dois tipos histológicos mais comuns do câncer de tireoide são o CPT e o carcinoma folicular de tireoide (CFT), denominados de carcinomas diferenciados da tireoide (CDT) e correspondendo a mais de 95% dos casos das neoplasias malignas da tireoide (8,12,13). O CPT é a forma mais comum na população pediátrica, representando mais de 90% dos casos (8). Em crianças mais novas (abaixo dos 10 anos), os subtipos esclerosante difusa e variante folicular do CPT são mais frequentes (14). Os CDT são originários das células foliculares e preservam as características das células foliculares normais, como a síntese e secreção de tireoglobulina (Tg), e captação de iodo (15).

O CDT é considerado uma neoplasia de comportamento indolente com baixas taxas de morbidade e mortalidade. O prognóstico nas crianças e adolescentes é considerado excelente, mesmo em casos de doença avançada (8,16,17). Porém, pacientes diagnosticados com CDT antes dos 10 anos de idade parecem ter um prognóstico pior (18,19). Um estudo populacional norte americano, realizado entre os anos 1992 e 2014, encontrou uma taxa de sobrevida em 20 anos, independente do estadiamento ao diagnóstico, de 96,3% e 99,7% no CFT e CPT, respectivamente (figura

2A) (9). Nos pacientes com doença localizada apenas na tireoide ou restrita a região cervical, as taxas de sobrevida em 20 anos foram de 98,9% e 98,0%, respectivamente (9). Nos pacientes com doença metastática ao diagnóstico, a sobrevida em 20 anos foi de 87,1% (figura 2B) (9). Cerca de 30 a 45% das crianças com metástases pulmonares desenvolvem doença persistente, porém estável, após terapia com iodo radioativo (RAI) (20,21). De forma interessante, parece ocorrer uma resposta clínica continuada, observada através do declínio dos níveis de Tg após o término do RAI em crianças com metástases pulmonares (22). No entanto, parte destes pacientes apresenta curso clínico mais agressivo, com altas taxas de doença persistente e recorrência com alta morbidade e aumento da mortalidade. De fato, um grande desafio no manejo do CDT é a identificação desta parcela de pacientes com maior risco de desfechos desfavoráveis.

O conhecimento e a identificação de fatores que auxiliem na avaliação de risco são de fundamental importância no manejo do CDT. A individualização do risco de morte e/ou recorrência no acompanhamento de pacientes com neoplasias malignas é uma tendência em praticamente todos os tipos de neoplasia (23). Recentemente, novas estratégias para individualização do risco dos pacientes com CDT têm sido propostas, como o uso de marcadores laboratoriais, moleculares e da resposta do paciente ao tratamento inicial, na tentativa de predizer o risco de cada paciente. O objetivo deste artigo é revisar criticamente o CDT em crianças e adolescentes, com ênfase nos tópicos de apresentação da doença, tratamento cirúrgico, avaliação de risco, acompanhamento e perspectivas futuras.

APRESENTAÇÃO CLÍNICA

A apresentação clínica mais comum do CDT é através de nódulo palpável de tireoide (24). Entretanto, o CPT frequentemente se apresenta com adenopatia cervical com ou sem nódulo detectável na tireoide, ou como achado incidental em exames de imagem não relacionados a tireoide (25). Ocasionalmente, o diagnóstico é feito apenas após a descoberta de metástases a distância (20,26,27).

Existem diferenças importantes na apresentação clínica do CPT e do CFT. O CPT costuma se apresentar com tumores multicêntricos e bilaterais, com metástases em linfonodos cervicais na maioria dos casos (20,27-37). Metástases hematogênicas podem acontecer em até 25% dos casos (25,38-44), porém geralmente estão associadas com

significativas metástases em região cervical (28,45). As variantes do CPT são: clássica, sólida, folicular e esclerosante difusa (46,47). O CFT geralmente se apresenta como tumor único e apresenta maior potencial para metástases hematogênicas para pulmões e ossos na apresentação inicial (24). Metástases para linfonodos cervicais são raras (24). Suas variantes histológicas são: células de Hurthle, células claras e carcinoma insular (pouco diferenciado) (46).

O CDT em crianças é, em vários aspectos, uma doença diferente daquela observada em adultos, com diferenças na sua patofisiologia, apresentação clínica e desfechos em longo prazo (16,24). Recentemente, a Associação Americana de Tireoide (ATA), reconhecendo essas diferenças, publicou dois guidelines separados de nódulos de tireoide e CDT específicos para crianças e adultos (24,48). A sua apresentação clínica em crianças costuma ser mais extensa e agressiva quando comparada à população adulta (1,16,25). O tamanho tumoral tende a ser maior nessa população e existe um envolvimento precoce da cápsula tireoidiana e tecidos adjacentes (49,50). Além disso, a multicentricidade também tende a ser mais comum, chegando a 40% das crianças (51,52). Por último, os pacientes pediátricos têm uma maior probabilidade de metástases em linfonodos e a distância (17). Envolvimento de linfonodos está presente em 40-90% das crianças, contra 20-50% dos adultos (53) e a prevalência de metástases a distância é de 20-30% em crianças, contra 2% nos adultos (25). Os locais mais comuns de acometimento são pulmão, osso e sistema nervoso central (30).

TRATAMENTO CIRÚRGICO

Por muitos anos, a recomendação de tratamento do CDT na população pediátrica seguiu as recomendações de tratamento dos adultos. Até aqui essa abordagem resultou em uma alta taxa de cura, mas exigiu que todas as crianças realizassem tratamento que incluía tireoidectomia total, seguida de terapia com RAI e terapia supressiva com levotiroxina (24). O objetivo era eliminar qualquer evidência de doença, documentadas pelo rastreamento corporal total (RCT) e pela Tg. Infelizmente, estudos recentes com acompanhamento de várias décadas revelaram um aumento na mortalidade por todas as causas de sobreviventes de CDT pediátrico, predominantemente devido a segundas neoplasias em crianças tratadas com radiação (54-56). Esses dados associados ao conhecimento do excelente prognóstico dessa neoplasia, fez com que a ATA publicasse

recomendações específicas para essa população. Deve ser ressaltado, porém, que a maior parte dessas evidências provém de coortes retrospectivas sujeitas a vieses e com tempo médio de acompanhamento em torno de 10 anos.

Assim, os dois objetivos principais do manejo do CDT na população pediátrica são: manter baixa a mortalidade específica da doença atualmente desfrutada pelas crianças e reduzir as potenciais complicações do tratamento (24). O ponto principal nesse processo é identificar a minoria de crianças que vai se beneficiar de tratamento mais agressivo e o melhor entendimento das características clínicas que predispõe a uma resposta a essas terapias (24). Por outro lado, esse tratamento menos agressivo pode aumentar o risco de doença persistente/recorrente e o número de sobreviventes com doença de baixo volume, persistente, porém livre de progressão (24). Para isso, dois pontos são fundamentais nesse processo: estadiamento pré e pós-operatório e uso do RAI em pacientes selecionados (24). Isso deverá reduzir a possibilidade de que o tratamento e o acompanhamento em longo prazo sejam mais agressivos do que o necessário ou até inadequados (24).

Na avaliação pré-operatória, todos os pacientes devem realizar ecografia cervical para avaliação de possíveis metástases em linfonodos cervicais (57,58). Para a maior parte dos pacientes pediátricos com CDT, a cirurgia recomendada é a tireoidectomia total (24). Essa recomendação é baseada na alta incidência de doença multifocal e bilateral (25,37,39,44,59), bem como em um aumento do risco de recorrência nos pacientes pediátricos submetidos a tireoidectomia subtotal ou lobectomia (31,34,37,39,43,54,60). A exploração cervical central é recomendada para crianças com citologia maligna e evidência clínica de invasão extratireoidiana grosseira no estadiamento pré-operatório ou durante o intraoperatório (28,39,61). A exploração cervical profilática pode ser seletivamente considerada com base na multifocalidade e tamanho do tumor e na experiência do cirurgião (24). Como regra, a exploração cervical só deve ser realizada mediante comprovação citológica de linfonodos metastáticos, não sendo indicada de forma profilática (24). A cirurgia da tireoide em crianças deve ser preferencialmente em centros com equipe multidisciplinar especializada, com endocrinologista, radiologista, médico nuclear, anestesista, cirurgião de tireoide alto volume (>30/ano – incluindo crianças e adultos) e unidade de cuidados intensivos (62,63).

AVALIAÇÃO DE RISCO

Fatores prognósticos

Atualmente, uma das etapas mais importantes na avaliação de crianças e adolescentes com CDT é a estratificação de risco para doença persistente e/ou recorrente (64). Vários fatores prognósticos são bem estabelecidos, sendo citados no guideline da ATA de CDT em adultos, como extremos de idade, tumores maiores, multicentricidade, extensão extratireoidiana, metástases em linfonodos, invasão vascular e tireoglobulina pós-operatória (POTg) (48). Entretanto, existem resultados conflitantes em relação a esses fatores prognósticos em crianças e adolescentes (tabela 1) (8,35,37,65-67). Estes fatores podem ser divididos em fatores relacionados ao paciente (idade ao diagnóstico, sexo) e relacionados ao tumor (tipo histológico, tamanho, multifocalidade, extensão da doença, estadiamento tumoral, metástases em linfonodos e à distância e ressecção da lesão).

A maioria desses fatores foi identificada em estudos que avaliaram coortes de pacientes seguidos nas décadas de 1990 e 2000 (8,35,37). É importante ressaltar algumas diferenças importantes em relação ao manejo contemporâneo do CDT, em especial o uso de métodos laboratoriais e exames de imagem com menor sensibilidade e acurácia. Outra limitação é que muitos dos fatores prognósticos identificados resultaram de análises nas quais a mortalidade foi o desfecho principal. Em pacientes com CDT, é importante considerar os riscos individualizados de doença persistente e mortalidade, uma vez que a maioria dos pacientes (em especial pacientes jovens) apresenta taxas de mortalidade muito baixas, porém taxas de doença persistente elevadas.

Relacionados ao paciente

Idade

No estudo de Jarzab e col. (37) os autores demonstraram que os pacientes com idade ao diagnóstico mais jovem (abaixo dos 10 anos) tinham pior prognóstico, sendo que todas as 14 crianças com idade entre 6 e 10 anos apresentaram recidiva da doença.

Dados similares foram mostrados por Mihailovic e col. (65) com crianças diagnosticadas com CDT entre 8 e 10 anos de idade apresentando maiores taxas de recorrência. Outro estudo também demonstrou que crianças com remissão completa da doença eram mais velhas do que as pacientes com doença persistente (14,7 vs. 17,1, P=0,002) (67). Entretanto, outros estudos (8,35,66) não encontraram associação entre idade e piora dos desfechos clínicos. De forma geral, os estudos com maior número de pacientes jovens (< 10 anos) encontraram associação entre idade mais baixa e doença persistente/recorrente, enquanto estudos com menos participantes jovens não encontraram essa associação (28,39,42,45,68,69). É necessário ressaltar que os regimes de tratamento podem ter variado, o que pode afetar os desfechos. Por exemplo, a cirurgia pode ter sido menos agressiva em crianças menores gerando um possível viés (24).

Sexo

Os resultados dos estudos em relação ao sexo e desfechos clínicos são bastante contraditórios (8,35,37,65-67). Wada e col. (35) mostrou que a proporção de pacientes do sexo masculino foi significativamente maior nos pacientes com recorrência da doença do que naqueles sem recorrência (33,3% vs. 4,8%, P=0,01). Além disso, outros 2 estudos também encontraram associação entre pacientes do sexo masculino e piora dos desfechos clínicos (66,67). Entretanto, outros estudos (8,37,65) não encontraram essa associação.

Relacionados ao tumor

Tipo Histológico

Os dois principais tipos de CDT, papilar e folicular, apresentam prognósticos muito similares, com altas taxas de sobrevida (99,7% vs. 96,3%) em 20 anos (9).

Entre os pacientes com CPT, algumas variantes histológicas apresentam pior prognóstico, tais como células altas, colunar, sólida ou trabecular e esclerosante difusa (24). A maioria dos estudos (8,35,37,65-67), entretanto, não conseguiu determinar uma associação entre o tipo histológico e a piora de desfechos clínicos. Provavelmente, isso deve-se a dois fatores principais: as variantes de pior prognóstico são muito raras e a maioria dos estudos apenas comparou os tipos papilar e folicular, sem considerar as variantes de cada um.

No CFT, a variante chamada de carcinoma de células de Hürthle parece estar associada ao pior prognóstico (70). Entretanto, essa informação é derivada de estudos em adultos, com poucos dados envolvendo a população pediátrica (24).

Tamanho

A maioria dos estudos que avaliou a associação do tamanho tumoral com desfechos clínicos não encontrou nenhuma associação (8,35,65). Uma possível explicação é que como o tamanho da tireoide varia durante a infância e adolescência, o tamanho tumoral isoladamente talvez não seja o melhor parâmetro de avaliação do risco.

Multifocalidade

Os pacientes com CDT, em especial os pacientes com CPT, frequentemente apresentam mais de um foco de doença (multifocalidade), entretanto, sua relação com piora do prognóstico nesses pacientes é contraditória (8,35,65,66). Wada e col. (35) mostrou que a proporção de tumores multifocais foi significativamente maior nos pacientes com recorrência em relação àqueles sem recorrência (60,0% vs. 21,4%, P=0,01). Outro estudo de Mihailovic e col. (65) também demonstrou aumento significativo da recorrência da doença em pacientes com tumores multifocais. Entretanto, outros dois estudos não encontraram nenhuma associação entre tumores multifocais e piora dos desfechos clínicos (8,66).

Extensão da doença

A maioria dos estudos que avaliou a relação entre extensão extratireoidiana com desfechos clínicos não encontrou essa associação (35,66). Esse achado vem ao encontro da mudança realizada no último *American Joint Committee on Cancer staging system of tumor size, nodal metastases and distant metastases* (8th TNM/AJCC), no qual a extensão microscópica deixou de ser um fator importante no estadiamento dos pacientes (71).

Estadiamento tumoral

Wada e col. (35) demonstraram que crianças com CDT com estadiamento T3 e T4a, em comparação com pacientes T1 e T2, apresentaram menores taxas de sobrevida livre de doença. Entretanto, outros estudos não encontram essa associação (65,67).

Metástases em linfonodos cervicais

O envolvimento de linfonodos cervicais na apresentação do CDT, especialmente no CPT, em crianças é bastante frequente, chegando até 80-90% em algumas séries (53). Entretanto, sua relação com piora dos desfechos clínicos também é controversa (8,35,37,65-67). Wada e col. (35) mostrou que a proporção de tumores com linfonodos comprometidos (clínicos e patológicos) foi significativamente maior nos pacientes com recorrência em relação àqueles sem recorrência (46,7% vs. 11,9%, P=0,009 e 86,7% vs. 57,1%, respectivamente). O estudo de Pires e col. (66) mostrou que os pacientes sem linfonodos positivos ao diagnóstico apresentaram uma razão de chance de 6,0 (3,6-9,7) de estarem livres de doença ao final do acompanhamento. Entretanto, outros estudos (37,65,67) não encontraram associação entre a presença de linfonodos cervicais metastáticos e piora dos desfechos clínicos. Alguns fatores podem, pelo menos parcialmente, justificar essa discrepância de resultados, como não categorização dos pacientes por faixa etária, modo de identificação da metástase (clinicamente vs. exame anatomopatológico), o número de linfonodos acometidos e presença de acometimento extranodal (14,72).

Metástases a distância

As metástases a distância são relativamente frequentes na população pediátrica, chegando a uma prevalência de 20-30% (25), sendo importantes determinantes do prognóstico e constituindo a principal causa de morte relacionada ao CDT (73,74). O estudo de Verburg e col. (67) mostrou que os pacientes que apresentavam resposta completa ao final do acompanhamento, em comparação àqueles com doença persistente, apresentavam menor prevalência de metástases a distância ao diagnóstico (10,6% vs. 54,5%, P<0,01). Além disso, o estudo de Pires e col. (66) mostrou que os pacientes sem metástases ao diagnóstico do CDT apresentaram uma razão de chance de 9,38 (4,29-20,5, P<0,001) de estarem livre de doença ao final do acompanhamento.

Cirurgia inicial

Dois estudos que avaliaram a relação entre o tipo de cirurgia inicial e desfechos clínicos, encontrou associação significativa (37,65). No primeiro, os autores mostraram

que os pacientes que realizaram tireoidectomia subtotal, em comparação àqueles que realizaram tireoidectomia total, apresentaram um risco relativo de 9,6 (2,3-39,1) para recorrência da doença (37). O segundo estudo mostrou que os pacientes submetidos a tireoidectomia total e que receberam dose de RAI, em comparação aos pacientes que realizaram tireoidectomia subtotal ou total sem RAI, apresentaram menores taxas de recidiva da doença (65).

TNM

Na tentativa de melhorar a predição do prognóstico dos pacientes com CDT, diversos sistemas de estadiamento combinando diversos dos fatores citados acima foram propostos. Em comum, todos têm como objetivo estimar o risco de mortalidade e/ou a recorrência, guiar o tratamento e o seguimento e garantir uma comunicação efetiva entre os diferentes profissionais, permitindo a comparação de dados entre diferentes centros (48,75).

A maioria dos sistemas foi desenvolvida para estratificar corretamente as taxas de mortalidade, porém são menos precisos para predição de recorrências e presença de doença persistente. Outra limitação é a falha na predição de desfechos para pacientes em estágios iniciais e considerados de baixo risco (estágios I e II na maioria deles), que compreendem a maior parte dos pacientes com CDT (49). Além disso, o fato de utilizarem somente informações da apresentação da doença (sem considerar a resposta ao tratamento) e a não validação em várias populações também limita o seu uso (76) .

A maioria dos sistemas inclui idade ao diagnóstico, tamanho do tumor, invasão extratireoideana e presença de metástases a distância. Diversos estudos já objetivaram comparar estes diferentes sistemas de estadiamento (77-80). Estes estudos demonstraram que o TNM/AJCC e o *Metastasis, Age, Completeness of ressection, Invasion and Size* (MACIS) são os dois sistemas com melhor desempenho para predizer desfechos em pacientes com CDT.

Entretanto, não existe nenhum sistema de estadiamento pós-operatório que tenha sido validado em crianças e adolescentes com CDT, e a utilidade da extrapolação dos sistemas de estadiamento dos adultos para o cenário pediátrico é limitado pela disparidade clínica observada entre os dois grupos (24).

O TNM/AJCC é o sistema de estadiamento mais comumente utilizado (48,81) e sugerido pelo guideline da ATA (24). Ele inclui como variáveis a idade do paciente (dicotomizada em 45 anos), o tamanho do tumor e a presença de invasão extratireoideana, a presença de metástases em linfonodos e a distância. Os pacientes são classificados em 4 estágios, com diminuição progressiva da sobrevida de acordo com os níveis mais elevados de estágio, sendo que as crianças e adolescentes são classificadas apenas nos estágios I (sem metástases a distância) e II (com metástases a distância), o que é um limitante em termos de determinar o prognóstico nessa população (24). Os pacientes classificados como TNM/AJCC I tem uma sobrevida de aproximadamente 100%, enquanto que os pacientes com classificação IV tem sobrevida de cerca de 45% (82,83). As principais críticas a este sistema consistem na não inclusão de variáveis que sabidamente influenciam na evolução e prognóstico dos pacientes (tipo histológico, multifocalidade, dados relacionados ao tratamento) e a sua inabilidade em predizer desfechos que não mortalidade (como recorrências e presença de doença persistente). O TNM/AJCC é atualizado periodicamente, sendo que a última versão (oitava) foi recentemente publicada (tabela 2) (71).

Classificação de risco da ATA em crianças e adolescentes com CDT

Conforme já foi colocado anteriormente, esses sistemas de estadiamento foram concebidos com o objetivo de avaliar a mortalidade relacionada ao CDT. Uma vez que as taxas de mortalidade nessa neoplasia são relativamente baixas, sistemas que avaliem também a chance de recidiva são considerados importantes nas definições do manejo destes pacientes. Com este objetivo, a ATA propôs um sistema que tem como objetivo identificar os pacientes em risco de doença persistente cervical e ajudar a identificar quais pacientes devem realizar estadiamento pós-operatório para avaliar a presença de metástases a distância (24). Nesse sistema, o paciente é categorizado em três grupos de risco: baixo, intermediário ou alto (tabela 3) (24).

Os pacientes de baixo risco são aqueles com doença grosseiramente confinada a glândula tireoide sem linfonodos comprometidos ou com micrometástases incidentais para um pequeno número de linfonodos centrais. Os pacientes de risco moderado são aqueles com linfonodos cervicais extensos em região central ou linfonodos em cadeias laterais. O grupo de pacientes de alto risco é composto por aqueles que apresentam linfonodos extensos em região cervical lateral, tumores localmente invasivos, com ou

sem metástases a distância. Entretanto, sua utilidade é limitada, uma vez que leva em conta apenas os dados histopatológicos, mas não considera a resposta a terapia.

ACOMPANHAMENTO

Avaliação pós-operatória

Para a maioria dos pacientes, a avaliação inicial pós-operatória é realizada cerca de 3 meses após a cirurgia (24). O objetivo desse estadiamento é avaliar a evidência de doença persistente loco regional e identificar os pacientes que poderão se beneficiar do RAI, tais como aqueles com metástases a distância conhecidas ou suspeitas. Os pacientes de baixo risco devem realizar exame de Tg em uso de levotiroxina (Tg-T4) (24). Por sua vez, os pacientes de risco intermediário e alto devem realizar Tg estimulada (sTg) e RCT para uma melhor estratificação de risco e determinação do tratamento com RAI (24). Assim, uma conduta mais individualizada e conservadora no tratamento e estadiamento pós-operatório irá diminuir a exposição desnecessária ao I^{131} em crianças sem evidência de doença, nas quais os riscos da terapia rotineira com I^{131} provavelmente superam quaisquer benefícios (24).

Terapias complementares

Iodo Radioativo

O objetivo da terapia com I^{131} é diminuir os riscos da recorrência do CDT e, teoricamente, reduzir a mortalidade eliminando a doença ávida pelo iodo (24). Com o aumento da conscientização dos potenciais efeitos colaterais a longo prazo do tratamento com I^{131}, há um aumento dos esforços para identificar pacientes que têm uma alta probabilidade de se beneficiar da terapia (24). A terapia com I^{131} está indicado para tratamento da doença nodal ou locorregional persistente que não possa ser ressecada cirurgicamente e nos pacientes com doença metastática presumível (84). Alguns autores recomendam a terapia rotineira com I^{131} para pacientes com tumores T3 ou envolvimento nodal cervical extenso (N1a extenso ou N1b). Pela falta de dados comparativos, não há uma definição entre realizar uma dose empírica de I^{131} ou calculada por dosimetria (24). Alguns autores preferem realizar a dose empírica por ser

mais prática na 1ª dose de I^{131} do paciente e reservar o uso de dosimetria para aqueles com metástases pulmonares difusas ou necessidade de mais de 1 dose de I^{131} (85-87). A dosimetria também pode ser considerada na 1ª dose naqueles pacientes com reserva limitada de medula óssea (85-87). O RCT pós dose é recomendado para todas as crianças 4 a 7 dias após o tratamento com I^{131} (88).

Supressão com levotiroxina

A supressão de TSH em crianças com CDT deve ser determinada pelo risco da ATA e seu status de doença atual (24). Em crianças com doença conhecida ou suspeita, deve-se manter a supressão do TSH, enquanto naquelas sem evidência de doença, o TSH pode ser normalizado para níveis dentro dos valores de referência normais/baixos (24).

Papel da tireoglobulina

A Tg é uma glicoproteína específica da tireoide que é sintetizada e secretada pela tireóide normal e por carcinomas diferenciados da tireóide (24). Após a cirurgia e terapia com I^{131}, os níveis séricos de Tg servem como um marcador sensível de doença recorrente (89-92); a magnitude da elevação da Tg sérica parece correlacionar-se com o(s) local(is) da doença metastática e com o subtipo de tumor (89). Foi demonstrado em estudos com adultos que ensaios ultrassensíveis de Tg sérica são mais sensíveis para a detecção de câncer de tireoide residual quando comparado com o RCT (24,90,93-95). Na ausência de anticorpos anti-tireoglobulina (TgAc), a Tg sérica tem um alto grau de sensibilidade e especificidade para detectar doença persistente/recorrente, com a mais alta sensibilidade observada após estimulação com TSH (sTg) (91). Existem poucos dados sobre a interpretação da Tg em crianças com CDT (24). Como os dados sugerem que os níveis séricos de Tg podem ser mais altos em crianças quando comparados com adultos com uma extensão semelhante da doença (22,96), a aplicação de dados de estudos em adultos para crianças é difícil. Portanto, ainda não está claro se níveis elevados de Tg têm o mesmo valor prognóstico para crianças, que podem ter um limiar de Tg diferente para o que seria considerado clinicamente relevante ou doença "acionável" (24).

Diante da escassez de dados na população pediátrica, nosso grupo realizou um estudo (97) para avaliar o papel da tireoglobulina estimulada pós-operatória (sPOTg) como fator prognóstico do CDT nessa população, sendo incluídas 32 crianças e adolescentes com diagnóstico do CDT antes dos 18 anos de idade. Nesse estudo, nós encontramos que o melhor valor de ponto de corte para predição de resposta excelente foi de 31,5 ng/mL, com sensibilidade e especificidade de 100%.

A dosagem da Tg sérica é um componente crítico no manejo do paciente pediátrico com CDT, tanto no momento do estadiamento pós-operatório inicial quanto durante o acompanhamento em longo prazo (24). Portanto, o monitoramento da Tg-T4 é a abordagem ideal para avaliar recorrência ou progressão da doença (24).

Anticorpos anti-tireoglobulina

O TgAc está presente em cerca de 25% dos pacientes com CDT, sendo que a sua principal importância é a possibilidade de interferir na dosagem da Tg (98-103). Em função disso, recomenda-se a mensuração dos níveis dos TgAc em todos os pacientes em seguimento de CDT (103). Como as concentrações de TgAc respondem a mudanças nos níveis de antígenos de Tg circulantes, e, portanto, representam indiretamente mudanças na massa do tecido da tireoide, o nível de TgAc pode servir como um marcador tumoral substituto para CDT (24,99,100).

A maioria dos estudos relatou que o reaparecimento, a persistência ou uma tendência crescente nas concentrações de TgAc no período pós-operatório são fatores de risco significativos para doença persistente ou recorrente (104-108). No entanto, não se sabe se um valor de TgAc positivo está correlacionado com a extensão/invasividade da doença ou com o prognóstico (24). Um declínio nos títulos de TgAc indica uma carga de doença em declínio, mas pode levar uma média de três anos para eliminar TgAc após a cura do CDT (109). Um aumento significativo nos anticorpos Tg sugere uma progressão da doença que merece uma avaliação mais detalhada (24). Semelhante à Tg, a tendência nas concentrações de TgAc é mais relevante para a detecção de doenças do que qualquer concentração única de TgAc (24).

Estratificação dinâmica de risco

Os estadiamentos de risco clínico-patológicos usam informações da avaliação inicial do paciente para categorização de risco individual e não há mudança dessa classificação ao longo do tempo. Nos últimos anos, a utilização da resposta ao tratamento inicial tem sido preconizada no intuito de estimar o risco de recorrência e morte, uma vez que os pacientes que apresentam uma boa resposta ao tratamento inicial teriam menor risco de recorrência e morte. A esta nova modalidade de estratificação de risco deu-se o nome de "estratificação dinâmica de risco (DRS)" uma vez que o risco do paciente muda com o tempo, de acordo com novos dados que vão sendo obtidos ao longo do seguimento (23). Os pacientes são classificados de acordo com a resposta ao tratamento em quatro categorias: resposta excelente (exames de imagem negativos, Tg-T4 <0,2 ng/mL ou sTg <1,0 ng/mL), resposta bioquímica incompleta (exames de imagem negativos, Tg-T4 >1,0 ng/mL ou sTg >10,0 ng/mL ou níveis de anticorpos antitireoglobulina (TgAc) em elevação), resposta estrutural incompleta (evidência funcional ou estrutural de doença independente dos valores de Tg e TgAc), resposta indeterminada (exames de imagem inespecíficos, valores de Tg-T4 entre 0,2 e 1,0 ng/mL, valores de sTg entre 1,0 e 10,0 ng/mL ou níveis de TgAc estáveis ou em declínio (tabela 4) (110,111).

O uso da classificação dinâmica de risco já se mostrou eficaz em diversos estudos em adultos (110-115). O estudo de Vaisman e col. (112) mostrou que os pacientes com resposta excelente apresentaram risco de apenas 1,4% de doença persistente/recorrente. Além disso, 34% dos pacientes inicialmente classificados como tendo resposta bioquímica incompleta após o tratamento inicial, evoluiu com resposta excelente ao final do acompanhamento, sem terapia adicional, exceto a supressão com levotiroxina. Por outro lado, nos pacientes com doença estrutural persistente somente 9% evoluíram com resposta excelente, mesmo após diversas terapias adicionais. Resultados semelhantes foram observados em uma coorte italiana de 512 pacientes (115), onde os autores demonstraram que a DRS teve maior valor preditivo negativo do que a classificação de risco da ATA para predição de doença persistente (72,8% e 96,3% vs. 39,2% e 90,6%, respectivamente). Estes dois estudos demonstram a habilidade desta nova estratégia em reclassificar os pacientes de todos os espectros de doença, aumentando assim a confiabilidade da predição de risco.

Entretanto, enquanto a DRS foi validada em pacientes adultos com CDT, ela foi avaliada em poucas coortes de crianças e adolescentes (116-117). Por essa razão, não existe recomendação para o seu uso no Guideline da ATA de crianças com CDT (24). O estudo de Lazar e col. (116) avaliou o DRS em uma coorte de 54 pacientes com uma mediana de idade ao diagnóstico de 13,9 anos e uma mediana de acompanhamento de 8,8 anos. Os autores observaram que aqueles pacientes classificados como resposta completa após o tratamento inicial apresentaram excelente prognóstico: 82,9% dos pacientes permaneceram no status de resposta excelente no acompanhamento. Por outro lado, todos os pacientes com resposta incompleta permaneceram com doença persistente. De maneira interessante, a proporção de variância associado ao DRS foi maior do que o da classificação de risco da ATA (0,79 vs. 0,25), sugerindo que o DRS é um preditor mais preciso para o desfecho da doença. O estudo de Sung e col. (117) incluiu uma coorte com 77 pacientes pediátricos com CDT e demonstrou que o DRS foi útil para predizer desfecho da doença no acompanhamento: o risco de doença persistente/recorrente foi significativamente maior no grupo com resposta indeterminada (HR = 10,2, P=0,045) e no grupo com resposta estrutural incompleta (HR = 98,7, P=0,005) quando comparados ao grupo com resposta excelente.

Para melhorar a avaliação da DRS em crianças e adolescentes, nosso grupo realizou um estudo multicêntrico (118), envolvendo 4 instituições de referência no tratamento do CDT. Foram incluídos 66 pacientes com diagnóstico da doença antes dos 18 anos de idade. Nesse estudo, demonstramos que a DRS parece ser um importante fator prognóstico para doença persistente/recorrente nessa população, uma vez que foi o único fator com associação significativa na análise multivariada.

Tempo de acompanhamento

A recorrência de CDT em crianças foi relatada por até 40 anos após a primeira terapia. Por essa razão, as crianças com CDT devem ser acompanhadas por toda a vida, embora com intensidade decrescente para aqueles sem evidência de doença (54,119).

PERSPECTIVAS FUTURAS

Marcadores moleculares

Alterações genéticas têm sido propostas como fatores prognósticos para o CPT (120,121). Esses avanços no perfil molecular do CDT pediátrico têm um potencial significativo para melhorar a abordagem do diagnóstico e tratamento desses pacientes. Há uma alta probabilidade de que um maior entendimento de como tumores com alterações oncogênicas semelhantes podem manter a diferenciação também afetará positivamente o cuidado fornecido aos pacientes com doença refratária (122). Com estes avanços, a determinação de um perfil personalizado do câncer poderá tornar-se viável no CDT pediátrico em um futuro próximo e poderá proporcionar uma terapia individualizada para esses pacientes (123).

Devido a sua grande importância biológica na regulação de diversos processos celulares, alterações genéticas em efetores da via de sinalização da mitogen-activated protein kinase (MAPK) (figura 3) são as mais bem relacionadas com o desenvolvimento e agressividade do CDT (123). Esta é uma via de sinalização intracelular que, quando ativada, desempenha um papel central no crescimento, divisão, proliferação, diferenciação e apoptose das células (123). Sua ativação é feita por fatores de crescimento, hormônios e citocinas em receptores celulares. Diversos rearranjos genéticos têm sido identificados em todos os níveis desta via de sinalização em pacientes com CDT (123). Dados do Cancer Genome Atlas Research (TGCA) demonstraram que os principais genes envolvidos na patogênese do CDT, em ordem decrescente, foram o BRAF, RAS, RET/PTC e NTRK (figura 4A) (124). Esse estudo incluiu quase 500 pacientes com CDT, porém apenas 9 tinham idade abaixo dos 20 anos ao diagnóstico. Outro estudo (125) com 512 pacientes avaliou a causa das mutações em pacientes com CDT e evidenciou que a troca de nucleotídeo é a causa mais comum em adultos, enquanto na população mais jovem existe um crescimento significativos de casos de rearranjos genéticos. Resultados de pequenas coortes de crianças e adolescentes demonstram que a prevalência das mutações nessa população é diferente em relação aos adultos (figura 4B) (126-147). O CPT pediátrico é caracterizado por um aumento na prevalência das mutações por rearranjos (24). Essas diferenças moleculares podem ser uma das razões para melhor resposta ao RAI em crianças com CPT e poderiam parcialmente explicar sua baixa mortalidade e rara progressão para tumores não diferenciados (24).

RET PTC

O proto-oncogene RET, localizado no cromossomo 10q11.2 codifica um receptor tirosina quinase (148). Pelo menos 12 tipos de rearranjos RET/PTC já foram descritos, sendo os tipos 1 e 3 os mais comuns (148).

Na população pediátrica, a mutação RET/PTC é a que apresenta maior prevalência, em torno de 43% (126-134). O primeiro estudo a avaliar a mutação RET/PTC em crianças sem exposição à radiação foi publicada em 2000 por Fenton e col. (126). Foram incluídos 33 pacientes, com uma prevalência geral de 45% (8 PTC-1; 2 PTC-2; 2 PTC-3; 3 PTC-1 e PTC-2). Entretanto, não foi encontrado uma correlação entre o tipo da mutação e idade, tamanho do tumor, extensão da doença ao diagnóstico e recorrência. Outro estudo (127) dos mesmos autores publicado alguns anos depois, encontrou uma prevalência de 58% (7/12). Uma coorte francesa (128) com 27 pacientes pediátricos com CPT encontrou uma prevalência de 29,6% na mutação RET/PTC. Nesse estudo, os autores não encontraram correlação entre a presença da mutação e agressividade do tumor. Nikita e col. (129) encontrou uma prevalência da mutação RET/PTC de 21,4% em um estudo com 28 crianças. De forma interessante, todos os pacientes com a mutação desse estudo tinham idade ao diagnóstico abaixo dos 15 anos. Apesar disso, a mutação não foi associada com tamanho tumoral, metástases linfonodais ou a distância. Em 2016, 4 coortes norte-americanas (130-133) foram publicadas, com número de pacientes entre 13 e 28 pacientes, demonstrando uma prevalência da mutação entre 15 e 22%. Nenhum dos 4 estudos correlacionou a presença da mutação com desfechos clínicos. Um estudo brasileiro (134) com 35 pacientes pediátricos com CPT encontrou uma prevalência da mutação de 37% (4 PTC-1; 1 PTC-2; 4 PTC-3). Os pacientes com a mutação RET/PTC-3 apresentaram tumores de maior tamanho, correlação com multifocalidade e tendência a extensão extra tireoidiana. Entretanto, não houve nenhuma associação com a presença de metástases cervicais e a distância.

BRAF

A BRAF quinase, cujo gene codificador foi localizado no cromossomo 7, é o mais potente ativador da via MAPK quinase (148). Mais de 40 mutações no gene do BRAF já foram identificadas, sendo a mutação T1799A a mais comum (148). Esta mutação é do tipo missense, devido a uma transversão somática de uma timina por uma adenina na posição 1799 no éxon 15 (T1799A), o que resulta em uma substituição de um aminoácido valina por um ácido glutâmico na posição 600 (BRAFV600E) (148).

Em crianças e adolescentes, é a segunda mutação mais prevalente, sendo encontrada em aproximadamente 28% dos casos (118-121,134,137-145). Entretanto, seu papel como agente de agressividade nesses tumores nessa população, diferentemente dos adultos, é incerto (128-131,133,137-145). Os primeiros trabalhos (127,135,136) que estudaram o papel do gene BRAF em crianças e adolescentes, encontraram a mutação em raros casos (0-3,2%).

A partir de 2012, após estudos em adultos, é que foi encontrado um aumento significativo na prevalência da mutação V600E do BRAF (128-131,134,137-145). O primeiro estudo de Sassolas (128) com 27 pacientes encontrou uma prevalência da mutação de 7,4%, porém não encontrou associação com desfecho clínico. Outra coorte de Ricarte-Filho (137), também com uma amostra de 27 pacientes, encontrou uma prevalência de 26%. Seis coortes americanas (129-131,138-140) foram publicas entre 2014 e 2017, contemplando ao total 164 pacientes e, embora com altas taxas de prevalência da mutação (31 a 68%), nenhum dos estudos conseguiu demostrar associação com desfechos clínicos desfavoráveis (extensão da doença, tamanho tumoral, invasão da cápsula, metástases cervicais ou a distância).

Entretanto, 2 estudos (141,142) mostraram associação entre a presença da mutação BRAF V600E e piora de desfecho clínico. No primeiro deles, Alzahrani e col. (141) mostraram uma prevalência da mutação BRAF V600E de 22,6% (12/53). Embora não tenha sido encontrada associação com tamanho tumoral, metástases cervicais ou a distância e taxa de persistência da doença após 6-12 meses do tratamento inicial, houve uma diferença significativa na taxa de doença persistente/recorrente na última avaliação dos pacientes. Em uma mediana de 6,7 anos de acompanhamento, as taxas de doença persistente/recorrente foram de 66,7% vs. 34,1%, nos pacientes com e sem a mutação BRAF V600E, respectivamente (P=0,05). No segundo estudo, de Onder e col. (142), foi encontrada uma prevalência de 30% da mutação BRAF V600E, em uma amostra de 50 pacientes. Nesse estudo, foi encontrado uma correlação entre a presença da mutação e multicentricidade (41 vs. 6%) e recorrência local (71 vs. 23%).

Por outro lado, um estudo chinês (143) avaliou o papel da mutação BRAF V600E, tendo encontrado uma prevalência de 41,5%. De forma interessante, a presença da mutação teve uma associação inversa com alguns desfechos clínicos, com menores taxas de multicentricidade e invasão extratireoidiana e MACIS mais baixo.

Outros 2 estudos recentes realizados em países árabes (144,145), com um total de 128 pacientes, encontraram prevalência da mutação BRAF V600E de 26,4 e 25%.

Ambos estudos não encontraram associação entre a presença da mutação e sexo, extensão extra-tireoidiana, invasão vascular, metástases em linfonodos ou a distância, doença persistente/recorrente.

Por fim, o único estudo brasileiro (134) que avaliou essa mutação, encontrou uma prevalência da mutação de 9%, em uma amostra de 35 pacientes. A presença da mutação foi associada com maior idade e tamanho tumoral.

NTRK

O gene do receptor de tirosina quinase neurotrófico tipo 1 (NTRK1), localizado no cromossomo 1, codifica o receptor do fator de crescimento nervoso (NGF) de alta afinidade e é ativado através da via da MAPK (146). ETV6-NTRK3 resulta de uma translocação intercromossômica t(12;15)(p13;q25) que justapõe os éxons 1–4 de ETV6 aos éxons 12–18 de NTRK3 (137).

Esse gene vem sendo recentemente estudado e vem ganhando importância, em função de sua relativa alta prevalência (atualmente o terceiro maior na população pediátrica), em torno de 12%, e sua possível relação com desfechos clínicos (130,132,134,137). O primeiro estudo a avaliar o papel dos oncogenes de fusão NTRK nessa população foi o de Ricarte-Filho e col. (137). Os autores encontraram uma prevalência de 7,4%, em uma amostra de 27 pacientes. Os 2 estudos que avaliaram a presença do rearranjo com desfechos clínicos, encontraram associação entre a presença da mutação e agressividade tumoral (130,132). O primeiro (130) identificou a presença dos oncogenes em 26% (7/27) da amostra, sendo 5 casos NTRK tipo 3 e 2 casos NTRK tipo 1. Em 5 desses casos, o tumor media mais de 2 cm e havia invasão vascular; invasão linfática foi identificada em todos os casos. Comparado aos pacientes com mutação BRAF V600E, aqueles com oncogene de fusão NTRK apresentaram doença mais extensa e agressiva. O segundo estudo (132) encontrou uma prevalência da doença de 22,2%, em uma amostra de 18 pacientes e demostrou associação com histologia agressiva. O único estudo brasileiro que pesquisou esse rearranjo nessa população, encontrou uma prevalência de 9% (3/35) na amostra de oncogenes de fusão NTRK tipo 3 (134).

RAS

Os genes RAS codificam proteínas G altamente relacionadas, que desempenham um papel central na transdução de sinal intracelular pela ativação da MAPK e outras

vias de sinalização, como PIK3/AKT (148). As mutações pontuais de RAS geralmente ocorrem nos códons 12, 13 ou 61 das proteínas H-RAS, K-RAS ou N-RAS (148).

As mutações no gene RAS foram as primeiras estudadas na população pediátrica com CDT, embora apresentem uma prevalência bem inferior em relação a população adulta, com taxa estimada de 2,7% (127-135,137,144,146). Fenton e col. (146) publicou um estudo com 38 crianças com câncer de tireoide e encontrou uma prevalência da mutação de apenas 6,5%, não conseguindo estabelecer uma relação com a agressividade da doença pelo pequeno número de pacientes. Alguns anos mais tarde, uma publicação do mesmo grupo (127) não encontrou nenhum paciente com a mutação RAS em um grupo de 14 crianças com CPT. Outros estudos (130,131,133-135), combinando uma população de 206 crianças e adolescentes, incluindo 1 estudo brasileiro (134), também não identificaram nenhum caso de mutação RAS. Em outros estudos (128,129,137,144), com uma população combinada de 179 pacientes, a prevalência da mutação variou de 2,5 a 7,4%, exceto no estudo de Picarsic (132), o único a encontrar uma taxa mais elevada da mutação de 16% (3/18).

CONCLUSÃO

A definição do risco e prognóstico individual é parte fundamental na avaliação e manejo dos pacientes pediátricos com CDT. Através dessa revisão é possível concluir que: 1) os dados de associação entre fatores prognósticos e desfechos da doença em crianças e adolescentes com CDT são conflitantes; 2) a maior parte das informações dos sistemas de estadiamento são baseadas em estudos com adultos e, devido as suas diferenças em relação a doença na população pediátrica, esses dados devem ser analisados com cautela; 3) os marcadores moleculares parecem ser uma perspectiva importante para avaliação e tratamento desses pacientes no futuro.

No nosso estudo que avaliou o papel da tireoglobulina estimulada pós-operatória (sPOTg) como fator prognóstico do CDT em crianças e adolescentes, demonstramos que esse exame possui alta acurácia para predizer o risco de doença persistente nessa população.

No nosso estudo que avaliou o papel da estratificação dinâmica de risco em crianças e adolescentes com CDT, encontramos que esta é um forte preditor de desfecho da doença, podendo ser útil na definição de estratégias de acompanhamento. Além

disso, reforçamos o papel da sPOTg e sua associação com doença persistente, sendo que o valor de ponto de corte com maior sensibilidade e especificidade foi de 37,8 ng/mL.

Tabela 1: Avaliação da associação entre fatores prognósticos e persistência do CDT.

Fatores do paciente	**Jarzab (2000)**	**Wada (2009)**	**Vaisman (2011)**	**Mihailovic (2014)**	**Verburg (2015)**	**Pires (2016)**
Idade	S	N	N	S	S	N
Sexo	N	S	N	N	S	S
Fatores do tumor						
Tamanho	NA	N	N	N	NA	NA
Multifocalidade	NA	S	N	S	NA	N
Tipo histológico	N	N	NA	N	N	N
Invasão extratireoideana	NA	N	NA	NA	NA	N
Estadiamento tumoral	NA	S	NA	N	N	NA
Metástases em linfonodos	N	S	S	N	N	S
Metástases a distância	NA	NA	S	N	S	S
Fatores do tratamento						
Cirurgia inicial	S	NA	NA	S	NA	NA

S = sim

N = não

NA = não avaliado

Tabela 2. Estadiamento TNM do CDT

Tx	Tumor primário não pode ser identificado
T0	Sem evidência de tumor primário
T1a	Tumor 1 cm ou menos, limitado a tireoide
T1b	Tumor entre 1 e 2 cm, limitado a tireoide
T2	Tumor entre 2 e 4 cm, limitado a tireoide
T3a	Tumor maior que 4 cm, limitado a tireoide
T3b	Tumor de qualquer tamanho com extensão extratireoidiana grosseira invadindo músculos do pescoço (esterno-hioideo, esternotireoideio, omo hioideo)
T4a	Tumor que se estende além da cápsula da tireoide e invade algum dos seguintes: tecidos moles subcutâneo, laringe, traqueia, esôfago, nervo laríngeo recorrente
T4b	Tumor que invade fáscia pré-vertebral, vasos mediastinais, artéria carótida
Nx	Linfonodos regionais não podem ser avaliados
N0	Sem metástases em linfonodos regionais
N1a	Metástases em nível VI ou mediastino superior (nível VII)
N1b	Metástases cervicais unilaterais, bilaterais ou contralaterais (níveis I, II, III, IV ou V) ou retrofaríngeos
M0	Sem metástases a distância
M1	Com metástases a distância

Estágio	**Idade < 55 anos**
I	Qualquer T, Qualquer N, M0
II	Qualquer T, Qualquer N, M1

T, tamanho

N, linfonodo

M, metástase

CDT, carcinoma diferenciado de tireoide

Adaptado de Brierley JD, et al. (71).

Tabela 3. Classificação de risco ATA em crianças e adolescentes com CDT

Risco	Definição
Baixo	Doença grosseiramente confinada a tireoide com No/Nx OU Pacientes com doença N1a incidental
Intermediário	Doença N1a extensa ou N1b mínima
Alto	Doença regionalmente extensa (N1b extensa) OU Doença localmente invasiva (T4), com ou sem metástases a distância

ATA, Associação Americana de Tireoide

CDT, Carcinoma diferenciado de tireoide

Adaptado de Francis GL, et al. (24).

Tabela 4. Estratificação dinâmica de risco

Resposta	Definição
Excelente	Exames de imagem negativos E Tg sob supressão <0,2 ng/mL OU Tg estimulada <1,0 ng/mL
Bioquímica incompleta	Exames de imagem negativos E Tg sob supressão ≥1,0 ng/mL OU Tg estimulada ≥10,0 ng/mL OU TgAc em elevação
Estrutural incompleta	Evidência de doença estrutural ou funcional independente dos níveis de Tg ou TgAc
Indeterminada	Achados de imagem não específicos OU Tg sob supressão entre 0,2 e 1,0 ng/mL OU Tg estimulada entre 1,0 e 10,0 ng/mL OU TgAc estável ou em queda

Tg, tireoglobulina

TgAc, anticorpos anti-tireolobulina

Adaptado de Tuttle et al. (110).

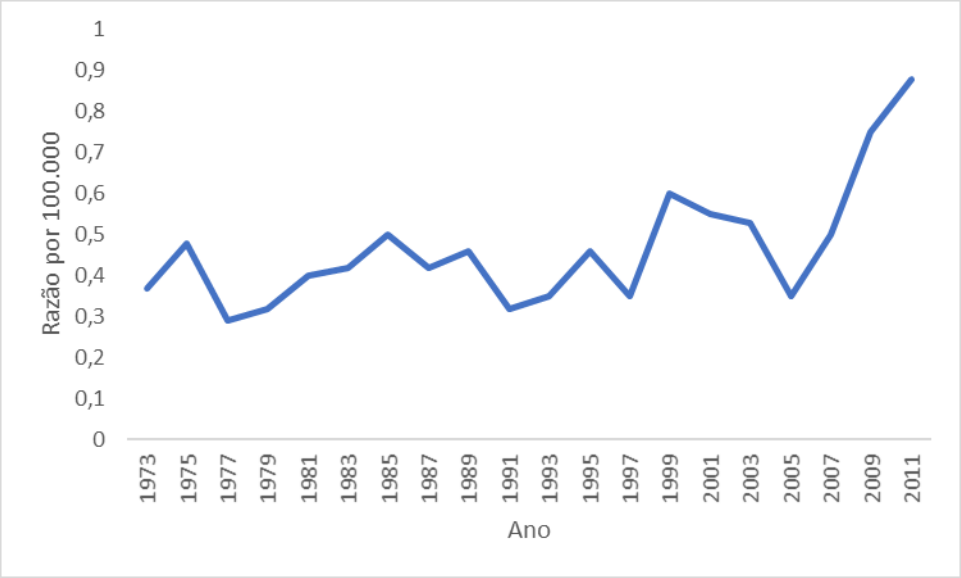

Figura 1. Incidência do carcinoma diferenciado de tireoide em uma base populacional norte-americana com 2504 pacientes entre 1973-2011. Adaptado de Golpanian S, et al. (7).

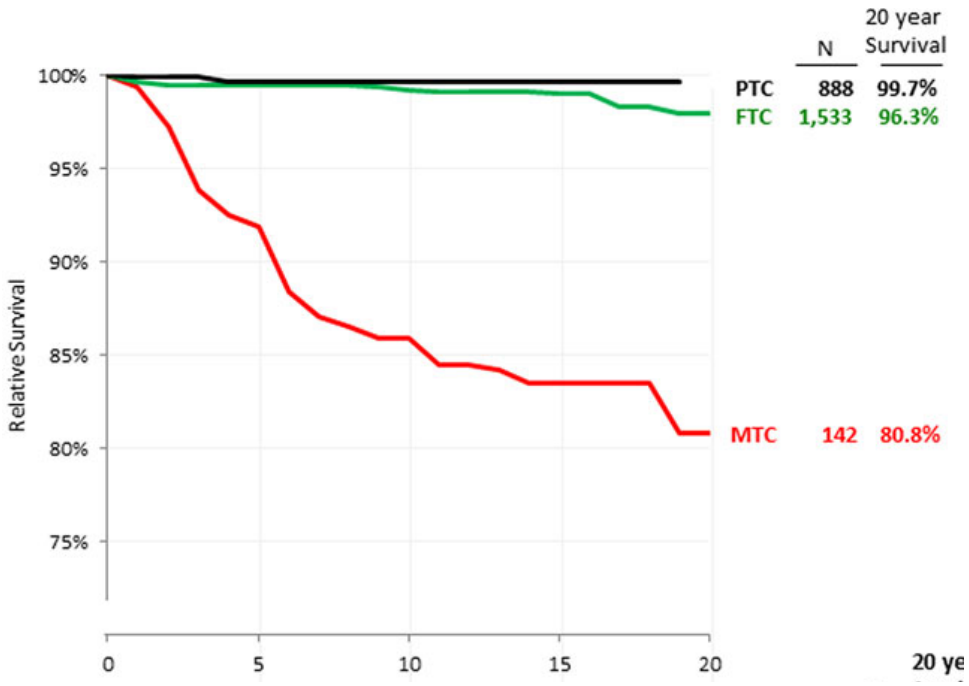

Figura 2A. Taxas de sobrevida em 20 anos de uma base populacional norte-americana entre os anos de 1992-2014 , de acordo com a histologia do câncer de tireoide. Adaptado de Massimino et al. (9).

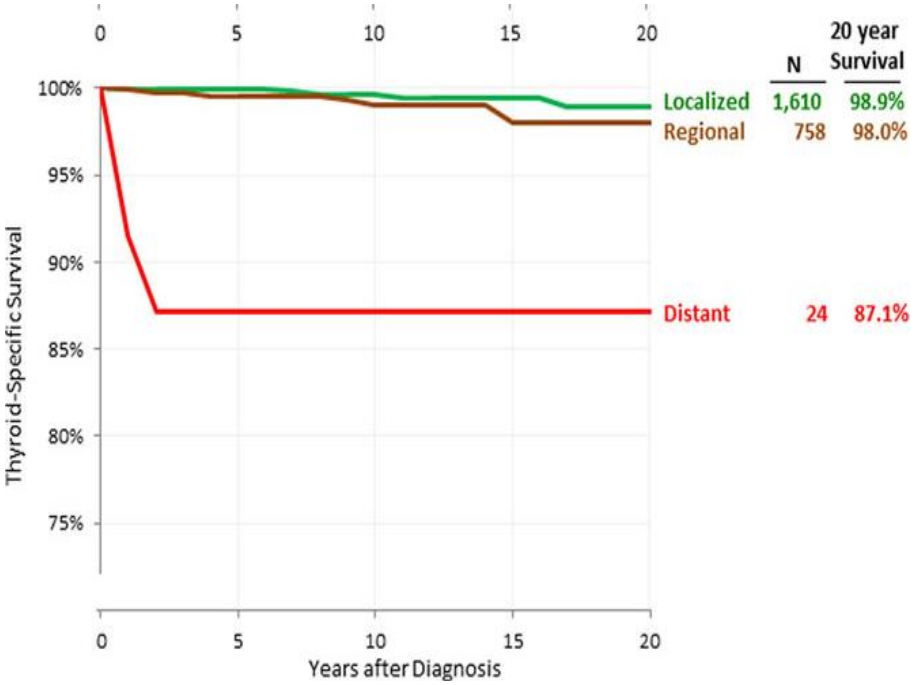

Figura 2B. Taxas de sobrevida em 20 anos de uma base populacional norte-americana entre os anos de 1992-2014 , de acordo com a localização do tumor inicial do câncer diferenciado de tireoide. Adaptado de Massimino et al. (9).

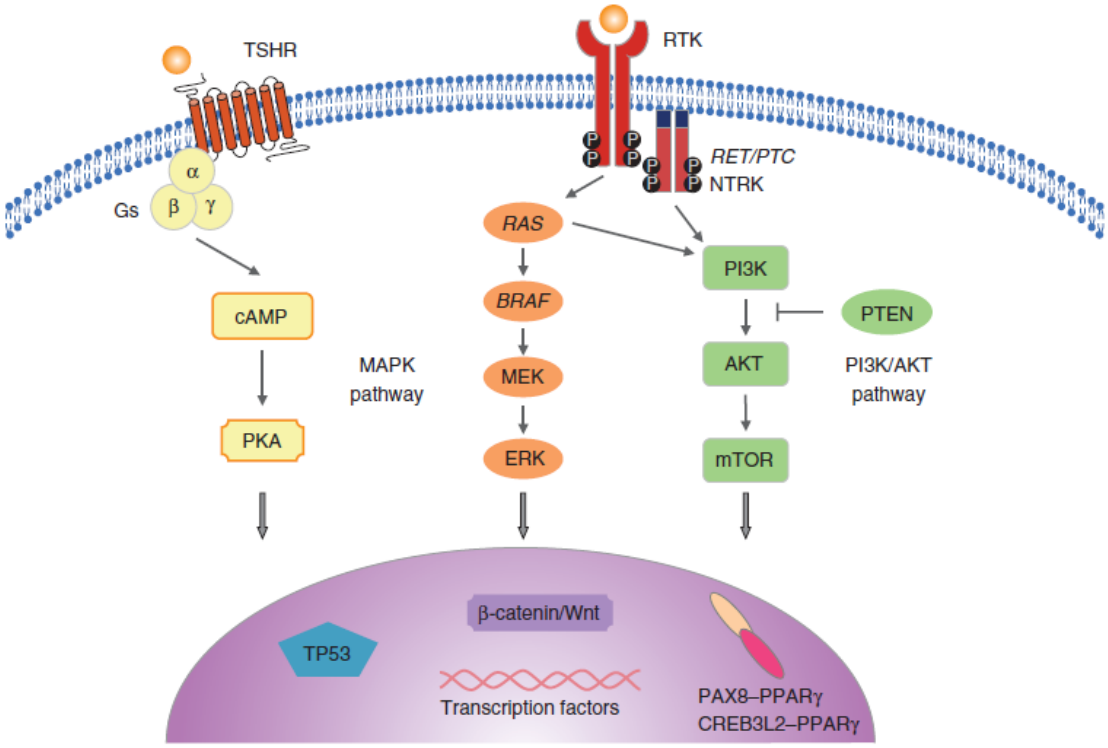

Figura 3. Via da *mitogen-activated protein kinase* (MAPK). Adaptado de Hsiao SJ (122).

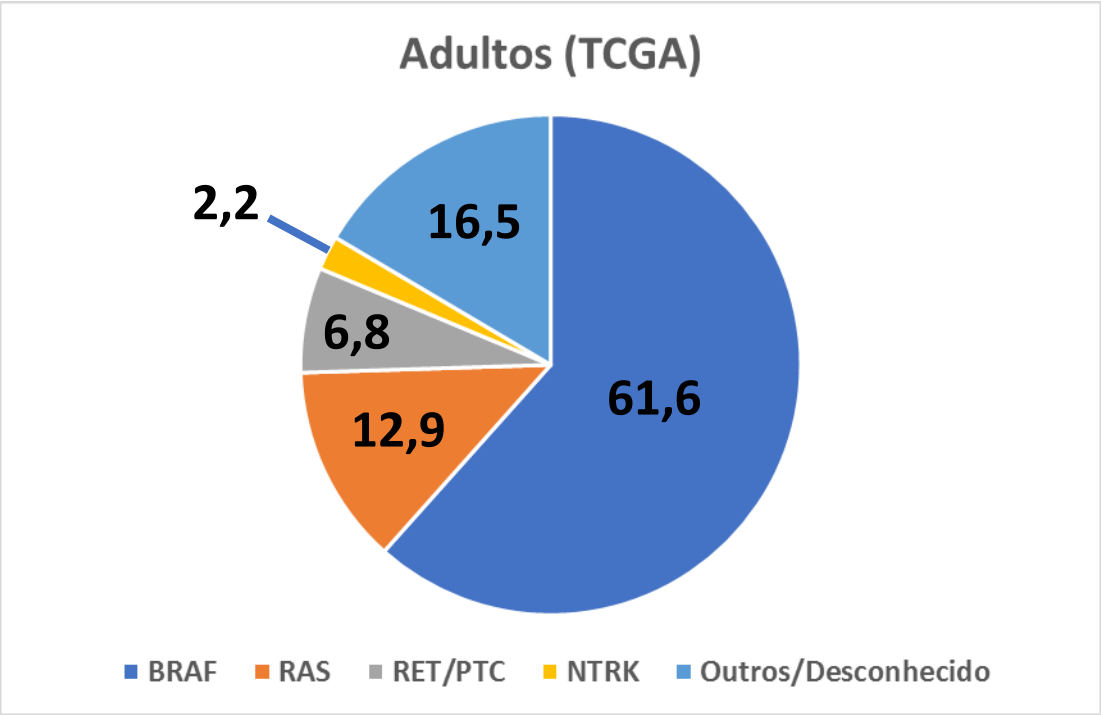

Figura 4A. Prevalência das mutações no carcinoma diferenciado de tireoide de acordo com dados do Cancer Genome Atlas Research (TGCA). (123)

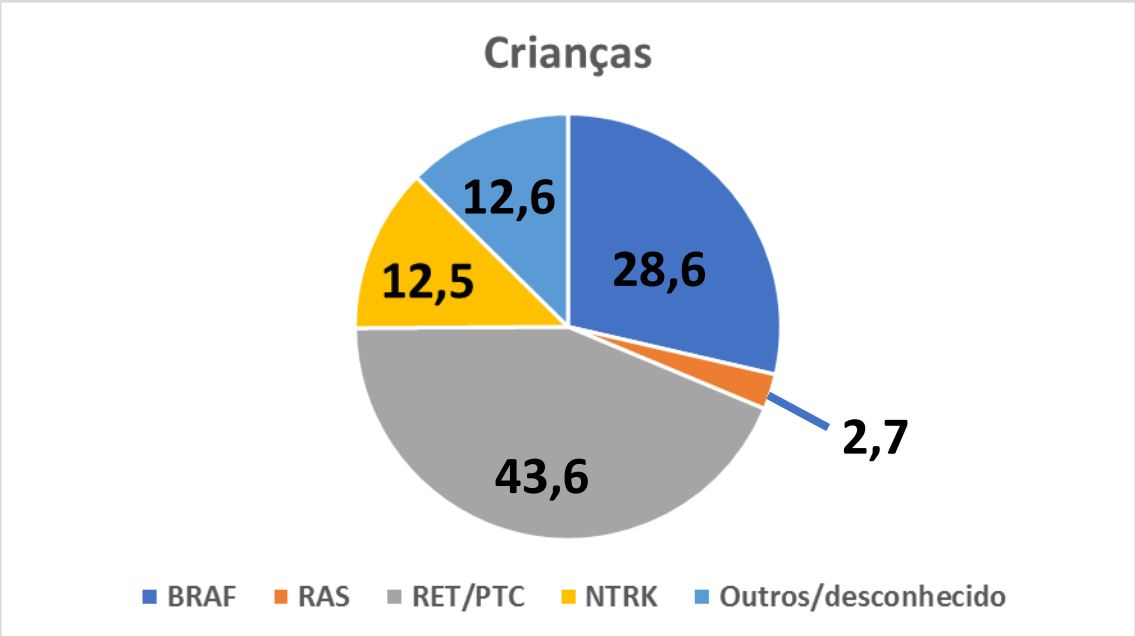

Figura 4B. Prevalência das mutações no carcinoma diferenciado de tireoide em crianças e adolescentes. (125-146).

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Parte II

Role of Postoperative Stimulated Thyroglobulin as Prognostic Factor for Differentiated Thyroid Carcinoma in Children and Adolescents

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Role of Postoperative Stimulated Thyroglobulin as Prognostic Factor for Differentiated Thyroid Cancer in Children and Adolescents

André Zanella, MD; Rafael Selbach Scheffel, MD, Ph.D.; Marina Weber Pasa; José Miguel Dora, MD, Ph.D.; and Ana Luiza Maia, MD, Ph.D.

Thyroid Unit, Endocrine Division, Hospital de Clínicas de Porto Alegre and Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

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Abstract

Background: Prognostic factors are essential for risk stratification in patients with differentiated thyroid carcinoma (DTC). The role of stimulated postoperative thyroglobulin (**s**POTg) has been well-established in adult DTC population but it remains unclear in children and adolescents. This study aimed to evaluate potential prognostic factors in children and adolescents with DTC, with special emphasis on sPOTg analysis.

Methods: Individuals aged ≤18 years at diagnosis were selected from a cohort of DTC patients attending the thyroid clinic of a tertiary university-based hospital. Baseline clinical and oncological characteristics, interventions, disease status and outcomes were obtained from medical records. Clinical variables included in the univariate analysis were sex, age at diagnosis, tumor size, presence of lymph node and distant metastasis and **s**POTg. Additionally, **s**POTg was evaluated using the area under the receiver operating characteristic curve analysis.

Results: Thirty-two children and adolescents with DTC (28 girls, 87.5%; the mean age at diagnosis = 14.7 ± 3.2 years) were included in this study. Thirty-one (96.9%) patients had papillary thyroid carcinoma. The median tumor size was 2.0 cm (P25-75 1.6-3.5), 22 patients (68.8%) had lymph node disease, and 5 (15.6%) had distant metastasis at diagnosis. All patients underwent total thyroidectomy, and 29 (90.6%) received radioactive iodine therapy. After a median follow-up of 5.0 years (P25-75 2.0-10.0), disease status was avalaible for 27 patients: 15 (55.6%) patients were disease free, six (22.5%) had biochemical disease and six (22.2%) had persistent structural disease (two cervical and four distant metastasis). Prognostic factors associated with persistent disease in the univariate analysis were lymph node and distant metastasis at diagnosis and **s**POTg. According to the receiver operating curve analysis (n=17 patients), the best **s**POTg cutoff to predict disease-free status was 31.5 ng/ml, with a sensitivity and specificity of 100%.

Conclusion: The data demonstrate that **s**POTg displayed high accuracy in predicting the risk of persistent disease in young patients with DTC.

Introduction

Thyroid cancer in childhood is rare. However, recent data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program have shown that thyroid cancer incidence is increasing in this population (1,2). In Brazil, thyroid cancer accounts for 2% of all pediatric cancers (3). Differentiated thyroid carcinoma (DTC), including papillary (PTC) and follicular (FTC) cancer, accounts for the majority (>95%) of all thyroid malignancies (4-6).

DTC in children is, in many ways, a distinct disease from DTC in adults (4-8). Although children most often present with extensive and aggressive disease and have a higher frequency of recurrence, their prognosis is excellent, with a low mortality rate even if advanced disease is present (4-9). Recently, the American Thyroid Association (ATA), recognizing these differences, released two separate guidelines for thyroid nodules and DTC specific to children and adults (10,11). The current recommendation for initial management of these young patients is total thyroidectomy followed by radioiodine therapy as indicated and levothyroxine suppressive therapy (4,5,10).

Currently, one of the most important steps in the evaluation of patients with DTC is risk stratification for recurrence (12). For that reason, the knowledge of possible prognostic factors is essential. Several prognostic factors have been well established and cited in the ATA Adult DTC Guidelines: extremes of age, larger tumors, multicentricity, extrathyroidal extension, lymph node metastasis, vascular invasion, and postoperative thyroglobulin (POTg) (11). In contrast, there are conflicting results related to these prognostic factors in children and adolescents (13-15).

One study published in 2011 by Mihailovic et al. (13) evaluated potential prognostic factors in children and concluded that younger age at diagnosis, less aggressive initial treatment, and tumor multifocality were associated with disease recurrence. These authors identified no association between DTC recurrence and sex or lymph node or distant metastasis (13). Conversely, Vaisman et al. (14) found that the only two factors associated with persistent disease were lymph node and distant metastasis. In this cohort, age, sex, tumor size and multicentricity were not predictors of the success of initial therapy (14). Of interest, the POTg – a well-stablished risk predictor for adults with DTC (16) - has not been evaluated in young patients.

The objective of the present study was to evaluate factors associated with persistent disease, with a particular focus on stimulated postoperative thyroglobulin

(sPOTg) analysis, in a contemporary DTC cohort of children and adolescents attending a referral center hospital in southern Brazil.

Materials and Methods

Patients and study design

Patients with a histological diagnosis of DTC before the age of 18 years, from a cohort of DTC patients attending the Thyroid Outpatient Clinic of the Endocrine Division of Hospital de Clínicas de Porto Alegre from 2000 to 2015, were included in this report. The institution is a tertiary-care, university teaching hospital in southern Brazil and is a referral center for DTC treatment.

Treatment protocol and follow-up

The DTC treatment protocol at the institution consists of performing total thyroidectomy, administering an ablative or therapeutic dose of radioactive iodine (RAI) as indicated, and levothyroxine suppression therapy (17-19). Decisions regarding cervical lymph node dissection were made at the discretion of the surgical team at the center where the patients underwent surgery. Follow-up duration was defined as the time between the thyroidectomy and the last medical visit to the clinic. During the first evaluation, the following data were recorded for each patient: patient demographics; tumor characteristics (date of diagnosis; histological features; extrathyroidal extension and lymph node involvement); and treatment (surgery, RAI, and other interventions). Each patient was classified using the 7th edition of the TNM/AJCC staging system (I or II). N0 status was determined by clinical examination of the neck, preoperative and postoperative neck ultrasound (US) imaging, macroscopic examination during surgery and pathological examination of patients with lymph node resection.

The follow-up protocol called for an initial assessment at three to six months post surgery, which included a physical examination of the neck and measurements of serum thyroglobulin (Tg) levels under thyrotropin (TSH) suppression (Tg-T4) and antithyroglobulin antibody (TgAb). In a second evaluation 6-12 months after the initial treatment, serum Tg was measured under conditions of a stimulated TSH (sTg) with endogenous hypothyroidism (TSH >30 mIU/L). Neck US was also performed during the first year of follow-up. Patients classified as disease-free (see below) were scheduled for annual visits that included a physical examination of the neck and measurements of Tg-T4 and TgAb. Patients with persistent disease were scheduled for

medical visits twice a year. Additional imaging studies (e.g. neck US, diagnostic I-131 whole body scan [WBS] and computed tomography [CT]) were undertaken as indicated when clinical or laboratory findings raised suspicion of persistent or recurrent disease.

sPOTg

sPOTg was measured post thyroidectomy and before administration of RAI. In patients not selected to receive RAI, the sPOTg was measured in the first year after thyroidectomy. In both groups, sPOTg measurement was made under stimulated conditions and was considered appropriate if TSH was >30 mIU/L (endogenous hypothyroidism). Serum levels of TgAb were accessed in the same blood sample from which sPOTg was measured, and patients with positive results were excluded from this analysis.

Outcomes

Disease status was defined based on clinical examination, Tg-T4 and sTg levels, neck US, post-RAI WBS (when available), and additional imaging exams when indicated.

Disease-free was defined as no clinical or imaging evidence of tumor (i.e. no uptake outside the thyroid bed on the post-treatment WBS, and no imaging evidence of tumor on neck US), undetectable (<1 ng/mL) Tg-T4 levels and sTg levels <2 ng/mL.

Persistent disease was subdivided into biochemical or structural disease. Biochemical disease was defined as Tg-T4 values ≥1 ng/ml or sTg levels ≥2 ng/mL without structural evidence of disease. Structural disease of the cervical lymph node was determined by imaging studies and biopsy-proven disease (cytology or histology) with or without abnormal Tg values. Patients diagnosed with persistent disease were evaluated for additional treatment (e.g. surgery or radioiodine), depending on the site involved.

Recurrence was defined as new biochemical or structural evidence of disease detected in a patient who had previously been determined to be disease free.

Laboratory analysis

Serum Tg measurements were performed using immunoradiometric assays (from 2000 to 2002, radioimmunoassay; 2002 to 2010, electrochemiluminescence; and 2010 until the present, chemiluminescence - ECLIA, Modular E-170, Roche) with

functional sensitivities of at least 1 ng/mL. TgAb measured using the passive agglutination method from 2000 to 2010 and chemiluminescence (Siemens Healthcare) from 2010 until the present. After each new technique had been implemented, necessary standardization and validation procedures were performed. TSH levels were measured by electrochemiluminescent immunoassay (ADVIA Centaur XP; Siemens Healthcare). All tests were conducted in the central laboratory of the Hospital de Clínicas de Porto Alegre.

Statistical analysis

Clinical and laboratory data are reported as the mean ± standard deviation or median and percentiles 25 and 75 (P25-75) for continuous variables and absolute numbers and percentages for categorical variables. Comparative analyses were performed using an unpaired Student's *t*, Mann-Whitney U-test, Fisher´s test or chi-square test, as appropriate.

Clinical variables, such as sex, age at diagnosis, tumor size, lymph nodal and distant metastases, and sPOTg were evaluated as potential prognostic factors for DTC by univariate analysis. sPOTg was also assessed using the area under the receiver operating characteristic (ROC) curve with sPOTg as a continuous prognostic variable and disease status at follow-up as the outcome variable.

All tests were two-tailed, and all analyses were performed using IBM SPSS Statistics for Windows v20.0 (IBM Corp., Armonk, NY). A two-tailed p-value <0.05 was considered statistically significant.

Results

Clinical characteristics

A group of 32 children and adolescents with DTC (28 girls, 87.5%; M age at diagnosis = 14.7±3.2 years) were included in this study. Thirty-one (96.9%) patients had PTC and one (3.1%) had FTC. The median tumor size was 2.0 cm (P25-75 = 1.6-3.5). Cervical metastasis was identified in 22 (68.8%) patients, and distant metastasis in five (15.6%) patients. Re**g**arding TNM staging, 27 (84.4%) were classified as stage I and five (15.6%) as stage II. Clinical and oncological characteristics of the 32 patients are described in Table 1.

All patients underwent total thyroidectomy**,** and 29 (90.6%) received RAI therapy with a median activity of 100 mCi (P25-75 = 100-150). Post-therapy WBS were

performed in 28 patients; 23 (82.1%) patients presented only cervical uptake**,** and 5 (17.9%) had distant metastases (all in the lung).

Disease Status

During the first year of follow-up, disease status was available for 27 patients (Fig. 1A): 14 (51.9%) patients were considered disease free, six (22.2%) had biochemical persistent disease, and seven (25.9%) had persistent structural disease (two cervical and five distant metastasis).

After a median follow-up of 5.0 years (P25-75 = 2.0-10.0), disease status was available for the 27 patients (Fig. 1B): 15 (55.6%) patients were considered disease free, six (22.2%) had persistent biochemical, and six (22.2%) had persistent structural disease (two cervical and four distant metastasis). No recurrence or deaths were registered.

Prognostic factors

To investigate factors associated with disease-free status at follow-up, patients were grouped into disease-free or persistent-disease categories. Univariate analysis indicated that patients with persistent disease had a higher proportion of lymph node metastasis (100.0 vs. 46.7%, p=0.003) and distant metastasis (41.6 vs. 0.0%, p=0.01). The sPOTg was significantly higher in the group of patients with persistent disease (638.0 vs. 8.5 ng/mL, p<0.001). Male sex, age at diagnosis, and tumor size were not associated with persistent disease (p=0.075, p=0.359**,** and p=0.338, respectively; Table 2).

sPOTg as a prognostic factor for DTC

Data for sPOTg and disease status at follow-up data were available for 19/32 patients included in this study. Of these, two were ex**c**luded from analysis due to positive TgAb levels at the time of sPOTg (TgAb titers of 1:409,600 and 1:1600). The first patient has distant metastasis and still displays high titers of TgAb after seven years of follow-up. The second patient has no evidence of structural disease and showed a significant drop in the TgAb levels during the 14 years of follow-up**.**

Thus, 17 patients were evaluated. The time interval between surgery and sPOTg was a median of 3.0 months (P25-75 = 1.5-8.0). All patients but one received RAI: a female, aged 15-year old at diagnosis, with a 2.0 cm PTC, without lymph node

metastasis or distant metastasis (low-risk, T1bN0M0). Her sPOTg was already undetectable one month after surgery and continued to be undetectable without evidence of disease after four years of follow-up.

The median value of sPOTg was 11.2 ng/mL (P25-75 = 7.5–418.5), with a median of 8.5 ng/mL (P25-75 = 5.2-11.1) for patients classified as disease free and 638.0 ng/mL (P25-75 = 125.0 – 2,297.0) for patients with persistent disease ($p<0.001$). The maximum value of sPOTg among patients considered disease free (n=10) was 13.5 ng/mL, whereas patients with persistent disease (biochemical or distant; n=7) had a minimum sPOTg value of 49.5 ng/mL. Table 3 shows the individual sPOTg levels, the time between surgery and its measurement**,** current disease status and follow-up data for these patients.

To evaluate the performance of sPOTg in predicting persistent disease, a ROC curve was used, which resulted in an area under the curve of 1.0 [confidence interval (CI) 1.0-1.0]. A sPOTg level of 31.5 ng/mL was determined as the optimal cutoff point to predict disease-free status, with a sensitivity and specificity of 100%.

No significant changes in the sPOTg values or ROC curve were observed when the patient who did not receive RAI was excluded from the analysis**.**

Discussion

Identification of patients who are at greater risk of adverse outcomes is a critical step in the management and follow-up of DTC patients. This study shows that sPOTg is a powerful prognostic tool to predict disease status at follow-up in children and adolescents with DTC.

POTg has been suggested as a prognostic factor in adult patients with DTC (16,20-25). A recent meta-analysis demonstrated POTg has a high negative predictive value (94.2% [CI 92.8-95.3]) for persistent disease, with the best cutoff value of 10 ng/mL for the prediction of the absence of biochemical or structural evidence of disease (16). However, the studies included in this meta-analysis involved mostly adult patients (average age ranging from 40.6 to 49.2 years). In fact, these data may not be applicable for pediatric patients, since this type of tumor in children differs from that identified in adult populations, not only in pathophysiology and clinical presentation but also in long-term outcomes (10). Additionally, the data suggests that serum Tg levels might be higher in children when compared with adults with a similar extent of disease (10,26,2**7**). Thus, differences can be expected in the analysis of POTg between children

and adults, particularly regarding optimal cutoff value for these populations. Nevertheless, no previous studies have evaluated the use of POTg as a prognostic marker specifically in a pediatric population.

The present results show a significant difference in sPOTg values in patients with disease-free status when compared to those with persistent disease at follow-up (8.5 vs**.** 638.0 ng/mL, respectively). Interestingly, the sPOTg cutoff value of 31.5 ng/mL is higher than those previously reported in adult populations studies, which ranged from 5.0 to 30.0 ng/mL (16). A potential explanation for the differences between adults and children/adolescents sPOTg cut-off values is the more aggressive presentation of DTC in young patients, with larger tumors, lymph node**,** and distant metastasis.

In the present cohort, the presence of lymph node metastasis and distant metastasis were associated with persistent disease in short- and long-term outcomes. These findings are similar to those found in a previous study (14) that identified lymph node metastasis and distant metastasis as the two most important prognostic factors in young patients with DTC. Furthermore, in agreement with the present results, these authors found no statistical significance between sex, tumor size, or age at diagnosis and persistent disease. In contrast, a recent study that included 118 children and adolescents (15) showed that sex and metastatic disease (lymph node and distant) are important prognostic factors in children with DTC. Moreover, they found ATA risk stratification useful in predicting early and long-term outcomes in the pediatric population.

Based on the present study, sPOTg results can help guide the follow-up of young patients with DTC. Those with POTg values <31.5 ng/mL had a better prognosis, requiring less intensive treatment and monitoring. Conversely, patients with **s**POTg >31.5 ng/mL were at high risk of persistent disease, a condition that warrants more agressive treatment and follow-up.

This study has some strengths. First, the fact that all patients included in this analysis were followed at the same institution ensures similar therapeutic and follow-up approaches. The exclusion of patients with TgAb-positive minimizes the possibility of false negatives sPOTg values. However, the relatively small number of patients and the fact that the analysis is restricted to only one center experience are limitations for the interpretation of the ROC curve analysis and the external validity of our findings, a fact that should be acknowledged. Another aspect to be considered is that although a median of five years is a reasonable time of follow-up for assessing clinical outcomes, a more extensive period should be observed for definitive conclusions. Notwithstanding,

considering the rarity of DTC in this population and the lack of effective risk stratification strategies, the role of sPOTg as a prognostic risk stratification tool in the pediatric population is of considerable interest.

In conclusion, this study demonstrates that lymph node metastasis, distant metastasis, and sPOTg are useful prognostic factors in young patients with DTC. Of particular interest, sPOTg seems to have a promising role as a tool for identifying children and adolescents with DTC at high risk of persistent disease.

Table 1. Characteristics of 32 children and adolescents with differentiated thyroid carcinoma

Age at diagnosis (years)	14.7 ± 3.2
Female sex, n (%)	28 (87.5)
Histology, n (%)	
Papillary	31 (96.90)
Follicular	1 (3.1)
Tumor size (cm)	2.0 (1.6-3.5)
Lymph node metastasis (N1), n (%)	22 (68.8)
Distant metastasis, n (%)	5 (15.6)
TNM AJCC stage, n (%)	
I	27 (84.4)
II	5 (15.6)
RAI therapy, n (%)	29 (90.6)
RAI activity (mCi)	100 (100-150)
Follow-up (years)	5.0 (2.7-10.2)

Data are expressed as the mean ± SD, median (percentiles 25-75) or frequencies. RAI, radioactive iodine.

Table 2. Univariate analysis of predictors of persistent disease status

	Disease Status		Univariate Analysis
	Disease-free	**Persistent Disease**	**p**
Male sex	0/15 (0.0)	3/12 (25.0)	0.075
Age at diagnosis (years)	15.0 ± 2.9	13.7 ± 4.0	0.359
Tumor size (cm)	2.0 (1.7-3.5)	2.9 (2.1-4.0)	0.338
Lymph node metastasis	7/15 (46.7)	12/12 (100)	0.003
Distant metastasis	0/15 (0.0)	5/12 (41.6)	0.010
Stimulated postoperative Tg (ng/mL)	8.5 (5.2-11.1)	638.0 (125.0-2297.0)	< 0.001

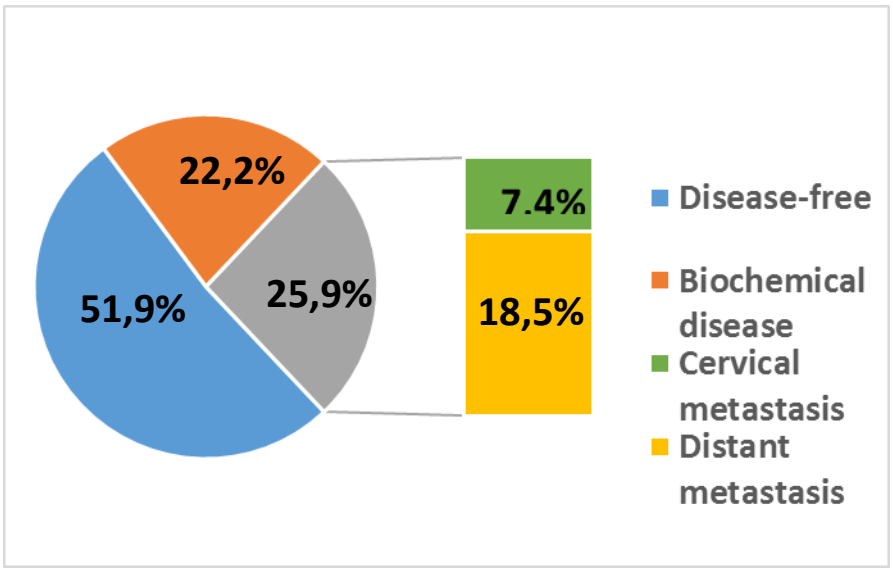
Data are expressed as the mean ± SD, median (percentiles 25-75) or frequencies. Tg, thyroglobulin.

Table 3. Individual characteristics of 17 patients with POTg level and disease status available

Patient	sPOTg (ng/mL)	Time after surgery (months)	Current stimulated Tg (ng/mL)	Current status	Follow-up (years)
1	0.1	1.0	0.1	Disease-free	3.0
2	0.5	3.0	0.1	Disease-free	5.0
3	6.8	3.0	0.6	Disease-free	5.0
4	7.0	34.0	0.5	Disease-free	6.0
5	8.0	2.0	0.1	Disease-free	4.0
6	9.0	3.0	0.1	Disease-free	4.0
7	10.0	7.0	0.1	Disease-free	8.0
8	11.1	1.0	0.1	Disease-free	11.0
9	11.1	8.0	0.1	Disease-free	5.0
10	13.5	2.0	0.1	Disease-free	5.0
11	125.0	1.0	32.7	Biochemical disease	2.0
12	2297.0	8.0	72.0	Biochemical disease	9.0
13	49.5	3.0	10.0	Structural Disease	2.0
14	638.0	13.0	8.6	Structural disease	2.0
15	199.0	1.0	3.0	Structural disease	1.0
16	1656.0	26.0	404.0	Structural disease	12.0
17	4493.0	2.0	20212.0	Structural disease	5.0

sPOTg, stimulated postoperative thyroglobulin.

1A.



1B.

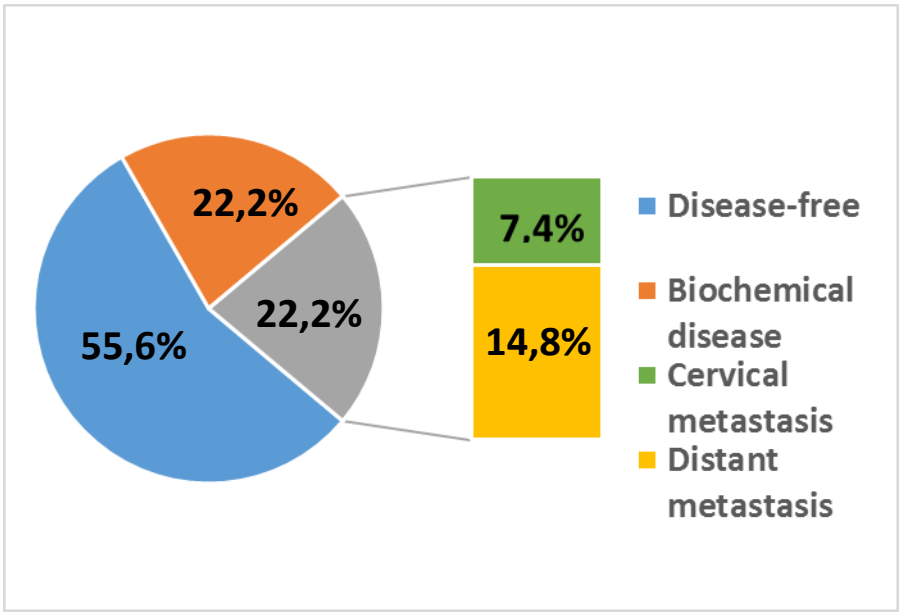


Fig. 1. Disease **s**tatus after a one-year follow-up (**A**) and after a median of 5.0 years of follow-up (P25-75 2.0-10.0) (**B**).

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Parte III

Dynamic Risk Stratification in the Follow-up of Children and Adolescents with Differentiated Thyroid Cancer

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Dynamic Risk Stratification in the Follow-up of Children and Adolescents with Differentiated Thyroid Cancer

André Borsatto Zanella[1,2], MD; Rafael Selbach Scheffel[1], MD, Ph.D.; Carla Fernanda Nava[1], MD; Lenara Golbert[3], MD, Ph.D.; Erika Laurini de Souza Meyer[3], MD, Ph.D.; Márcia Punales[4] MD, Ph.D.; Iracema Gonçalves[4], MD; José Miguel Dora[1], MD, Ph.D.; and Ana Luiza Maia[1], MD, Ph.D.

Thyroid Unit, Endocrine Division, Hospital de Clínicas de Porto Alegre and Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

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Abstract

Background: Risk stratification for persistent disease is an important step in pediatric differentiated thyroid cancer (DTC) management. The dynamic risk stratification (DRS) is a well validated system for adults, but not yet for children and adolescents. This study evaluated the DRS as well as other prognostic factors in pediatric DTC.

Methods: Patients aged ≤ 18 years from four DTC tertiary teaching hospitals in Southern Brazil were included. Clinical characteristics were systematically retrieved, and all patients were classified according to risk stratification system of the 2015 ATA Children DTC guidelines (ATA Risk) and according to DRS (excellent, indeterminate, biochemical, or structural incomplete responses). Disease status was evaluated after initial therapy and at last follow-up visit.

Results: Sixty-six patients aged 14.5±3.0 years were studied of whom 54 (81.8%) were girls and 62 (93.9%) had papillary thyroid carcinomas. Tumor size was 2.3cm (P25-75; 1.6-3.5), 41 (63.1%) had cervical and 18 (27.7%) distant metastasis at diagnosis. All patients underwent total thyroidectomy and 63 (95.5%) received radioiodine. Patients were classified according to DRS after initial therapy (n=63) as follows: 21 (33%) excellent, 13 (21%) indeterminate, 6 (9%) biochemical, and 23 (37%) structural incomplete responses. Notably, after six years (P25-75; 2.7-10.0), most patients remained in the same category. Interestingly, the cutoff analysis of stimulated postoperative thyroglobulin **(**sPOTg**)** through receiver operating characteristic curve showed that the value of 37.8 ng/mL showed 81% sensitivity and 100% specificity to predict an excellent response. Prognostic factors associated with persistent disease in the univariate analysis were TNM, ATA risk, DRS and sPOTg.

Conclusion: DRS after initial therapy and sPOTg are strong predictors of disease outcome and might be helpful on defining follow-up strategies in pediatric DTC.

Introduction

Differentiated thyroid cancer (DTC), which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), is the most common endocrine tumor during childhood (1-3). PTC is the most common form of thyroid cancer in both children and adults and represents >90% of all DTC diagnoses. Notably, DTC incidence in children and adolescents is increasing at a rate of 1.1% per year (4-9). In Brazil, thyroid cancer currently accounts for 2% of all pediatric cancers (10).

DTC has distinct presentations in pediatric patients compared to adults (3,11-14). Although children and adolescents more often present with extensive and aggressive disease and display a higher frequency of persistence/recurrence, their prognosis is excellent, with a low mortality rate, even for those presenting with advanced disease at diagnosis (3, 11-15).

Currently, one of the most important steps in the management of adult patients with DTC is risk stratification for persistent/recurrent disease (16,17). However, there is no single postoperative staging system that has been validated for children and adolescents with DTC, and the utility of extrapolating adult risk and staging systems into the pediatric setting is limited by the observed clinical disparity between the two age groups (18,19). The American Joint Committee on Cancer (AJCC) TNM classification system is widely used for describing the extent of disease and prognosis in the adult population (20). However, as it was developed to predict mortality and not persistence/recurrence, the TNM classification system remains limited in terms of determining prognosis in children and adolescents (18). The most recent 2015 American Thyroid Association (ATA) guideline for children with DTC suggest using the TNM system to categorize patients into three risk groups, which also provide guidance for postoperative management: low, intermediate and high (18). However, its utility is limited, since it only takes into account the histopathological data, but does not consider response to therapy.

A novel risk stratification system was recently described, which stratifies response to therapy following initial treatment and during follow-up. This approach has been termed “dynamic risk stratification” (DRS) (21-25). Nevertheless, while the response to therapy assessment has been validated for adult patients with DTC, it has only been evaluated in a few cohorts of children and adolescents (26-27). Of interest, it was recently demonstrated that stimulated postoperative thyroglobulin (sPOTg) after

initial treatment seems to have a promising role as a tool for identifying children and adolescents with DTC at high risk of persistent disease (19).

The primary objective of the present study was to evaluate the DRS as a prognostic tool to stratify risk for persistent and/or recurrent disease in a contemporary DTC cohort of children and adolescents attending four DTC referral centers in southern Brazil. The secondary objective was to evaluate the role of sPOTg as prognostic factor in this population.

Materials and Methods

Patients and study design

Sixty-six children and adolescents with histological diagnosis of DTC before the age of 18 years were included in this retrospective study. This number corresponds to all consecutive pediatric patients who were followed at four referral centers for DTC treatment in southern Brazil from 2000 to 2016: *Hospital de Clínicas de Porto Alegre* (n=31), *Hospital Nossa Senhora da Conceição* (n=24), *Santa Casa de Porto Alegre* (n=9) and *Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul* (n=2).

Treatment protocol and follow-up

The DTC treatment protocol used in these institutions consists of performing total thyroidectomy, administering or not administering an ablative or therapeutic dose of radioactive iodine (RAI) as indicated, and levothyroxine suppression therapy (18,19,28,29). Decisions regarding cervical lymph node dissection were made at the discretion of the surgical team at the center where the patients underwent surgery. Of the 66 patients, 44 have been operated in the four institutions included in this study. However, 22 patients were referred to these institutions after the surgical procedure. The surgical notes and the referral report were reviewed, and data about the lymph node was registered. Follow-up duration was defined as the time between the thyroidectomy and the last medical visit to the clinic. During the first evaluation, the following data were recorded for each patient: patient demographics; tumor characteristics (date of diagnosis; histological features; extrathyroidal extension and lymph node involvement); and treatment (surgery, RAI, and other interventions).

The follow-up protocol called for an initial assessment at 3 to 6 months post-surgery, which included a physical examination of the neck and measurements of serum

thyroglobulin (Tg) levels under thyrotropin (TSH) suppression (Tg-T4) and antithyroglobulin antibody (TgAb). In a second evaluation, 6 to 12 months after the initial treatment, serum Tg was measured under conditions of a stimulated TSH (sTg) with endogenous hypothyroidism (TSH >30 mIU/L). Neck ultrasound (US) was also performed during the first year of follow-up. Patients classified as disease free (see below) were scheduled for annual visits that included a physical examination of the neck and measurements of Tg-T4 and TgAb. Patients with persistent disease were scheduled for medical visits twice a year and evaluated for additional therapy as needed. Additional imaging studies [e.g. neck US, diagnostic I-131 whole body scan (WBS) and computed tomography (CT)] were performed as indicated when clinical or laboratory findings raised suspicion of persistent or recurrent disease.

Risk stratification and Outcomes

To evaluate the initial risk for this pediatric population, all patients were classified according the eighth AJCC TNM staging system (I or II) (20). N0 status was determined by clinical examination of the neck or pre- and postoperative neck US imaging or macroscopic examination during surgery and pathological examination of patients with lymph node resection. Additionally, they were stratified according to the 2015 ATA pediatric guideline (18) into three thyroid cancer risk levels: low, intermediate and high.

Disease status was defined based on clinical examination, Tg-T4 and sTg levels, neck US, post-RAI WBS (when available), and additional imaging exams when indicated. Patients were classified into four categories: excellent response, indeterminate response, biochemical incomplete response, or structural incomplete response.

In patients submitted to RAI, an excellent response was defined as negative imaging and Tg-T4 <0.2 ng/mL or sTg <1.0 ng/mL (21). A biochemical incomplete response was defined as negative imaging and Tg-T4 >1.0ng/mL or sTg >10.0 ng/mL or rising TgAb levels. A structural incomplete response was defined as structural or functional evidence of disease with any Tg or TgAb level. An indeterminate response was defined as non-specific findings on imaging studies or Tg-T4 between 0.2 to 1.0 ng/mL or sTg between 1.0 and 10.0 ng/mL or TgAb stable or declining.

In patients not submitted to RAI, excellent response was defined as negative imaging and Tg-T4 <0.2 ng/mL or sTg <2.0 ng/mL (21). A biochemical incomplete

response was defined as negative imaging and Tg-T4 >5.0ng/mL or sTg >10.0 ng/mL or increasing Tg levels over time or rising TgAb levels. Structural incomplete response was defined as structural or functional evidence of disease with any Tg or TgAb level. An indeterminate response was defined as non-specific findings on imaging studies or Tg-T4 between 0.2 to 5.0 ng/mL or sTg between 2.0 and 10.0 ng/mL or TgAb stable or declining.

Recurrence was defined as new biochemical or structural evidence of disease detected in a patient who had previously been determined to be disease free.

DRS

The response to treatment, based on the criteria described above, was evaluated after initial treatment**,** which includes surgery and RAI**,** and at the last follow-up visit. The patients were classified into the four categories of DRS: excellent response, indeterminate response, biochemical incomplete response, or structural incomplete response.

sPOTg

sPOTg was measured before administration of RAI in those patients who received this treatment and in the first year after thyroidectomy in those patients who did not receive RAI. In both groups, sPOTg measurements were made under stimulated conditions following four weeks of thyroid hormone withdrawal (endogenous hypothyroidism) and sPOTg was considered appropriate if TSH was >30mIU/L. Serum levels of TgAb were evaluated in the same blood sample from which sPOTg was measured, and patients with positive results were excluded from this analysis (n=5).

Statistical analysis

Clinical and laboratory data are reported as the mean ± standard deviation (SD) or median and percentiles 25 and 75 (P25-75) for continuous variables and absolute numbers and percentages for categorical variables. Comparative analyses were performed using an unpaired Student's *t*, Mann-Whitney U-test, Fisher´s test or chi-square test as appropriate.

Clinical variables, such as sex, age at diagnosis, tumor size, histological subtype, multicentricity, lymph node and distant metastasis, sPOTg, ATA risk and DRS after

initial treatment were evaluated as potential prognostic factors for DTC persistent disease by univariate analysis. sPOTg was also assessed using the area under the receiver operating characteristic (ROC) curve with sPOTg as a continuous prognostic variable and disease status at follow-up as the outcome variable.

All tests were two-tailed, and all analyses were performed using IBM SPSS Statistics for Windows v20.0 (IBM Corp., Armonk, NY). A two-tailed p-value <0.05 was considered statistically significant.

Results

Clinical characteristics

Sixty-six children and adolescents with DTC (81.8% of girls) with a mean age at diagnosis of 14.5 ± 3.0 years were included in this study. Of these, 62 (93.9%) had PTC and four (6.1%) had FTC. The median tumor size was 2.3 cm (P25-75 1.6-3.5). Cervical metastasis was identified in 41 (63.1%) patients (N1a=11; N1b=30) and distant metastasis in 18 (27.7%). The clinical and oncological characteristics of the studied patients are described in Table 1.

All patients underwent total thyroidectomy; 12 have been submitted only to central neck dissection and 33 to central and lateral neck dissection. Of the 66 patients, information about the surgical lymph node status was available for 45 subjects. Using the TNM classification, it was possible to classify those patients as follows: 4 with N0, 11 with N1a and 30 with N1b. Of the 30 patients classified as N1b, 19 presented unilateral disease, 8 presented bilateral disease and 3 extensive invasive burden disease.

In terms of RAI therapy, 63 (95.5%) patients received RAI being 42 therapeutic (mean 124.2 ± 38.5 mCi) and 21 ablative (mean 89.7 ± 37.0 mCi). In relation to the three patients who did not receive any RAI, all were classified as T1N0M0, and hence were in the ATA low risk category. Post-therapy WBS were performed in 60 patients; 3 (5%) patients had no uptake, 39 (65.0%) patients only had cervical uptake, and 18 (30.0%) patients were found to have distant metastases that were localized in the lung in all of them.

DRS

Data concerning the disease status after initial therapy were available for 63 patients: 21 (33%) had an excellent response, 13 (21%) an indeterminate response, 6

(9%) a biochemical persistent disease, and 23 (37%) a structural incomplete response (Fig. 1).

After a median follow-up of 6.0 (2.7-10.0) years, 19 (90%) of the patients with an excellent response in the first evaluation remained disease free, two (10%) were reclassified to indeterminate response, and none had persistent disease (biochemical or structural).

Those patients with an indeterminate response after initial therapy showed similar results: the majority (n=8; 62%) remained in the indeterminate response category, four (31%) were reclassified as having an excellent response, and only one (7%) developed structural disease (cervical lymph node metastasis).

Among the six patients with biochemical disease after the initial therapy, one (17%) displayed an excellent response at follow-up, one (17%) was considered to have indeterminate response, and the majority (66%) remained in the biochemical disease group (Fig. 1). Notably, only one of the patients not initially classified as having structural persistent disease developed a metastasis (a cervical lymph node metastasis in a patient with indeterminate response after initial treatment).

All patients with structural persistent disease were evaluated for additional therapy (i.e., surgical interventions and/or RAI) at the discretion of the attending physician. Among the patients (n = 23) diagnosed with structural persistent disease after the initial treatment, only three (13%) reached an excellent response status after additional treatment (two patients underwent surgical intervention for cervical persistent disease, and one patient had a pulmonary metastasis that resolved after a cumulative dose of 350 mCi of RAI). Most of the patients classified as having structural persistent disease after initial therapy continued with structural disease (n=14; 61%), and six (26%) exhibited an indeterminate response (Fig. 1). No deaths were recorded.

Additional treatment

Among the patients with an excellent response after initial treatment (n=21), only one was submitted to a new neck exploration (negative for metastasis), and none received additional RAI. Among the 13 patients with indeterminate response after initial treatment, three of them were submitted to revisional cervical surgery (all three positives for lymph node metastasis) and one received a second RAI treatment. Related to patients with a biochemical incomplete response (n=6) after initial therapy, two of

them were submitted to revisional surgery for cervical lymph node metastasis and three received additional RAI. Among the 23 patients with structural persistent disease after initial treatment, 12 underwent revisional new neck exploration (11 positive and 1 negative for lymph node metastasis), and 16 received at least one more RAI treatment.

ATA pediatric risk classification versus DRS after initial therapy

Next, the ATA pediatric risk classification and DRS were compared after initial therapy. It was observed that both systems had a good correlation, with 59% of low, 31% of intermediate, and 5% of high-risk patients showing excellent response to therapy (Table 2). On the other hand, only 8% of low-risk patients, 19% of intermediate-risk patients, and 81% of high-risk patients had a structural incomplete response to therapy.

DRS after initial treatment and excellent response

Next, the proportion of patients in the ATA pediatric risk classification and DRS systems who achieved an excellent response at the last follow-up was analyzed. As expected, differences were observed in these rates according to the ATA pediatric risk stratification. Patients achieved an excellent response in 79% for low-risk, 31% for intermediate-risk, and 9% for high-risk patients (p=0.007). This difference was also observed in DRS categories after response to the initial treatment. Excellent response rates were 90% for excellent response, 30% for indeterminate response, 16% for biochemical persistent disease and 13% for structural persistent disease (p=0.01).

Role of sPOTg as predictor of disease status

Data on sPOTg and disease status at follow-up were available for 43/66 (65%) patients included in this study, and five were excluded for the presence of positive TgAb. The median value of sPOTg was 18.9 ng/mL (P25–75, 9.0–221). The time interval between surgery and sPOTg was a median of 2.0 months (P25–75 = 1.0–4.0). To evaluate the performance of sPOTg in predicting persistent disease (biochemical or structural), a ROC curve was used (Fig. 2), which resulted in an area under the curve of 0.92 [confidence interval 0.83–1.00]. A sPOTg level of 37.8 ng/mL was determined as the optimal cutoff point to predict persistent disease, with a sensitivity of 81% and specificity of 100%. Of interest, all patients with an excellent response (n=20) had a

sPOTg <37.8 ng/mL, and 92% of patients with structural persistent disease had a sPOTg above the cutoff level (Table 2).

Prognostic factors and univariate and multivariate analysis

To investigate factors associated with persistent disease at follow-up, patients were grouped into disease-free or persistent disease categories. Univariate analysis indicated that tumor size, lymph node and distant metastasis, ATA pediatric risk, DRS after initial treatment, and sPOTg were all associated with persistent disease (Table 3). The variables sex, age at diagnosis, histological subtype, and multicentricity were not associated with persistent disease. An additional analysis using a multivariate model that included all variables with p-values <0.05 in the univariate analysis and disease status as the dependent variable showed that only DRS after initial therapy was an independent prognostic factor for persistent disease (Table 4). Unfortunately, the statistical model did not support the sPOTg variable.

Discussion

Risk stratification systems for recurrence/persistence of disease are critical for providing the best care available for DTC patients, but these tools are not yet well validated for the pediatric population. This study shows that both DRS and sPOTg are powerful prognostic tools to predict disease status at follow-up in children and adolescents with DTC.

Identifying patients at greater risk of adverse outcomes is as important step in the management of DTC patients. Since DTC is known to be an indolent neoplasia, the ‘‘over follow-up effect’’ with unnecessary surveillance, diagnostic tests and medical appointments is a concern (17). This issue may have even more impact in the pediatric population, since these patients are expected to have a lifelong follow-up. Another important aspect regarding children and adolescents with DTC is the paucity of data and studies in this population. DTC in pediatric patients has a distinct presentation and prognosis. Thus, extrapolating results from studies of adult population might lead to equivocal conclusions.

The DRS has been validated by a seminal study of Tuttle et al. in 2010 (21). Several studies have further corroborated the DRS as an important instrument for risk stratification in adult patients with DTC (22-25). A central aspect of this system is to

contemplate the dynamic response of the patient to the initial treatment and follow-up treatment. The DRS, based on information from imaging studies and serum Tg levels, provides a better prediction of the risk of recurrent/persistent disease and allows the individualization of patient's management and follow-up.

Despite all these observations that qualify DRS as one of the major tools in the follow-up of patients with DTC, it has been poorly studied in children. Accordingly, there is no recommendation for its use in ATA management guidelines for children with thyroid cancer (18). In fact, to the best of the author´s knowledge, only two studies have evaluated the DRS in the pediatric DTC population. In the first study, Lazar *et al*. (26) evaluated the DRS system in a cohort of 54 patients with median age at diagnosis 13.9 years and a median of 8.8 year follow-up. The authors observed that those patients classified as having a complete response after initial treatment displayed a good prognosis: 82.9% of the patients remained in the excellent response status on long-term follow-up. On the other hand, all the patients with an incomplete response remained with persistent disease. Of interest, the proportion of variance associated with DRS was greater than that explained by ATA risk-stratification system (0.79 vs. 0.25), suggesting that DRS is a more precise predictor for disease outcome. The second study evaluated a cohort of 77 pediatric DTC patients and also demonstrated that DRS was useful to predict disease outcome at a long-term follow-up: the risk of recurrent/persistent disease was significantly higher in the indeterminate group (hazard ratio [HR] = 10.2; p=0.045) and in the structural incomplete group (HR = 98.7; p=0.005) compared to the group with an excellent response (27).

The present study shows that in a cohort of 66 pediatric patients with DTC, the DRS after initial therapy is an excellent tool on predicting disease status. Notably, the DRS status category after initial therapy remained unchanged for most patients during a median follow-up of six years. These findings are especially important for the group of patients with excellent response after the initial treatment, since 90% (21/23) of them remained disease-free during long-term follow-up.

Another important finding of this study is the demonstration of the usefulness of sPOTg as a prognostic factor for DTC in the pediatric population. Tg is a specific and sensitive marker of the presence of follicular thyroid cells, and serum Tg measurement is a cornerstone tool in the follow-up of DTC patients and is considered the most accurate method to detect persistent or recurrent disease. Moreover, sPOTg has been suggested as a prognostic factor in adult patients with DTC by many studies (30-35).

Recently, the usefulness of sPOTg as a prognostic factor was demonstrated in a small DTC pediatric population followed at the author´s institution (19). Here, including patients from four referral centers, a similar sPOTg cutoff level to predict disease status (37.8 ng/mL) was observed. Of note, this value is much higher than that found in the adult population with DTC, indicating different cutoff values for these two populations. According to a recent metanalysis (30), the best cutoff of sPOTg for predicting persistent disease in adult DTC patients is 10.0 ng/mL. These observations might help to guide the follow-up of young patients with DTC, differentiating those that require a less intensive treatment from those that are candidates for more aggressive treatment and follow-up.

This study has some strengths: first, the large number of patients of this rather uncommon disease in children; and second, its multicenter design, which strengths the external validity of the results. However, it should be noted that although six years is a reasonable length of follow-up to assess clinical outcomes, observations for longer periods should be studied to reach more definitive conclusions. Another possible limitation is that there was no standardization of surgical treatment to address lymph node disease. On the other hand, the data reflect real-life clinical practice, enhancing the external validity of the findings. However, this possible limitation may be partially mitigated by the fact that the surgery report of all patients were reviewed and that they underwent a clinical examination of the neck and postoperative neck US, which allowed the presence of suspicious lymph nodes to be identified.

In conclusion, adequate risk stratification in DTC is crucial to avoid, on one hand, the overtreatment of low-risk patients and, on the other hand, the under-treatment of high-risk patients. This study demonstrates that the DRS after initial therapy and sPOTg are reliable prognostic factors in children and adolescents with DTC. Performing sPOTg and the DRS are acceptable, widely available, practical, timely, low cost and high-value strategies that should be used consistently in the management of pediatric DTC patients.

Table 1. Characteristics of 66 children and adolescents with differentiated thyroid carcinoma

Age at diagnosis (years)	14.5 ± 3.0
Female sex, n (%)	54 (81.8)
Histology, n (%)	
Papillary	62 (93.9)
Follicular	4 (6.1)
Tumor size (cm)	2.3 (1.6-3.5)
Lymph node metastasis (N1), n (%)	41 (63.1)
Distant metastasis, n (%)	18 (27.7)
TNM AJCC stage, n (%)	
I	47 (72.3)
II	18 (27.7)
RAI therapy, n (%)	63 (95.5)
RAI activity (mCi)	100 (100-150)
Follow-up (years)	6.0 (2.7-10.0)

Data are expressed as the mean ± SD, median (percentiles 25-75), or frequencies.

AJCC, American Joint Committee on Cancer; RAI, radioactive iodine.

Table 2. ATA pediatric risk stratification and dynamic risk stratification based on response to initial treatment in pediatric thyroid cancer

Response to initial treatment	ATA risk stratification			sPOTg (ng/mL)	
	Low (n=24)	Intermediate (n=16)	High (n=22)	<37.8	>37.8
Excellent response (n=20)	14 (59%)	5 (31%)	1 (5%)	14 (100%)	0 (0%)
Indeterminate response (n=13)	6 (25%)	5 (31%)	2 (9%)	5 (71%)	2 (29%)
Biochemical incomplete response (n=6)	2 (8%)	3 (19%)	1 (5%)	1 (25%)	3 (75%)
Structural incomplete response (n=23)	2 (8%)	3 (19%)	18 (81%)	1 (8%)	12 (92%)

ATA, American Thyroid Association; sPOTg, stimulated postoperative thyroglobulin .

Table 3. Univariate analysis of predictors of persistent disease status

	Disease Status		Univariate Analysis
	Disease-free	**Persistent Disease**	**p**
Male sex	2/27 (7.4)	9/36 (25.0)	0.058
Age at diagnosis (years)	14.5 ± 2.7	14.3 ± 3.3	0.839
Tumor size (cm)	2.0 (1.2-2.6)	2.7 (1.8-4.0)	0.019
Lymph node metastasis	8/26 (30.7)	32/36 (88.8)	<0.001
Distant metastasis	1/26 (3.8)	17/36 (47.2)	<0.001
sPOTg (ng/mL)	8.8 (3.1-14.6)	167.0 (11.9-508.9)	< 0.001
Follicular cancer	3/27 (11.1)	1/36 (2.7)	0.177
Multicentricity	6/20 (30.0)	15/29 (51.7)	0.128
ATA pediatric risk			
Low	19/26 (73.1)	5/36 (13.9)	
Intermediate	5/26 (19.2)	11/36 (30.5)	<0.001
High	2/26 (7.7)	20/36 (55.6)	
DRS after initial treatment			
Excellent	19/27 (70.4)	2/36 (5.5)	
Indeterminate	4/27 (14.8)	9/36 (25.0)	<0.001
Biochemical persistent	1/27 (3.7)	5/36 (13.9)	
Structural persistent	3/27 (11.1)	20/36 (55.6)	

Data are expressed as the mean ± SD, median (percentiles 25-75), or frequencies.
DRS, dynamic risk stratification.

Table 4. Multivariate analysis of predictors of persistent disease status.

	OR [CI]	p
Tumor size (cm)	1.5 [0.8-3.0]	0.17
Lymph node metastasis	16.8 [0.6-523.9]	0.08
Distant metastasis	1.7 [0.01-136.0]	0.79
ATA pediatric risk		
Low	1.0	
Intermediate	1.0 [0.4-27.3]	0.73
High	2.0 [0.03-164.1]	0.17
DRS after initial treatment		
Excellent	1.0	
Indeterminate	35.2 [3.7-762.5]	0.006
Biochemical persistent	54.9 [2.5-3933.1]	0.027
Structural persistent	13.9 [1.1-313.7]	0.05

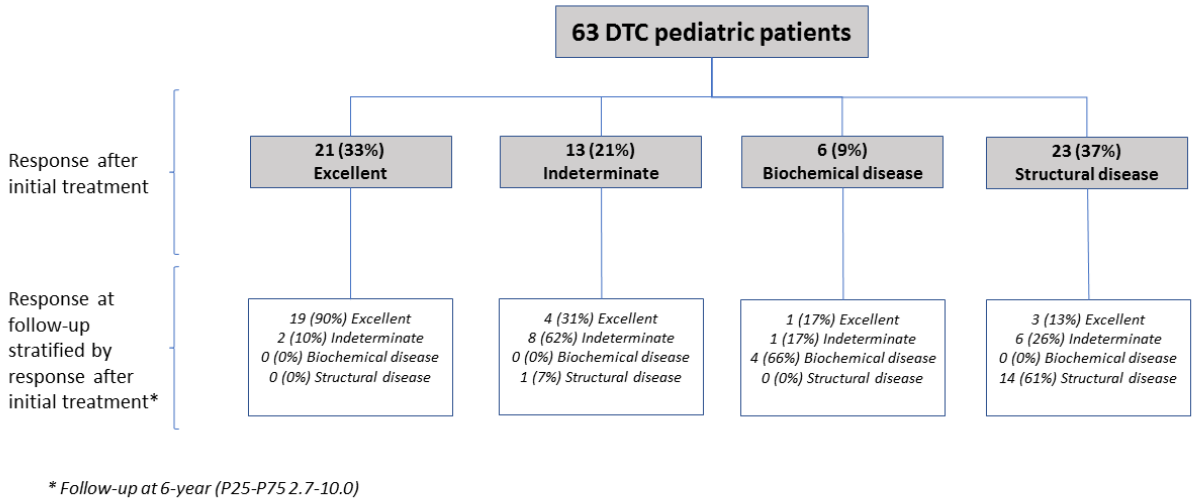

FIG. 1. Follow-up outcomes, according to the dynamic risk stratification (DRS). DTC, differentiated thyroid cancer.

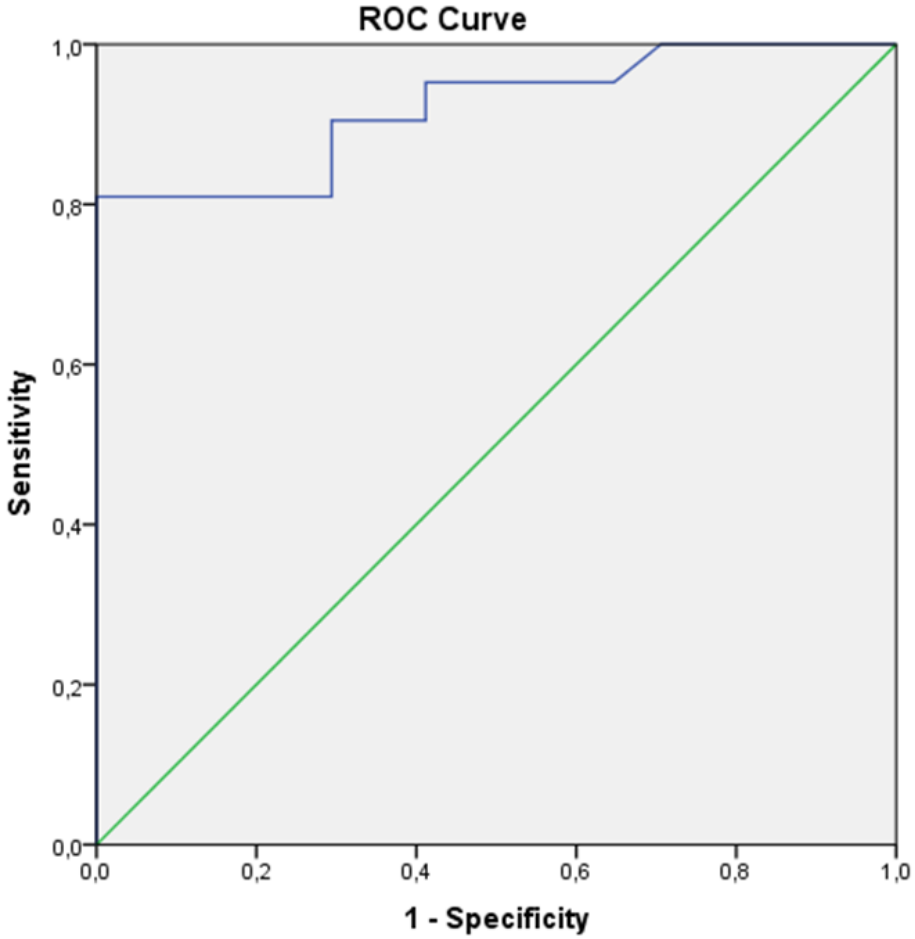

FIG. 2. Receiver operating characteristic curve of sPOTg for excellent response. sPOTg, stimulated postoperative thyroglobulin.

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CONSIDERAÇÕES FINAIS

O CDT em crianças e adolescentes é uma doença rara, mas que vem aumentando sua incidência ao longo dos últimos anos. Por essa razão, os estudos nessa população são escassos. O melhor conhecimento dessa patologia é fundamental para que possamos oferecer o melhor tratamento e acompanhamento desses pacientes.

O prognóstico do CDT em crianças e adolescentes é excelente na maioria dos casos, com taxas de sobrevida em 20 anos acima de 95%. Entretanto, uma parcela desses pacientes pode apresentar uma doença mais agressiva, tanto na sua apresentação inicial quanto durante o acompanhamento. Sendo assim, o ponto fundamental é tentar identificar de forma precoce quem são esses pacientes, para oferecer um tratamento e acompanhamento diferenciado.

Nos 2 estudos apresentados aqui tivemos a oportunidade de aumentar nosso conhecimento nessa área. Mostramos que existem alguns fatores prognósticos associados a doença persistente, como metástases em linfonodos, metástases a distância, sPOTg, classificação de risco da ATA e DRS. Além disso, demonstramos o papel da sPOTg e da DRS, ferramentas amplamente testadas e comprovadas na população adulta com CDT, em crianças e adolescentes.