Universidade Federal do Rio Grande Do Sul

Faculdade de Medicina

Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Rafael Selbach Scheffel

Fatores Prognósticos do Carcinoma Diferenciado da Tireóide

Porto Alegre
2014

Rafael Selbach Scheffel

Fatores Prognósticos do Carcinoma Diferenciado da Tireóide

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul como requisito parcial para obtenção do título de Doutor em endocrinologia.

Orientadora: Prof[a]. Dr[a]. Ana Luiza Maia

Porto Alegre
2014

CIP - Catalogação na Publicação

AGRADECIMENTOS

À Prof^a. Dr^a. Ana Luiza Maia, os meus agradecimentos pela oportunidade de convivência e aprendizado. Obrigado não só pela orientação, mas também pela amizade e companheirismo destes quatro anos.

Ao colega, amigo e coautor desses trabalhos José Miguel Dora pela parceria destes últimos anos. Tua contribuição foi muito importante para esta conquista.

Aos colegas e amigos do Grupo de Tireóide – Mirian Romitti, Lucieli Ceolin, Carla Vaz Ferreira, Simone Wajner, Érika Méier, Rafaela Vanin Pinto Ribeiro, Helena Cecin Rohenkohl, Carla Krause, Shana Weber, Juliano Dalla Costa, Clarissa Capp, Leonardo Leiria, Debora Rodrigues Siqueira, Nadja Zennig, André Zanella, Carla Brauner Blom, Walter Escouto, Josi Vidart, Denise Antunes e Kharina Dias pelas contribuições na elaboração deste trabalho e pelos momentos maravilhosos compartilhados.

Ao Prof. Dr. Luis Henrique Canani pela orientação na fase de iniciação científica, base que foi muito útil para a realização deste trabalho.

Aos meus pais, Regina Maria Scheffel e Paulo Ricardo Scheffel, e aos meus irmãos, Augusto Selbach Scheffel e Josué Selbach Scheffel, por todo o carinho e apoio, por ser o porto seguro da minha vida. Ao meu avô, José Adolfo Selbach, o primeiro médico que conheci e que sempre será um exemplo da profissão.

À minha companheira e maior incentivadora, Lisiane Meneghini, que não apenas entendeu os sacrifícios que essa tarefa exigiu, mas sempre foi uma apoiadora incondicional.

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:** Fatores Prognósticos do Câncer Diferenciado de Tireóide.

- **Artigo original:** Low Recurrence Rates in Differentiated Thyroid Carcinoma: a Single Institution Experience.

- **Artigo original:** Prognostic Value of Postoperative Thyroglobulin in Differentiated Thyroid Carcinoma: a Prospective Study.

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

- Scheffel RS, Dora JM, Siqueira DR, Burttet LM, Cerski MR, Maia AL. Toxic Cardiomyopathy leading to fatal acute cardiac failure related to vandetanib: a case report with histopathological analysis. European Journal of Endocrinology, v. 99, p. 99, 2013.

- Maia AL, Scheffel RS, Meyer EL, Mazeto GMFS, Carvalho GA, Graf H, Vaisman M, Maciel LMZ, Ramos HE, Tincani AJ, Andrada NC, Ward LS. Consenso brasileiro para o diagnóstico e tratamento do hipertireoidismo: recomendações do Departamento de Tireóide da Sociedade Brasileira de Endocrinologia e Metabologia. Arquivos Brasileiros de Endocrinologia e Metabologia, v. 57, p. 205-232, 2013.

- Dora JM, Machado WE, Scheffel RS, Andrade VA, Maia AL. Increasing the Radioiodine Dose Does Not Improve Cure Rates in Severe Graves' Hyperthyroidism: A Clinical Trial with Historical Control. Journal of Thyroid Research, v. 2013, p. 1-5, 2013.

- Bertoldi EG, Severo MD, Scheffel RS, Foppa M, Azevedo MJ, Maia AL. Left Atrial Metastases of Poorly Differentiated Thyroid Carcinoma Diagnosed by Echocardiography and Magnetic Resonance Imaging-Case Report and Review of Literature. Echocardiography, v. 2, 2012.

LISTA DE ABREVIATURAS E SIGLAS

AATg – anticorpo anti-tireoglobulina

AGES – Age, histologic grade, tumor extent and size of the primary tumor

AMES – Age, Metastatses, Extent and Size of the primary tumor

ATA – American Thyroid Association

BRAF – Serine/threonine-protein kinase B-Raf

CDT – Carcinomas Diferenciados da Tireóide

CFT – Carcinoma Folicular de Tireóide

CPT – Carcinoma Papilar de Tireóide

CT – Computed Tomography

DTC – Differentiated Thyroid Carcinoma

ERK – Extracellular-signal-regulated kinase

EORTC – European Organization for Research on Treatment of Cancer

ETA – European Thyroid Association

FTC – Follicular Thyroid Carcinoma

HCPA – Hospital de Clínicas de Porto Alegre

IQR – Interquartile Range

LATS – Latin American Thyroid Society

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

MAPK – Mitogen-activated protein kinase

MSK – Memorial Sloan-Kettering Cancer Center

NTCTS: National Thyroid Cancer Treatment Cooperative Study

PTC – Papillary Thyroid Carcinoma

RAI – Radioactive Iodine

RCT – Rastreamento Corporal Total

RET – RE arrangement during transfection

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

ROC – Receiver Operator Characteristics

RR – Risco Relativo

SBEM – Sociedade Brasileira de Endocrinologia e Metabologia

SD – Stantard Deviation

SPSS – Statistical Package for Social Science Professional Software

sTg – Stimulated Thyroglobulin

Tg – Thyroglobulin; tireoglobulina

TgAb – Antithyroglobulin Antibodies

Tg-T4 – Thyroglobulin Levels Under TSH Supression

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

TSH – hormmônio estimulante da tireóide; thyroid stimulating hormone

US – Ultrasound

WBS – Whole Body Scan

SUMÁRIO

Parte I

Fatores Prognósticos do Câncer Diferenciado de Tireóide

Fatores Prognósticos do Câncer Diferenciado de Tireóide

Rafael Selbach Scheffel, MD, José Miguel Dora, MD, PhD,

André B. Zanella, MD, and Ana Luiza Maia, MD, PhD

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

Palavras-chave: câncer diferenciado de tireóide, fatores prognósticos, mortalidade.

Contagem de palavras: Texto 5.323; Resumo 260; Tabelas 3, Figuras 3.

Conflitos de interesse: R.S.S., J.M.D., A.B.Z e A.L.M. não têm conflitos a declarar.

RESUMO

O carcinoma diferenciado de tireóide (CDT) constitui a neoplasia maligna mais comum do sistema endocrinológico, respondendo por aproximadamente 95% dos casos. O CDT é considerado uma neoplasia de comportamento indolente com baixas taxas de morbidade e mortalidade. No entanto, alguns pacientes apresentam doença mais agressiva e a identificação desses pacientes (com maior risco de recorrência, morbidade e mortalidade) permanece como um dos grandes desafios no manejo dessa neoplasia. Na tentativa de individualizar o risco e identificar esse grupo de pacientes mais propensos a desfechos desfavoráveis, diversos fatores prognósticos já foram descritos. Os primeiros fatores identificados foram derivados de estudos que avaliaram características clínicas e patológicas dos pacientes e, mais recentemente, novas estratégias, como uso de marcadores laboratoriais e moleculares, e resposta ao tratamento inicial têm sido propostas. Neste artigo revisamos criticamente os principais fatores prognósticos descritos na literatura, discutindo as suas aplicações e limitações na prática clínica. Observamos que praticamente todos os fatores prognósticos descritos até o momento apresentam limitações: 1) os fatores clínico-patológicos são derivados de estudos antigos, nos quais o curso da doença parece diferir do padrão atual, e utilizam a mortalidade como desfecho principal; 2) a determinação da tireoglobulina sérica, o mais estudado fator prognóstico laboratorial, advém de estudos com limitações metodológicas que dificultam a sua interpretação e aplicação; 3) os fatores moleculares ainda carecem de dados que demonstrem superioridade na individualização dos pacientes, quando comparados aos fatores disponíveis. Na análise comparativa, a avaliação da resposta ao tratamento inicial parece apresentar o melhor desempenho como fator prognóstico para a evolução do paciente em médio e longo prazo.

INTRODUÇÃO

O câncer de tireóide é considerado uma neoplasia maligna incomum sendo responsável por 1% do total de neoplasias (0,5% do total de cânceres nos homens e 1,5% nas mulheres) (1). No entanto, constitui a neoplasia maligna mais comum do sistema endocrinológico, respondendo por aproximadamente 95% dos casos de carcinomas desse sistema (1, 2). A incidência de neoplasia maligna da tireóide em Porto Alegre (RS) é de 1,1/100.000 habitantes para homens e 2,7/100.000 habitantes para mulheres e no Brasil, a estimativa para o câncer da tireóide em mulheres para o ano de 2014 é de 9.200 casos novos, sendo o 4º tumor maligno mais frequente em mulheres e o 13º em homens (3, 4). Nas últimas três décadas tem se observado um aumento da incidência deste tipo de neoplasia em praticamente todos os países do mundo (5). Estudos realizados nos Estados Unidos demonstraram que a incidência praticamente triplicou de 1975 a 2009 (4,9 para 14,3 casos por 100.000 habitantes, respectivamente) (6). No Brasil, um levantamento realizado na cidade de Florianópolis (7) e outro em São Paulo (8), também demonstraram um aumento da incidência, inclusive com taxa superior a observada nos estudos americanos.

Os dois tipos histológicos mais comuns do câncer de tireóide são o carcinoma papilar de tireóide (CPT), carcinoma folicular de tireóide (CFT), denominados de carcinomas diferenciados da tireóide (CDT) e correspondendo a cerca de 94% dos casos das neoplasias malignas da tireóde (2). Os CDT são originários das células foliculares e preservam as características das células foliculares normais, como a síntese e secreção de tireoglobulina, e captação de iodo (1).

O CDT é considerado uma neoplasia de comportamento indolente com baixas taxas de morbidade e mortalidade. A sobrevida média em 10 anos é de 93 a 98%, caracterizando o CDT como uma das neoplasias malignas com maior chance de cura (2, 9, 10). No entanto, parte destes pacientes apresenta curso clínico mais agressivo, com altas taxas de doença persistente e recorrência que levam a morbidade e 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 identificação 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 (11). Recentemente, novas estratégias para individualização do risco dos pacientes com CDT têm sido propostas, como 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 os principais fatores prognósticos descritos na literatura, discutindo as suas principais aplicações e limitações na prática clínica.

FATORES DE PROGNÓSTICO CLÍNICOS E PATOLÓGICOS

A maioria desses fatores foi identificada em estudos que avaliaram coortes de pacientes seguidos nas décadas de 80 e 90 (10, 12). 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. Além disso, nesses estudos as taxas de recidiva e mortalidade (cerca de 30% e 8%, respectivamente) são maiores do que as observadas nos estudos contemporâneos (cerca de 5-15% e 5%, respectivamente), possivelmente refletindo modificações na epidemiologia, no curso da doença e/ou no tratamento e seguimento da doença (10, 12, 13). 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) apresentará taxas de mortalidade muito baixas, porém taxas de doença persistente elevadas.

Estes fatores podem ser divididos em fatores relacionados ao paciente (idade ao diagnóstico, gênero) e relacionados ao tumor (tipo histológico, tamanho, extensão da doença).

Relacionados ao paciente
Idade

A idade no momento do diagnóstico é considerada um fator prognóstico para predição de mortalidade: pacientes com idade superior a 45 anos apresentam taxas de mortalidade mais elevadas quando comparados a pacientes mais jovens, sendo a diferença acentuada nos indivíduos com mais de 60 anos (sobrevida em 10 anos de 97% nos pacientes < 45 anos; 85% nos pacientes com 45 a 59 anos e 65% nos pacientes com

60 a 69 anos) (9, 10, 14-17). Esse padrão de comportamento também é válido para crianças e adolescentes, que tendem a apresentar tumores em estágios mais avançados, porém o curso da doença costuma ser indolente e a mortalidade extremamente baixa (sobrevida de 100% em 20 anos e de 94-100% em 30 anos) (18-20).

Gênero

Apesar do CDT ser mais comum em mulheres, homens com CDT apresentam uma taxa maior de invasão extratireoideana (51 vs. 39%), envolvimento de linfonodos (40 vs. 32%) e metástases a distância (9 vs. 4%) (21). Os dados sobre a influência do gênero sobre desfechos desfavoráveis são controversos. Na coorte publicada por Mazzaferri em 1994, os pacientes do sexo masculino apresentam quase o dobro de mortalidade quando comparados com as mulheres (45% vs. 29%, P < 0,01) (10). No entanto, outros estudos não demonstraram associação do gênero masculino com diminuição de sobrevida (17), mas sim com menor sobrevida livre de doença (21).

Relacionados ao tumor

Tipo Histológico

Os dois principais subtipos de CDT, papilar e folicular, apresentam diferenças em relação ao prognóstico. A sobrevida dos pacientes com CPT em 10 anos é de cerca de 98%, enquanto que os pacientes com CFT apresentam sobrevida de 90-92% (9, 16).

Entre os pacientes com CPT, algumas variantes histológicas apresentam pior prognóstico. Entre essas se destaca a variante de células altas, caracterizada histologicamente por células duas vezes mais altas do que largas. Esse tipo histológico apresenta risco cerca 4 e 14 vezes maior de recorrência e morte, respectivamente, quando comparado com o CPT clássico (22). Outras variantes histológicas do CPT (colunar, sólida ou trabecular, esclerosante difusa) são raras e, apesar do numero limitado de dados disponíveis sobre o seu comportamento, são consideradas variantes mais agressivas quando comparadas com o CPT clássico (23).

No CFT, a variante chamada de carcinoma de células de Hürthle parece estar associada ao pior prognóstico. Esta variante, quando comparada ao CFT, apresenta maiores taxas de metástases para linfonodos (27,2% vs. 8,5%, P < 0,05) (24). Adicionalmente, a sobrevida livre de doença em 10 anos é de 41-76% nos pacientes com carcinoma de células de Hürthle (2, 24, 25).

Tamanho

Tumores maiores estão associados a maiores taxas de metástases cervicais e/ou à distância. Em relação a desfechos, o risco de recorrência e mortalidade aumenta linearmente com o tamanho do tumor (10, 26). Na coorte publicada por Mazzaferri (10), tumores < 1,5 cm apresentaram mortalidade em 30 anos de 0,4%, enquanto que tumores maiores do que 4,5 cm apresentaram mortalidade de 22% (10). Em outro estudo realizado no Japão, que incluiu 1.740 pacientes, tumores maiores do que 4 cm apresentaram taxas mais elevadas de mortalidade quando comparado a neoplasias menores (0,2% de taxa de mortalidade nos pacientes com tumores < 1 cm; 0,4% nos pacientes com tumores de 1,1 a 2 cm; 1% nos pacientes com tumores de 2,1 a 3 cm; 2% nos tumores de 3,1 a 4 cm e 4% pacientes com tumores > 4 cm) (21). Estes dados foram corroborados por achados semelhantes em um estudo realizado na China, no qual o melhor ponto de corte para predição de mortalidade foi de 3,5 cm (17).

Multifocalidade

Os pacientes com CDT, em especial os pacientes com CPT, frequentemente apresentam mais de um foco de doença (multifocalidade). Em um estudo com 2.095 pacientes com CPT, a multifocalidade (RR 1,45; IC95% 1,01-2,10) e o número de tumores (RR 1,75; RR 1,04-2,97) foram associados à recorrência tumoral (27). Apesar de a multifocalidade ser frequentemente interpretada como a disseminação de um mesmo tumor, dois estudos questionam esse conceito. No primeiro, em uma amostra de 10 mulheres com CDT, em 5 a origem clonal dos tumores não era a mesma (28). No segundo, quando avaliado o padrão de mutação do BRAF, este diferiu em 40% dos pacientes (29). Estes achados sugerem que pacientes com tumores multifocais podem, na verdade, estar apresentando mais de um tumor e, por isso, explicar o fato desse achado estar relacionado a maior agressividade da doença.

Extensão da doença

A extensão da doença é considerada um importante fator prognóstico. A extensão do tumor além da cápsula tireoideana é encontrada em cerca de 10-30% dos pacientes com CDT (10). A presença de envolvimento tumoral macroscópico, com invasão de estruturas cervicais, está associada a alto risco de doença persistente e/ou recorrência do tumor (30). Além disso, em um estudo que envolveu 2.011 pacientes com CDT demonstrou que aqueles com mais de 45 anos e envolvimento macroscópico

importante (invasão de estruturas adjacentes a tireóide) apresentavam diminuição da sobrevida (16). A extensão microscópica também aumenta a chance de recorrência e de envolvimento de linfonodos (31, 32), apesar de alguns estudos não demonstrarem essa associação (33, 34).

O envolvimento de linfonodos acontece em cerca de 30 a 40% dos pacientes com CPT, sendo mais comum em crianças (até 80%) (1, 35). A importância no prognóstico deste envolvimento é motivo de controvérsia, com estudos demonstrando associação com o aumento de mortalidade (36) e outros que não identificam essa associação (26, 37). Os resultados discrepantes podem ser parcialmente explicados pela não categorização dos pacientes por faixas etárias. De fato, um estudo que utilizou este recurso demonstrou que a presença de metástases em linfonodos não influenciava o prognóstico em pacientes com menos de 45 anos, enquanto que naqueles com mais de 45 anos a presença de metástases em linfonodos aumentava a chance de morte em 46% (38). Outros fatores que parecem ser importantes e podem explicar parte da discrepância dos resultados destes estudos são o modo de identificação da metástase (clinicamente vs. exame anatomopatológico), o número de linfonodos acometidos e presença de acometimento extranodal (38, 39). Além da simples descrição da presença de linfondos com metástases, também pode ser utilizada a taxa de linfonodos metastáticos/ linfonodos negativos. Um estudo que avaliou cerca de 11.000 pacientes demonstrou que o ponto de corte de 0,42 linfonodos metastáticos/ linfonodos negativos identificava os pacientes com maior risco de mortalidade por CDT (40).

Apesar de pouco frequentes (5-10%), as metástases à distância são importantes determinantes do prognóstico e constituem a principal causa de morte relacionada ao CDT (41, 42). A sobrevida média dos pacientes com metástase à distância no momento do diagnóstico é de 30-50% em 5 anos (16, 42, 43) e as taxas de mortalidade são ainda maiores na presença de metástases no sistema nervoso central (mediana de sobrevida de 1 ano) (44). Os principais fatores prognósticos em pacientes com metástase à distância são a idade, o local da metástase e a capacidade de captar iodo (45).

SISTEMAS DE ESTADIAMENTO

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, garantir uma comunicação efetiva entre os diferentes profissionais, permitindo a comparação de dados entre diferentes centros (46, 47).

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 (48). 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 (49).

A maioria dos sistemas inclui idade ao diagnóstico, tamanho do tumor, invasão extratireoideana e presença de metástases à distância (tabela 1). Diversos estudos já objetivaram comparar estes diferentes sistemas de estadiamento (50-53). Estes estudos demonstraram que o *American Joint Committee on Cancer staging system of tumor size, nodal metastases and distant metastases* (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.

O TNM/AJCC é o sistema de estadiamento mais comumente utilizado (46, 54, 55). 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 à distância. Os pacientes são classificados em 4 estágios, com diminuição progressiva da sobrevida de acordo com os níveis mais elevados de estágio. 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% (12, 56). As principais críticas a este sistema consistem a 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 (sétima) foi publicada em janeiro de 2010 (57).

Outro sistema amplamente utilizado é o *Metastasis, Age, Completeness of ressection, Invasion and Size* (MACIS). Esse sistema utiliza um cálculo que inclui as

seguintes variáveis: idade do paciente, tamanho do tumor primário, completude da ressecção, presença de invasão e presença de metástases à distância. O paciente é classificado em 4 grupos (1-4) de acordo com o escore obtido. Os pacientes com escore < 6 são classificados como grupo 1, apresentando mortalidade relacionada ao CDT < 1%. Os pacientes do grupo 2 são aqueles com escores de 6 a 6,99, com mortalidade de ~11%. O grupo 3 compreende os pacientes com pontuação de 7 a 7,99 e apresenta mortalidade de 44%, enquanto que os pacientes com escore > 7,99 são incluídos no grupo 4 e apresentam mortalidade de 76% (26).

Em 1998 foi publicado um sistema de estadiamento derivado de um registro de 14 instituições, o *National Thyroid Cancer Treatment Cooperative Study* (NTCTCS) (58). Neste sistema foram incluídas as variáveis idade ao diagnóstico, tipo histológico do tumor, tamanho do tumor, multifocalidade, invasão extratireoideana, presença de metástases e desdiferenciação tumoral. Quanto maior o estadiamento, pior o prognóstico de 1.562 pacientes seguidos entre 1987 a 1995, tanto em relação à sobrevida quanto a chance de estarem livres de doença em 5 anos.

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 (5 a 10%), sistemas que avaliem também a chance de recidiva são considerados importantes nas definições do manejo destes pacientes. Com este objetivo, a *American Thyroid Association* (ATA), propôs um sistema que tem como objetivo avaliar o risco de recorrência (46). Neste sistema o paciente é classificado como de baixo, moderado ou alto risco. Os pacientes de baixo risco são aqueles com diagnóstico de carcinoma papilar sem histologia agressiva, sem invasão vascular, que não apresentam extensão extratireoideana ou metástases, tiveram todo o tumor ressecado e rastreamento com iodo demonstrando captação restrita a região cervical. Os pacientes de risco moderado são aqueles que pelo menos um dos critérios: invasão microscópica de tecido extratireoideano, metástases em linfonodos cervicais, captação fora do leito da tireóide no rastreamento ou tumores com histologias mais agressivas. O grupo de pacientes de alto risco é composto por aqueles que apresentam metástases à distância ou tumor parcialmente ressecado ou invasão macroscópica no momento da cirurgia. Uma coorte retrospectiva que incluiu 588 pacientes com CDT demonstrou que pacientes classificados como de baixo risco pela ATA apresentaram uma taxa de doença persistente estrutural ou recorrência de 3%,

enquanto que os pacientes classificados como risco intermediário tiveram uma taxa de 21% e os pacientes de alto risco 68% (59).

Além deste, a *Latin American Thyroid Society* (LATS), a *European Thyroid Association* (ETA) e Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) desenvolveram sistemas semelhantes (47, 60, 61). As principais diferenças entre estes sistemas é que nas propostas da LATS, da ETA e da SBEM os pacientes classificados como baixo risco pela ATA são subdivididos em muito baixo risco (tumores menores do que 1 cm) e baixo risco (os demais considerados de baixo risco pela ATA). Além disso, nos sistemas da ETA e da LATS todos os pacientes não classificados como muito baixo ou baixo risco são considerados de alto risco, enquanto que nos sistemas da ATA e da SEM existe a categoria de risco intermediário (tabela 2). Um estudo que comparou os sistemas propostos pela ATA e pela LATS demonstrou que os dois apresentam resultados semelhantes: pelo sistema da ATA a taxa doença persistente e recorrência foi, respectivamente, de 13 e 8% nos pacientes de baixo risco, 27 e 21% nos pacientes de risco intermediário e 48,5 e 20% nos de alto risco. Com a utilização dos critérios da LATS essas taxas foram de 18,5 e 4,5% nos pacientes de muito baixo risco, 14 e 0% nos de baixo risco e 30 e 22% nos de alto risco (62).

RESPOSTA AO TRATAMENTO INICIAL

Os estadiamentos de risco clinico-patológicos usam informações da avaliação inicial do paciente para categorização de risco de 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 "classificação dinâmica de risco" uma vez que o risco do paciente muda com o tempo, de acordo com novos dados que vão sendo obtidos ao longo do seguimento (11). Os pacientes são classificados de acordo com a resposta ao tratamento como tendo resposta excelente (ausência de evidência de doença clínica, bioquímica e estrutural), resposta aceitável (níveis de tireoglobulina estimulada < 10 ng/mL e alterações inespecíficas em exames de imagem) e resposta incompleta (níveis positivos da tireoglobulina sob supressão ou tireoglobulina estimulada > 10 ng/mL ou achados compatíveis com doença estrutural em exames de imagem) (59).

O uso da classificação dinâmica de risco já se mostrou eficaz em diversos estudos. Em uma coorte de 588 pacientes a taxa de doença estrutural quando os pacientes eram classificados de acordo com os grupos de risco da ATA eram de 3% para os pacientes de baixo risco, 21% para os pacientes de risco intermediário e 68% para os pacientes de alto risco. Quando foi aplicada a classificação dinâmica de risco, observou-se que os pacientes de baixo risco com resposta excelente mantinham a taxa de doença persistente estrutural em 2%, porém naqueles com resposta incompleta essa taxa aumentava para 13%. Já no grupo de pacientes de risco intermediário, a taxa de doença persistente caía para 2% naqueles com resposta excelente e aumentava para 41% nos pacientes com resposta incompleta. De forma semelhante, os pacientes de alto risco apresentaram taxa de doença persistente estrutural de 14% e 79% quando apresentavam resposta excelente e incompleta, respectivamente (Figura 1) (59). Resultados semelhantes foram observados em uma coorte italiana de 548 pacientes, com redução das taxas de recorrência dos pacientes que apresentavam resposta excelente ao tratamento, independente do grupo de risco que pertenciam anteriormente (63) (Figura 2). Nesse estudo cerca de 50% dos pacientes classificados anteriormente como de risco intermediário ou alto tiveram a sua faixa de risco revisada para baixo risco depois da avaliação dinâmica. 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.

MARCADORES LABORATORIAS

Tireoglobulina

A tireoglobulina (Tg) é um marcador específico do tecido tireoidiano e uma ferramenta importante no seguimento dos pacientes com CDT (46, 47). Diversas séries da literatura já demonstraram a importância da Tg no acompanhamento dos pacientes com CDT (64, 65). Baseados nestes dados, os consensos atuais de tratamento de CDT recomendam a dosagem da Tg estimulada 6 a 12 meses após o tratamento inicial em todos os pacientes, com intuito de avaliar a eficácia do tratamento e guiar o seguimento do paciente (46, 47).

Além deste importante papel no seguimento em longo prazo dos pacientes com CDT, diversos estudos têm demonstrado que a Tg pode ser utilizada como marcador de prognóstico precoce (tabela 3). Utilizando-se o conceito de Tg pós-operatória (dosagem do nível sérico de Tg após estímulo com TSH após o tratamento cirúrgico inicial) tem

sido demonstrado que a Tg pós-operatória é um fator prognóstico independente, apresentando um alto valor preditivo negativo para diversos desfechos desfavoráveis (rastreamento corporal positivo após dose de iodo, elevação da tireoglobulina sérica no seguimento, presença de metástases, recorrência de doença, mortalidade) (tabela 3). Uma metanálise com 15 estudos que incluiu 3.947 pacientes confirmou estes achados, atribuindo ao teste um valor preditivo negativo de 94,2% (IC 95% 92,8-95,3) (66).

Algumas limitações dos estudos que avaliaram o uso da Tg pós-operatória dificultam a sua aplicação na prática clínica como diferenças importantes nos critérios de inclusão e principalmente na definição de desfechos, algumas vezes utilizando como desfecho o resultado do rastreamento corporal total após a dose de iodo, outras vezes dosagens de Tg no seguimento dos pacientes e mais raramente desfechos clínicos (tabela 3). Além disso, estes estudos apresentam limitações metodológicas, uma vez que a maioria deles tem desenho retrospectivo e nem todos utilizaram o método de curva ROC (*receiver operator characteristics*) para definição do ponto de corte da tireoglobulina. Outra importante limitação da aplicabilidade destes dados é o fato de quase a totalidade dos pacientes incluídos na análise terem realizado tratamento com iodo radioativo.

Dois estudos já testaram a estratégia de selecionar os pacientes para o tratamento ablativo com iodo através da dosagem da Tg estimulada pós-operatória. No primeiro deles, 104 pacientes de baixo risco (CDT limitado a tireóide e sem variante histológica agressiva) foram avaliados com Tg pós-operatória e aqueles que apresentassem nível sérico <1 ng/mL (59 pacientes; 59,6% da amostra) não receberam iodo. Em um seguimento médio de 3,3 anos nenhum dos pacientes apresentou recidiva (67). No segundo estudo, 136 pacientes com CPT de baixo risco (variantes histológicas não agressivas, estágio TNM/AJCC 1b-3N0M0) com Tg pós-operatória <1 ng/mL e ecografia cervical sem anormalidades foram incluídos. Durante acompanhamento médio de 44 meses (variação 12-72 meses), apenas 2 pacientes apresentaram recorrência do CPT (68). Estes dois estudos demonstram que a utilização do nível de Tg pós-operatória para selecionar pacientes de baixo risco para o uso de dose ablativa de iodo parece ser uma estratégia eficiente e, de fato, a *National Comprehensive Cancer Network* incorporou esta recomendação seu último consenso (15).

Anticorpo Anti-tireoglobulina

De uma maneira semelhante à Tg, a dosagem do anticorpo anti-tireoglobulina (AATg) tem seu principal papel no seguimento dos pacientes com CDT. O AATg está presente em cerca de 10% da população em geral, porém é descrito em até 25% dos pacientes com CDT (69). A sua principal importância é possibilidade de interferir na dosagem da Tg, causando resultados falsos negativos e falsos positivos (69). Em função disso recomenda-se a mensuração dos níveis dos AATg em todos os pacientes em seguimento de CDT (46, 47).

Alguns estudos sugerem que a positividade do AATg constitui um importante fator prognóstico. Os pacientes que apresentam níveis de AATg em descenso, especialmente aqueles que negativam, parecem apresentar melhor prognóstico do que os pacientes que permanecem com o AATg positivo (em especial em valores elevados ou em ascensão) (70-72). Em um estudo italiano, os pacientes com AATg positivo nos quais os níveis negativaram apresentaram taxas menores de doença persistente do que aqueles que permaneceram com AATg positivos por todo o seguimento (8,2% vs. 17,3%; P=0,05) (73).

Outro aspecto que pode apresentar significado prognóstico é a simples positividade para o AATg. Em um estudo publicado em 2002, a taxa de recorrência nos pacientes que apresentavam AATg positivo foi de 49% enquanto que os pacientes com AATg negativo apresentaram 3,4% de recorrência (74). Em outro estudo, os pacientes com AATg positivo mensurado 6 a 12 meses após o tratamento inicial apresentaram sobrevida livre de doença de 80%, enquanto que nos pacientes com AATg negativo esta taxa foi de 95% (75). Nesses dois estudos foram incluídos somente pacientes com Tg indetectável e os níveis de AATg foram determinados no seguimento dos pacientes. Recentemente, um estudo multicêntrico realizado na Itália, avaliou o papel prognóstico do nível de AATg na primeira avaliação após o tratamento cirúrgico. Foram incluídos 220 pacientes com AATg positivo e 1.020 pacientes com AATg negativo. Os pacientes com AATg positivo apresentavam tumores mais frequentemente classificados de alto risco pela ATA (6,9 vs. 3,2%) e apresentavam extensão extratireoideana macroscópica mais comumente (4,1% vs. 0%). Após 1 ano de seguimento, o grupo de pacientes com AAT positivo apresentou taxas mais elevada de doença persistente (13,6% vs. 7,1%; P=0,002) e recorrência de doença no seguimento a longo prazo (5,8% vs. 1,4%; P=0,0003) (73).

O uso do AATg como marcador prognóstico apresenta algumas limitações. A primeira delas é que existe controvérsia em relação ao ponto de corte que deve ser

considerado como positivo. Os pontos de corte disponibilizados pelos fabricantes em geral são calculados para o diagnóstico de doenças autoimunes da tireóide e não para avaliar a possibilidade de interferência do AATg sobre a dosagem da tireoglobulina ou como marcador prognóstico em pacientes com CDT (76). Outro problema é que existem discordâncias de resultados nos diversos métodos de aferição do AATg, podendo causar resultados diferentes em um mesmo paciente no mesmo momento (77).

MARCADORES MOLECULARES

Recentemente, marcadores moleculares têm sido propostos como marcadores prognósticos individuais com potencial vantagem de possibilitar a predição de risco de recorrência para cada paciente, sendo úteis para nortear a terapêutica e o acompanhamento no CPT.

As mutações na via da *mitogen-activated protein kinase* (MAPK) são as mais bem relacionadas com o desenvolvimento e agressividade do CPT. Esta é uma via de sinalização intracelular que, quando ativada, desempenha um papel central no crescimento, divisão, proliferação, diferenciação e apoptose das células (Figura 3). A ativação fisiológica 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 CPT (78-80). No entanto, dois pontos desta via são particularmente implicados na gênese e comportamento do CPT: mutações no gene do BRAF e no gene do RET.

Gene BRAF

Um dos principais componentes dessa via é a Raf quinase que desencadeia a fosforilação sequencial e a ativação do MEK e ERK. Três isoformas funcionais da Raf foram descritas na espécie humana, A-Raf, B-Raf ou BRAF e C-Raf (81). Entre elas, a BRAF quinase, cujo gene codificador foi localizado no cromossomo 7, é o mais potente ativador da via MAPK (82). Mais de 40 mutações no gene do BRAF já foram identificadas, sendo a mutação T1799A a mais comum (83). 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). As mutações deste gene parecem induzir ou facilitar um estado de instabilidade genômica, alta

invasividade e desdiferenciação tumoral com supressão mais significativa da apoptose, além de uma redução significativa da expressão da maquinaria do metabolismo do iodo intratireoideano (83). A ocorrência desta alteração genética nos CPT tem uma prevalência que varia de 29 a 83% (média de 44%), dependendo da origem da população em estudo.

Diversos estudos nos últimos anos descreveram a associação desta mutação com características clínico-patológicas mais agressivas nos pacientes com CPT (83, 84). De fato, uma meta-análise que incluiu 2.470 pacientes demonstrou que a presença da mutação aumentava o risco de metástases para linfonodos (RR 1,32; IC95% 1,20-1,45), invasão extratireoideana (RR 1,71; IC95% 1,50-1,94) e diagnóstico em estágios avançados (RR 1,70; IC95% 1,45-1,99) (85).

A associação da mutação com desfechos clínicos desfavoráveis (presença de doença persistente, recorrência e mortalidade) é mais controversa. Algumas coortes demonstraram um claro efeito da mutação com aumento da mortalidade (83, 86-88). Em um estudo retrospectivo multicêntrico que incluiu 1.890 pacientes com mediana de seguimento de 33 meses a mutação do BRAF foi associada com aumento significativo da mortalidade (7,1% vs. 5,3%, P<0,01). Entretanto quando esta análise foi ajustada para outros fatores clínicos e histológicos, a associação perdeu a significância. Além disso, a maioria dos pacientes com mutação positiva apresentou tumores com comportamento indolente (89). A interpretação destes dados nos leva a pensar que a presença da mutação no gene do BRAF é um marcador de agressividade e pior prognóstico em pacientes com CPT, porém não adiciona informações a outros marcadores já descritos e conhecidos.

Gene RET

O RET é um receptor extracelular que tem funções na regulação do crescimento, diferenciação celular e morte celular programada. Rearranjos no RET constituem uma das mais prevalentes alterações genéticas encontradas em pacientes com CPT, envolvendo a fusão de dois genes heterólogos que resultam em proteínas quiméricas e ativação permanente do receptor. Pelo menos 11 tipos desta alteração genética (chamada de RET/PTC) já foram identificados e são descritas em 30 a 60% dos pacientes com CPT. A presença do rearranjo RET/PTC está associada ao diagnóstico em pacientes mais jovens, a CPT com histologia clássica e presença de metástases em linfonodos (78, 79).

Em relação ao CFT, mutações no gene RAS parecem estar associadas a neoplasias mais agressivas e maior mortalidade (90), porém com dados mais limitados quando comparados com os descritos acima para CPT.

CONCLUSÃO

A definição do risco individual de evolução desfavorável é parte importante no manejo pacientes com CDT. Diversos fatores prognósticos já foram avaliados, mas uma revisão crítica identifica limitações importantes para a aplicação na prática clínica. Observamos que praticamente todos os fatores prognósticos descritos até o momento apresentam limitações: 1) os fatores clínico-patológicos são derivados de estudos antigos, nos quais o curso da doença parece diferir do padrão atual, e utilizam a mortalidade como desfecho principal; 2) a determinação da tireoglobulina sérica, o mais estudado fator prognóstico laboratorial, advém de estudos com limitações metodológicas que dificultam a sua interpretação e aplicação; 3) os fatores moleculares ainda carecem de dados que demonstrem superioridade na individualização dos pacientes, quando comparados aos fatores disponíveis. Na análise comparativa, a avaliação da resposta ao tratamento inicial parece apresentar o melhor desempenho como fator prognóstico para a evolução do paciente em médio e longo prazo.

Tabela 1: Comparação entre os diversos sistemas de estadiamento para o CDT.

	EOTRC (1979)	AGES (1987)	AMES (1988)	MACIS (1993)	MSK (1995)	NTCTCS (1998)	TNM/ AJCC (2010)
Fatores do Paciente							
Idade	X	X	X	X	X	X	X
Sexo	X		X				
Fatores do Tumor							
Tamanho		X	X	X	X	X	X
Multicentricidade						X	
Grau do tumor		X			X		
Invasão extratireoideana	X	X	X	X	X	X	X
Metástases em linfonodos					X	X	X
Metástases à distância	X	X	X	X	X	X	X
Fatores do Tratamento							
Completude da Ressecção				X			

EORTC: *European Organization for Research on Treatment of Cancer*

AGES: *Age, histologic grade, tumor extent and size of the primary tumor*

AMES: *Age, Metastatses, Extent and Size of the primary tumor*

MACIS: *Metastasis, Age, Completeness of ressection, Invasion and Size*

MSK: *Memorial Sloan-Kettering Cancer Center*

NTCTS: *National Thyroid Cancer Treatment Cooperative Study*

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

X: variáveis incluídas no sistema

Tabela 2: Comparação dos diferentes sistemas de classificação de risco propostos pelas sociedades americana, europeia e latino-americana de tireóide.

Risco	ATA	ETA	LATS	SBEM
Muito baixo risco	NA	Tumor unifocal com menos de 1 cm, sem invasão extratireoideana, sem metastases	Tumor unifocal com menos de 1 cm, sem invasão extratireoideana, sem metástases	Tumor com menos de 1 cm, sem invasão extratireoideana, sem metástases ou 1-2 cm unifocal.
Baixo risco	Tumor intratireoideano Sem histologia agressiva Sem invasão vascular Sem metástases para linfonodos ou à distância Sem captação fora do leito da tireóide no RCT	Tumor multifocal Tamanho de 1 a 4 cm Sem metástases para linfonodos ou à distância	Tumor multifocal Tamanho de 1 a 4 cm Sem metástases para linfonodos ou à distância Sem histologia agressiva Sem invasão vascular Sem captação fora do leito da tireóide no RCT	Tumor com menos de 2 cm com invasão mínima, sem metástases. Tumor menor que 2 cm sem invasão e com 1 a 3 linfonodos acometidos, sem metástases a distância. Tumor menor que 4 cm sem metastaeses em linfonodos ou a distância.
Risco intermediário	Metástase para linfonodo Invasão extratireoideana mínima	NA	NA	Tumor com 2-4 cm com invasão extratioredeana mínima. Tumor com 2-4 cm sem invasão extratioredeana

				e com acometimento linfonodal. Tumor maior que 4 cm. Acometimento linfonodal. Subtipo histológico agressivo ou invasão vascular.
	Invasão Vascular Histologia Agressiva Captação fora do leito tireoideana no RCT			
Risco Elevado	Invasão extratireoideana importante Ressecção incompleta do tumor Metástases à distância Tireoglobulina inapropriadamente elevada no seguimento	Tumor com mais de 4 cm Invasão extratireoideana importante Metástases para linfonodos Metástases à distância	Metástases para linfonodos Metástases à distância Presença de doença residual Histologia agressiva Invasão extratireoideana Tumor maior do que 4 cm em pacientes com mais de 45 anos	Tumor com invasão extratireoideana extensa. Acometimento linfonodal extenso. Metástases à distância. Ressecção incompleta. RCT com captação à distância.

ATA: *American Thyroid Association*

ETA: *European Thyroid Association*

LATS: *Latin American Thyroid Society*

SBEM: Sociedade Brasileira de Endocrinologia e Metabologia

NA: Não se aplica

RCT: rastreamento corporal total

Tabela 3: Estudos que avaliaram a dosagem de tireoglobulina sérica após a tireoidectomia total e antes da dose ablativa de iodo em pacientes com CDT.

Referência	N	Desenho	Desfecho	Ponto de corte
Ruiz-Garcia, 1991 (91)	98	Prospectivo	Recorrência	23,0 ng/mL
Filesi et al, 1998 (92)	69	Retrospectivo	Metástases	60,0 ng/mL
Ronga et al, 1999 (93)	334	Retrospectivo	Metástases	30,2 ng/mL
Oyen et al, 2000 (94)	254	Retrospectivo	Metástases	10,0 ng/mL
Lima et al, 2002 (95)	42	Transversal	Estágio TNM	2,3 ng/mL
Lin et al, 2002 (96)	847	Retrospectivo	Mortalidade	10,0 ng/mL
Hall et al, 2003 (97)	213	Retrospectivo	Recorrência	20,0 ng/mL
Toubeau et al, 2004 (98)	212	Retrospectivo	Recorrência	30,0 ng/mL
Kim et al, 2005 (99)	268	Prospectivo	Tg + Recorrência	10,0 ng/mL
Rosario et al, 2005 (100)	212	Prospectivo	RCT	10,0 ng/mL
Bernier et al, 2005 (101)	407	Retrospectivo	RCT + Tg	5,0 ng/mL
Giovanella et al, 2005 (102)	156	Retrospectivo	Status da doença	3,2 ng/mL
Heemstra et al, 2007 (103)	366	Prospectivo	Remissão	27,5 ng/mL
Lee et al, 2007 (104)	81	Retrospectivo	Tg	10,0 ng/mL
Sawaka, 2007 (105)	141	Retrospectivo	Tg	2,0 ng/mL
Familiar et al, 2009 (106)	63	Retrospectivo	Status da doença	10,0 ng/mL
Piccardo et al, 2010 (107)	237	Retrospectivo	Status da doença	10,0 ng/mL
Pelttari et al, 2010 (108)	468	Retrospectivo	Recorrência	1 ng/mL
Rosario et al, 2011 (109)	237	Prospectivo	Status da doença	10,0 ng/mL
Tamilia et al, 2011 (110)	193	Retrospectivo	RCT + Tg	6,0 ng/mL

Polachek et al, 2011 (111)	420	Prospectivo	Status da doença	10,0 ng/mL
Webb et al, 2012 (66)	74	Retrospectivo	Status da doença	10,0 ng/mL
Melo et al, 2013 (112)	293	Prospectivo	Status da doença	7,2 ng/mL
González et al, 2014 (113)	133	Retrospectivo	Remissão	8,55 ng/mL

N: número de pacientes incluídos no estudo

RCT: rastreamento corporal total

TNM: *American Joint Committee on Cancer staging system of tumor size, nodal metastases and distant metastases*

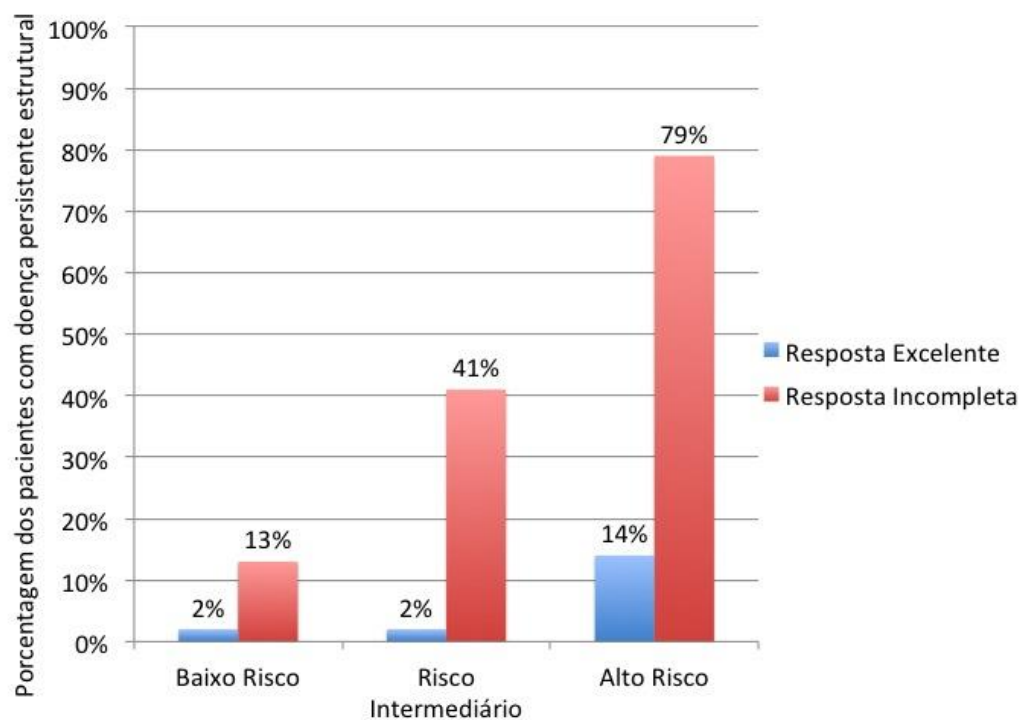Tg: tireoglobulina estimulada no seguimento

Figura 1: Reclassificação dos pacientes com CDT conforme a resposta ao tratamento em uma coorte de 588 pacientes. Adaptado de Tuttle et al. (59).
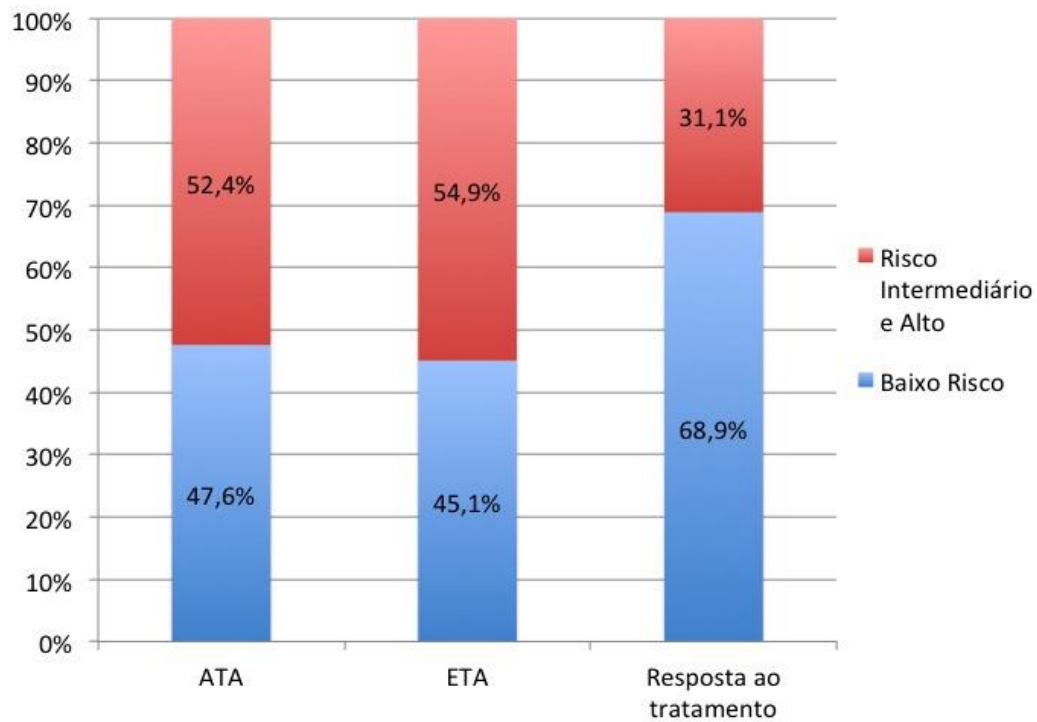
Figura 2: Classificação dos pacientes do estudo de Castagna et al (63) demonstrando que a resposta ao tratamento reclassifica cerca de 50% dos pacientes classificados com alto risco em sistemas de classificação da *American Thyroid Association* (ATA) e da *European Thyroid Association* (ETA).
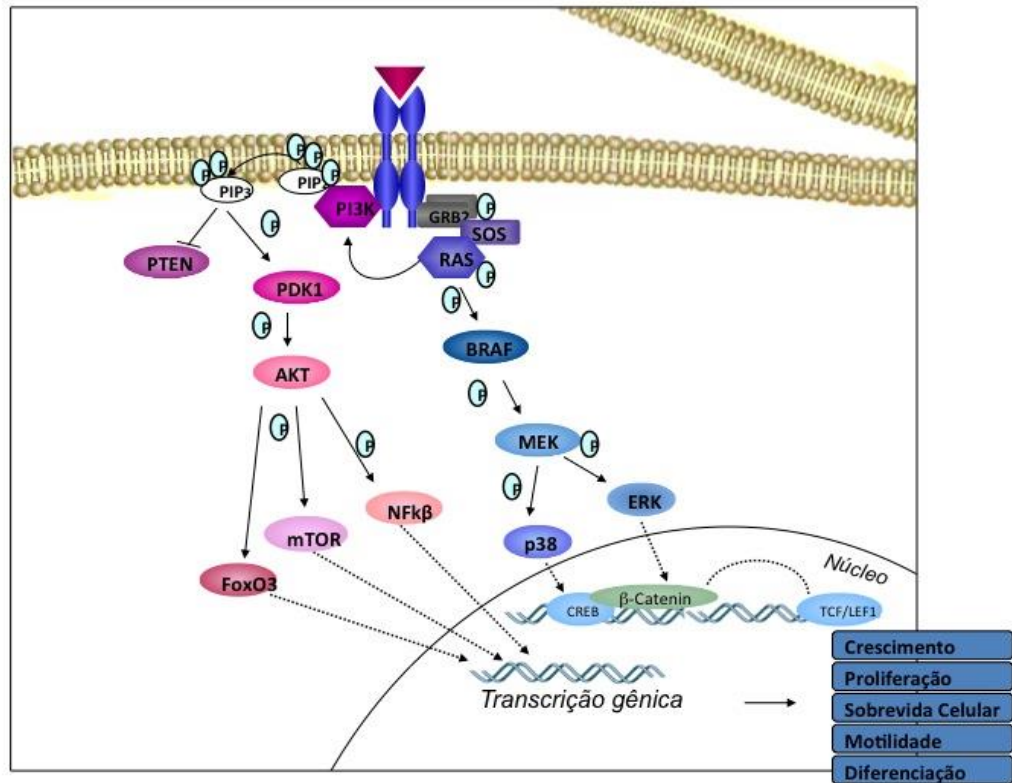
Figura 3: Via da *mitogen-activated protein kinase* (MAPK). Aptado de Romitti et al (80).

REFERÊNCIAS

1.   Sherman SI. Thyroid carcinoma. Lancet. 2003;361(9356):501-11.

2.   Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer. 1998;83(12):2638-48.

3.   Coeli CM, Brito AS, Barbosa FS, Ribeiro MG, Sieiro AP, Vaisman M. [Incidence and mortality from thyroid cancer in Brazil]. Arq Bras Endocrinol Metabol. 2005;49(4):503-9.

4.   INCA INdC-. Incidência 2014 - Incidência de Câncer no Brasil 2014 (acessado em 19/08/2014). Disponível em: http://www.inca.gov.br/estimativa/2014/.

5.   Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes & Control: CCC. 2009;20(5):525-31.

6.   Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngology. 2014;140(4):317-22.

7.   Cordioli MI, Canalli MH, Coral MH. Increase incidence of thyroid cancer in Florianopolis, Brazil: comparative study of diagnosed cases in 2000 and 2005. Arq Bras Endocrinol Metabol. 2009;53(4):453-60.

8.   Veiga LH, Neta G, Aschebrook-Kilfoy B, Ron E, Devesa SS. Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the U.S. SEER program, 1997-2008. Thyroid. 2013;23(6):748-57.

9.   Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. Cancer. 1997;79(3):564-73.

10.   Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(5):418-28.

11.   Tala H, Tuttle RM. Contemporary post surgical management of differentiated thyroid carcinoma. Clinical Oncology. 2010;22(6):419-29.

12.   DeGroot LJ, Kaplan EL, Straus FH, Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? World Journal of Surgery. 1994;18(1):123-30.

13.   Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-

1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World Journal of Surgery. 2002;26(8):879-85.

14. Ito Y, Miyauchi A, Kihara M, Takamura Y, Kobayashi K, Miya A. Relationship between prognosis of papillary thyroid carcinoma patient and age: a retrospective single-institution study. Endocrine Journal. 2012;59(5):399-405.

15. Network NCC. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Thyroid Carcinoma 2014 (acessado em 27/07/2014). Disponível em http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.

16. Verburg FA, Mader U, Tanase K, Thies ED, Diessl S, Buck AK, et al. Life expectancy is reduced in differentiated thyroid cancer patients >/= 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. J Clin Endocrinol Metab. 2013;98(1):172-80.

17. Lang BH, Lo CY, Chan WF, Lam KY, Wan KY. Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging. Ann Surg Oncol. 2007;14(2):730-8.

18. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World Journal of Surgery. 2010;34(6):1192-202.

19. Markovina S, Grigsby PW, Schwarz JK, DeWees T, Moley JF, Siegel BA, et al. Treatment approach, surveillance, and outcome of well-differentiated thyroid cancer in childhood and adolescence. Thyroid. 2014;24(7):1121-6.

20. Vaisman F, Corbo R, Vaisman M. Thyroid carcinoma in children and adolescents-systematic review of the literature. Journal of Thyroid Research. 2011;2011:845362.

21. Ito Y, Miyauchi A, Jikuzono T, Higashiyama T, Takamura Y, Miya A, et al. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. World Journal of Surgery. 2007;31(4):838-48.

22. Jalisi S, Ainsworth T, Lavalley M. Prognostic outcomes of tall cell variant papillary thyroid cancer: a meta-analysis. Journal of Thyroid Research. 2010;2010:325602.

23. Jung TS, Kim TY, Kim KW, Oh YL, Park do J, Cho BY, et al. Clinical features and prognostic factors for survival in patients with poorly differentiated thyroid

carinoma and comparison to the patients with the aggressive variants of papillary thyroid carcinoma. Endocrine Journal. 2007;54(2):265-74.

24.   Kushchayeva Y, Duh QY, Kebebew E, D'Avanzo A, Clark OH. Comparison of clinical characteristics at diagnosis and during follow-up in 118 patients with Hurthle cell or follicular thyroid cancer. American Journal of Surgery. 2008;195(4):457-62.

25.   Kushchayeva Y, Duh QY, Kebebew E, Clark OH. Prognostic indications for Hurthle cell cancer. World Journal of Surgery. 2004;28(12):1266-70.

26.   Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114(6):1050-7.

27.   Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. World Journal of Surgery. 2013;37(2):376-84.

28.   Shattuck TM, Westra WH, Ladenson PW, Arnold A. Independent clonal origins of distinct tumor foci in multifocal papillary thyroid carcinoma. N Engl J Med. 2005;352(23):2406-12.

29.   Giannini R, Ugolini C, Lupi C, Proietti A, Elisei R, Salvatore G, et al. The heterogeneous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92(9):3511-6.

30.   Gemsenjager E, Heitz PU, Seifert B, Martina B, Schweizer I. Differentiated thyroid carcinoma. Follow-up of 264 patients from one institution for up to 25 years. Swiss Medical Weekly. 2001;131(11-12):157-63.

31.   Jukkola A, Bloigu R, Ebeling T, Salmela P, Blanco G. Prognostic factors in differentiated thyroid carcinomas and their implications for current staging classifications. Endocr Relat Cancer. 2004;11(3):571-9.

32.   Lee SH, Lee SS, Jin SM, Kim JH, Rho YS. Predictive factors for central compartment lymph node metastasis in thyroid papillary microcarcinoma. The Laryngoscope. 2008;118(4):659-62.

33.   Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. World Journal of Surgery. 2006;30(5):780-6.

34.   Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Minimal extrathyroid extension does not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the age of 45 years. Surgery Today. 2006;36(1):12-8.

35.   Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med. 1993;328(8):553-9.

36.   Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. The American Surgeon. 2005;71(9):731-4.

37.   Bhattacharyya N. A population-based analysis of survival factors in differentiated and medullary thyroid carcinoma. Otolaryngology. 2003;128(1):115-23.

38.   Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab. 2005;90(10):5723-9.

39.   Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22(11):1144-52.

40.   Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. Ann Surg Oncol. 2013;20(6):1906-11.

41.   Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-9.

42.   Lee J, Soh EY. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors. Annals of Surgery. 2010;251(1):114-9.

43.   Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer. 2007;110(7):1451-6.

44.   Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab. 1997;82(11):3637-42.

45. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab. 1988;67(3):501-8.

46. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.

47. Rosario PW, Ward LS, Carvalho GA, Graf H, Maciel RM, Maciel LM, et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol. 2013;57(4):240-64.

48. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86(4):1447-63.

49. Hannequin P, Liehn JC, Delisle MJ. Multifactorial analysis of survival in thyroid cancer. Pitfalls of applying the results of published studies to another population. Cancer. 1986;58(8):1749-55.

50. D'Avanzo A, Ituarte P, Treseler P, Kebebew E, Wu J, Wong M, et al. Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. Thyroid. 2004;14(6):453-8.

51. Davis NL, Bugis SP, McGregor GI, Germann E. An evaluation of prognostic scoring systems in patients with follicular thyroid cancer. American Journal of Surgery. 1995;170(5):476-80.

52. Rios A, Rodriguez JM, Ferri B, Matinez-Barba E, Febrero B, Parrilla P. Are prognostic scoring systems of value in patients with follicular thyroid carcinoma? Eur J Endocrinol. 2013;169(6):821-7.

53. Verburg FA, Mader U, Kruitwagen CL, Luster M, Reiners C. A comparison of prognostic classification systems for differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2010;72(6):830-8.

54. Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer. 1997;79(12):2414-23.

55. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab. 1997;82(11):3553-62.

56.   Hay ID. Papillary thyroid carcinoma. Endocrinology and Metabolism Clinics of North America. 1990;19(3):545-76.

57.   Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

58.   Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, et al. Prospective multicenter study of thyroiscarcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer. 1998;83(5):1012-21.

59.   Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341-9.

60.   Pitoia F, Ward L, Wohllk N, Friguglietti C, Tomimori E, Gauna A, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol. 2009;53(7):884-7.

61.   Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154(6):787-803.

62.   Pitoia F, Bueno F, Urciuoli C, Abelleira E, Cross G, Tuttle RM. Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American thyroid association and Latin American thyroid society risk of recurrence classification systems. Thyroid. 2013;23(11):1401-7.

63.   Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur J Endocrinol. 2011;165(3):441-6.

64.   Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab. 2005;90(9):5047-57.

65.   Torrens JI, Burch HB. Serum thyroglobulin measurement. Utility in clinical practice. Endocrinology and Metabolism Clinics of North America. 2001;30(2):429-67.

66.   Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, et al. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. J Clin Endocrinol Metab. 2012;97(8):2754-63.

67.   Vaisman A, Orlov S, Yip J, Hu C, Lim T, Dowar M, et al. Application of post-surgical stimulated thyroglobulin for radioiodine remnant ablation selection in low-risk papillary thyroid carcinoma. Head Neck. 2010;32(6):689-98.

68.   Rosario PW, Mineiro Filho AF, Prates BS, Silva LC, Calsolari MR. Postoperative stimulated thyroglobulin of less than 1 ng/ml as a criterion to spare low-risk patients with papillary thyroid cancer from radioactive iodine ablation. Thyroid. 2012;22(11):1140-3.

69.   Spencer CA. Clinical review: Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC). J Clin Endocrinol Metab. 2011;96(12):3615-27.

70.   Pacini F, Mariotti S, Formica N, Elisei R, Anelli S, Capotorti E, et al. Thyroid autoantibodies in thyroid cancer: incidence and relationship with tumour outcome. Acta Endocrinologica. 1988;119(3):373-80.

71.   Rubello D, Casara D, Girelli ME, Piccolo M, Busnardo B. Clinical meaning of circulating antithyroglobulin antibodies in differentiated thyroid cancer: a prospective study. Journal of Nuclear Medicine. 1992;33(8):1478-80.

72.   Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB, Singer PA, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1998;83(4):1121-7.

73.   Durante C, Tognini S, Montesano T, Orlandi F, Torlontano M, Puxeddu E, et al. Clinical Aggressiveness and Long-Term Outcome in Patients With Papillary Thyroid Cancer and Circulating Anti-Thyroglobulin Autoantibodies. Thyroid. 2014.

74.   Chung JK, Park YJ, Kim TY, So Y, Kim SK, Park DJ, et al. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. Clin Endocrinol (Oxf). 2002;57(2):215-21.

75.   Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, et al. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in

thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2008;93(12):4683-9.

76.   Dufour DR. Thyroglobulin antibodies--failing the test. J Clin Endocrinol Metab. 2011;96(5):1276-8.

77.   Pitoia F, Bueno MF, Abelleira E, Salvai ME, Bergoglio L, Luster M, et al. Undetectable pre-ablation thyroglobulin levels in patients with differentiated thyroid cancer: it is not always what it seems. Arq Bras Endocrinol Metabol. 2013;57(4):300-6.

78.   Trovisco V, Soares P, Preto A, Castro P, Maximo V, Sobrinho-Simoes M. Molecular genetics of papillary thyroid carcinoma: great expectations. Arq Bras Endocrinol Metabol. 2007;51(5):643-53.

79.   Kato MA, Fahey TJ, 3rd. Molecular markers in thyroid cancer diagnostics. Surg Clin North Am. 2009;89(5):1139-55.

80.   Romitti M, Ceolin L, Siqueira DR, Ferreira CV, Wajner SM, Maia AL. Signaling pathways in follicular cell-derived thyroid carcinomas (review). International Journal of Oncology. 2013;42(1):19-28.

81.   Kolch W. Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. Biochem J. 2000;351 Pt 2:289-305.

82.   Mercer KE, Pritchard CA. Raf proteins and cancer: B-Raf is identified as a mutational target. Biochim Biophys Acta. 2003;1653(1):25-40.

83.   Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev. 2007;28(7):742-62.

84.   Basolo F, Torregrossa L, Giannini R, Miccoli M, Lupi C, Sensi E, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. J Clin Endocrinol Metab. 2010;95(9):4197-205.

85.   Tufano RP, Teixeira GV, Bishop J, Carson KA, Xing M. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine. 2012;91(5):274-86.

86.   Lee X, Gao M, Ji Y, Yu Y, Feng Y, Li Y, et al. Analysis of differential BRAF(V600E) mutational status in high aggressive papillary thyroid microcarcinoma. Ann Surg Oncol. 2009;16(2):240-5.

87.   Elisei R, Ugolini C, Viola D, Lupi C, Biagini A, Giannini R, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab. 2008;93(10):3943-9.

88.   Elisei R, Viola D, Torregrossa L, Giannini R, Romei C, Ugolini C, et al. The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. J Clin Endocrinol Metab. 2012;97(12):4390-8.

89.   Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013;309(14):1493-501.

90.   Garcia-Rostan G, Zhao H, Camp RL, Pollan M, Herrero A, Pardo J, et al. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J Clin Oncol. 2003;21(17):3226-35.

91.   Ruiz-Garcia J, Ruiz de Almodovar JM, Olea N, Pedraza V. Thyroglobulin level as a predictive factor of tumoral recurrence in differentiated thyroid cancer. Journal of Nuclear Medicine. 1991;32(3):395-8.

92.   Filesi M, Signore A, Ventroni G, Melacrinis FF, Ronga G. Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. Journal of Nuclear Medicine. 1998;39(9):1542-6.

93.   Ronga G, Fiorentino A, Paserio E, Signore A, Todino V, Tummarello MA, et al. Can iodine-131 whole-body scan be replaced by thyroglobulin measurement in the post-surgical follow-up of differentiated thyroid carcinoma? Journal of Nuclear Medicine. 1990;31(11):1766-71.

94.   Oyen WJ, Verhagen C, Saris E, van den Broek WJ, Pieters GF, Corsten FH. Follow-up regimen of differentiated thyroid carcinoma in thyroidectomized patients after thyroid hormone withdrawal. Journal of Nuclear Medicine. 2000;41(4):643-6.

95.   Lima N, Cavaliere H, Tomimori E, Knobel M, Medeiros-Neto G. Prognostic value of serial serum thyroglobulin determinations after total thyroidectomy for differentiated thyroid cancer. J Endocrinol Invest. 2002;25(2):110-5.

96.   Lin JD, Huang MJ, Hsu BR, Chao TC, Hsueh C, Liu FH, et al. Significance of postoperative serum thyroglobulin levels in patients with papillary and follicular thyroid carcinomas. Journal of Surgical Oncology. 2002;80(1):45-51.

97.   Hall FT, Beasley NJ, Eski SJ, Witterick IJ, Walfish PG, Freeman JL. Predictive value of serum thyroglobulin after surgery for thyroid carcinoma. The Laryngoscope. 2003;113(1):77-81.

98.   Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, et al. Predictive value for disease progression of serum thyroglobulin levels measured in the

postoperative period and after (131)I ablation therapy in patients with differentiated thyroid cancer. Journal of Nuclear Medicine. 2004;45(6):988-94.

99.   Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, et al. Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(3):1440-5.

100.   Rosario PW, Borges MA, Fagundes TA, Franco AC, Purisch S. Is stimulation of thyroglobulin (Tg) useful in low-risk patients with thyroid carcinoma and undetectable Tg on thyroxin and negative neck ultrasound? Clin Endocrinol (Oxf). 2005;62(2):121-5.

101.   Bernier MO, Morel O, Rodien P, Muratet JP, Giraud P, Rohmer V, et al. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2005;32(12):1418-21.

102.   Giovanella L, Ceriani L, Ghelfo A, Keller F. Thyroglobulin assay 4 weeks after thyroidectomy predicts outcome in low-risk papillary thyroid carcinoma. Clin Chem Lab Med. 2005;43(8):843-7.

103.   Heemstra KA, Liu YY, Stokkel M, Kievit J, Corssmit E, Pereira AM, et al. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2007;66(1):58-64.

104.   Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, et al. Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation 131I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma. Am J Clin Oncol. 2007;30(1):63-8.

105.   Sawka AM, Orlov S, Gelberg J, Stork B, Dowar M, Shaytzag M, et al. Prognostic value of postsurgical stimulated thyroglobulin levels after initial radioactive iodine therapy in well-differentiated thyroid carcinoma. Head Neck. 2008;30(6):693-700.

106.   Familiar C, Moraga I, Anton T, Gargallo MA, Ramos A, Marco AL, et al. Risk factors of persistent disease at 5 years from diagnosis in differentiated thyroid cancer: study of 63 patients. Endocrinologia y nutricion. 2009;56(7):361-8.

107.   Piccardo A, Arecco F, Morbelli S, Bianchi P, Barbera F, Finessi M, et al. Low thyroglobulin concentrations after thyroidectomy increase the prognostic value of undetectable thyroglobulin levels on levo-thyroxine suppressive treatment in low-risk differentiated thyroid cancer. J Endocrinol Invest. 2010;33(2):83-7.

108. Pelttari H, Valimaki MJ, Loyttyniemi E, Schalin-Jantti C. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. Eur J Endocrinol. 2010;163(5):757-63.

109. Rosario PW, Xavier AC, Calsolari MR. Value of postoperative thyroglobulin and ultrasonography for the indication of ablation and (1)(3)(1)I activity in patients with thyroid cancer and low risk of recurrence. Thyroid. 2011;21(1):49-53.

110. Tamilia M, Al-Kahtani N, Rochon L, Hier MP, Payne RJ, Holcroft CA, et al. Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. Nuclear medicine communications. 2011;32(3):212-20.

111. Polachek A, Hirsch D, Tzvetov G, Grozinsky-Glasberg S, Slutski I, Singer J, et al. Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. J Endocrinol Invest. 2011;34(11):855-60.

112. Melo M, Costa G, Ribeiro C, Carrilho F, Martins MJ, da Rocha AG, et al. Stimulated thyroglobulin at recombinant human TSH-aided ablation predicts disease-free status one year later. J Clin Endocrinol Metab. 2013;98(11):4364-72.

113. Gonzalez C, Aulinas A, Colom C, Tundidor D, Mendoza L, Corcoy R, et al. Thyroglobulin as early prognostic marker to predict remission at 18-24 months in differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2014;80(2):301-6.

114. Brito JP, Gionfriddo M, Morris JC, Montori VM. Overdiagnosis of thyroid cancer and graves' disease. Thyroid. 2014;24(2):402-3.

115. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab. 2013;98(2):636-42.

116. Brito JP, Davies L, Zeballos-Palacios C, Morris JC, Montori VM. Papillary lesions of indolent course: reducing the overdiagnosis of indolent papillary thyroid cancer and unnecessary treatment. Future Oncol. 2014;10(1):1-4.

117. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid. 2013;23(7):885-91.

Parte II

Very Low Recurrence Rates in Differentiated Thyroid Carcinoma Patients with Complete Response to Initial Therapy: a Referral Center Experience

Very Low Recurrence Rates in Differentiated Thyroid Carcinoma Patients with Complete Response to Initial Therapy: a Referral Center Experience

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

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

Running title: *Response to treatment in differentiated thyroid carcinoma*

Keywords: differentiated thyroid carcinoma, recurrence, initial therapy

Word Count: Text, 2715; Abstract, 253; Tables, 4; Figures, 1.

Disclosure Statement: R.S.S., J.M.D., D.A., A.B.Z, and A.L.M. have nothing to declare.

Abstract

Context: Current guidelines advise life-long surveillance for all patients with differentiated thyroid cancer (DTC). Changes in the epidemiological profiles of DTC patients may jeopardize this recommendation.

Objective: To estimate the recurrence rates in DTC patients.

Design, setting and patients: A cohort of DTC patients who attended a single institution.

Main outcome measures: Disease free was defined as having no clinical, imaging or biochemical evidence of tumors. Recurrence was defined as evidence of disease in a patient who had been previously classified as disease free.

Results: A total of 786 patients were included in the study. Papillary thyroid cancer accounted for 86.6% of the cases. The mean age at diagnosis was 45.8±15.1 years, and 81.6% of the patients were female. The median tumor size was 2.0 cm, 28.5% of the patients had lymph node involvement, and 6.1% had distant metastases. Disease status after the initial therapy was available for 548 patients: 357 (65.1%) patients were considered to be disease free, and 191 (34.9%) patients had persistent disease (90 with biochemical and 101 with structural disease). After a 4-year follow-up (2-8 years), 97.2% of the patients who had been classified as disease free in the first evaluation remained in disease remission status. Of the 10 (2.8%) patients with persistent disease, 8 (80%) presented biochemical whereas 2 (20%) had cervical structural disease.

Conclusions: The majority of the DTC patients who were considered to be disease free after the initial treatment maintained this status at long-term follow-up. Active, life-long surveillance may not be required for these patients.

Introduction

Differentiated thyroid cancer (DTC), including papillary (PTC) and follicular cancer (FTC), accounts for the majority (>90%) of all thyroid malignancies. The incidence of DTC has increased remarkably in many countries (1-5), a finding that has been, at least partially, attributed to the early detection of sub-clinical tumors of uncertain significance (6). Early diagnosis has led to a trend toward a more favorable profile of DTC disease, with less frequent lymph node involvement, extrathyroidal extension, and distant metastasis (1, 7-9). The overtime DTC shift to a less aggressive spectrum of disease was demonstrated in a recent published retrospective study that included eight Italian centers; the recurrence rate at 10.4 years was approximately 1.4% (10).

Several different risk stratification systems have been proposed for DTC patients based on clinicopathological findings that are available soon after surgical therapy and have been developed to predict the risk of death but not of recurrence (11). The TNM staging system of the American Joint Committee on Cancer (TNM/AJCC) and the Metastasis, Age, Completeness of Resection, Invasion and Size (MACIS) are the most used systems. Both of them have limitations, as not considering the response to treatment as a prognostic factor and the inability to accurate predict persistent disease and recurrence. In the last years, some authors have suggested that risk stratification can be further improved if the initial risk estimate systems are actively modified over time based on the response to therapy and the course of the disease. These novel risk stratification systems have been shown to identify those patients with a greater likelihood of progressing toward long-term remission after initial therapy (12-15).

The current thyroid cancer management guidelines advise that patients with DTC should be followed at least annually for an undetermined period of time (16, 17). Because of improvements in the medical armamentarium with high-sensitive thyroglobulin measurements and high-resolution ultrasonography, the long-term follow-up is primarily based on the likelihood of late recurrences (18). This strategy, which lacks evidence of benefit in terms of survival or well being, adds the burden of unnecessary examinations and medical appointments to patients and health systems.

We describe a cohort followed in a tertiary care hospital in southern Brazil. The objectives of the present study are to estimate recurrence rates, identify the prognostic factors for recurrence and to identify those patients who are considered to be at low risk for recurrence.

Materials and Methods

Patients and study design

We evaluated a cohort of DTC patients who attended the Thyroid Outpatient Clinic of the Endocrine Division of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care, university-teaching hospital in southern Brazil from 2000 to 2014. The inclusion criterion was the histological diagnosis of DTC, and there were no exclusion criteria. Our institution is a reference center that uses radioactive iodine (RAI) to treat patients; therefore, not all patients underwent surgery at our center. The study was approved by the Institution Ethical Committee of the HCPA, Porto Alegre, Brazil.

Treatment protocol and follow-up

Our DTC treatment protocol consists of performing a total thyroidectomy, administering an ablative or therapeutic dose of RAI, as indicated, and using levothyroxine suppression. Decisions regarding cervical lymph node dissection were made based on the discretion of the surgeon team at the center in which the patients underwent the first surgery. The follow-up duration was defined as the time between the thyroidectomy and the last medical visit to the clinic.

Our ablation protocol used RAI activities prescribed at the attending physician's discretion. A low-iodine diet was prescribed for 2 weeks before the RAI administration until 2 days afterward. The dose was administered in stimulated TSH condition on endogenous hypothyroidism (TSH>30 mUI/L), after withdrawing levothyroxine (at least 3-4 weeks without thyroid hormone). A post-therapy whole body scan (WBS) was performed seven to ten days after the RAI administration.

In the first evaluation, the following data were recorded for each patient: patient demographics, tumor characteristics (e.g., the date of diagnosis, histological features, extension and lymph node involvement) and treatment (e.g., surgery, RAI and other interventions). Each patient was classified using the 7th edition of TNM/AJCC staging system (I, II, III, or IV) (11). N0 status was defined considering the clinical examination of the neck, preoperative and postoperative neck ultrasound (US) imaging, macroscopic examination during surgery and pathological examination in patients with lymph node resection. We also defined the baseline tumor stage and the risk for persistent/recurrent disease based on the proposed classification using the American Thyroid Association (ATA) guidelines (17).

The follow-up protocol called for an initial assessment at 3 to 6 months after the initial treatment, which included a physical examination of the neck and measurements of the serum thyroglobulin levels under TSH suppression (Tg-T4) and anti-thyroglobulin antibody (TgAb). Six to 12 months after the initial treatment, serum Tg under stimulated TSH condition on endogenous hypothyroidism (TSH>30 mIU/L) (sTg) and TgAb were measured. The patient was classified according to his or her response to therapy. Patients who were classified as disease free were scheduled for annual visits, during which a physical examination of the neck and measurements of Tg-T4 and TgAb were performed. Patients with persistent disease were scheduled for the same examination twice a year. Additional imaging studies [e.g., dx-WBS, computed tomography (CT)] were performed, as needed, whenever the clinical or laboratory findings raised the suspicion of persistent or recurrent disease.

Outcomes

In the first year of follow-up, the response to initial therapy was assessed based on the serum Tg levels, neck US, post RAI WBS and appropriate additional imaging.

"Disease free" was defined as having 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) serum Tg-T4 levels and sTg levels <2 ng/mL.

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

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

Laboratory analysis

Serum Tg measurements were conducted using various immunoradiometric assays that indicated functional sensitivities of at least 1 ng/mL. Antithyroglobulin antibodies were measured using the passive agglutination method (Siemens Healthcare,

Diagnostics Products Ltd. Llanberis, Gwynedd LL55 4EL, United Kingdom). TSH levels were measured by electrochemiluminescent immunoassay (ADVIA Centaur XP – Siemmens, Tarrytown, NY, USA). These tests were all conducted in the central laboratory of the HCPA.

Statistical analysis

The clinical and laboratory data, which are reported as the mean±standard deviation (SD) values, or as the median and percentiles 25 and 75 (continuous variables) or as absolute numbers and percentages (categorical variables), were compared using an unpaired Student's *t* test, Mann-Whitney U test or χ^2, as appropriate.

Generalized linear models with a log link and Poisson errors were used to estimate relative risks and 95% confidence intervals for persistent disease. Using univariate regression analysis, clinical variables, such as gender, age at the time of diagnosis, histological subtype, multicentricity, tumor size, lymph nodal and distant metastases, ATA risk and TNM AJCC stage, were evaluated as potential prognostic factors of DTC. The factors that presented P<0.10 in the univariate analysis were included in the multivariate models.

All tests were two-tailed, and all analyses were performed using the Statistical Package for Social Science professional software version 20.0 (SPSS, Chicago, IL, USA). A two-tailed P<0.05 was considered to be statistically significant.

Results

Clinical characteristics

The clinical and oncological characteristics of the 786 patients are described in Table 1. The mean patient age at the time of diagnosis was 45.8±15.1 years, and there were 641 (81.6%) women. PTC was diagnosed in 681 (86.6%) patients. The median tumor size measured 2.0 cm; 224 (28.5%) patients had lymph node metastases, and 48 (6.1%) patients had distant metastases. The TNM/AJCC classification was as follows: 484 (61.6%) patients were stage I; 92 (11.7%) patients were stage II; 93 (11.8%) patients were stage III and 96 (12.2%) patients were stage IV. The TNM/AJCC stage was unknown for 21 patients. According to the ATA classification, the risk level was low in 388 (49.4%) patients, intermediate in 327 (41.6%) patients and high in 71 (9.0%) patients. Seventy-two (9.2%) patients were positive for TgAb.

All patients underwent surgery with curative intent (total thyroidectomy and neck dissection, as necessary). Ablative or therapeutic RAI was administered in 658 (83.7%) patients (mean dose, 109.4±38.0 mCi; range, 30-250 mCi). Post-therapy WBS was performed in 566 patients; it showed no uptake in 28 (4.9%) patients, cervical uptake in 506 (89.4%) patients and distant metastases in 32 (5.7%) patients.

Response to initial therapy

Data concerning the disease status after the initial therapy (response to therapy) were available for 548 patients: 357 (65.1%) patients were considered to be disease free, and 191 (34.9%) patients had persistent disease. Of those patients diagnosed with persistent disease, 90 patients had biochemical disease, and 101 patients had structural disease (62 patients with cervical metastasis and 39 patients with distant metastasis).

To investigate the factors associated with the disease status after the initial treatment, the patients were grouped into disease free or persistent disease categories. Univariate analysis indicated that male gender, multicentric tumors, larger tumor size, lymph node and distant metastases and intermediate and high ATA risk classifications were all associated with persistent disease (Table 2). An additional analysis using a multivariate model that included all variables with P<0.10 in the univariate analysis and disease status as the dependent variable, showed that male gender, lateral lymph nodal involvement, distant metastasis and ATA high-risk classification were independent prognostic factors for persistent disease (Table 3).

Recurrence rate

All these 548 patients were reevaluated after a median 4-year follow-up (interquartile range, 2-8 years). Of the 357 patients who were considered to be disease free in the first evaluation, 347 (97.2%) continued to be disease free. Remarkably, only 10 (2.8%) patients presented recurrences (8 patients with biochemical disease and 2 patients with cervical structural disease) (Table 4). All structural recurrences were limited to the cervical lymph nodes.

All patients with persistent disease (biochemical or structural) could receive additional therapy (i.e., surgical interventions or RAI) at the discretion of the attending physician. Among the 90 patients with biochemical disease after the initial therapy, 14 (15.6%) were considered to be disease free; 70 (77.8%) patients remained with biochemical disease, and only 6 (6.6%) patients evolved to cervical structural disease at

the 4-year follow-up. Among the patients (n=101) diagnosed with structural disease, only 11 (10.9%) became disease free; 15 (14.9%) patients exhibited biochemical disease, and 75 (75.2%) patients continued with structural disease (Figure 1). Additional analyses, including only those patients (n=292) with at least 5 years of follow-up, showed similar results.

Discussion

Recently, it has been suggested that DTC might be overdiagnosed because the incidence is increasing, but the mortality rate is stable (6, 19). Changes in the epidemiological profile and advances in the follow-up management of these patients could also lead to a similar result, the "over follow-up effect" with unnecessary surveillance, diagnostic tests (thyroglobulin measurements, imaging studies and fine-needle aspiration biopsies) and medical appointments because the majority of the patients can be defined as disease free in the first evaluation after initial therapy, and they remain disease free in the long term.

The primary purpose of surveillance after initial therapy in patients with malignant neoplasia is the early identification of those patients with recurrent disease who might potentially have more favorable outcomes with additional interventions. The recurrence timing and patterns, particularly in the case of metastatic disease, vary according to the type and stage of cancer at the time of diagnosis. There are several malignancies with follow-up guidelines (20, 21), and even in these more aggressive cancers, in the majority of cases, life-long testing to evaluate for recurrent or metastatic disease is not recommended in otherwise asymptomatic cancer survivors. In the case of DTC, the optimal follow-up strategy has not been determined, and the majority of the patients are followed for an undetermined time period and submitted to biochemical and radiological examinations even when these patients are asymptomatic.

The discrepancy highlighted above is greater when we consider the low recurrence rate in patients with DTC. We demonstrated that the recurrence rate in patients who had been classified as disease free after the initial therapy was only 2.8% after a median follow-up of 4 years. Notably, the recurrence rate for structural disease was even lower, 0.6% (2 of 357 patients). Our results align with the findings of other contemporary studies that showed that the actual recurrence rate for CDT is approximately 1% to 4% (10, 12, 15, 22-26). All these studies defined recurrence as newly detected biochemical or structural disease following any period of no evidence of

disease; consequently, only a patient who had achieved a disease-free status could be classified as having disease recurrence. When analyzing the group of patients diagnosed with persistent biochemical disease, we observed that only 6.6% (6 patients) evolved to cervical structural disease, a finding that raises the clinical significance of detectable thyroglobulin without structural disease in the follow-up of DTC.

Our study has some limitations. Although a median 4-year period is a reasonable follow-up for assessing clinical outcomes, some professionals may be concerned that a longer follow-up is required to assess the risk of late recurrences and death. However, as already demonstrated by other groups, disease recurrence occurs mostly in the first 2 to 5 years of follow-up (10, 26). Another possible limitation is that the majority of our patients received RAI and the disease course may be different in low-risk patients who do not receive RAI, as currently advocated. On the other hand, the fact that all patients included in the present study were followed at a single institution ensures a similar therapeutic approach and follow-up strategy, thereby enhancing the validity of our data. Furthermore, the non-exclusion of patients with positive TgAb and those at high risk for recurrence enhances the external validity of our findings.

In conclusion, the majority of patients who were defined as disease free after the initial treatment remained disease free after a long follow-up and might not require active, life-long surveillance. We believe that our data, combined with similar results published, provide evidence to discontinue follow-up to patients with no structural or biochemical signs of persistent disease after the initial evaluation. This approach allows a more effective follow-up strategy for DTC patients, with more efforts and resources directed at those patients at high risk for recurrence and progressive disease.

Table 1. Characteristics of 786 patients with differentiated thyroid carcinoma

Age at time of diagnosis (years)	45.8±15.1
Female gender	641 (81.6%)
Papillary histology	681 (86.6%)
Tumor size (cm)	2.0 (1.1–3.4)
Lymph node metastasis	
N0	561 (71.5%)
N1	224 (28.5%)
Distant metastasis	48 (6.1%)
TNM AJCC stage	
I	484 (61.6%)
II	92 (11.7%)
III	93 (11.8%)
IV	96 (12.2%)
Unknown*	21 (2.7%)
ATA risk level	
Low	388 (49.4%)
Intermediate	327 (41.6%)
High	71 (9.0%)
Positive TgAb during follow-up	72 (9.2%)
Follow-up (years)	4.0 (1.0–8.0)

TgAb: anti-thyroglobulin antibody.

ATA: American Thyroid Association.

*The tumor size was unavailable in these patient subgroups (all patients were older than 45 years).

Table 2. Univariate analysis of predictors of disease status after the initial treatment.

	Disease Status after Initial Treatment		Univariate Analysis	
	Disease Free	**Persistent Disease**	**RR (95% CI)**	**P**
Male gender	46/357 (12.9)	61/191 (31.9)	1.93 (1.55-2.41)	<0.001
Age at the time of diagnosis	45.7 ± 13.9	45.7±16.0	0.99 (0.99-1.00)	0.955
Follicular histology	52/357 (14.6)	29/191 (15.2)	1.04 (0.76-1.43)	0.737
Multicentricity	95/291 (32.6)	68/133 (51.1)	1.67 (1.27-2.21)	<0.001
Tumor size	1.7 (2.0)	2.8 (3.0)	1.17 (1.11-1.22)	<0.001
Lymph node metastasis				
0	287/357 (80.4)	93/190 (48.9)	1.00	
1a	18/357 (5.0)	13/190 (6.8)	1.71 (1.09-2.68)	<0.001
1b	52/357 (14.6)	84/190 (44.2)	2.52 (2.02-3.14)	
Distant metastasis	0/357 (0)	41/190 (21.6)	3.39 (2.97-3.88)	<0.001
ATA risk				
Low	209/357 (58.5)	47/181 (24.6)	1.00	
Intermediate	141/357 (39.5)	90/181 (47.1)	2.12 (1.56-2.88)	<0.001
High	7/357 (2.0)	54/181 (28.3)	4.82 (3.66-6.34)	
Positive TgAb	26/356 (7.3)	22/189 (11.6)	1.36 (0.98-1.90)	0.123

TgAb: anti-thyroglobulin antibody.
ATA: American Thyroid Association.

Table 3. Multivariate analysis of predictors of persistent disease status after the initial treatment.

	RR (95% CI)	P
Male gender	1.48 (1.14-1.94)	0.003
Multicentricity	1.28 (0.98-1.67)	0.067
Tumor size	1.06 (0.99-1.14)	0.062
Lymph node metastasis		
0	1.00	
1a	1.52 (0.91-2.54)	0.106
1b	1.55 (1.09-2.20)	0.013
Distant metastasis	1.58 (1.12-2.22)	0.008
ATA risk		
Low	1.00	
Intermediate	1.41 (0.91-2.21)	0.125
High	2.17 (1.24-3.78)	0.006
Positive TgAb	1.17 (0.82-1.67)	0.387

TgAb: anti-thyroglobulin antibody.
ATA: American Thyroid Association.

Table 4. Clinical characteristics of 10 patients who demonstrated disease recurrence after successful initial therapy.

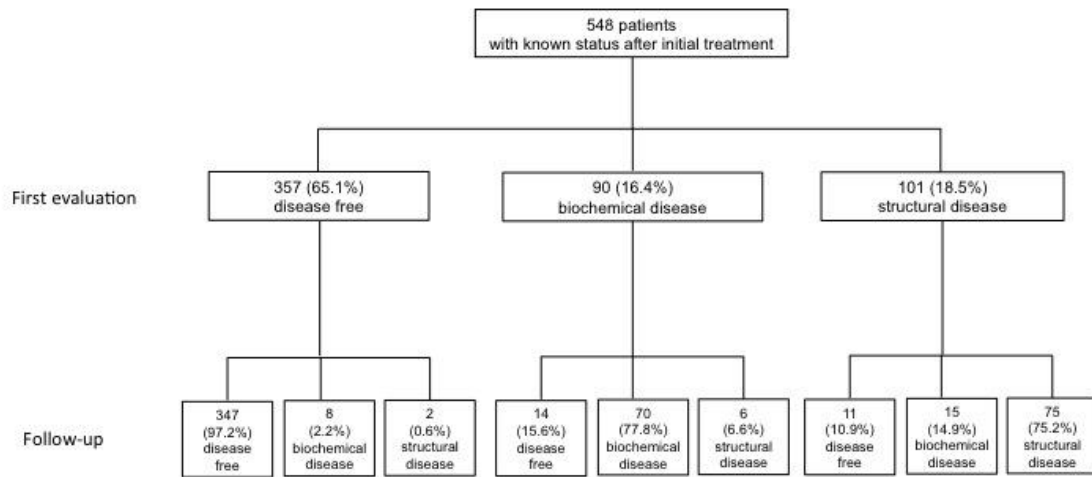| N	Gender	Age	AJCC stage	ATA risk	Treatment	Time of recurrence (years)	Type of recurrence
1	Male	51	IV	High	Thyroidectomy + RAI	2	Biochemical
2	Female	58	II	Low	Thyroidectomy + RAI	2	Biochemical
3	Female	24	I	Intermediate	Thyroidectomy + RAI	3	Biochemical
4	Female	31	I	Intermediate	Thyroidectomy + RAI	3	Biochemical
5	Male	35	I	Intermediate	Thyroidectomy + RAI	3	Biochemical
6	Female	32	I	Low	Thyroidectomy + RAI	6	Structural
7	Male	41	I	Low	Thyroidectomy + RAI	6	Biochemical
8	Female	57	IV	Intermediate	Thyroidectomy + RAI	7	Biochemical
9	Female	60	IV	High	Thyroidectomy + RAI	11	Structural
10	Male	31	I	Intermediate	Thyroidectomy + RAI	12	Biochemical

Figure 1. Follow-up outcomes, according to the patients' responses to therapy.

References

1.   Davies L, Ouellette M, Hunter M, Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? Laryngoscope. 2010;120(12):2446-51.

2.   Olaleye O, Ekrikpo U, Moorthy R, Lyne O, Wiseberg J, Black M, et al. Increasing incidence of differentiated thyroid cancer in South East England: 1987-2006. Eur Arch Otorhinolaryngol. 2011;268(6):899-906.

3.   Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer causes & control : CCC. 2009;20(5):525-31.

4.   Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev. 2009;18(3):784-91.

5.   Cordioli MI, Canalli MH, Coral MH. Increase incidence of thyroid cancer in Florianopolis, Brazil: comparative study of diagnosed cases in 2000 and 2005. Arq Bras Endocrinol Metabol. 2009;53(4):453-60.

6.   Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ. 2013;347:f4706.

7.   Reynolds RM, Weir J, Stockton DL, Brewster DH, Sandeep TC, Strachan MW. Changing trends in incidence and mortality of thyroid cancer in Scotland. Clin Endocrinol (Oxf). 2005;62(2):156-62.

8.   Leenhardt L, Grosclaude P, Cherie-Challine L. Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid. 2004;14(12):1056-60.

9.   Elisei R, Molinaro E, Agate L, Bottici V, Masserini L, Ceccarelli C, et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. J Clin Endocrinol Metab. 2010;95(4):1516-27.

10.   Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab. 2013;98(2):636-42.

11.   Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

12.   Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341-9.

13.   Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. Thyroid. 2011;21(12):1317-22.

14.   Vaisman F, Shaha A, Fish S, Tuttle R. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol (Oxf). 2011.

15.   Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur J Endocrinol. 2011;165(3):441-6.

16.   Rosario PW, Ward LS, Carvalho GA, Graf H, Maciel RM, Maciel LM, et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol. 2013;57(4):240-64.

17.   Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.

18.   Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(5):418-28.

19.   Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid. 2013;23(7):885-91.

20.   Desch CE, Benson AB, 3rd, Somerfield MR, Flynn PJ, Krause C, Loprinzi CL, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2005;23(33):8512-9.

21.   Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(7):961-5.

22.   Nascimento C, Borget I, Al Ghuzlan A, Deandreis D, Chami L, Travagli JP, et al. Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. Endocr Relat Cancer. 2011;18(2):R29-40.

23.   Crocetti U, Durante C, Attard M, Maniglia A, Tumino S, Bruno R, et al. Predictive value of recombinant human TSH stimulation and neck ultrasonography in differentiated thyroid cancer patients. Thyroid. 2008;18(10):1049-53.

24.   Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Wartofsky L. Does an undetectable rhTSH-stimulated Tg level 12 months after initial treatment of thyroid cancer indicate remission? Clin Endocrinol (Oxf). 2011;74(1):111-7.

25.   Han JM, Kim WB, Yim JH, Kim WG, Kim TY, Ryu JS, et al. Long-term clinical outcome of differentiated thyroid cancer patients with undetectable stimulated thyroglobulin level one year after initial treatment. Thyroid. 2012;22(8):784-90.

26.   Brassard M, Borget I, Edet-Sanson A, Giraudet AL, Mundler O, Toubeau M, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. J Clin Endocrinol Metab. 2011;96(5):1352-9.

Parte III

Prognostic Value of Postoperative Thyroglobulin in Differentiated Thyroid Carcinoma: a Prospective Study

Prognostic Value of Postoperative Thyroglobulin in Differentiated Thyroid Carcinoma: a Prospective Study

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

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

Running title: *Postoperative Thyroglobulin as Prognostic factor*

Keywords: differentiated thyroid carcinoma, thyroglobulin, prognostic

Word Count: Text, 2973; Abstract, 327; Tables, 3; Figures, 2.

Disclosure Statement: R.S.S., J.M.D., A.B.Z, and A.L.M. have nothing to declare.

Abstract

Background: Thyroglobulin (Tg) is a specific marker of thyroid tissue and Tg after total thyroidectomy (postoperative-Tg) had been suggested as a prognostic marker in patients with differentiated thyroid carcinoma (DTC).

Objectives: To evaluate whether postoperative-Tg adds in risk stratification of DTC.

Methods: Three-hundred-and-thirty DTC patients who underwent total thyroidectomy were included. Postoperative-Tg was measured under stimulated TSH condition. Persistent disease was defined as clinical or imaging evidence of tumor (structural disease) and/or Tg values under TSH suppression ≥ 1 ng/mL or stimulated Tg levels ≥ 2 ng/mL (biochemical disease). The postoperative-Tg performance was evaluated using the ROC curve. Multiple logistic regression analysis was performed using persistent disease as dependent variable and gender, tumor size, lymph node and distant metastasis, ATA risk classification and postoperative-Tg as independent variables.

Results: Of the 330 patients included, 273 (82.7%) were women, 286 (84.7%) had papillary thyroid carcinoma. The mean age at the time of diagnosis was 46.5 ± 14.9. After a median follow-up of 4.0 years, 101 (30.4%) patients showed persistent disease. The median value of postoperative-Tg was 5.16 ng/mL (range 0.1 to 35185 ng/mL; IQR 19.85). The ROC curve resulted in an AUC of 0.85 (95% CI 0.81-0.90) and the optimal cutoff point for predicting persistent disease was 7.0 ng/mL (sensibility 81% and specificity 72%). Using the optimal cutoff point, 147 patients (44.5%) showed positive postoperative-Tg. Of them, 82 (55.7%) have persistent disease on follow-up. Of the remaining 183 patients with negative postoperative-Tg only 19 (10.4 %) presented persistent disease on long-term follow-up (P<0.001). Of note, only 2 patients out of 85 (2.35%) with postoperative-Tg < 1.0 ng/mL have persistent disease on the follow-up (1 of them with biochemical disease and one with cervical disease). In the multivariate model, male gender, ATA high-risk classification and postoperative-Tg above 7.0 ng/mL remained as significant risks factor for persistent disease.

Conclusion: Postoperative-Tg level is an independent prognostic factor for persistent disease and might be used on defining the best therapeutic approach for DTC patients.

Introduction

Differentiated thyroid cancer (DTC), including papillary and follicular cancer, accounts for the majority (90%) of all thyroid malignancies. Although the disease is characterized by an **indolent course** and favorable prognosis, about 20-30% of the patients have a more aggressive clinical course leading to increased morbidity and mortality. At present, a major challenge in DTC management is to identify those patients at risk for persistent or recurrent disease to allow a more individualized therapeutic approach and follow-up. The current guidelines for DTC recommend treatment with total thyroidectomy, followed by radioactive iodine (RAI) ablation, and TSH suppression by levothyroxine for the majority of patients. Life-long follow-up is the standard care for all patients with DTC (1, 2).

Thyroglobulin (Tg) is a specific marker of thyroid tissue and serum Tg measurement is a cornerstone tool in the long-term follow-up of DTC patients, being considered the most accurate method to detect persistent or recurrent disease (1, 2, 3). As the sensitivity of Tg assays has improved, it is apparent that the majority of patients once thought to have recurrent DTC are better classified as having persistent disease that has progressed to the limits of detection for structural or functional imaging.

Previous studies have suggested that elevated levels of Tg after total thyroidectomy and previous to radioiodine (postoperative-Tg) is a prognostic marker for persistent or recurrent disease (4-10). Indeed, a recent meta-analysis demonstrated a high negative predictive value of postoperative-Tg (94.2%; 95% CI 92.8-95.3) (11). Notwithstanding, these studies differ regarding selection of patients, duration of follow-up and definitions for recurrence. Moreover, methodological flaws like retrospective design, use of surrogate endpoints and lack of standardized criteria to interpret the postoperative-Tg (not all the studies used a receiver operator characteristics to define the cut-off of Tg) preclude the widespread applicability of the findings in clinical practice.

The objective of the present study is to evaluate whether postoperative-Tg adds in risk stratification of patients with DTC using a prospective study design with clinical outcomes in a single center cohort.

Materials and Methods

Patients and study design

Patients with diagnosis of DTC, attending at the Thyroid Outpatient Clinic of the Endocrine Division of Hospital de Clínicas de Porto Alegre (HCPA, a tertiary care, university-teaching hospital in southern Brazil), were considered for the study. The only inclusion criterion was the histological diagnosis of DTC. Patients with positive antithyroglobulin antibodies (TgAb) or lacking data on postoperative-Tg were excluded. Our institution is a reference center for radioactive iodine (RAI) administration and, therefore, not all patients underwent surgery at our center. The study was approved by the Institution Ethical Committee of the HCPA, Porto Alegre, Brazil.

Treatment protocol and follow-up

The initial DTC treatment protocol at our Division consists of total thyroidectomy, administration of ablative or therapeutic dose of RAI, as indicated, and levothyroxine suppression. Decision regarding cervical lymph node dissection was made based on the discretion of the surgeon team. The follow-up period was defined as the time between the thyroidectomy and the last medical visit to the clinic.

The ablation protocol follows RAI activities recommended by the attending physician's discretion. A low-iodine diet was prescribed for 2 weeks before the RAI administration until 2 days afterward. The dose was administered in stimulated TSH condition on endogenous hypothyroidism (TSH > 30 mUI/L), after withdrawing levothyroxine (at least 3-4 weeks without thyroid hormone). A post-therapy whole body scan (WBS) was performed 7 to 10 days after the RAI administration.

In the first evaluation, the following data were recorded for each patient: patient demographics, tumor characteristics (e.g., histological features, extension and lymph node involvement) and treatment (e.g., surgery, RAI and other interventions). Each patient was classified using the 7th edition of the TNM staging system of the American Joint Committee on Cancer (TNM/AJCC) staging system (I, II, III, or IV). N0 status was defined considering the clinical examination of the neck, preoperative and postoperative neck ultrasound (US) imaging, macroscopic examination during surgery and pathological examination in patients with lymph node resection. We also defined the baseline tumor stage and the risk for persistent/recurrent disease based on the proposed classification using the American Thyroid Association (ATA) guidelines (2).

The follow-up protocol called for an initial assessment at 3 to 6 months after the initial treatment, which included a physical examination of the neck, measurements of the serum Tg levels under T4 therapy (Tg-T4) and TgAb. Six to 12 months after the

initial treatment, serum Tg under stimulated TSH condition on endogenous hypothyroidism (TSH > 30 mUI/L) (sTg) and TgAb were measured. The patient was then classified according to the response to therapy. Patients who were classified as disease free were scheduled for annual visits, during which a physical examination of the neck and measurements of Tg-T4 and TgAb were performed. Patients with persistent disease were scheduled for the same examination twice a year. Additional imaging studies [e.g., dx-WBS, computed tomography (CT)] were performed, as needed, whenever the clinical or laboratory findings raised the suspicion of persistent or recurrent disease.

Postoperative-Tg

The postoperative-Tg was measured before the administration of RAI. In those patients selected to not receive RAI, the postoperative-Tg was measured 3 to 6-months after thyroidectomy. In both groups, the measurement was made on endogenous hypothyroidism (TSH > 30 mUI/L) and serum levels of TgAb were measured in the same blood sample.

Outcomes

"Disease free" was defined as having 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) serum Tg-T4 levels and sTg levels <2 ng/mL.

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

Laboratory analysis

Measurements of serum Tg were made by eletrochemoluminescent method (ECLIA, Modular E-170 Roche); with values above 1 ng/mL considered as positive. TgAb were measured using the passive agglutination method (Siemens Healthcare,

Diagnostics Products Ltd. Llanberis, Gwynedd LL55 4EL, United Kingdom). TSH levels were measured by electrochemiluminescent immunoassay (ADVIA Centaur XP – Siemmens, Tarrytown, NY, USA). These tests were all conducted in the central laboratory of the HCPA.

Statistical analysis

The clinical and laboratory data are reported as the mean±standard deviation (SD) values, or as the median and interquartile interval (continuous variables) or as absolute numbers and percentages (categorical variables), were compared using an unpaired Student's *t* test, Mann-Whitney U test or χ^2, as appropriate.

Generalized linear models with a log link and Poisson errors were used to estimate relative risks and 95% confidence intervals for persistent disease. Using univariate and multivariate regression analysis, clinical variables, such as gender, age at the time of diagnosis, histological subtype, multicentricity, tumor size, lymph nodal and distant metastases, ATA risk and postoperative-Tg were evaluated as potential prognostic factors of DTC. To evaluate the postoperative-Tg we used the area under the receiver operator characteristics (ROC) curve, with a confidence interval of 95%.

All tests were two-tailed, and all analyses were performed using the Statistical Package for Social Science professional software version 20.0 (SPSS, Chicago, IL, USA). A two-tailed P < 0.05 was considered to be statistically significant.

Results

Clinical characteristics

From the 718 patients with DTC followed at the Thyroid Outpatient Clinic of the HCPA, 65 were excluded because they had positive TgAb. Of the remaining 653 patients, 330 have data on postoperative-Tg and disease status on the follow-up and were included (Figure 1).

The clinical and oncological characteristics of the 330 patients are described in Table 1. The mean age at the time of diagnosis was 46.5±14.9 years, and 273 (82.7%) were women. Papillary thyroid cancer (PTC) was diagnosed in 286 (86.7%) patients. The median tumor size measured 2.0 cm (range 0.2 to 10.0 cm; IQR 2.4); 100 (30.3%) patients had lymph node metastases, and 18 (5.5%) patients had distant metastases. The TNM/AJCC classification was as follows: 194 (58.8%) patients were stage I; 44 (13.3%) patients were stage II; 42 (12.7%) patients were stage III and 44 (13.3%)

patients were stage IV. The TNM/AJCC stage was unknown for 6 patients. According to the ATA classification, the risk level was low in 160 (48.5%) patients, intermediate in 140 (42.4%) patients and high in 30 (9.1%) patients.

All patients underwent surgery with curative intent (total thyroidectomy and neck dissection, as indicated by the attending surgeon). Ablative or therapeutic RAI was administered in 297 (90.0%) patients (mean dose, 113.2±30.4 mCi; range, 30-200 mCi). Post-therapy WBS was performed in 279 patients; it showed no uptake in 10 (3.5%) patients, cervical uptake in 254 (91.1%) patients and distant metastases in 15 (5.4%) patients.

Postoperative-Tg

The median value of postoperative-Tg was 5.16 ng/mL (range 0.1 to 35185 ng/mL; IQR 19.85). To evaluate the performance of postoperative-Tg in predicting persistent disease we used a ROC curve. This resulted in an area under the curve of 0.85 (95% CI 0.81-0.90). The postoperative-Tg level of 7.0 ng/mL was the optimal cut-off point with sensibility of 81% and specificity of 72% (Figure 2). Using this cut-off point, 147 patients (44.5%) were classified as having positive postoperative-Tg. After a median follow-up of 4.0 years, 82 patients (55.7%) have persistent disease. In contrast, only 19 (10.4%) of the remaining 183 patients considered as having negative postoperative-Tg presented with persistent disease (P<0.001). Remarkably, only 2 out of 85 (2.3%) patients with postoperative-Tg <1.0 ng/mL have persistent disease (1 with biochemical disease and 1 with cervical disease).

Clinical Outcomes

After a median follow-up of 4.0 years, 229 (69.6%) patients were considered to be disease free, and 101 (30.4%) patients had persistent disease. Of those patients diagnosed with persistent disease, 58 (57.4%) patients had biochemical disease, and 43 (42.5%) patients had structural disease (28 patients with cervical metastasis and 15 patients with distant metastasis).

To investigate the factors associated with disease status on the follow-up, the patients were grouped into disease free or persistent disease categories. Univariate analysis indicated that the group with persistent disease have a higher proportion of men (29.7 vs. 11.8%, P<0.001), higher proportion of multicentric tumors (47.4 vs. 33.0%, P=0.025), larger tumors (3.0 vs. 1.5 cm, P<0.001), higher proportion of central (8.9 vs.

6.6%, P=0.046) and lateral (43.6 vs. 14.0%, P<0.001) lymph node and distant metastasis (17.8 vs. 0%, P<0.001). The proportion of patients classified as high-risk on ATA risk classification was also higher (27.7 vs. 0.9%, P<0.001). The mean postoperative-Tg levels were significantly higher in patients with persistent disease (32.8 vs. 2.2 ng/mL, P<0.001) (Table 2).

Additional analyses using a multivariate model including disease status as the dependent variable and gender, tumor size, lymph node and distant metastasis, ATA risk classification, and postoperative-Tg above 7.0 ng/mL as independent variables are show in table 3. Male gender, ATA high-risk classification and postoperative-Tg above 7.0 ng/mL remained as significant risk factor for persistent disease.

Patients without use of RAI

To evaluate whether the role of postoperative-Tg in patients who did not receive RAI ablation, we made an additional analysis including 33 patients (10% of the total sample of the study). These patients have mean age at the time of diagnosis of 53.3±14.3 years, and 29 (87.9%) were women. PTC was diagnosed in 30 (90.9%) patients. The median tumor size measured 1.3 cm (range 0.3 to 5.5 cm; IQR 1.8); only 1 patient had lymph node metastases, and none patient had distant metastases. TNM/AJCC classification was as follows: 22 (66.7%) patients were stage I; 44 (12.1%) patients were stage II; 6 (18.2%) patients were stage III and 1 (3%) patient was stage IV. According to the ATA classification, the risk level was low in 25 (75.8%) patients and intermediate in 8 (24.2%).

The median value of postoperative-Tg in this subgroup was 0.75 ng/mL (range 0.1 to 7.6 ng/mL; IQR 1.34). Of the 33 patients, 21 (63.6%) have postoperative-Tg <1 ng/mL and only 1 have postoperative-Tg >7 ng/mL. After a median follow-up of 1.0 year (range 0 to 4.0 years; IQR 1.0), 27 patients (81.8%) were disease-free. Of note, all patients classified as having persistent disease had postoperative-Tg >1 ng/mL and none have identified structural disease.

Discussion

In the last years, estimation of individual risk has been emphasized on the management of patients with DTC in attemtp to tailor the recommendations for initial therapy and follow-up strategies. The ATA risk of recurrence classification system and the proposed model of response to therapy or ongoing risk assessment are examples of

such efforts. Although these two initiatives overcome some flaws of the classic risk stratification systems, such as the inability to adequately predict disease recurrence, both require at least 6-12 months of patient follow-up to be used.

The measurement of serum Tg is the most important tool in the follow-up of patients with DTC (1, 2, 3). The postoperative-Tg has been suggested as prognostic factor for persistent or recurrent disease (4, 5, 7, 8, 10, 15-19) with the advantage of be available at a very early stage of the patient evaluation, supporting decision-making for treatment (e.g. use or RAI) and follow-up strategies. Indeed, a meta-analysis of 15 studies that included 3,947 patients confirmed these findings with a negative predictive value of 94.2% (95% CI 92.8 to 95.3) (11). In this study, we found a negative predictive value of 89.6% using a prospective design, ROC curve to define the optimal cut-off point (7.0 ng/mL) and disease status as outcome, laboratorial and clinical parameters that help on the clinical applicability of the postoperative-Tg in the management of the DTC patients. Of note, the postoperative-Tg displayed the higher relative risk in the multivariate analysis; overcoming classic risk factors (as gender, age, tumor size, lymph node and distant metastasis) and even the ATA risk classification. Of note, only two patients (2.3%) with postoperative-Tg <1 ng/mL presented persistent disease on follow-up.

Another important question for the applicability of the postoperative-Tg refers to the fact that almost all patients included in the previous studies underwent RAI administration, raising the concern whether this marker would be valid for those patients who did not receive RAI. Two previous studies have evaluated the strategy of selecting patients for treatment with RAI through the postoperative-Tg. In the first study, 104 low-risk patients (CDT limited to thyroid and without aggressive histological variant) were evaluated with postoperative-Tg. Patients with serum postoperative-Tg levels <1 ng/mL (59 patients, 59.6% of the sample) did not receive RAI. After a median follow-up of 3.3 years, none of these patients had a recurrence of CDT (62). The second study had a similar strategy, including 136 low-risk patients with postoperative-Tg <1 ng/mL and negative cervical ultrasound. After a mean follow up period of 44 months (range 12-72 months), only 2 (%) patients had recurrence of the CPT. Here, we evaluated the performance of postoperative-Tg in a subgroup of 33 patients who did not receive RAI. Remarkably, 63.6% have postoperative-Tg <1 ng/mL and none of them have persistent disease on short–term follow-up. Albeit not a large sample, these

findings are of importance since it included also patients classified as intermediate risk. Taken together, these results suggest that the use of postoperative-Tg to select patients for RAI administration can be a safe and effective strategy. In fact, the National Comprehensive Cancer Network has incorporated the recommendation to use postoperative-Tg in the selection of patients for RAI in their consensus (13).

In conclusion, this prospective cohort study demonstrates that postoperative-Tg level is an independent prognosis factor for DTC. Notably, the group with undetectable levels of postoperative-Tg had a highly favorable prognosis, and probably can be spare RAI ablation. These findings might have important implications in the follow-up of patients with DTC and could be used to minimize treatment-related morbidity in this indolent disease.

Table 1. Characteristics of 330 patients with differentiated thyroid carcinoma.

Age at time of diagnosis (years)	46.5 ± 14.9
Female gender	273 (82.7%)
Papillary histology	286 (86.7%)
Tumor size (cm)	2.0 (2.4)
Lymph node metastasis	
N0	230 (69.7%)
N1	100 (30.3%)
Distant metastasis	18 (5.5%)
TNM AJCC stage	
I	194 (58.8%)
II	44 (13.3%)
III	42 (12.7%)
IV	44 (13.3%)
Unknown*	6 (1.8%)
ATA risk level	
Low	160 (48.5%)
Intermediate	140 (42.4%)
High	30 (9.1%)
RAI administration	297 (90.0%)
Postoperative-Tg	5.16 (19.16)
Follow-up (years)	4.0 (5.0)

ATA: American Thyroid Association.

RAI: radioactive iodine

Tg: thyroglobulin

*The tumor size was unavailable in these patient subgroups (all patients were older than 45 years).

Table 2. Univariate analysis of predictors for disease status.

	Disease Status		Univariate Analysis	
	Disease Free	Persistent Disease	RR (95% CI)	P
Male gender	27/229 (11.8)	30/101 (29.7)	2.02 (1.47-2.73)	<0.001
Age at the time of diagnosis	46.9 ± 13.7	45.2 ± 17.2	0.99 (0.98-1.01)	0.332
Follicular histology	197/229 (14.0)	12/101 (11.9)	0.87 (0.52-1.46)	0.641
Multicentricity	63/191 (33.0)	37/78 (47.4)	1.52 (1.05-2.20)	0.025
Tumor size	1.5 (1.8)	3.0 (2.8)	1.22 (1.16-1.30)	<0.001
Lymph node metastasis				
0	182/229 (79.5)	48/101 (47.5)	1.00	
1a	15/229 (6.6)	9/101 (8.9)	1.80 (1.01-3.19)	0.046
1b	32/229 (14.0)	44/101 (43.6)	2.77 (2.02-3.80)	<0.001
Distant metastasis	0/229 (0)	18/101 (17.8)	3.76 (3.12-4.52)	<0.001
ATA risk				
Low	133/229 (58.1)	27/101 (26.7)	1.00	
Intermediate	94/229 (41.0)	46/101 (45.5)	1.95 (1.28-2.95)	0.002
High	2/229 (0.9)	28/101 (27.7)	5.53 (3.87-7.90)	<0.001
Postoperative-Tg	2.2 (8.3)	32.8 (88.0)	1.00 (1.00-1.00)	<0.001

ATA: American Thyroid Association.

Tg: Thyroglobulin.

Table 3. Multivariate analysis of predictors for persistent disease status.

	RR (95% CI)	P
Male gender	1.30 (0.97-1.74)	0.083
Tumor size	1.08 (1.03-1.15)	0.004
Lymph node metastasis		
0	1.00	
1a	1.42 (0.83-2.43)	0.197
1b	1.40 (0.99-1.97)	0.051
Distant metastasis	1.18 (0.83-1.68)	0.338
ATA risk		
Low	1.00	
Intermediate	1.23 (0.78-1.94)	0.363
High	1.82 (1.04-3.17)	0.034
Postoperative-Tg > 7.0 ng/mL	3.74 (2.33-5.98)	<0.001

ATA: American Thyroid Association.
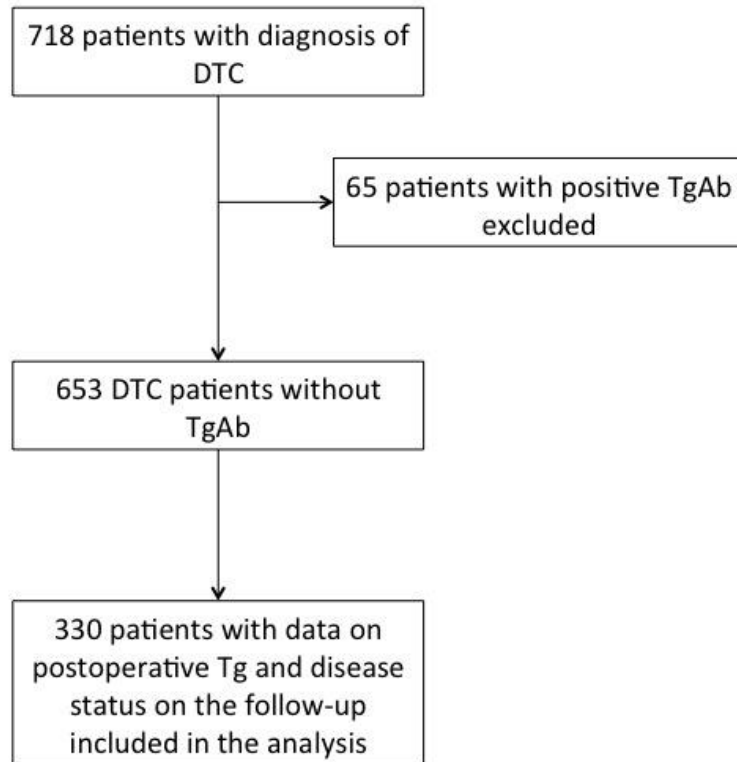
Tg: Thyroglobulin.

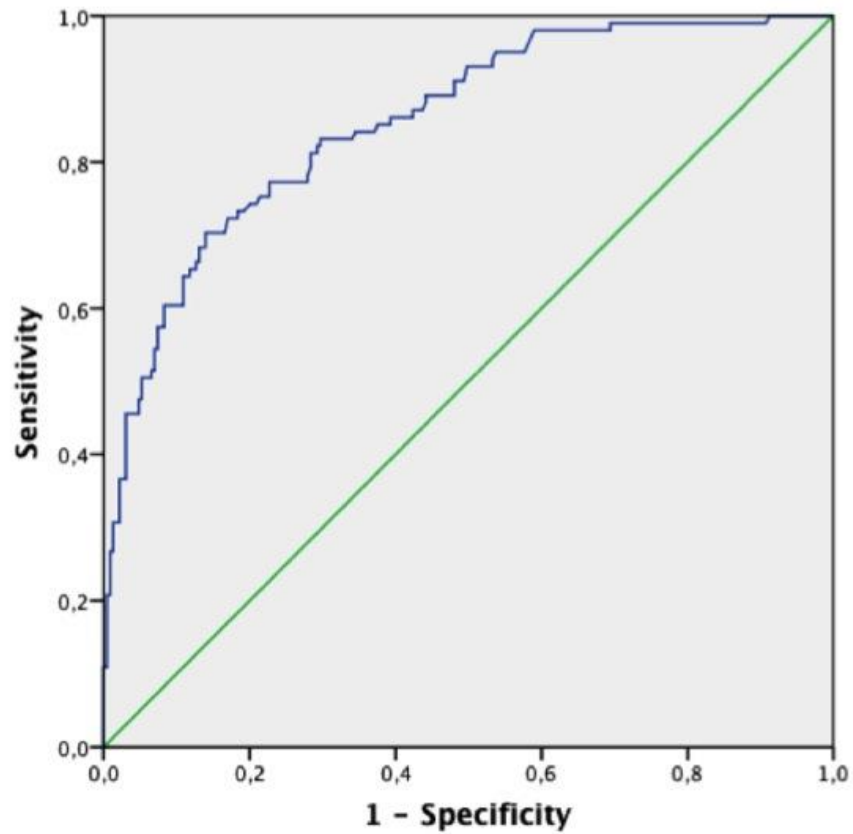**Figure 1: Flowchart of the patients included in the study.**

Figure 2: Receiver operator characteristics (ROC) curve of postoperative thyroglobulin for persistent disease.

References

1. Rosario PW, Ward LS, Carvalho GA, Graf H, Maciel RM, Maciel LM, et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol. 2013;57(4):240-64.

2. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.

3. Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(4):1433-41.

4. Bernier MO, Morel O, Rodien P, Muratet JP, Giraud P, Rohmer V, et al. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. European journal of nuclear medicine and molecular imaging. 2005;32(12):1418-21.

5. Rosario PW, Borges MA, Fagundes TA, Franco AC, Purisch S. Is stimulation of thyroglobulin (Tg) useful in low-risk patients with thyroid carcinoma and undetectable Tg on thyroxin and negative neck ultrasound? Clin Endocrinol (Oxf). 2005;62(2):121-5.

6. Hall FT, Beasley NJ, Eski SJ, Witterick IJ, Walfish PG, Freeman JL. Predictive value of serum thyroglobulin after surgery for thyroid carcinoma. The Laryngoscope. 2003;113(1):77-81.

7. Heemstra KA, Liu YY, Stokkel M, Kievit J, Corssmit E, Pereira AM, et al. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2007;66(1):58-64.

8. Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, et al. Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(3):1440-5.

9. Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, et al. Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation 131I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma. Am J Clin Oncol. 2007;30(1):63-8.

10. Ronga G, Fiorentino A, Paserio E, Signore A, Todino V, Tummarello MA, et al. Can iodine-131 whole-body scan be replaced by thyroglobulin measurement in the post-

surgical follow-up of differentiated thyroid carcinoma? Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1990;31(11):1766-71.

11.   Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, et al. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. J Clin Endocrinol Metab. 2012;97(8):2754-63.

12.   Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341-9.

13.   Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. Thyroid. 2011;21(12):1317-22.

14.   Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur J Endocrinol. 2011;165(3):441-6.

15.   Lin JD, Huang MJ, Hsu BR, Chao TC, Hsueh C, Liu FH, et al. Significance of postoperative serum thyroglobulin levels in patients with papillary and follicular thyroid carcinomas. Journal of surgical oncology. 2002;80(1):45-51.

16.   Piccardo A, Arecco F, Morbelli S, Bianchi P, Barbera F, Finessi M, et al. Low thyroglobulin concentrations after thyroidectomy increase the prognostic value of undetectable thyroglobulin levels on levo-thyroxine suppressive treatment in low-risk differentiated thyroid cancer. J Endocrinol Invest. 2010;33(2):83-7.

17.   Pelttari H, Valimaki MJ, Loyttyniemi E, Schalin-Jantti C. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. Eur J Endocrinol. 2010;163(5):757-63.

18.   Gonzalez C, Aulinas A, Colom C, Tundidor D, Mendoza L, Corcoy R, et al. Thyroglobulin as early prognostic marker to predict remission at 18-24 months in differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2014;80(2):301-6.

19.   Melo M, Costa G, Ribeiro C, Carrilho F, Martins MJ, da Rocha AG, et al. Stimulated thyroglobulin at recombinant human TSH-aided ablation predicts disease-free status one year later. J Clin Endocrinol Metab. 2013;98(11):4364-72.