

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

IMPACTO DO TNM-8 E DO RASTREIO CORPORAL TOTAL PÓS-DOSE DE
RADIOIODO NO MANEJO DE PACIENTES COM CARCINOMA DIFERENCIADO
DE TIREOIDE

Dissertação de Mestrado

Carla Fernanda Nava

Porto Alegre, 2019

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CARLA FERNANDA NAVA

Dissertação apresentada ao curso
de Pós-Graduação em Ciências
Médicas: Endocrinologia, UFRGS
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Orientador: Professor Dr. José Miguel Dora
Co-orientadora: Professora Dra. Ana Luiza Maia

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- Artigo original referente ao trabalho de pesquisa: Impact of the update TNM staging criteria on prediction of persistent disease in a differentiated thyroid carcinoma cohort; publicado na *Archives of Endocrinology and Metabolism* 2019 Feb;63(1):5-11.
- Artigo original referente ao trabalho de pesquisa: Reappraising the Diagnostic Accuracy of Post-Treatment Whole-Body Scan for Differentiated Thyroid Carcinoma (não publicado)

Além dos artigos já citados, ao longo do período do mestrado foram desenvolvidos os seguintes trabalhos:

- Dynamic Risk Stratification in the Follow-up of Children and Adolescents with Differentiated Thyroid Cancer. Zanella AB, Scheffel RS, **Nava CF**, Golbert L, Laurini de Souza Meyer E, Punaes M, Gonçalves I, Dora JM, Maia AL. *Thyroid*. 2018 Oct;28(10):1285-1292.
- Impact of neoadjuvant multikinase inhibitors in response to therapy in patients with locally advanced unresectable thyroid carcinoma: case report and systematic review. **Carla Fernanda Nava**; Rafael Selbach Scheffel; Ana Patrícia Cristo; Carla Vaz Ferreira; Shana Weber; André Borsatto Zanella; Francisco Costa Paixão; Alceu Migliavaca; José Ricardo Guimarães; Marcia Graudenz; José Miguel Dora; Ana Luiza Maia. *Submitted to Thyroid Journal*

LISTA DE ABREVIATURAS E SIGLAS

AJCC/UICC - American Joint Committee on Cancer/Union for International Cancer Control

ATA - American Thyroid Association

CAAE - certificado de apresentação para apreciação ética

CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CDT - carcinoma diferenciado de tireoide

CFT - carcinoma folicular de tireoide

CPT - carcinoma papilar de tireoide

CNPq - Conselho Nacional de Pesquisas

CT - computed tomography

DSS - disease specific survival

DTC - differentiated thyroid carcinoma

DxWBS - diagnostic whole-body scan

FAPERGS - Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul

FIPE - Fundo de Incentivo à Pesquisa

FN - false-negative

FP - false-positive

FTC - follicular thyroid carcinoma

HCPA - Hospital de Clínicas do Porto Alegre

I-131 - iodine-131

MRI - magnetic resonance

NA - not available

NC - not calculable

NCDB - National Cancer Database

neck US - neck ultrason

NIS - sodium/iodine symporter

NR - non-reactive

PRONEX - Programa de Apoio aos Núcleos de Excelência

PTC - papillary thyroid carcinoma

ptWBS - post-treatment whole-body scan

RA - reactive

RAI - radioactive iodine

RCT - rastreio corporal total

RIT - radioiodoterapia

SD - standard deviation

SEER - Surveillance, Epidemiology and End Results

sPOTg - stimulated post-operative thyroglobulin

sTg - thyroglobulin under stimulated TSH condition

Tg - thyroglobulin

Tg-T4 - thyroglobulin under TSH suppression

TgAb - anti-thyroglobulin antibody

TNM - 7 - 7th TNM system edition

TNM - 8 - 8th TNM system edition

TNM - tumor, node, metastasis system

TP - true-positive

TSH - thyroid stimulating hormone

US - ultrasound

WBS - whole-body scan

WGS - weighted generalized score

SUMÁRIO

RESUMO	9
ABSTRACT	12
INTRODUÇÃO	14
ANEXO - TABELA 1	16
CONCLUSÃO	18
REFERÊNCIAS BIBLIOGRÁFICAS	19
 PARTE I - IMPACT OF THE UPDATE TNM STAGING CRITERIA ON PREDICTION OF PERSISTENT DISEASE IN A DIFFERENTIATED THYROID CARCINOMA COHORT (<i>publicado na Archives of Endocrinology and Metabolism 2019 Feb;63(1):5-11</i>)	21
 PARTE II - REAPPRAISING THE DIAGNOSTIC ACCURACY OF POST-TREATMENT WHOLE-BODY SCAN FOR DIFFERENTIATED THYROID CARCINOMA	44

RESUMO

O carcinoma diferenciado de tireoide (CDT) inclui os subtipos papilar (CPT) e folicular (CFT) e é responsável pela maioria das neoplasias malignas tireoidianas. Aproximadamente 85% dos CDT são CPT, atingindo principalmente mulheres, nas faixas etárias entre 40-59 anos. O CDT é geralmente um tumor indolente, usualmente diagnosticado em estágio I e com excelente prognóstico. O manejo do CDT tem mudado nos últimos anos, em janeiro de 2018 foi incorporado à prática clínica a oitava edição do sistema de estadiamento do *American Joint Committee on Cancer - Tumor, node, metastasis* (AJCC/TNM-8) que traz duas principais mudanças com relação à antiga classificação (sétima edição do tumor, linfonodos e metástases - TNM-7): o corte de idade ao diagnóstico passa dos 45 anos para os 55 anos e os critérios de classificação de T3 e T4. Essa atualização objetiva melhorar a predição de doença e sobrevida dos pacientes, separando os pacientes em risco de persistência e/ou recorrência de doença em estágios mais avançados do TNM. Com objetivo de avaliar o impacto da mudança do TNM-7 para o TNM-8 em uma população brasileira de CDT fizemos uma análise comparativa das classificações e dos desfechos relacionados à doença que se encontra no artigo intitulado "*Impact of the update TNM staging criteria on prediction of persistent disease in a differentiated thyroid carcinoma cohort*". Comparamos as classificações do TNM-7 e do TNM-8 em uma coorte de pacientes brasileiros, do sul do país, com carcinoma diferenciado de tireoide. Foram incluídos no trabalho 419 pacientes, quando comparadas às distribuições dos pacientes dentro das classificações notamos que as diferenças entre o TNM-7 e o TNM-8 são estatisticamente significativas e levaram os pacientes, com o TNM-8, a 37% de reclassificações para estágios de menor risco de mortalidade relacionada à doença. Mais da metade (56%) das reclassificações foi atribuída a mudança do corte de idade ao diagnóstico para 55 anos. Com a classificação TNM-8 os pacientes de menor risco foram alocados em estágios mais baixos, sugerindo que o novo sistema é melhor em distribuir os pacientes de acordo com suas categorias de risco. Durante o seguimento mediano de 4,4 anos, os achados referentes à resposta ao tratamento são coerentes com essa

interpretação. Evidenciando assim que o TNM-8 é melhor em estratificar os pacientes com CDT, alocando os pacientes dentro das categorias de risco correspondentes, o que leva ao tratamento mais adequado, menos agressivo, sem expô-los a tratamentos desnecessários e excessivos.

Corroborando com condutas mais conservadoras no manejo dos pacientes com CDT, o consenso Americano no Manejo de Pacientes Adultos com CDT publicado em dezembro de 2015 deixa de indicar tratamento com radioiodo (RIT) aos pacientes de baixo risco. Para todos os outros pacientes que recebem tratamento RIT, a realização do exame de rastreamento corporal total (RCT) após a dose de iodo é mandatória. Diante da incerteza dos benefícios da realização do RCT e dos potenciais risco do exame, fazia-se necessária uma releitura da sua utilidade para os pacientes com CDT que receberam RAI. No artigo intitulado *"Reappraising the Diagnostic Accuracy of Post-Treatment Whole-Body Scan for Differentiated Thyroid Carcinoma"* usamos a mesma coorte de pacientes para avaliar a acurácia diagnóstica do RCT, onde foram avaliados 268 pacientes após sua primeira dose de RAI. Foram revisadas todas as imagens de RCT e os pacientes com diagnóstico documentado de metástases à distância ou captação à distância no RCT foram revisados independentemente por dois especialistas em carcinoma de tireoide. Vinte e nove pacientes possuíam metástases à distância, destes 20 apresentaram captação à distância no RCT (verdadeiro-positivos) e 9 não apresentaram captação à distância (falso-negativos). Vinte e oito pacientes apresentaram captação à distância ao RCT, 9 deles falso-positivos. Estratificando o RCT de acordo com a classificação de risco da *American Thyroid Association* (ATA) notamos que para pacientes de risco baixo e intermediário o exame apresenta baixa sensibilidade no diagnóstico de metástase à distância. Quando excluídos os pacientes de baixo risco, que atualmente não tem indicação de tratamento com RIT, a performance do exame mostrou-se ainda pior. No entanto, para o grupo de alto risco da ATA, o RCT foi melhor em prever presença de metástase à distância, com boa sensibilidade, especificidade e valor preditivo positivo (82%, 100% e 100%, respectivamente), com significância estatística. Em resumo, em pacientes com baixa probabilidade pré-teste o exame deve ser reconsiderado, já para os pacientes de alto risco da ATA nos quais a probabilidade pré-teste é alta,

o RCT se mostra uma ferramenta útil para diagnóstico de metástases à distância.

ABSTRACT

Differentiated thyroid carcinoma (DTC) includes the papillary (PTC) and follicular (FTC) subtypes and is responsible for most thyroid malignancies. Approximately 85% of DTC are PTC, afflicting mainly women aged 40-59 years. DTC is usually an indolent tumor, diagnosed in stage I and with excellent prognosis.

The management of DTC has changed in recent years. Released in January 2018, the eighth edition of the *American Joint Committee on Cancer - Tumor, node, metastasis* (AJCC/TNM-8) staging system included two main changes from the previous classification (the seventh edition, TNM-7): the age range at diagnosis of 45 years to 55 years old and the classification criteria for T3 and T4. These updates aim to improve disease prediction and survival of patients, separating patients at risk of persistence and/or recurrence of disease in more advanced stages of TNM. In order to evaluate the impact of the change from TNM-7 to TNM-8 in a Brazilian population of DTC, we performed a comparative analysis of the classifications and outcomes related to the disease found in the article titled *Impact of the update TNM staging criteria on prediction of persistent disease in a differentiated thyroid carcinoma cohort*. We compared the TNM-7 and TNM-8 classifications in a cohort of 419 Brazilian DTC patients from the south of the country. The differences in the distributions of patients between TNM-7 and TNM-8 were statistically significant and led to 37% of patients classified under TNM-8 being moved to stages with a lower risk of mortality related to the disease. More than half (56%) of the reclassifications were attributed to changing the age cut-off to 55 years. With the TNM-8 classification, the lowest risk patients were placed in lower stages, suggesting that the new system is better at distributing patients according to their risk categories. During the median follow-up of 4.4 years, findings regarding treatment response were consistent with this interpretation and showed that TNM-8 is better at stratifying patients with DTC, which leads to more appropriate and less aggressive treatment, thereby not exposing them to unnecessary or excessive treatments.

Corroborating the more conservative management of DTC patients, the U.S. consensus given in the Management of Adult Patients with DTC

published in December 2018 no longer indicates treatment with radioiodine (RAI) for low-risk patients. For all other patients receiving RAI treatment, a whole-body scan (WBS) following the iodine dose is mandatory. Given the uncertainty of the benefits of WBS and the potential risk of the test, a re-reading of its usefulness was necessary for patients with DTC who received RAI. In the article entitled *Reappraising the Diagnostic Accuracy of Post-Treatment Whole-Body Scan for Differentiated Thyroid Carcinoma*, we used the same cohort of patients to assess the diagnostic accuracy of the WBS, where 268 patients were evaluated after their first dose of RAI. All WBS images were reviewed and the patients with documented diagnosis of distant metastases or remote uptake in the WBS were independently reviewed by two specialists in thyroid carcinoma. Twenty-nine patients had distant metastases, of which 20 had remote uptake in the WBS (true-positive) and 9 had no distant uptake (false-negative). Twenty-eight patients presented remote uptake in the WBS, nine of them false-positive. Stratifying the WBS according to the American Thyroid Association (ATA) risk classification, we note that for low-risk and intermediate-risk patients, the test presents low sensitivity in the diagnosis of distant metastases. When low-risk patients, who currently do not have an indication for RAI treatment, were excluded, the performance of the exam was even worse. However, for the high-risk ATA group, WBS was better at predicting presence of distant metastases with statistically significant sensitivity, specificity, and positive predictive value (82%, 100%, and 100%, respectively). In summary, for patients with a low pre-test probability the exam should be reconsidered, whereas for high-risk patients in whom the pre-test probability is high, the WBS is a useful tool for the diagnosis of distant metastases.

INTRODUÇÃO

O carcinoma de tireoide é a neoplasia endócrina mais comum com uma incidência global estimada de 3,1% em 2018 (Bray, et al. 2018). O carcinoma diferenciado de tireoide (CDT), incluindo os subtipos carcinoma papilar (CPT) e carcinoma folicular (CFT), é derivado das células foliculares da glândula tireoide, sendo responsável pela maioria das neoplasias malignas tireoidianas. Aproximadamente 84% dos CDT são CPT, atingindo principalmente mulheres, nas faixas etárias entre 40-59 anos (Shah, et al. 2015; Lim, et al. 2017). O CDT é geralmente um tumor indolente, usualmente diagnosticado em estágio inicial e com excelente prognóstico. Nesse contexto, o manejo do CDT tem mudado nos últimos anos, visto que as condutas preconizadas para tumores pequenos e de menor risco são mais conservadoras. (Haugen, et al. 2016; Ito, et al. 2018; Tuttle and Fagin, et al. 2017).

Recentemente, em janeiro de 2018 foi incorporado à prática clínica a oitava edição do *American Joint Committee on Cancer - Tumor, node, metastasis* (AJCC/TNM8) (Tuttle, et al. 2017). O TNM-8 traz duas principais mudanças com relação à antiga classificação do TNM-7 (sétima edição do tumor, linfonodos e metástases) (Edge, et al. 2010): o corte de idade ao diagnóstico passa dos 45 anos para os 55 anos e a classificação de T3 e T4. Pacientes que antes eram considerados de maior risco de morte relacionada ao CDT se estivessem acima de 45 anos e apresentassem metástases à distância, agora passam a ter o mesmo risco se estiverem acima de 55 anos. Tumores com extensão extratireoidiana mínima passam a ser incluídos nos tumores confinados a tireoide, fazendo com que tumores maiores que 4cm sejam considerados T3a e os maiores que 4cm e de extensão extratireoidiana grosseira sejam considerados T3b. Tumores classificados com T4a passaram a ser os que apresentam invasão grosseira de tecidos subcutâneos, laringe, traqueia, esôfago ou nervo laringeo recorrente e o T4b passa a ser para tumores com invasão grosseira da fáscia pré-vertebral ou vasos cervicais. (Tuttle and Fagin, et al. 2017) (**Tabela 1**). A atualização para o TNM-8 objetiva melhorar a predição de doença e sobrevida dos pacientes, separando os pacientes em risco de persistência e/ou recorrência de doença

em estágios mais avançados do TNM. Com objetivo de avaliar o impacto da mudança do TNM-7 para o TNM-8 em uma população brasileira de CDT fizemos uma análise comparativa das classificações e dos desfechos relacionados à doença representada pelo artigo integrante da parte I desta tese de mestrado.

Outra mudança foi o consenso Americano no Manejo de Pacientes Adultos com CDT em dezembro de 2015, que não mais indica radioiodoterapia (RIT) aos pacientes de baixo risco, em pacientes de intermediário risco ele pode ser considerado se associado a exames de imagem e laboratoriais e para os de alto risco é sempre indicado (Haugen, et al. 2016). Para os pacientes que recebem RIT, a realização do exame de rastreamento corporal total (RCT) após a dose de iodo é mandatória. Diante da incerteza dos benefícios da realização do RCT e dos potenciais risco do exame, faz-se necessária uma releitura da sua utilidade para os pacientes com CDT que receberam RIT. Exames com resultados falso-positivos são uma preocupação, visto que geram estresse psicológico ao paciente e custos financeiros na busca da confirmação da presença de metástase antes não suspeitada, com a realização de exames e consultas adicionais, com novos deslocamentos ao hospital que seriam desnecessários. Como limitação do método, há também que se considerar os exames falso-negativos, onde a metástase está presente e o RCT não foi capaz de diagnosticá-la.

Com o avanço das técnicas diagnósticas, faz-se necessária constante reavaliação dos métodos utilizados no manejo dos pacientes com CDT. Com objetivo de avaliar o desempenho do exame RCT após a primeira dose de RAI na população de CDT, concebemos estudo para avaliar a acurácia diagnóstica do exame no contexto atual, considerando como método padrão-ouro a presença de metástases confirmadas em exames de imagem (tomografia computadorizada, ressonância nuclear magnética, cintilografia óssea e ecografia cervical), biópsias ou exames anatomopatológicos pós-operatórios. Trabalho esse integrante da parte II desta tese de mestrado.

Tabela 1. Comparação entre o TNM-7 e TNM-8.

TNM-7		TNM-8	
Tx	Tamanho do tumor não pôde ser avaliado mas sem extensão extratireoidiana	Tx	Tamanho do tumor não pôde ser avaliado
T1	Tumor ≤ 2cm	T0	Sem evidência de tumor primário
		T1a	Tumor ≤ 1cm restrito à tireoide
		T1b	Tumor > 1cm ≤ 2cm restrito à tireoide
T2	Tumor > 2 cm ≤ 4cm	T2	Tumor > 2cm ≤ 4cm restrito à tireoide
T3	Tumor > 4cm restrito à tireoide ou EET mínima	T3a	Tumor > 4cm restrito à tireoide
		T3b	Tumor de qualquer tamanho com EET grosseira, invadindo músculos do pescoço (esterno hioide, esterno tireoide, tireo hioide ou omohioide)
T4a	Tumor de qualquer tamanho com EET grosseira - invadindo tecido subcutâneo, laringe, traquéia, esôfago ou n laringeo recorrente	T4a	Tumor de qualquer tamanho com EET grosseira - invadindo tecido subcutâneo, laringe, traquéia, esôfago ou n laringeo recorrente
T4b	Tumor de qualquer tamanho com EET grosseira - invadindo fáscia pré-vertebral, art carótida ou vasos mediastinais	T4b	Tumor de qualquer tamanho com EET grosseira - invadindo fáscia pré-vertebral, art carótida ou vasos mediastinais
Nx	LNFs não avaliados na cirurgia	Nx	Linfonodos (LNFs) não foram avaliados
N0	Sem evidência de metástases para LNFs	N0	Sem evidência de metástases para LNFs
		N0a*	Um ou mais LNFs com citologia ou histologia benigna
		N0b*	Sem evidência clínica ou radiológica de metástases para LNFs
N1a	Metástase para nível VI (pré-traqueal, paratraqueal ou perilaringeal/Delfiano)	N1a	Metástase para LNFs níveis VI ou VII (pré-traqueal, paratraqueal ou perilaringeal/Delfiano ou mediastino superior). Doença uni ou

			bilateral	
N1b	Metástase para LNFs unilateral, bilateral, contralateral ou mediastino superior		N1b	Metástase unilateral, bilateral ou contralateral para LNFs níveis I, II, III, IV ou V ou retrofaríngeanos.
Mx	Metástase à distância desconhecida		Mx	Metástase à distância desconhecida
M0	Sem metástase à distância		M0	Sem metástase à distância
M1	Presença de metástase à distância		M1	Presença de metástase à distância
Estágio	TNM-7		TNM-8	
	< 45 anos	≥ 45 anos	< 55 anos	≥ 55 anos
I	Qualquer (QQ) T, N, M0	T1 N0 M0	QQ T, N, M0	T1-2 N0/Nx M0
II	QQ T, N, M1	T2 N0 M0	QQ T, N, M1	T1-2 N1 M0 T3a-b QQ N M0
III		T3 N0 M0 T1-3 N1a M0		T4a QQ N M0
IVA		T4a N0 M0 T4a N1a M0 T1-4a N1b M0		T4b QQ N M0
IVB		T4b QQ N M0		QQ T, QQ N, M1
IVC		QQ T, QQ N, M1		

CONCLUSÃO

Os trabalhos acima corroboram dados da literatura, sendo que o primeiro valida a nova classificação do TNM-8 na população brasileira de CDT e mostra que a atualização para a oitava edição do TNM classifica melhor os pacientes quanto ao risco de mortalidade relacionada à doença, fazendo com que a intensidade do tratamento adjuvante e o seguimento sejam mais adequados aos riscos da doença de base. O segundo trabalho levanta questão importante no manejo do CDT sobre exame obrigatório no acompanhamento dos pacientes que receberam RIT. Reavaliando a acurácia diagnóstica do RCT na primeira dose de RIT, confirmamos suspeita da prática clínica. Nos pacientes com risco baixo ou intermediário pela ATA o RCT deve ser reconsiderado e provavelmente contra-indicado. A baixa probabilidade pré-teste da presença de metástases à distância nesta população eleva o número de exames falsos positivos e não acrescenta dados ao seguimento. Já os pacientes de alto risco são beneficiados pelo exame, que pode ser uma ferramenta útil na detecção precoce de metástases à distância. Esses dados trazem grande potencial para mudar o consenso e o manejo do CDT no futuro.

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PARTE I

**IMPACT OF THE UPDATE TNM STAGING CRITERIA ON PREDICTION OF
PERSISTENT DISEASE IN A DIFFERENTIATED THYROID CARCINOMA
COHORT***

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Impact of the updated TNM staging criteria on prediction of persistent disease in a Differentiated Thyroid Carcinoma Cohort*

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Abstract

Background: The 8th TNM system edition (TNM-8) released in 2018 presents significant changes when compared to the 7th edition (TNM-7). The aim of this study was to assess the impact of changing the TNM staging criteria on the outcomes in a Brazilian cohort of differentiated thyroid carcinoma (DTC).

Methods: DTC patients, attending a tertiary, University-based hospital, were classified by TNM-7 and TNM-8. Prediction of disease outcomes status of the two systems was compared in a retrospective cohort study design.

Results: 419 DTC patients were evaluated, comprised by 82%(345/419) women, with mean age at diagnosis of 46.4±15.6 years, 89%(372/419) papillary thyroid carcinoma, with a median tumor size of 2.3cm(P25-P75, 1.3-3.5). One hundred and sixty patients (38%) had lymph node metastases and 47(11%) distant metastases at diagnosis. Using the TNM-7 criteria, 236(56%) patients were classified as Stage I, 50(12%) as Stage II, 75(18%) as Stage III and 58(14%) as Stage IV. When evaluated by the TNM-8, 339(81%) patients were classified as Stage I, 64(15%) as Stage II, 2(0.5%) as Stage III and 14(3%) as Stage IV. After a median follow-up of 4.4years(P25-P75 2.6-6.6), the rate of incomplete biochemical and/or structural response was 54% vs 92%(P=0.004) and incomplete structural response was 42% vs 86%(P=0.009) for patients classified as stage IV by TNM-7 vs TNM-8, respectively. Only 4(1%) disease-related deaths were recorded.

Conclusions: In our cohort, 37% of DTC patients were down staged with the application of TNM-8 (vs TNM-7). Additionally, TNM-8 seems to better stratify the risk of structural incomplete response at follow-up.

Introduction

Differentiated thyroid carcinoma (DTC), comprising papillary (PTC) and follicular carcinoma (FTC), accounts for the majority (>90%) of all thyroid malignancies (1). In recent years, an increasing incidence of DTC diagnosis has been documented worldwide (2). The incremental use of imaging resources in medical practice, along with the continuous development of more sensitive techniques, led to the pandemic observation of “overdiagnosis” of DTC (2). Most of the increment in DTC diagnosis can be credited to increased detection of pre-clinical indolent tumors restricted to the thyroid gland, that present a more favorable disease profile (3,4).

The current 2015 ATA Management Guidelines for Adult Patients with DTC advise that “AJCC/UICC staging is recommended for all patients with DTC, based on its utility in predicting disease mortality, and its requirement for cancer registries” (5). In response to the change in DTC epidemiology, staging systems are being revised, to ensure a more balanced delivery of therapy for DTC, specially for those at low risk of disease-related morbidity/mortality.

The 8th edition (TNM-8) of the American Joint Committee on Cancer; Tumor, Lymph Nodes, Metastasis (AJCC/TNM) system, was incorporated into the management of DTC in January of 2018 (6). The most significant changes were the age at diagnosis cut-off (from 45 to 55 years) and the redefinition of the T3b and T4a classifications. In the TNM-7, microscopic extrathyroidal extension of the tumor warranted a T3 classification. In the TNM-8, T3 is now comprised of tumors greater than 4 cm and confined to the thyroid gland (T3a) or gross extrathyroidal extension of the strap muscles (T3b). T4a is now defined as gross invasion of the subcutaneous tissue, larynx, trachea, esophagus or recurrent laryngeal nerve and T4b as gross invasion of the prevertebral fascia or major vessels (6,7).

The update in the TNM staging criteria aims to improve prediction of disease specific and overall survival, allocating patients at risk of persistent/recurrent disease for more advanced TNM stages, qualifying diagnostic work up and interventions at follow-up (8).

In Brazil we have scarce data on the clinical impact of updating the TNM criteria. Thus, the objective of this study was to assess how changing

the TNM staging criteria affects the prediction of long term outcomes in a cohort of Brazilian DTC patients in tertiary, University-based hospital.

Subjects and Methods

Patients and study design

The patients included were followed in a retrospective cohort of DTC patients from the Thyroid Outpatient Clinic of the Thyroid Unit, Endocrine Division of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care, university teaching hospital in southern Brazil. From 2009 to 2015, all consecutive patients with a histological diagnosis of DTC and data available to be classified by TNM-7 and TNM-8 staging systems were included. The study was approved by the ethics committee of the institution (CAAE 68434617.5.0000.5327/GPPG 17-0482).

Treatment protocol and follow-up

Our DTC treatment protocol consists of performing total thyroidectomy and administration of radioactive iodine (RAI) remnant ablation activity according to the ATA risk assessment. Decisions regarding cervical lymph node dissection were made at the discretion of the surgical team from the center where the patients underwent the first surgery. Duration of follow-up was defined as the time between the first surgery and the last medical visit to the clinic.

Our ablation protocol used RAI activities prescribed at the attending physician's discretion. The RAI was administered in a stimulated TSH condition of endogenous hypothyroidism (TSH>30 mUI/L), after withdrawing levothyroxine (at least 3-4 weeks without thyroid hormone). A post-treatment whole body scan (post-treatment WBS) was performed seven to ten days after RAI administration.

In the first evaluation, the following data were recorded for each patient: demographics, tumor characteristics (e.g., histological features [papillary thyroid carcinoma or follicular thyroid carcinoma - including Hurthle cell carcinoma], extension and lymph node involvement) and treatment (e.g., surgery, RAI remnant ablation, and other interventions). Each patient was

classified using the 7th and 8th editions of the TNM/AJCC staging system (I, II, III, or IV) (6,9). N0 status was defined with postoperative neck ultrasound (US) imaging or pathological examination of patients with lymph node resection. Distant metastasis (M1) was considered present when there was a lesion outside the cervical bed on imaging (CT, MRI or scintigraphy) with: histological confirmation or post-treatment WBS uptake and/or elevated Tg. The risk of persistent/recurrent disease was assessed based on the proposed risk stratification system by the American Thyroid Association (ATA) guidelines, with patients classified into three risk groups: low, intermediate and high (5).

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). In a second evaluation, 6 to 12 months after the initial treatment, serum thyroglobulin (Tg) under stimulated TSH condition in endogenous hypothyroidism (TSH>30 mIU/L) (sTg) and TgAb were measured. Neck ultrasound was performed in this first year of follow-up. At this point, the patient was classified according to disease outcome to initial therapy (see below in the outcomes section). Patients classified as having an excellent response were scheduled for annual visits, during which a physical examination of the neck and measurements of Tg-T4 and TgAb were performed. Patients with indeterminate or incomplete responses were scheduled for the same examination at least twice a year. Additional imaging studies [e.g. x-ray, bone scintigraphy, computed tomography (CT), magnetic resonance (MR)] 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 disease outcome of initial therapy was assessed based on the serum Tg-T4 or sTg levels, neck US, and additional imaging exams, whenever indicated.

An excellent response was defined as having no clinical or imaging evidence of tumor (i.e., no imaging evidence of tumor on neck US or CT),

undetectable (<0.2 ng/mL) serum Tg-T4 levels and/or sTg levels <1 ng/mL. Indeterminate response was defined as nonspecific findings on imaging studies, Tg-T4 detectable but < 1 ng/mL, sTg detectable but < 10 ng/mL or TgAb stable or declining in the absence of structural or functional disease. Biochemical incomplete response was defined as negative imaging and Tg-T4 \geq 1 ng/ml or sTg levels \geq 10 ng/mL or rising TgAb levels. Structural incomplete response was defined as structural or functional evidence of disease at any Tg-T4 level with or without TgAb. Patients who were diagnosed with persistent disease were evaluated for additional treatment (e.g., surgery, RAI, external-beam radiation or multi-kinase inhibitors), depending on the site involved and disease progression.

All patients with biochemical incomplete and structural incomplete responses were considered to have persistent disease. Recurrence was defined as new biochemical or structural evidence of the disease detected in a patient who had been previously classified as having an excellent response. Disease specific survival (DSS) was considered the time from initial surgery to last follow-up or death related to DTC.

Laboratory analysis

Serum Tg measurements were conducted using immunoradiometric assays (from 2000 to 2002 radioimmunoassay; 2002 to 2010 electrochemiluminescence and 2010 until the present chemiluminescence) that indicated functional sensitivities of at least 0.2 ng/mL. Antithyroglobulin antibodies were measured using the passive agglutination method from 2000 to 2010 and by chemiluminescence from 2010 until the present. After each new technique had been implemented, the necessary procedures for standardization and validation were performed. TSH levels were measured by chemiluminescence assay from 2000 to 2006 (Immulite 2000 SIEMENS), electrochemiluminescence from 2006 to 2010 (Modular E ROCHE), chemiluminescence assay from 2010 to 2014 (Centaur XP SIEMENS) and electrochemiluminescence from 2014 until the present (Cobas E602 ROCHE). These tests were all conducted in the central laboratory of the HCPA.

Statistical analysis

The clinical and laboratory data are reported as the mean \pm standard deviation (SD) values or as the median and percentiles 25 and 75 (P25-75) for continuous variables, or as absolute numbers and percentages for categorical variables. Comparative analyses of frequencies were performed using Pearson Chi-Square or Fisher's Exact Test, as appropriate. Agreement for qualitative (categorical) variables was assessed using the *Cohen's Kappa* coefficient.

All tests were two-tailed, and all analyses were performed using the Statistical Package for Social Science Professional software version 20.0 (IBM Corp., Armonk, NY). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Patients

Four hundred and nineteen DTC patients were evaluated. Clinical and oncological characteristics of these patients are described in **Table 1**. The mean age at diagnosis was 46.4 ± 15.6 years, 345 (82%) were women and PTC was diagnosed in 372 (89%) patients. The median tumor size was 2.3 cm (P25-75 1.3-3.5cm). One hundred and sixty patients (38%) had lymph node metastases, and 47 (11%) patients had distant metastases. All patients underwent total thyroidectomy \pm lymph node dissection and received RAI remnant ablation. The mean RAI activity was 112.3 ± 38.1 mCi.

TNM-7 vs TNM-8: staging comparison

Using the TNM-7 criteria, 236 (56%) patients were classified as stage I, 50 (12%) as stage II, 75 (18%) as stage III and 58 (14%) as stage IV. When evaluated by the TNM-8, 339 (81%) patients were classified as stage I, 64 (15%) as stage II, 2 (0.5%) as stage III and 14 (3%) as stage IV (**Table 2**).

The distribution of stage frequencies from TNM-7 to TNM-8 were statistically significant ($p \leq 0.0001$), and distributed as follows: 236 (100%) patients who were stage I remained the same; of the 50 previously in stage II, 36 (72%) were reclassified to stage I and only 14 (28%) maintained the classification. Of the 75 that were stage III, 49 (65%) were reclassified to

stage I, 26 (35%) to stage II and none remained in this classification; of the 58 patients in stage IV, 19 (33%) were reclassified to stage I, 24 (41%) to stage II, 2 (3%) to stage III, and only 14 (24%) remained in stage IV. One hundred and fifty-five (37%) patients with DTC were downstaged with the application of TNM-8 (vs TNM-7), 87 (56%) being due to the change in the age at diagnosis cut-off from 45 to 55 years and 68 (44%) to change in T3 definition (**Table 3**).

TNM-7 vs TNM-8: ATA Risk

Using TNM-7, 163/233 (70%) stage I patients were classified as low risk, 63/233 (27%) as intermediate risk and 7/233 (3%) as high risk. Stage II patients were classified as follows: 31/50 (62%) as low risk, 6/50 (12%) as intermediate risk and 13/50 (26%) as high risk. Of those in stage III, 30/75 (40%) were classified as low risk, 44/75 (59%) as intermediate risk and 1/75 (1%) as high risk. Of those in stage IV, 8/58 (14%) were stratified as low risk, 23/58 (40%) as intermediate risk and 27/58 (47%) as high risk.

Applying the TNM-8, stage I patients were stratified as low risk in 212/335 (63%) cases, as intermediate risk in 113/335 (34%) and as high risk in 10/335 (3%). Those in stage II were classified as low risk in 20/65 (31%), as intermediate risk in 23/65 (35%) and as high risk in 22/65 (34%). All stage III (n=2) and stage IV (n=14) patients were classified as high risk (100%) (**Table 4**). The greater number of reclassifications in ATA low and intermediate risk patients led to a weak level of agreement between TNM-7 and TNM-8 (*Kappa* 0.14 and 0.13, respectively; $p \leq 0.0001$ for both comparisons). In ATA high-risk patients, the agreement between the two classifications was considered moderate (*Kappa* 0.54, $p \leq 0.0001$).

TNM-7 vs TNM-8: disease outcomes

Regarding disease outcomes after initial therapy, we verified an excellent response status in 47/223 (21%), 9/49 (18%), 21/71 (30%) and 6/58 (10%) for patients at stage I, II, III and IV of TNM-7, respectively. While using the TNM-8 at the same point in time, an excellent response status was as follows: 76/322 (24%), 7/63 (11%), 0/2 (0%) and 0/14 (0%) for patients at stage I, II, III and IV, respectively. Indeterminate status was observed in 99/223 (44%), 10/49 (20%), 29/71 (41%) and 18/58 (31%) for patients at

stage I, II, III and IV of TNM-7, respectively; and using the TNM-8 we found 135/322 (42%), 19/63 (30%), 1/2 (50%) and 1/14 (7%) for patients at stage I, II, III and IV, respectively. Biochemical incomplete response was the disease status in 40/223 (18%), 13/49 (27%), 11/71 (15%) and 7/58 (12%) for patients at stage I, II, III and IV of TNM-7, respectively; and while using TNM-8 62/322 (19%), 8/63 (13%), 1/2 (50%) and 0/14 (0%) for patients at stage I, II, III and IV, respectively. Structural incomplete response frequencies were 37/223 (17%), 17/49 (35%), 10/71 (14%) and 27/58 (47%) for patients at stage I, II, III and IV using TNM-7, respectively; and in 49/322 (15%), 29/63 (46%), 0/2 (0%) and 13/14 (93%) for patients at stage I, II, III and IV using TNM-8 (**Table 5**).

After a median follow-up of 4.4 years (P25-P75 2.6-6.6), the majority of the patients maintained the same response to therapy status or were downgraded to a more favorable status, a finding observed with both TNM staging systems ($p \leq 0.001$). The rate of excellent response in stage I patients was 39% vs. 38% for TNM-7 and TNM-8; in stage II patients it was 26% vs 17%, in stage III patients it was 36% vs 0% and in stage IV patients 14% vs 0%. The rate of indeterminate responses was 40% vs 41% in stage I patients; 36% vs 34% in stage II patients; 45% vs 50% in stage III patients and 32% vs 7% in stage IV patients. The rate of biochemical incomplete response was 13% vs 12% in stage I patients; 14% vs 6% in stage II patients; 3% vs 50% in stage III patients and 12% vs 7% in stage IV patients. The rate of structural incomplete response was 8% vs 8% in stage I patients, 24% vs 42% in stage II patients; 16% vs 0% in stage III patients and 42% vs 86% ($p = 0.009$) in stage IV patients for TNM-7 and TNM-8, respectively (**Table 6, Figure 1**). The agreement level was considered moderate only for patients with incomplete structural response (*Kappa* 0.51, $p \leq 0.0001$).

Recurrence was observed only on 3/419 (0.7%) patients during follow-up period with a median time of 2.6 years.

It was not possible to access the impact of the reclassification on DSS due to the low mortality rate observed in our cohort ($n=4$, 1%). The four deaths occurred in TNM-7 stage IV patients ($n=4$, 100%), and in TNM-8 stage II ($n=2$, 50%) and stage IV ($n=2$, 50%) patients.

Discussion

The classification of DTC patients using staging systems is a crucial step in the care of these patients, since it allowed the healthcare team to determine the best therapeutic and follow-up approach. This study examined the impact of updating the TNM staging system from TNM-7 to TNM-8 on the reclassification of DTC patients in a Brazilian cohort, showing that the TNM-8 reclassified 37% of patients to lower stages. We also compared the prognostic information from both systems, and observed that TNM-8 was superior in predicting disease status at follow-up.

In recent years the incidence of DTC has been increasing with a more frequent diagnosis of low-risk and indolent tumors (2). These patients do not benefit from an aggressive approach, but may be exposed to the risks of overtreatment. The impact of updating the TNM-7 staging system to TNM-8 has been explored by some studies (8,10,11). In our study the majority of reclassifications occurred due to age at the diagnosis cut-off change (n=87, 56%). The change in age at the diagnosis cut-off was proposed and validated by Nixon et al in a multicenter study of 9500 patients (12,13). Older patients with more advanced disease tend to have a worse prognosis and this is usually proportional to age at diagnosis. Nixon et al showed that increasing the age cut-off point from 45 to 55 years resulted in a better prediction of outcomes, and prevented low risk patients from being overstaged and, consequently, overtreated. The results of Kim et al (14) corroborate these findings, and showed that a cut-off of 55 years was better at predicting DSS. In our population age cut-off numbers were in accordance with other reports, and seem to better stratify low and high risk patients. Twenty percent of all patients in our study were downstaged because of the change in cut-off for age at diagnosis, which is in line with data from Kim et al (10) that found 27%, and Pontius et al results of 26% (SEER cohort) and 26% (NCDB cohort) (11).

Using TNM-8, we observed that stage I patients are mostly classified as ATA low risk group, stage II patients are evenly distributed between low, intermediate, and high risk and patients in stages III and IV are exclusively at ATA high risk. When we compared these figures with the classification obtained using TNM-7, we noticed that patients in stage I were also mostly in the low-risk group, while patients in stage II were distributed between low and

high risk, those in stage III between low and intermediate risk and those in stage IV distributed in all three groups. Taken together these findings suggest that the TNM-8 serves as a good predictor for relapses and complications related to the disease.

Regarding the prediction of disease outcomes of the TNM-8, initially and after a median of 4.4 years (P25-P75 2.6-6.6) follow-up, we observed that patients with an excellent response were only those initially classified as stage I and II, those with indeterminate response were mainly patients in stage I and II, also including some stage III and IV. The groups of patients with biochemical incomplete and structural incomplete responses were comprised by patients with TNM-8 stage I to IV. It is worth mentioning that 86 to 93% of TNM-8 stage IV patients were on incomplete structural response and none of them had an excellent response. While comparing the two staging systems, TNM-8 classifies patients with a more severe disease spectrum as stages III and IV, identifying groups that benefit from a more aggressive treatment and follow-up approaches.

Our study has some limitations. The fact that only two patients remained in stage III after reclassification to TNM-8, makes it difficult to evaluate disease outcome prediction for this subgroup. Also, all patients included in this study underwent total thyroidectomy and received radioiodine, which limits the extrapolation of our results to patients submitted to partial thyroidectomy and to those who did not receive radioiodine. Notwithstanding, one should note that our data reflect a real clinical practice scenario at a tertiary care center, where all patients have access to standardized treatment protocols. Additionally, our data comprise a considerable number of patients, and it is one of the first studies providing Brazilian information on the subject.

In summary, 37% of DTC patients were downstaged with the application of TNM-8 (vs TNM-7). The TNM-8 incorporates a large number of patients to lower stages, retaining the favorable prediction performance for stages I and II. It also selects more advanced DTC disease to stages III and IV. These findings confirm that the application of TNM-8 to our population is valid, and superior to TNM-7, regarding prediction of poor DTC outcomes. The use of TNM-8 has the potential to benefit a large number of patients,

helping deliver the appropriate intensity of care according to disease prognosis.

Table 1. Characteristics of 419 patients with differentiated thyroid carcinoma.

Age at diagnosis (years)	46.4 ± 15.6
Female sex – n (%)	345 (82.3)
Histology – n (%)	
Papillary	372 (88.8)
Follicular	47 (11.2)
Tumor size (cm)	2.3 (1.3-3.5)
Lymph node metastasis (N1) – n (%)	160 (38.2)
Distant metastasis – n (%)	47 (11.2)
RAI therapy – n (%)	419 (100)
RAI activity (mCi)	112.3 ± 38.1
Follow-up (years)	4.4 (2.6-6.6)

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

RAI, Radioactive iodine.

Table 2. Modifications of differentiated thyroid carcinoma staging from the TNM-7 to the TNM-8 system.

DTC Staging		TNM-8			
		I (n=339)	II (n=64)	III (n=2)	IV (n=14)
TNM-7	I (n=236)	236 (100%)	0 (0%)	0 (0%)	0 (0%)
	II (n=50)	36 (72%)	14 (28%)	0 (0%)	0 (0%)
	III (n=75)	49 (65%)	26 (35%)	0 (0%)	0 (0%)
	IV (n=58)	19 (33%)	24 (41%)	2 (3%)	14 (24%)

DTC, differentiated thyroid carcinoma.

Chi-square of $p \leq 0.0001$ for TNM-7 vs TNM-8.

Table 3. Comparison of Tumor classification of TNM-7 and TNM-8 systems.

		TNM-8							
		T1a	T1b	T2	T3a	T3b	T4a	T4b	Total
TNM-7	T1	69	85	-	-	-	-	-	154
	T2	-	-	111	-	-	-	-	111
	T3	6	24	37	63	2	-	-	132
	T4a	-	-	-	-	-	13	-	13
	T4b	-	-	-	-	-	-	4	4
	Total	75	109	148	63	2	13	4	414

Table 4. ATA risk according to differentiated thyroid carcinoma staging using the TNM-7 and TNM-8 systems.

ATA risk	TNM-7 Stage				TNM-8 Stage			
	n (%)				n (%)			
	I	II	III	IV	I	II	III	IV
Low	163 (70)	31 (62)	30 (40)	8 (14)	212 (63)	20 (31)	0 (0)	0 (0)
Intermediate	63 (27)	6 (12)	44 (59)	23 (40)	113 (34)	23 (35)	0 (0)	0 (0)
High	7 (3)	13 (26)	1 (1)	27 (47)	10 (3)	22 (34)	2 (100)	14 (100)

Kappa for TNM-7 vs TNM-8 according to ATA risk: 0.14 for low risk ($p \leq 0.0001$); 0.13 for intermediate risk ($p \leq 0.0001$) and 0.54 for high risk ($p \leq 0.0001$).

Table 5. Disease outcomes after initial treatment according to differentiated thyroid carcinoma staging using the TNM-7 and TNM-8 systems.

Treatment response	TNM-7 Stage					TNM-8 Stage			
	n (%)					n (%)			
	I	II	III	IV		I	II	III	IV
Structural incomplete	37 (17)	17 (35)	10 (14)	27 (47)		49 (15)	29 (46)	0 (0)	13 (93)
Biochemical incomplete	40 (18)	13 (27)	11 (15)	7 (12)		62 (19)	8 (13)	1 (50)	0 (0)
Indeterminate	99 (44)	10 (20)	29 (41)	18 (31)		135 (42)	19 (30)	1 (50)	1 (7)
Excellent	47 (21)	9 (18)	21 (30)	6 (10)		76 (24)	7 (11)	0 (0)	0 (0)

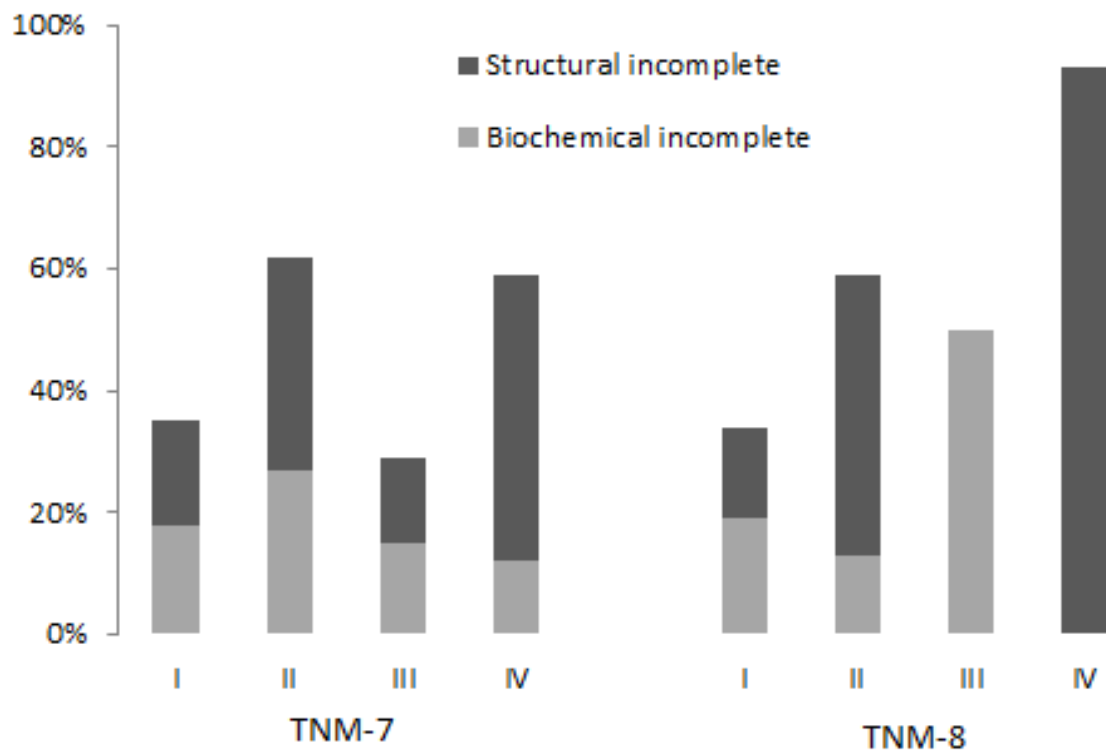
Kappa for TNM-7 vs TNM-8 according to initial treatment response: 0.13 for excellent response ($p = 0.006$); 0.19 for indeterminate response ($p \leq 0.0001$); 0.07 for biochemical incomplete response ($p = 0.26$) and 0.56 for structural incomplete response ($p \leq 0.0001$).

Table 6. Disease outcomes at long-term follow-up according to differentiated thyroid carcinoma staging using the TNM-7 and TNM-8 systems.

Treatment response	TNM-7 Stage					TNM-8 Stage			
	n (%)					n (%)			
	I	II	III	IV		I	II	III	IV
Structural incomplete	18 (8)	12 (24)	12 (16)	24 (42)		27 (8)	27 (42)	0 (0)	12 (86)
Biochemical incomplete	29 (13)	7 (14)	2 (3)	7 (12)		39 (12)	4 (6)	1 (50)	1 (7)
Indeterminate	87 (40)	18 (36)	34 (45)	18 (32)		133 (41)	22 (34)	1 (50)	1 (7)
Excellent	86 (39)	13 (26)	27 (36)	8 (14)		123 (38)	11 (17)	0 (0)	0 (0)

Kappa for TNM-7 vs TNM-8 according to treatment response at long-term follow-up: 0.13 for excellent response ($p \leq 0.001$); 0.13 for indeterminate response ($p \leq 0.001$); 0.26 for biochemical incomplete response ($p = 0.002$) and 0.51 for structural incomplete response ($p \leq 0.0001$).

Figure 1. Differentiated thyroid carcinoma biochemical incomplete and structural incomplete responses to therapy at long term follow-up, according to TNM-7 and TNM-8.



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