



ORIGINAL ARTICLE

Impact of TNM® 8th edition on thyroid cancer retrospective staging

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Abstract

Introduction: Thyroid carcinoma has a global survival close to 97% in 15 years. The 8th TNM® has recently been proposed, with changes that include an increase in the cut-off age from 45 to 55 years, a change in the role of microscopic extra-thyroidal tumor invasion (which is no longer considered a criterion for the classification of T3 tumors), and the presence of cervical metastases as a criterion for staging. As a result, a large proportion of patients are transferred to earlier stages. **Methods:** Retrospective descriptive cross-sectional study carried out through analysis of the medical records of patients undergoing thyroidectomy at HC-UFPR from January 2014 to December 2017. Inclusion criteria were patients with a postoperative pathological anatomic diagnosis of well-differentiated thyroid carcinoma (DTC) who underwent primary surgery in the study period. **Results:** 197 patients underwent thyroidectomy during the period considered, 58 with thyroid neoplasia and 34 with DTC. Eight patients had lymph node metastasis, five (14.70%) as N1a and three (8.83%) as N1b. Of the total sample, six (12.5%) patients presented downstaging from the 7th to the 8th edition of the TNM®. One of the re-staged patients had bone metastasis during follow-up and died during surgery to correct a pathological fracture. **Conclusion:** In this study sample, the update of the TNM® in its 8th edition resulted in the downstaging of six (12.5%) patients with DTC. A longer follow-up and a larger sample are necessary to correctly assess the impact of this change on patient prognosis.

Keywords: thyroid diseases; thyroidectomy; neoplasm staging.

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Introduction

Worldwide, the estimated annual incidence of thyroid cancer is 300,000 cases a year: 230,000 among women and 70,000 among men¹. There are several histological types of thyroid cancer. Among the well-differentiated tumors, the papillary and follicular subtypes stand out, being present in approximately 90% of cases².

Disease prognosis can be assessed by a wide range of risk stratification and staging systems, such as MACIS (distant metastasis, age, completeness of primary tumor resection, local invasion, tumor size), AMES (age, distant metastasis, tumor extent, tumor size), AGES (age, grade, tumor extent, tumor size), and TNM® (tumor, node metastasis, distant metastasis)³. The last system

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was developed in France by Pierre Denoix in 1940, and is currently the most used globally for the treatment, study, and research of malignant neoplasms.

In recent decades, the incidence of thyroid cancer has increased markedly in high-income countries. Despite the large increase in the number of cases, no major change in mortality has been observed⁴. This is because several studies have shown that the increase in incidence was limited to papillary carcinoma - the most frequent and indolent histological form of the tumor, and the thyroid cancer-specific mortality rate has remained stable or declined slightly. An increase in incidence largely confined to the most indolent histological subtype of the tumor in its earlier stages, with no concomitant increase in mortality, suggests overdiagnosis, which is the detection of indolent forms of cancer that will not cause symptoms during a person's lifetime, nor reduce life expectancy. Thus, it became necessary to create less aggressive staging systems aiming to perform less invasive treatments for diseases with a better prognosis.

Typically, patients with well-differentiated thyroid cancer (DTC) present a favorable clinical course, and several classification scores have been defined to correctly identify patients with worse prognoses. Patients with DTC have an excellent prognosis, with an estimated 15-year overall survival close to 97%. In October 2016, the American Joint Committee on Cancer (AJCC) proposed an update to its TNM® cancer staging system, which includes the DTC classification, and it has been introduced in clinical practice since January 2018. This change emerged as a less aggressive staging proposal, in line with the excellent prognoses observed in clinical practice.

The main changes in the updated TNM® 8th edition include a rise in the cut-off age from 45 to 55 years and the division into T3a as tumors >4 cm and T3b as extra-thyroidal extension tumors invading strap muscle; in addition, microscopic extra-thyroidal extension and the presence of lymph node metastases are no longer considered for staging. As a result⁵, a large proportion of patients are transferred to early stages. Using the new classification, patients with advanced disease (stages III and IV) compose an even smaller fraction of thyroid cancer cases. Therefore, patients previously considered to be in advanced disease stages can be treated less aggressively, and are able to undergo surgeries that are less radical and less invasive complementary treatments, such as with no need for use of adjuvant radioactive iodine therapy. This study aimed to evaluate the rate of cases whose clinical staging changed from the 7th to the 8th edition of the TNM® in patients previously treated primarily for DTC at the *Hospital de Clínicas* of the Federal University of Paraná (HC/UFPR).

Materials and methods

This is a retrospective, descriptive, cross-sectional study carried out through analysis of the medical records of patients undergoing thyroidectomy at HC-UFPR between January 2014 and December 2017. All surgery reports of patients submitted to total thyroidectomy were assessed. The reports were selected from the database of the Institution's surgical center, and the complete medical records of 197 patients were obtained and included

in the study sample. The study was approved by the Human Research Ethics Committee (CEP) of HC-UFPR in October 2019 under protocol no. 18878919.0.0000.0096.

The medical records were reviewed and their epidemiological, surgical and outcome data were tabulated in Excel® spreadsheets from Google forms. The following epidemiological data were studied: sex, age, histological type of thyroid cancer, and associated comorbidities. Surgical information included type and year of surgery performed. The patients were followed up at the outpatient clinic and Endocrinology Department of HC-UFPR, and information regarding postoperative laboratory tests (TSH, free T4, and thyroglobulin) was evaluated, as well as the need for adjuvant treatment: radioactive iodine therapy, its dosages, and number of sessions performed.

After tabulation in Excel® spreadsheet, the data were statistically analyzed using the SPSS® 2.0 software. The studied variables are presented as mean and standard deviation. The Kolmogorov-Smirnov test was applied to characterize data distribution. As the data presented parametric distribution, the Student's *t*-test for paired samples was used to compare the numerical variables and the Wilcoxon test was applied to compare the subjective variables. A significance level of 5% ($p < 0.05$) was adopted for all statistical analyses.

Inclusion criteria were patients with a postoperative anatomopathological diagnosis of DTC who underwent total thyroidectomy as primary therapy during the study period. All other patients were excluded from the study.

In the final sample, patients were re-staged according to the TNM® 8th edition, and these data were compared with the results of the 7th edition, which was in force at the time these patients were treated.

Results

Of the 197 patients who underwent total thyroidectomy at the HC-UFPR in the study period, 173 (87.81%) were women and 24 (12.19%) were men. Mean age of patients was 51.47 years (median=52) and mean length of hospital stay was 3.52 days (median=3).

Of the total sample (197), 58 patients presented malignant thyroid neoplasia, but only 34 patients (58.62%) were included in the study because they had an anatomopathological diagnosis of DTC: 29 (85.29%) with papillary carcinoma and five (14.71%) with follicular carcinoma. Regarding the total sample, 63 (31.97%) patients had multinodular colloid goiter, 16 (8.12%) presented follicular adenoma, 12 (6.09%) Hashimoto's disease, two (1.01%) Graves' disease, and one (0.50%) had diffuse large B-cell lymphoma. These data are shown in Figure 1. The other patients presented different results: oncocytic adenoma, follicular hyperplasia, metastasis of poorly-differentiated carcinoma of other location, lymphocytic thyroiditis, and hyperplastic nodular goiter.

Twenty-two patients were excluded from the sample because they were outside the study period and two because they did not undergo surgery as a primary treatment. Of the total number of patients with an anatomopathological diagnosis of DTC according to the TNM® 7th edition staging system, 26 (76.47%)

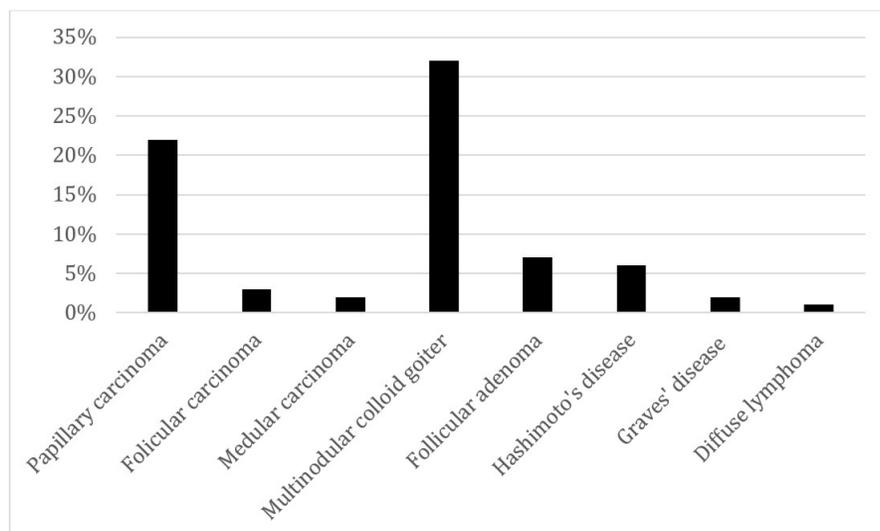


Figure 1. Distribution of the main anatomopathological diagnoses of total thyroidectomy.

were in stage I, one (2.94%) was in stage II, five (14.70%) were in stage II, and two (7.69%) were in stage IV.

Regarding tumor size (classification T of TNM®), considering the 34 evaluated cases that presented a diagnosis of DTC, 29 (85.29%) were women and five (14.71%) were men. Mean tumor size was 2.71 cm. Sizes of the smallest and largest tumors were 0.09 cm and 12 cm, respectively. The mean age of these patients was 44.25 years. As for the presence of lymph node metastasis (classification N of TNM®), 26 (76.47%) patients presented no local invasion, five (14.70%) cases had central lymph node chain metastasis (level VI, N1a), and three (8.83%) patients showed lateral lymph node chain invasion (levels II-V, N1b). There were only two cases of distant metastases (5.88%).

Among all patients with DTC (follicular and papillary), six presented downstaging from the 7th to the 8th edition TNM® - their main characteristics are shown in Table 1. Of these six patients, three were diagnosed with papillary carcinoma (50%) and three with follicular carcinoma (50%), two of latter were presented with the Hurthle cell variant. These patients were aged between 46 and 81 years, with mean age of 63.83 years. There were five (83.83%) women and only one (16.17%) man. At anatomopathological examination, two patients presented microscopic extra-thyroidal extension. In addition, four (66.67%) patients had no lymph node involvement and two (33.33%) presented central lymph node involvement (N1a). None of the six cases had distant metastases.

A comparison between the total sample and the six patients who were downstaged according to the TNM® 8th edition, statistically significant difference was observed between age of patients ($p=0.012$) and mean tumor size ($p=0.026$).

The mean time of outpatient follow-up of patients was 34.29 months - shortest time of 13 months and longest time of 55 months. During follow-up, four (66.66%) patients were referred to radioactive iodine therapy, but one of them did not perform it because he moved abroad in that period. In addition, two

patients underwent only one session of radioactive iodine therapy and one patient underwent three sessions, and the latter presented high thyroglobulin levels (>1000) even after the two initial sessions and, therefore, chose to prolong the treatment. Values of TSH, free T4, and thyroglobulin during follow-up are listed in Table 2.

Of the six patients who were down-staged, two were classified in stage III on the 7th TNM® and were transferred to stage I by the 8th TNM®, one was reclassified from stage III to stage II, one was transferred from stage II to I, and two patients were reclassified from stage III to stage II. Thus, six out of 34 patients with DTC were re-staged, corresponding to 12.5% of the sample.

Table 1. Patients down-staged with the TNM® update.

	TNM® 7 th edition	CS	TNM® 8 th edition	CS	Reason
	TNM		TNM		
Patient 1	T3N0M0	III	T1bN0M0	I	Microscopic invasion
Patient 2	T3N1aM0	III	T3aN1aM0	I	Age
Patient 3	T3N0M0	II	T3aN0M0	I	Age
Patient 4	T3N0M0	III	T3aN0M0	II	Minimal extrathyroidal extension
Patient 5	T3N1aM0	III	T2N1aM0	II	Lymph node metastasis
Patient 6	T3N0M0	III	T3aN0M0	II	Minimal extrathyroidal extension

Captions: TNM: malignant tumor classification; CS: clinical stage.

Table 2. Values of TSH, T4L, and Tg found 3, 6, and 12 months post-operatively.

Patient	A	B	C	D	E	F
TSH – 3m	1.27	0.18	0.07	30	0.455	1.52
TSH – 6m	4.49	0.008	> 100	0.3	41	-
TSH – 12m	3.19	0	63.31	0.01	0.21	0.33
T4F – 3m	1.17	1.6	1.5	< 0.4	1.46	1.2
T4F – 6m	1.13	1.6	< 0.4	1.5	0.46	-
T4F – 12m	1.3	1.58	0.79	1.11	1.5	1.39
Tg – 3m	-	< 0.2	< 0.2	-	107.1	4.6
Tg – 6m	-	< 0.2	< 0.2	0.24	1.1	-
Tg – 12m	261.5	0.2	-	< 0.2	< 0.2	-

Captions: 3m (up to 3 months after surgery), 6m (up to 6 months after surgery), 12m (up to 12 months after surgery), T4F (free T4), Tg (thyroglobulin).

This difference in staging from the 7th to the 8th TNM® showed statistically significant difference between the groups ($p=0.0185$). These data are shown in Table 3.

Table 3. Downstaging of patients with DTC in the comparison between the 7th and 8th editions of the TNM®.

Stage	TNM® 7 th edition		TNM® 8 th edition	
	N	%	N	%
I	26	76.47	29	85.29
II	1	2.94	3	8.82
III	5	14.7	0	0
IV	2	5.89	2	5.89

Captions: N: number of patients.

Since the beginning of follow-up to date, one of the patients died as a result of pulmonary thromboembolism during orthopedic surgery to correct a pathological fracture due to DTC bone metastasis (evolved as M1 during follow-up).

Discussion

DTC, which includes papillary and follicular cancer, comprises the majority (90%) of thyroid cancers, and presents a favorable prognosis. In this study, 90.57% of the patients had DTC: papillary carcinoma (81.14%) and follicular carcinoma (9.43%). However, a minority of these patients presented locoregional recurrence, including cervical lymph node metastases¹. Despite the increased incidence of DTC, no change in the mortality rate was observed, and this may be due to the fact that the increased diagnosis of small tumors may not influence the prognosis¹. The enormous increase in the incidence of small and early stage tumors is leading to a less aggressive therapeutic approach¹.

There is growing evidence that a cut-off age of 45 years has led to over-staging in many DTC patients, and the use of a cut-off age of 55 years in the 8th edition of the TNM® staging system may prevent staging in low-risk patients. This new classification may also provide a more realistic assessment of disease mortality in high-risk patients³. A significant number of patients aged 45-55 years can be reclassified to stage I or II with application of the TNM® 8th edition³. In this study, there was a statistical relationship between age >55 years and presence of malignant disease ($p=0.0422$), indicating that this change in age group may avoid less aggressive therapies in younger patients because of the better prognosis of thyroid cancer at earlier ages.

A recent study conducted in South Korea⁶ showed that, based on the TNM® 7th edition, the number of patients in the T1, T2, T3 and T4 classifications was

534 (33%), 210 (13%), 774 (48%), and 95 (6%), respectively. When the TNM® 8th edition was applied, the number of patients in the T1 and T2 classifications increased to 895 (55%) and 339 (21%), respectively. The 490 patients (30%) classified as T3 were down-staged to T1 (n=361, 22%) and T2 (n=129,8%) according to the TNM® 8th edition. No change in the number of patients classified as T3 and T4 between the TNM® 7th and 8th editions was observed in the study. Applying the TNM® 8th edition, the N classification was changed to N1a in five patients originally classified as N1b according to TNM® 7th edition because of their level VII lymph node metastases. Among the 165 patients with N1b disease according to the TNM® 8th edition, 18 (11%) had only lateral lymph node metastasis, with no central lymph node involvement². Similarly, in this study, three patients were reclassified from stage III to II, two from stage III to I, and one from stage II to I.

A disadvantage of using different prognostic systems is that it hinders the application of study conclusions in populations classified differently, as well as the grouping of data in review and consensus articles or meta-analyses³. The TNM 8th edition maintains the worldwide acceptability of the traditional TNM® staging paradigm, and seems to be satisfactory⁴. Recent studies conducted by independent researchers have shown that the mortality risk conferred by increasing age at diagnosis has log-linear characteristics, becoming much more important with patient aging⁵.

There is a new proposal for the staging of DTC, called TNM-Recursive Partitioning Analysis (RPA), a variation of the TNM®, but which stratifies the prognostic groups according to age group, once the 8th edition of the traditional TNM® only separates into age groups. Using this new reclassification, a study⁵ was carried out with a cohort of 6,342 DTC patients who were followed up for an average of 11.4 years. Groups with higher TNM-RPA were associated with increased risk of death⁵.

Hulse and collaborators⁷ evidenced a lower stage reclassification after the introduction of the 8th edition of the AJCC/UICC® staging system. Using this new classification, patients with advanced disease (stages III and IV) compose a small fraction of thyroid cancers (2%). A significant increase in stage I disease and a substantial reduction in advanced stage disease are expected with re-staging. In total, 119/361 (33%) patients were re-staged when the AJCC/UICC® 8th edition system was applied. The number of patients classified as advanced stage (III/IV) fell from 76 (21%) to eight (2%). Of this total, 3/119 (2.5%) patients who were subsequently down-staged died of metastatic disease⁷. A patient who was down-staged from stage IV to stage II had ambiguous tumor pathology reported as probable metastatic papillary carcinoma, but possible high-grade squamous cell carcinoma. Patients also died only five months after the initial surgery, suggesting the presence of particularly aggressive disease or pre-existing metastases that were not detected in the initial staging⁷. The present study suggests that not only age, but also evidence of lymph node invasion, are related to the long-term prognosis, emphasizing the importance of the new staging system.

Many studies published in the PubMed database have shown the impact of thyroid cancer re-staging brought by the new edition of the TNM®. A previous study⁸ outlined a redistribution from stage III to lower stages, affecting

206 (9.1%) patients. In the present study, there was also a change in the staging of patients from more advanced stages (III and IV) to earlier stages (I and II), reflecting their low risk of death related to thyroid cancer, with statistical significance ($p=0.0185$).

A study conducted by van Velsen et al.⁹ assessed 792 patients with DTC (79% papillary and 21% follicular) with mean age of 49 years. Mean follow-up was 7.2 years. A reclassification was performed using the TNM® 8th edition, which resulted in the downstaging of 282 (36%) patients, an increase in the number of patients in stages I and II, and an equivalent decrease in the number of patients in stages III and IV. In the present study, downstaging occurred in six of the 34 cases of DTC (12.5%). This lower proportion compared with that reported in the literature may have occurred as a result of the smaller sample size, the probably younger age of the participants, and of the fact that this study was not carried out in a specific cancer reference center.

A study conducted in Italy¹ with T1-T3 patients (n=84) showed that the decrease in the number of patients, according to the TNM® 8th edition, does not necessarily reflect a less aggressive disease: two lymph node recurrences (40%) were reported in the five patients who were down-staged from pT3 to pT2, with the lymph node recurrence rate for stage I increasing from 0% with application of the 7th edition of the TNM® to 5.3% with application of its 8th edition¹. Similarly, in this study, one of the patients who was down-staged developed bone metastasis during follow-up and died from pulmonary thromboembolism during surgery to correct a pathological fracture.

The main limitation of this study is its small sample size. A longer follow-up and a larger sample are needed to correctly assess the impact of this change on patient prognosis.

Conclusion

The update of the TNM® in its 8th edition resulted in the downstaging of six of the 34 (12.5%) patients with DTC in the present sample. This result is slightly lower than that found in the literature, probably because of the reduced sample size and the younger age of the participants.

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