RESEARCH

TNM 8th edition in thyroid cancer staging: is there an improvement in predicting recurrence?

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Abstract

TNM 8th edition introduces changes in the staging of patients with differentiated thyroid carcinoma (DTC). This study aims at assessing the value of TNM 8th edition in predicting response to therapy and structural recurrence of DTC. Four hundred and eighty DTC patients were retrospectively evaluated by 7th and 8th editions of TNM staging system in relationship with risk stratification, response to therapy and recurrence of disease as defined by 2015 ATA guidelines. As compared to the 7th edition, TNM 8th led to downstage 136 patients (28.3%), with 97.5% of patients falling into lower stages (I–II) and only 2.5% remaining in higher stages (III–IV) ($P < 0.001$). Patients who were downstaged in stages I–II by TNM 8th were classified more frequently at intermediate-high risk ($P < 0.001$), had more frequently structural incomplete response to therapy ($P = 0.009$) and had higher risk of structural recurrence ($P = 0.002$) as compared to patients who were in the same TNM stages but were not downstaged. Specifically, the risk of structural recurrence was significantly higher in patients in whom the downstaging was induced by changes in tumour classification (hazard ratio (HR) 6.18, 95% CI 2.20–17.40; $P = 0.001$) but not in those who were downstaged for the increase in age cut-off (HR 2.80, 95% CI 0.86–9.19; $P = 0.09$). In conclusion, TNM 8th edition did not show reliability in predicting aggressiveness of DTC. In fact, the downstaging of DTC patients especially when performed due to changes in tumour classification may overlook patients predisposed to structural recurrence, potentially causing uncertainty in the therapeutic decision-making at the time of disease's diagnosis.

Key Words

- differentiated thyroid cancer
- TNM staging
- response to therapy
- ATA risk stratification
- recurrence

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Introduction

Differentiated thyroid carcinoma (DTC) represents about 90% of all thyroid cancers and is the most frequent endocrine tumour. Although incidence of DTC has been rising steadily in most areas of the world over the last few decades, mortality has changed minimally, mainly as a result of increased use of diagnostic

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imaging and surveillance (Haugen *et al.* 2016, Amin *et al.* 2017, Schmidbauer *et al.* 2017, Pacini *et al.* 2018). Facing the important increase in incidence and stable mortality of thyroid carcinoma, the 8th edition of the AJCC (American Joint Commission on Cancer)/ TNM (Tumor Node Metastasis) manual, released in 2017, brings about important changes in the staging of patients with DTC. The main changes include an increase of the age threshold from 45 to 55 years to define patients with high risk of thyroid cancer-related death and a decrease in the negative prognostic value given to histopathological findings such as lymph node metastases and microscopic extrathyroidal extension (ETE). In fact, microscopic ETE was removed from the definition of T3 disease. These changes were proposed in order to increase the specificity and positive predictive value of TNM staging system in identifying patients with poor prognosis and low disease-specific and overall survival (Amin *et al.* 2017).

TNM staging is certainly useful in predicting disease mortality (Kim *et al.* 2017*a*,*c*, 2018*b*, Tam *et al.* 2018) and it is recommended for all DTC patients (Haugen *et al.* 2016). Since an objective of the staging systems is to guide the clinician in the planning of treatment (Brierley *et al.* 2017), one could argue that this planning cannot be solely based on the disease-related mortality that is relatively low in patients with DTC. However, the risk of recurrence is not negligible in DTC and many patients require repetitive treatments over the years, with a high clinical burden (Schmidbauer *et al.* 2017). Therefore, since disease-free survival has become a widely accepted endpoint for development of drugs and treatment procedures (Fiteni *et al.* 2014), it is reasonable to hypothesize that it may be valid also for the staging system like TNM. The current American Thyroid Association (ATA) guidelines proposed a risk stratification system and response to therapy categories with the intent to identify more aggressive tumours and to predict recurrence of disease in DTC patients (Haugen *et al.* 2016). Although the TNM is one of the major players for the classification of the ATA risk level, it is still unclear whether the new edition of TNM staging system may provide some information to predict the aggressiveness of DTC in addition to mortality (Lamartina *et al.* 2018, Nam *et al.* 2018, Nava *et al.* 2019).

Therefore, in this retrospective-longitudinal study we aimed at assessing a new possible role to the 8th edition of TNM staging system in predicting the response to therapy and recurrence of DTC.

Materials and methods

Study group

This study was carried out in two tertiary care Endocrine Units of Milan, Italy (Humanitas Research Center, IRCCS and IRCCS Ca' Granda Ospedale Maggiore Policlinico). This multicenter retrospective observational study was approved by Humanitas Clinical and Research Center and IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethical Committees, a written consent was not needed due to the observational and retrospective nature of the study.

The inclusion criteria were: (1) age >18 years, (2) histological diagnosis of DTC, (3) ≥6 months-follow-up post-thyroid surgery, and (4) availability of clinical data used by the TNM staging systems (Edge *et al.* 2010, Amin *et al.* 2017) and ATA classification of DTC (Haugen *et al.* 2016). Exclusion criteria were: (1) presence of concomitant non-thyroid cancers and (2) foci of poorly differentiated carcinoma at histology of thyroid specimens. From the internal databases, we retrospectively evaluated 503 patients with a diagnosis of DTC, who underwent thyroid surgery in the aforementioned Institutions from March 1980 to June 2018. Medical charts were reviewed and the following clinical variables were collected for each patient: sex, age at diagnosis, type of surgery, histopathologic findings (including histotype, tumour size, presence of angioinvasion, and extrathyroidal extension), duration of follow-up, and TNM staging (7th and 8th edition). The ATA risk stratification (low, intermediate, and high) and ATA response to initial therapy categories (excellent, indeterminate, biochemical incomplete, and structural incomplete) were retrospectively evaluated on the basis of available data.

Patients were followed up according to current guidelines at the time of clinical evaluations and then retrospectively stratified according to the latest ATA guidelines (Haugen *et al.* 2016). Biochemical evaluation of basal thyroglobulin (Tg), stimulated Tg postoperatively, and anti-Tg antibodies associated with neck ultrasound were carried out in all patients during the follow-up. In specific cases, other radiological tests (CT, PET, magnetic resonance, and bone scan) were performed.

Out of the 503 patients treated for DTC at our institutions, 480 DTC patients met the inclusion criteria and were included in the study. The median follow-up was 59 months (range 6–441). The clinical and pathological characteristics of the sample are summarized in Table 1. All patients were staged by the 7th and 8th edition of the TNM systems and results were compared each other

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Table 1 Clinical and histopathological characteristics of the study group.

	Characteristics	Patients (n)/value
Patient characteristics	Total	480
	Female (%)	364 (75.8)
	Male (%)	116 (24.2)
	Mean age at diagnosis (S.D.)	49 (±14)
	Median follow up, months (range)	59 (6–441)
Histopathological findings	Histology:	
	Papillary (%)	438 (91.2)
	Follicular (%)	33 (6.9)
	Papillary and follicular (%)	9 (1.9)
	Median tumour diameter, mm (range)	12 (1–100)
	Angioinvasion (%)	83 (17.3)
	Minimal extrathyroid extension (%)	78 (16.3)
	Gross extrathyroid extension (%)	16 (3.3)
	Lymph node metastases, N1 (%)	115 (24)
	Distant metastases, M1 (%)	5 (1)
Treatment	Surgical:	
	Total/near-total thyroidectomy (%)	454 (94.6)
	Lobectomy (%)	26 (5.4)
	Neck dissection (%)	182 (38)
	Post-surgical:	
	Radioiodine ablation (%)	322 (67.1)
	Median first dose, MBq (range)	2960 (1110–7740)
	Repeat radioiodine ablation (%)	40 (12.4)
	Median cumulative dose, MBq (range)	2960 (1110–28,090)
	Reoperation (%)	29 (6)
	Second line treatments (%)	10 (2.1)
Follow-up	Relapses (%)	41 (9.2)
	Deaths from thyroid cancer (%)	0 (0)
Initial ATA risk stratification	Low risk (%)	251 (52.3)
	Intermediate risk (%)	196 (40.8)
	High risk (%)	33 (6.9)
ATA response to therapy	Excellent response (%)	444 (92.5)
	Biochemical incomplete response (%)	8 (1.7)
	Structural incomplete response (%)	13 (2.7)
	Indeterminate response (%)	15 (3.1)

and were related with the risk stratification, response to therapy, and recurrence of disease as defined by the 2015 ATA guidelines.

The primary end-point was to assess the ability of 8th edition of TNM staging system in predicting structural recurrences in patients with DTC. The secondary end-points were: (1) to assess the correlation between TNM 8th edition and response to therapy, (2) to assess the correlation between TNM 8th edition and ATA risk stratification, and (3) to compare the 7th and 8th editions of TNM.

TNM staging systems

Each DTC patient was staged according to the 7th and 8th editions of AJCC/TNM as stage I, II, III, or IV (Edge *et al.* 2010, Amin *et al.* 2017). The criteria to define the stage in TNM 7th and TNM 8th edition are summarized in Table 2 (Lamartina *et al.* 2018).

ATA initial risk stratification and response to therapy categories

Based on clinical, histological, and molecular characteristics of DTC, each patient was classified according to the Initial Risk Stratification System proposed by 2015 ATA guidelines into three risk categories: low, intermediate, and high (Haugen *et al.* 2016).

The response to initial therapy in patients treated with total thyroidectomy and radioiodine remnant ablation was classified and continually assessed during follow-up, according to ATA guidelines (Haugen *et al.* 2016) as follows: (1) excellent response without evidence of clinical, biochemical (suppressed Tg <0.2 ng/mL or stimulated Tg <1 ng/mL, negative anti-Tg antibodies), or structural disease; (2) indeterminate response with nonspecific biochemical (suppressed Tg detectable, but <1 ng/mL or stimulated Tg detectable, but <10 ng/mL, declining or stable anti-Tg antibodies) or structural

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Table 2 Comparison of the 7th and 8th editions of TNM staging system.

7th edition Age <45 years				**8th edition Age <55 years**			
I	**Any T**	**Any N**	**M0**	**I**	**Any T**	**Any N**	**M0**
II	**Any T**	**Any N**	**M1**	**II**	**Any T**	**Any N**	**M1**
7th edition Age ≥45 years				**8th edition Age ≥55 years**			
I	Tumour ≤2 cm limited to the thyroid (**T1**)	**Nx/N0**	**M0**	**I**	Tumour ≤4 cm limited to the thyroid (**T1/T2**)	**Nx/N0**	**M0**
II	Tumour ≤4 cm limited to the thyroid (**T2**)	**Nx/N0**	**M0**	**II**	Tumour >4 cm (**T3a**) *or* with gross ETE invading only strap muscles (omohyoid, sternohyoid, sterno-thyroid, thyrohyoid) (**T3b**) *or* Any T with lymph node metastases (**N1**)		**M0**
III	Any T with lymph node metastases of central compartment (**N1a**) *or* with minimal ETE (**T3**) with or without lymph node metastases of the central compartment		**M0**	**III**	Any T with gross ETE invading subcuta-neous soft tissues, larynx, trachea, oesophagus or RLN (**T4a**)	**Any N**	**M0**
IVa	Any T with lymph node metastases of lateral compartment (**N1b**) *or* with gross ETE invading sub-cutaneous soft tissues, larynx, trachea, oesophagus, or RLN (**T4a**) with or without lymph node metastases		**M0**	**IVa**	Any T with gross ETE invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (**T4b**)	**Any N**	**M0**
IVb	Any T with gross ETE invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (**T4b**)	**Any N**	**M0**	**IVb**	**Any T**	**Any N**	**M1**
IVc	**Any T**	**Any N**	**M1**	-	-	-	-

ETE, extrathyroidal extension; RLN, recurrent laryngeal nerve.

findings; (3) biochemical incomplete response (suppressed Tg ≥1 ng/mL or stimulated Tg ≥10 ng/mL or abnormal Tg or rising anti-Tg antibodies) in the absence of localizable disease; and (4) structural incomplete response with evidence of persistent or new loco-regional or distant metastases. The response to initial therapy in patients treated with total thyroidectomy without radioiodine remnant ablation was defined as follows: (1) excellent response without evidence of clinical, biochemical (suppressed Tg <0.2 ng/mL or stimulated Tg <2 ng/mL, negative anti-Tg antibodies), or structural disease; (2) indeterminate response with nonspecific biochemical (suppressed Tg 0.2–5 ng/mL or stimulated Tg 2–10 ng/mL, declining or stable anti-Tg antibodies) or structural findings; (3) biochemical incomplete response (suppressed Tg >5 ng/mL or stimulated Tg >10 ng/mL or increasing Tg values with stable TSH levels or rising anti-Tg antibodies) in the absence of localizable disease; and (4) structural incomplete response with evidence of persistent or new loco-regional or distant metastases (Momesso & Tuttle 2014, Momesso *et al*. 2016). The response to initial therapy in patients treated with lobectomy alone was classified as follows: (1) excellent response without evidence of clinical, biochemical (suppressed Tg <30 ng/mL, negative anti-Tg antibodies), or structural disease; (2) indeterminate response with declining or stable anti-Tg antibodies) without structural and functional disease or nonspecific structural findings in imaging studies; (3) biochemical incomplete response with suppressed Tg >30 ng/mL, increasing Tg values with stable TSH level, or rising anti-Tg antibodies in the absence of localizable disease; and (4) structural incomplete response with evidence of persistent or new loco-regional or distant metastases (Momesso & Tuttle 2014, Momesso *et al*. 2016).

For the assessment of response to therapy, patients were firstly evaluated 6 months after the initial therapy and then monitored every 6–12 months during the follow-up. Patients with incomplete or indeterminate disease at the first clinical evaluation were monitored until an excellent response was achieved or a second treatment was performed. Patients who had initial incomplete or indeterminate response to therapy and did not achieve excellent response, as well as those undergoing a second treatment of DTC, were classified as having persistent disease.

Definition of recurrences

Only patients with excellent response (Haugen *et al*. 2016) were eligible for evaluation of disease recurrence, which was defined as a new appearance of disease after more than 12 months of follow-up. Biochemical recurrence was diagnosed in patients with elevated Tg (suppressed or stimulated) and/or appearance or progressive increase

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of anti-Tg antibodies levels without structural findings, in accordance to the surgical and radioablative treatment received, as previously mentioned. Structural recurrences were defined by the following conditions: (1) presence of suspicious lymph nodes in the central or lateral neck compartments or suspicious tissue in the thyroid bed confirmed by fine-needle aspiration biopsy and (2) positive findings on radioactive iodine (RAI) scans, 18F-FDG-PET scans, or other imaging suspicious for metastatic disease with or without histological/cytological confirmation. In order to avoid potential pitfalls in the retrospective analysis of data supporting the definition of biochemical recurrences, structural recurrences were considered as first end-point of the study.

Statistical analysis

Data were described as number and percentage if categorical or mean and if continuous. An independent *t*-test was used to evaluate the differences between the means of groups. Comparisons between groups were made with Chi-Square test or Fisher's Exact test, as appropriate. When these comparisons were multiple, Bonferroni's correction was performed. Logistic regression analysis was performed, and the odds ratios (OR) along with 95% confidence intervals (95% CI) were calculated, to evaluate the determinants of excellent response to therapy. Disease-free survival time was calculated from first RAI therapy (or date of surgery for patients who did not undergo RAI therapy) to first recurrence date, defined as the presence of structural disease, or last visit date for not recurrent patients. The determinants of disease-free survival were sought using the Cox regression analysis with calculation of the hazard ratios (HR) and 95% CI. A P value of <0.05 was considered as significant. All analyses were made with Stata13 and INSTAT GraphPad Prism 5.0 software.

Results

TNM staging

According to the 7th edition of TNM, the distribution of patients was as follows: 70.0%, 7.3%, 14.4%, and 8.3% in stage I, stage II, stage III, and stage IV, respectively. By restaging the same patients according to the 8th edition of TNM, the distribution changed to 89.2%, 8.3%, 0.8%, and 1.7% for stages I, II, III and IV, respectively ($P < 0.001$ vs TNM 7th), thus with downstaging of 136 patients (28.3%) (Fig. 1). Specifically, using the TNM 8th edition, 92 patients were downstaged to stage I (35 from stage II, 42 from stage III, and 15 from stage IV), 40 to stage II (27 from stage III and 13 from stage IV), and 4 patients were downstaged from stage IV to stage III. In 66 patients (48.5%), the downstaging was caused by the increase in the age cut-off (63 cases in stage I and 3 in stage II), whereas the remaining 70 patients (51.5%) were downstaged due to changes in criteria of tumour classification (29 cases in stage I, 37 in stage II, and 4 in stage III).

ATA risk stratification and TNM staging

In the whole group, according to the ATA risk stratification, 251 patients (52.3%) fell into the low-risk category, 196 (40.8%) into the intermediate category, and 33 patients (6.9%) into the high-risk category. Applying the TNM 7th staging system, the prevalence of intermediate-high ATA risk was significantly higher in stages III and IV as

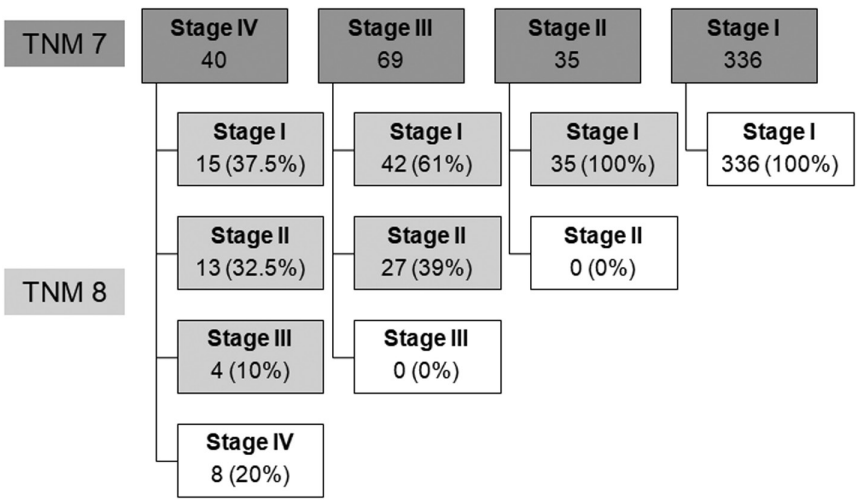

Figure 1
Redistribution of patients among stages, when switching from TNM 7th to TNM 8th. The gray boxes included the downstaged patients.

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compared to stages I and II ($P<0.001$), without significant differences between stages I and II and between stages III and IV (Fig. 2A). Applying the TNM 8th staging system, the prevalence of intermediate-high ATA risk was higher in stages II, III, and IV as compared to the stage I (Fig. 2B).

Restricting the analysis to the patients who were classified in the lowest stages (i.e. stages I–II) by TNM 8th edition, the prevalence of intermediate-high risk ATA category was significantly higher in patients who were downstaged as compared to those who were not downstaged (80.3% vs 33.1%; $P<0.001$). The prevalence of intermediate-high ATA risk category was not significantly different between downstaged patients for increase in the age cut-off and those in whom the downstaging was caused by changes in criteria of tumour classification (77.3 vs 83.3%; $P=0.38$).

Response to therapy and TNM staging

Six months after the initial therapy, according to the ATA's criteria of response to therapy, 348 patients (72.5%) showed an excellent response, 59 patients (12.3%) an indeterminate response, 45 patients (9.4%) a biochemical incomplete response, and 28 patients (5.8%) had a structural incomplete response. During the follow-up, other 96 patients achieved excellent response (overall 444 cases, 92.5%), whereas 36 patients had persistent disease (8 cases with biochemical incomplete response, 13 cases with structural incomplete response, and 15 cases with indeterminate response). The percentage of excellent biochemical response was significantly lower in patients classified in the intermediate-high ATA risk category as compared to those in the low-risk ATA category (89.5% vs 95.2%; $P=0.02$). Applying the TNM 7th staging system, the excellent response was less frequent in patients with stage IV as compared to the other stages, without significant differences among stages I, II, and III (Fig. 3A). Applying the TNM 8th staging system, the rate of excellent response was significantly higher in stage I as compared to stage IV, without significant differences among stages II and III (Fig. 3B). In the multivariate logistic regression analyses, excellent response maintained the significant association with TNM 8th, but not with TNM 7th and ATA stratification risk (Table 3). Similar results were obtained when the

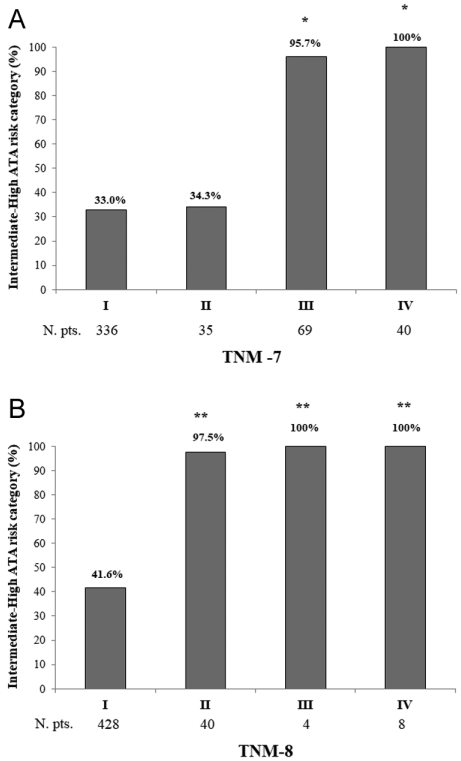

Figure 2
Distribution of intermediate-high ATA risk categories in different stages by TNM 7th (A) and TNM 8th (B) systems. The number of patients within each group was specified underneath the bars. *$P<0.001$ vs TNM 7th stages I and II; **$P<0.001$ vs TNM 8th stage I.

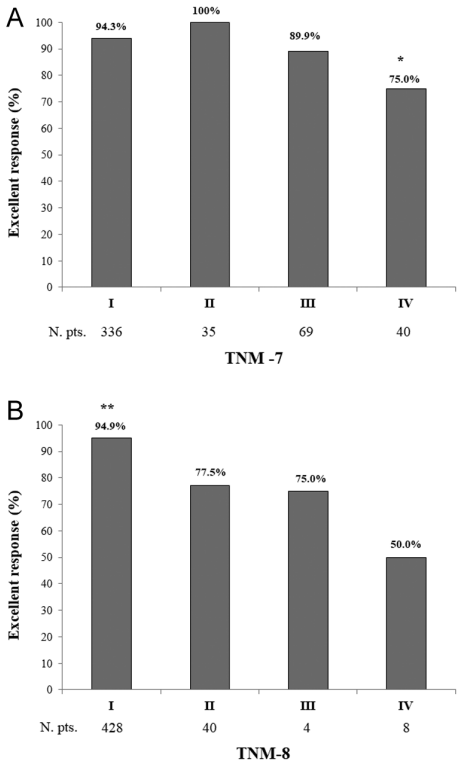

Figure 3
Distribution of excellent response to therapy in different stages by TNM 7th (A) and TNM 8th (B) systems. The number of patients within each group was specified underneath the bars. *$P<0.001$ vs TNM 7th stages I, II and III; **$P<0.001$ vs TNM 8th stage IV.

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Table 3 Results of univariate and multivariate logistic regression analyses evaluating the determinants of excellent response to therapy.

	Whole population (480 cases)		
	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)	
		Model#1	Model#2
Age	0.98 (0.96–1.01; *P*=0.12)	-	-
Sex (males vs females)	1.87 (0.91–3.82; *P*=0.09)	-	-
ATA risk stratification (intermediate-high risk vs low risk)	0.42 (0.25–0.69; *P*=0.01)	0.60 (0.31–1.16; *P*=0.13)	0.77 (0.39–1.48; *P*=0.43)
TNM-7th staging system	0.59 (0.45–0.79; *P*<0.001)	0.71 (0.31–1.16; *P*=0.07)	-
TNM-8th staging system	0.34 (0.22–0.52; *P*<0.001)	-	0.39 (0.23–0.69; *P*=0.001)
	Patients in stages I–II by TNM-8th (468 cases)		
	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)	
		Model#1	Model#2
Age	0.99 (0.97–1.012; *P*=0.58)	-	-
Sex (males vs females)	1.58 (0.72–3.47; *P*=0.25)	-	-
ATA risk stratification (intermediate-high risk vs low risk)	0.56 (0.31–0.99; *P*=0.05)	0.75 (0.36–1.55; *P*=0.44)	0.79 (0.40–1.55; *P*=0.48)
TNM-7th (III–IV vs I–II stages)	0.38 (0.18–0.82; *P*=0.01)	0.47 (0.19–1.20; *P*=0.11)	-
TNM-8th (II vs I stage)	0.19 (0.08–0.44; *P*<0.001)	-	0.22 (0.08–0.57; *P*=0.002)

Model#1: TNM-7th and ATA risk stratification; Model#2: TNM-8th and ATA risk stratification.

patients were classified in a two-tiered staging system (i.e. TNM 7th/8th stages I–II vs TNM 7th/8th stages III–IV) and the regression analyses were restricted in the subgroup of patients (*468 cases*) with the stages I–II according to TNM 8th (Table 3). The multivariate logistic analyses performed in this subgroup of patients showed that only TNM 8th (i.e. stages I vs stage II) was associated with excellent response to therapy, whereas neither TNM 7th (stage I–II vs II-IV) nor the ATA risk stratification (intermediate-high risk vs low risk) maintained the significant associations found in the univariate analysis. Moreover, in patients with stages I–II defined by TNM 8th edition, the prevalence of persistent disease with biochemical and structural incomplete response was significantly higher in downstaged cases as compared to those who were not downstaged (6.8% vs 2.1%; *P*=0.009). The percentage of persistent disease with incomplete response (either biochemical or structural) was comparable between downstaged patients for increase in the age cut-off and those in whom the downstaging was caused by changes in criteria of tumour classification (7.6% vs 6.0%; *P*=0.92).

Disease recurrence and TNM staging

The analysis of recurrence was performed in 444 patients who had achieved excellent response after treatment of DTC. During the follow-up, 41 patients (9.2%) experienced a recurrence of DTC: biochemical recurrence in 19 patients and structural recurrence in 22 patients (lymph nodes alone in 18 cases and distant metastases in 4 cases). In the univariate Cox analysis, structural recurrences were predicted by ATA risk stratification and both TNM staging systems (Table 4). In the multivariate Cox regression analyses, risk of structural recurrence was predicted only ATA risk stratification, whereas the associations with TNM staging systems were lost (Table 4). However, when the patients were classified in a two-tiered staging system (i.e. TNM 7th/8th stages I–II vs TNM 7th/8th stages III–IV) and the regression analyses were restricted in the subgroup of patients (468 cases) with the TNM 8th stages I–II, both TNM 8th (i.e. stages II vs stage I) and higher ATA risk categories (intermediate-high risk vs low risk) maintained the significant correlations with structural recurrences (Table 4). Moreover, in the TNM 8th stages I and II, the risk of structural recurrences was higher in downstaged patients as compared to those who were not downstaged (HR 4.23, 95% CI 1.71–10.42; *P*=0.002). Specifically, the risk of structural recurrence was statistically significant in patients in whom the downstaging was induced by changes in tumour classification (HR 6.18, 95% CI 2.20–17.40; *P*=0.001), but not in those who were downstaged due to increase in age cut-off (HR 2.80, 95% CI 0.86–9.19; *P*=0.09) (Fig. 4).

Discussion

In this retrospective study, patients who were downstaged by TNM 8th were classified more frequently as intermediate-high ATA risk, more frequently had persistent disease,

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Table 4 Results of univariate and multivariate Cox analyses evaluating the determinants of structural recurrences.

	Whole population (480 cases)		
	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)	
		Model#1	Model#2
Age	1.01 (0.98–1.04; *P*=0.55)	-	-
Sex (males vs females)	0.78 (0.28–2.14; *P*=0.63)	-	-
ATA risk stratification (intermediate-high risk vs low risk)	2.93 (1.62–5.29; *P*<0.001)	2.28 (1.04–4.99; *P*=0.04)	2.68 (1.33–5.38; *P*=0.006)
TNM-7th staging system	1.72 (1.23–2.39; *P*=0.001)	1.24 (0.80–1.93; *P*=0.32)	-
TNM-8th staging system	2.03 (1.22–3.38; *P*=0.006)	-	1.17 (0.62–2.19; *P*=0.62)
	Patients in stages I–II by TNM-8th (468 cases)		
	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)	
		Model#1	Model#2
Age	1.00 (0.97–1.04; *P*=0.74)		
Sex (males vs females)	0.75 (0.27–2.07; *P*=0.58)		
ATA risk stratification (intermediate-high risk vs low risk)	3.42 (1.76–6.64; *P*<0.001)	2.41 (1.08–5.38; *P*=0.03)	2.70 (1.32–5.52; *P*=0.006)
TNM-7th (III–IV vs I–II stages)	5.27 (2.11–13.16; *P*<0.001)	2.76 (0.95–7.98; *P*=0.06)	-
TNM-8th (II vs I stage)	8.29 (3.09–22.19; *P*<0.001)		4.82 (1.69–13.72; *P*=0.003)

Model#1: TNM-7th and ATA risk stratification; Model#2: TNM-8th and ATA risk stratification.

and showed higher risk of structural recurrence when compared to patients who were in the same TNM stages but not downstaged. The risk of structural recurrence was particularly higher in patients in whom the downstaging was induced by changes in tumour classification. Interestingly, patients in the TNM 8th stage II showed lower probability of excellent response and higher risk of structural recurrences as compared to patients with stage I.

The 8th edition of TNM staging system brought a series of changes in the management of DTC in order to appropriately identify patients at higher risk of disease-specific death (Kim *et al.* 2017*c*) and classify patients into the lower stages as being at low risk of dying (Kim *et al.* 2017*a*,*c*). In agreement with previous studies (Pontius *et al.* 2017, Kim *et al.* 2018*a*, Lamartina *et al.* 2018, Shteinshnaider *et al.* 2018, Tam *et al.* 2018), TNM 8th resulted in the downstaging of 28.3% of our patients. Noteworthy, similar to other experiences (Ganly *et al.* 2015, Kim *et al.* 2017*b*, 2018*a*), the restaging left only 2.5% of patients in the highest stages (III–IV), with respect to 22.7% in the previous edition. The increase in age threshold to 55 years at diagnosis, a decrease in the negative prognostic value given to lymph node metastases, and the removal of microscopic ETE from the definition of T3 disease were the variables responsible for the downstaging of DTC patients by TNM 8th edition (Amin *et al.* 2017). Different from previous reports (Pontius *et al.* 2017), in our study there was an equilibrium between the variables responsible for the downstaging of DTC patients, making it possible to discriminate for the first time between the impact of decrease in age cut-off and that of change in tumour classification on predicting response to therapy and recurrence of disease.

The TNM staging system was designed to predict mortality but not recurrence. As a matter of fact, the risk of death in DTC patients does not effectively reflect the risk of recurrence (Tuttle *et al.* 2010, Vaisman *et al.* 2012), a much more frequent event with respect to the extremely low disease-specific mortality (i.e. only 2–4%) (Haugen *et al.* 2016). For this reason, ATA guidelines proposed evaluation of the initial risk stratification subdividing

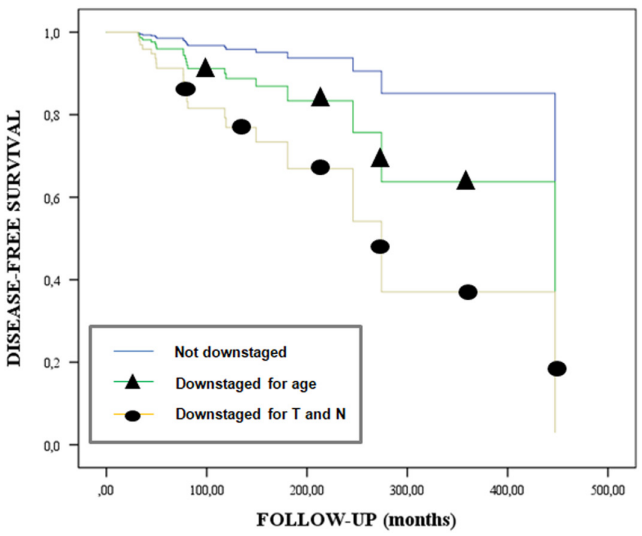

Figure 4
Disease-free survival (DFS) in patients re-classified in the TNM 8th stages I–II and stratified for the downstaging. A full color version of this figure is available at https://doi.org/10.1530/ERC-19-0412.

DTC patients into low, intermediate, and high-risk categories. Our study confirmed that ATA risk stratification was the main predictor of recurrence in DTC patients as compared to TNM staging systems. Indeed, the ATA risk classification is based on several clinicopathological and molecular findings, not all of which are contemplated in the TNM staging system (Tuttle *et al.* 2010, Haugen *et al.* 2016). In our study, the application of TNM 8th led to an increase in the number of patients classified as intermediate-high ATA risk in the lowest TNM stages. Specifically, the percentage of intermediate-high risk was higher in downstaged patients as compared to those who were not downstaged. This finding supports the working hypothesis that the downstaging of DTC patients by TNM 8th may underestimate the risk of recurrence, consistently with the concept that ATA risk stratification is an useful tool for predicting disease recurrence (Tuttle *et al.* 2010, Vaisman *et al.* 2012, Lee *et al.* 2017).

The risk of recurrence in DTC patients not only correlates with the initial ATA risk stratification, but it also depends on the response to initial therapy (Tuttle *et al.* 2010). In fact, the ATA risk stratification system is considered as a static parameter and only the integration of ATA risk with the patient's response to therapy provides a dynamic risk assessment which may change continuously during the follow-up and accurately predict the risk of relapse of DTC (Tuttle & Leboeuf 2008, Tuttle *et al.* 2010, Castagna *et al.* 2011, Haugen *et al.* 2016). Applying TNM 8th, the percentage of excellent response was higher in patients falling into stage I, whereas patients in stage II did not show significant differences as compared to the highest stages. As a matter of fact, the downstaged patients by TNM 8th more frequently showed an incomplete response to therapy as compared to patients who were not downstaged.

Although DTC is frequently an indolent disease, the rate of relapse is up to 30% and distant metastases occur in about 10% of DTC patients during follow-up (Sampson *et al.* 2007, Schmidbauer *et al.* 2017). Recurrences affect prognosis of DTC patients with a mortality that reaches about 11% in patients with a loco-regional recurrence and incomplete response to additional treatment and up to 55% in patients with identifiable distant metastases (Sugitani *et al.* 2008, Haugen *et al.* 2016). In our study group, about 9% of patients experienced recurrence of DTC, during a median follow-up of 59 months: 54% of patients with structural recurrence and the remaining 46% of patients with biochemical recurrence. Different from previous experiences (Nam *et al.* 2018), in our patients, TNM 8th did not improve the prediction of recurrence, since several patients with aggressive disease were re-classified into lower stages (Shteinshnaider *et al.* 2018, Verburg *et al.* 2018). Noteworthy, when the analyses were performed in the early-stage DTC according to the TNM 8th edition, the risk of structural recurrences resulted to be higher in patients with stage II as compared to those in stage I. This finding suggests that the downstaging of patients with aggressive disease by the TNM 8th occurred predominantly in the stage II. Interestingly, the risk of recurrence was higher mainly in patients whose downstaging was induced by changes in tumour classification as compared to those who were downstaged due to the increase in age cut-off. One could argue that this result may reflect the potential negative impact of microscopic ETE on the outcome of DTC (Amin *et al.* 2017), even though data on this issue are still a matter of controversy (Ito *et al.* 2006*a*,*b*, Sugitani *et al.* 2008, Shin *et al.* 2013, Santos & Bugalho 2016, Al-Qurayshi *et al.* 2017, Youngwirth *et al.* 2017, Kim *et al.* 2018*b*, Tran *et al.* 2018). However, the risk of recurrence in the presence of microscopic ETE is not negligible as highlighted in the ATA guidelines in which microscopic ETE is considered a criterion for classifying patients at intermediate risk of recurrence and candidates for post-surgical radioiodine ablation (Haugen *et al.* 2016). Moreover, results of a metanalysis reported that microscopic ETE may have a negative impact on the prognosis of patients with papillary thyroid carcinoma, especially in patients with larger tumour size and higher presence of lymph node metastases (Yin *et al.* 2016). Similarly, in a recent study, microscopic ETE was considered an unfavourable prognostic factor in larger tumours without lymph node metastases at diagnosis (Castagna *et al.* 2018). Therefore, the negative value of microscopic ETE can explain our increased risk of recurrences in downstaged patients for tumour classification using TNM 8th edition. These data further justify the proposal for a subcategorization of T categories on the basis of presence or absence of microscopic ETE in order to guide the management of DTC patients (Schmid *et al.* 2019). Another change in tumour classification is correlated to the decrease in the negative prognostic value given to lymph node metastases. In the latest TNM, the decrease in the unfavourable prognostic significance attributed to cervical lymph node metastases in patients ≥55 years and the lack of distinction between N1a and N1b were responsible for the downstaging of many patients (Edge *et al.* 2010, Amin *et al.* 2017). This has been questioned by several authors, concerned that

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TNM 8th may underestimate disease severity in older patients (Kim *et al.* 2018*a*,*c*). In fact, the presence and location of metastatic lymph nodes may affect the prognosis of DTC patients and increase the risk of recurrence (Adam *et al.* 2015, Kim *et al.* 2018*b*). These changes can explain our increased rate of recurrence in lower stages of TNM 8th and support the proposal to amend TNM staging system by re-evaluating lymph node involvement, in order to not underestimate relapses and mortality in this setting (Kim *et al.* 2018*c*).

Our study had some limitations; due to the small size of our sample and the lack of disease-specific mortality events, we were not able to evaluate overall survival and disease-specific survival, but we were able to evaluate disease-free survival. Another limitation is linked to the lack of information on the number and size of the removed lymph nodes, which could make the ATA risk stratification less accurate. Moreover, molecular characterization of tumours that had potential effects in the stratification of risk of recurrences was not available in our study group (Haugen *et al.* 2016). The retrospective design of our study did not allow to evaluate the real impact of TNM 8th edition on the therapeutic decision-making in patients with DTC. Indeed, re-classification of the tumours according to TNM 8th did not influence the treatment modalities of our patients. It is quite likely that, if the same patient cohort were collected in a prospective setting and classified primarily by TNM 8th, many patients would have received less aggressive treatment. One could argue that this approach may be cost-effective in limiting the use of potentially harmful therapies (Klein Hesselink *et al.* 2013, Mazziotti *et al.* 2018) in patients with higher overall survival. On the other hand, less aggressive treatment would eventually lead to even higher recurrence (Biondi & Cooper 2010), with consequent increase in the clinical and therapeutic burden.

In conclusion, TNM 8th edition did not show reliability in predicting aggressiveness of DTC and the ATA risk stratification appears to be more accurate than the TNM in predicting the recurrences of disease. Moreover, the downstaging of DTC patients, especially when performed due to changes in tumour classification, may overlook patients predisposed to structural recurrence, potentially causing uncertainty in the therapeutic decision-making at the time of disease diagnosis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M Arosio and A G A Lania are senior authors who contributed equally.

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