Editorial Commentary

The new AJCC/TNM Staging System (VIII ed.) in papillary thyroid cancer: clinical and molecular impact on overall and recurrence free survival

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Differentiated thyroid cancer (DTC) is the most common endocrine malignancy (1,2) and over 85% of DTC cases have a papillary histotype (PTC). Its incidence, relatively stable until the early 1990s, has rapidly grown in recent decades, more than any other cancer (3), due mostly to an increase of low-risk thyroid cancer (TC).

DTC is generally associated with an excellent prognosis: the 5-year survival rate is near 100% for localized disease, 98% for regional disease and 56% for metastatic disease.

Additionally, the death rate for TC has increased slightly in recent years, from 0.50 (per 100,000) in 2007 to 0.54 in 2016, in spite of earlier diagnosis and better treatment (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf) (4). Although DTC has a good prognosis, in some patients tumor behavior is aggressive and associated with poor outcome. A major issue, therefore, is finding characteristics and criteria that identify these tumors for appropriate management.

Recently American guidelines (5) introduced a new risk stratification system with additional prognostic variables for tailored management. Moreover, the TNM (Tumor, Node, Metastasis) classification was changed in 2018 to better predict DTC survival. Most of the changes in the 8th edition (TNM-8) downstaged a significant number of patients into lower stages to more accurately reflect their low risk of dying.

The changed American Thyroid Association (ATA) risk stratification and TNM staging have a significant impact on both the initial therapeutic decision and subsequent follow-up management. For this purpose, as recently suggested (6), molecular analysis data would be helpful in identifying the most aggressive DTC cases, thus influencing treatment decision making and subsequent follow-up.

Recently, Lee and colleagues describe a retrospective cohort of 505 PTC cases analyzed from The Cancer Genome Atlas (TCGA) database portal (7).

The objectives of the study were:

(I) To assess the accuracy of TNM-8 compared to TNM-7 in predicting PTC overall survival (OS) and recurrent free survival (RFS);

(II) To compare gene expression data, copy number alterations and somatic mutation profiles according to age at time of cancer diagnosis in order to evaluate the efficacy of TNM-8, not only on a clinical but also a genomic level.

The authors analyzed four major points:

Age cut-off and risk factors: PTC patients were subdivided on the basis of age at diagnosis using the previous cut-off of 45 years (TNM-7) and the new one of 55 years (TNM-8). Among the analyzed risk factors,

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multifocality, site of tumor and BRAF gene mutation showed no significant difference in outcome for either age group whereas a statistical difference was found for minimal extrathyroidal extension (mETE) using both age cut-offs. Male gender and larger tumors were predictors of the worst outcome using the 55-year cut-off.

Many reports analyzed the effect of changing the age cut-off, showing that an age cut-off higher than 45 years was a better indicator of cancer-related death risk.

Tam *et al.* (8) evaluated the effect on disease-specific survival (DSS) and OS of downstaging due to different age cut-offs in a retrospective series of 2,579 DTC. The 10-year DSS of the 45–54-year age group was 97.6%, which is higher (but not statistically significant) than for patients aged <45 years and lower than for patients aged ≥55 years (significant only with univariate analysis). They concluded that the survival discrimination power between TNM-7 and TNM-8 systems was no different and that both editions have the same ability to estimate survival among the stages.

In contrast, results from Kim *et al.* (9), analysing a large cohort of 3,176 DTC patients, and Kim *et al.* (10), including 1,613 DTC patients, suggested that TNM-8 has a higher ability to differentiate patients of different stages and therefore to predict DSS.

Regarding the choice of the new age cut-off, Mazurat and colleagues (11) showed an optimal age cut-off of 55 years but Kim *et al.* (12), with 35,323 patients from the Surveillance, Epidemiology and End Results (SEER) database, found that the optimum cut-off point for disease-related death was 57 years.

Moreover, as shown by several studies, mortality increases progressively with advancing age and any single cut-off point for age is less 'performant' than models that consider age as a continuous variable.

mETE is a controversial prognostic factor and several studies have evaluated its role on DSS and OS. Some authors (13-16) revealed similar clinical outcomes of patients with mETE and those with no ETE. However, Castagna *et al.* (17) showed poorer outcome (persistent structural or recurrent disease or tumor-related death) in patients with ETE compared with tumors larger than 1.5 cm with negative margins (11.8% *vs.* 5.1%), concluding that only small mETE tumors should be classified as low-risk tumors.

Tran *et al.* (18) found no association between tumor size and RFS in patients aged <55 years but that it was an independent predictor in patients aged ≥55 years, concluding that the impact of tumor size on RFS was limited to older patients.

We agree with the better prognostic accuracy of the shifted age cut-off supported by several studies (10-12).

However, with regard to the mETE prognostic value we are more cautious as it still remains controversial. Recently an expansion of TNM-8 has been published (telescoping) with the objective of collecting additional data without altering the definitions of the current TNM categories in order to better classify each tumor category according to the presence or absence of mETE and to test the subcategories for prognosis and treatment planning considerations. In the next few years, we shall have more information on the importance of mETE for each tumor category from several groups of authors.

RFS and OS in both age groups

RFS was not statistically different using the cut-off of 45 years but it was significantly worse for older patients with the cut-off at 55 years. OS was statistically lower for older patients using both age cut-offs.

Kim *et al.* (10) showed that age ≥55 years (but not 45–54 years) was a significant predictor of recurrence and overall mortality (P<0.005). Both TNM-7 and TNM-8 were predictive of RFS and OS (P<0.001) but TNM-8 better discriminated the tumor classification and overall TNM stage than TNM-7.

Nixon (19) showed that the shift of the age cut-off to 55 years also improved prediction of the 10-year DSS; survival improved from 99% to 76% for stages I–IV at an age cut-off of ≥45 years and from 99% to 67% at an age cut-off of ≥55 years, respectively.

Comparison of TNM-7 and TNM-8

Among 493 patients, 41% were downstaged into lower stages and unavoidably more cases of recurrences and deaths were found in the lower stages. In particular, 17% of patients downstaged from stage III to stage II had recurrent disease; 25% of cases downstaged from stage IV to III, 13.6% from stage IV to II and 18.4% from stage IV to stages III and II died for PTC.

The Kaplan-Meier plot for stage-dependent RFS and OS showed a statistically significant value for both editions. However, RFS had a more significant P value using the TNM-8 staging system than the TNM-7 system and for OS the value was higher for TNM-7 (but significant value for both eds.).

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Recently, several studies have been conducted to compare TNM-7 and TNM-8, and better predictability in patients with DTC by TNM-8 has been suggested (10,20,21). When TNM-8 is applied, a significant number of patients with DTC are reclassified to lower stages and more accurate survival predictions are provided compared with TNM-7. Therefore, the changes in TNM-8 are expected to provide a more realistic assessment of disease mortality in high-risk patients.

TNM-8, on the one hand, suggests an improved allocation of patients at high risk of dying from DTC into more advanced TNM stages and, on the other hand, induces a wrong belief of less aggressive disease. However, it should be emphasized that the risk of death is not always related to the risk of recurrence in many patients.

Tam *et al.* (8) showed that the 10-year DSS for stages I–IV for TNM-7 ranged from 100% to 82.6% (P<0.001) and for TNM-8 from 99.8% to 71.9% (P<0.001). The 10-year OS for stages I–IV based on TNM-7 ranged from 95.8% to 59.7% and for TNM-8 from 94.3% to 34.6%. The power of survival prediction for DSS in TNM-7 and TNM-8 is similar, although the 10-year DSS appears more appropriate between stages using the updated TNM-8.

Kim *et al.* (10), analysing1,613 patients, showed that using TNM-8, 38% of patients were reclassified into lower stages and 63% of patients with T3 classification were restaged as T1 or T2. The DSS results for patients in stages III and IV according to TNM-8 were worse than those according to TNM-7 (98.8% and 83.2%, respectively, for TNM-7; 72.3% and 48.6%, respectively, for TNM-8). They concluded that TNM-8 improves the prediction of both recurrence and survival in patients with PTC from the previous TNM-7 staging system.

In the study by Shteinshnaider *et al.* (21), the proportion of intermediate/high-risk patients in stages I–II according to TNM-8 increased considerably compared to TNM-7. Patients reclassified according to TNM-8 in stage II had more lymph node metastases, more recurrence risk, more reoperations, more persistency of disease and a non-significant increase in disease-specific mortality compared to TNM-7. This study underlines that TNM-8 provides a more accurate system to discriminate mortality and persistence in DTC patients but that the severity of disease, especially in the 45–55-year age group and in stage II patients, should not be underestimated following the important down-staging of these patients.

From our point of view, although the new TNM-8 in comparison to TNM-7 would seem to better discriminate mortality, the significant downstaging could underestimate the severity of disease in many patients and cause a non-negligible treatment burden, as for patients with latero-cervical metastases at diagnosis (22), especially when of large size and numerous (23).

Specific gene signature among the three groups of patients (<45, 45–55 and ≥55 years)

Lee and colleagues found that there were no specific molecular subtypes between the three age groups. There were 14 specific genes found in patients aged <45 years, none in patients aged 45–54 years and 103 in patients aged ≥55 years. These data showed that raising the cut-off age from 45 to 55 years more effectively predicts the disease prognosis of PTC and supports the use of TNM-8, making it clinically and genetically appropriate. No difference was found in copy number alteration or somatic mutation patterns. Moreover, there was no statistically significant difference in seven of the most frequently mutated genes (*BRAF*, *HRAS*, *NRAS*, etc.) according to each age group.

In summary, the authors evaluated the potential signalling pathways activated in each age group of patients: for example, those older than 55 years had alterations in the sirtuin signaling pathway, ATM signaling, the FXR/RXR activation pathway and the transforming growth factor-β pathway.

This study is the first to evaluate clinical and gene expression data in all patients and according to previous and recent age cut-offs and shows clinical and genetic evidence supporting the age of 55 years as being the better cut-off.

There are several limitations to this excellent study. It is a retrospective analysis using TCGA data and the impact of these specific genes in different ages cannot be defined due to the lack of correlation between molecular and clinical data.

Currently, none of the mortality risk systems incorporate molecular testing results. This may need to be re-evaluated because several studies have shown that molecular testing, including *BRAF* V600E, *TERT* and *TP53* or combinations of markers, has an important impact on the risk of recurrence and mortality.

Xing *et al.* (24) showed in 1,849 PTC patients that the presence of a *BRAF* mutation was associated with increased disease-specific mortality, although this was not significantly associated with mortality in a multivariate analysis. However, a significant interaction between *BRAF* mutation and several conventional clinicopathological risk

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factors was seen: lymph node metastases, distant metastases and American Joint Committee on Cancer (AJCC) stage IV disease.

In a systematic review and meta-analysis of 14 publications (25), including 2,470 PTC patients, the *BRAF* mutation was associated with a significantly higher risk of recurrence than *BRAF* wild-type tumors.

Two other molecular markers, *TP53* and *TERT* mutations, appear to confer an increased risk of tumor recurrence and tumor-related mortality. In one study that analyzed more than 400 DTC cases (26), the presence of a *TERT* mutation was found to be an independent predictor of mortality.

Another study (6) showed that the PTC recurrence rate for patients with coexisting *BRAF* and *TERT* mutations was significantly higher than that associated with either mutation alone, demonstrating an incremental and synergistic effect of the coexisting two mutations.

Recently Gan and colleagues (27) investigated the significance of the *BRAF* V600E mutation in predicting prognostic and aggressive clinicopathological characteristics according to a new age-based stratification. In the ≥55-year age group, *BRAF* V600E was found to be significantly associated with aggressive PTC characteristics, including tumor size, PTC subtype, radioactive iodine dose, follow-up time, recurrence, recurrence risk stage, advanced tumor stage, advanced node stage and AJCC stage III/IV (all P<0.05). Recurrence-free survival rate was statistically different in the ≥55-year age group (P=0.04) but there was no significant difference in the <55-year age group (P=0.76), according to the *BRAF* V600E mutation status. They therefore concluded that the *BRAF* V600E mutation was found to better predict aggressive and recurrent PTC based on age stratification with the cut-off age of 55 years.

In a recent paper, Yan and colleagues (28) analyzed the relationship between *BRAF* V600E and clinical features in PTC; with regard to age categories, they showed a significant difference of *BRAF* V600E incidence between patients aged ≤45 and >45 years (79.7% *vs.* 88.4%, P<0.001), concluding that PTC patients were more prone to be *BRAF* V600E positive with increasing age but that *BRAF* V600E has no independent prognostic value of risk in connection with outcome.

Regarding the impact of ATM (critical in the process of recognizing and repairing DNA lesions) and the FXR/RXR pathways (members of the nuclear family of receptors and key players in the control of numerous metabolic *pathways*), many reports have supported the association with PTC prognosis and survival (29-31).

Giaginis and colleagues (31) showed that enhanced farnesoid X receptor (FXR) was more frequently observed in PTC compared with hyperplastic nodules, and that in malignant lesions high levels were associated with capsular and vascular invasion, increased follicular cell proliferative rate, larger tumor size, presence of lymph node metastases, lymphatic invasion and increased recurrence rate risk.

Because of the clinical implications of this incremental improvement in risk stratification of *BRAF* and other mutations such as *TERT*, research on mutational status is not routinely recommended but could help to refine risk estimates when interpreted in the context of other clinicopathological risk factors.

Very recently, the importance of the impact of molecular signatures has been increasing and will allow a more specific detection of well-differentiated TC cases that have high risks of tumor recurrence and cancer-related mortality.

To date, none of the current molecular markers were considered to have sufficient independent prognostic significance to be included in the new staging system; moreover, Lee and colleagues do not indicate the mean follow-up of analyzed patients, which is a crucial point to better establish the real impact of mutation status on short- and long-term follow-up. It may be the case, mainly for some tumors with specific mutations, that a long follow-up is needed to disclose their aggressiveness.

In conclusion, TNM-8 staging should have greater accuracy in identifying patients at higher risk of dying of TC, but careful follow-up is also needed for downstaged patients. Even though molecular profiling of tumors has the potential to better estimate cancer aggressiveness and other risk factors, further studies are needed.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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