RESEARCH LETTER

8th edition of the AJCC/TNM staging system of thyroid cancer: what to expect (ITCO#2)

Dear Editor,

Differentiated thyroid cancer (DTC) has become one of the most frequently diagnosed malignancies, especially among women and young adults (Davies & Welch 2014). The outcomes are generally very good: disease recurrence rates are low (Durante *et al.* 2013), and survival rates are excellent (Tuttle *et al.* 2017*a*). Evidence-based management is crucial to avoid overtreatment of these low-risk tumors, which can reduce quality of life and yet identify accurately those requiring more aggressive therapy. Several staging systems have been generated to inform DTC management. One of the most widely used is the tumor-node-metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), which allows to predict the risk of cancer-related death. The 8th edition of the AJCC staging system for thyroid cancer (AJCC-8) was recently published (Tuttle *et al.* 2017*b*) and is scheduled to be implemented on 1 January 2018. Revision of the system was undertaken to address several specific limitations identified in the 7th edition (AJCC-7), which has been in use since 2009 (Tuttle *et al.* 2017*a*,*b*). The main changes (described in detail below and summarized in Table 1) are as follows: (1) an increase in the age threshold for defining high risk of thyroid cancer-related death and (2) a decrease in the unfavorable prognostic significance attributed to certain findings (i.e., cervical lymph node metastases and microscopic extrathyroidal extension (ETE), which has been re-defined to include only invasion of the perithyroidal muscle).

To assess the impact of transitioning to the new AJCC-8 in terms of stage distribution and prevalence of each stage class, we analyzed data extracted from the web-based database of the Italian Thyroid Cancer Observatory (ITCO) (www.itcofoundation.org), a network of thyroid cancer centers (including primary and tertiary centers) located throughout Italy. The database includes prospectively updated, observational data provided by ITCO member centers on patients consecutively diagnosed with thyroid cancer since 2013 (Lamartina *et al.* 2017). Cases included in our study met all the following criteria: (1) histological diagnosis of thyroid cancer of follicular origin; (2) date of diagnosis between 1 January 2013 and 1 March 2017; (3) complete data on primary tumor pathology, including minimal ETE, and initial treatment.

The selected cohort analyzed included 1765 patients, 76% of whom were females. The median age at diagnosis was 48 years (range: 10–87). Total thyroidectomy (or lobectomy + completion thyroidectomy) was performed in 1727 (98%) cases and followed by radioiodine remnant ablation in 954 (55%). Neck dissection was performed in 711 (40%) of the 1765 patients. Most of the tumors (n = 1657, 94%) were papillary thyroid cancers; the remaining 108 (6%) were follicular or Hürthle cell carcinomas. Estimated risks of recurrence calculated according to the criteria recommended in 2015 by the American Thyroid Association were low in 1046 (59%), intermediate in 612 (35%) and high in 107 (6%) of the cases. Microscopic ETE was found in 410 (23%), but only 40 (2%) of these patients had gross invasion of the strap muscles (sternohyoid, sternothyroid, thyroidhyoid and/or omohyoid muscles). Lymph node status for the 711 patients who underwent lymph node dissection was as follows: pN0 (no metastasis) in 338 (19%); pN1a (central compartment metastases) in 221 (12%) and pN1b (lateral compartment metastases) 152 (9%). Distant metastases were found in 32 (1.8%) patients.

As noted above, in the AJCC-8, the age threshold for high risk of disease-specific mortality was raised from 45 years – the median age at diagnosis in several published series – to 55 years (Nixon *et al.* 2016). This change increases the proportion of relatively young patients whose mortality risk can be defined solely on the basis of the absence or presence of distant metastases (stages I and II, respectively) (Table 1). As shown in Fig. 1A, the percentage of patients classified as 'younger' in our

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Table 1 AJCC TNM staging: 7th and 8th editions.

7th edition	Age <45 years			8th edition	Age <55 years		
I	Any tumor size	Any lymph node status	Absence of distant metastases (M0)	I	Any tumor size	Any lymph node status	Absence of distant metastases (M0)
II	Any tumor size	Any lymph node status	Presence of distant metastases (M1)	II	Any tumor size	Any lymph node status	Presence of distant metastases (M1)
7th edition	**Age ≥45 years**			**8th edition**	**Age ≥55 years**		
I	Tumor of ≤2 cm limited to the thyroid (T1)	Absence of lymph node metastases (Nx/N0)	Absence of distant metastases (M0)	I	Tumor of ≤4 cm limited to the thyroid (T2)	Absence of lymph node metastases (Nx/N0)	Absence of distant metastases (M0)
II	Tumor of ≤4 cm limited to the thyroid (T2)	Absence of lymph node metastases (Nx/N0)	Absence of distant metastases (M0)	II	Tumor of any size with lymph node metastases (N1) *or* with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyroidhyoid, omohyoid) with/without lymph node metastases (T3b)		Absence of distant metastases (M0)
III	Tumor of any size with lymph node metastases of the central compartment (N1a) *or* with minimal extrathyroid extension (T3) with/without lymph node metastases of the central compartment		Absence of distant metastases (M0)	III	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a)	Any lymph node status	Absence of distant metastases (M0)
IVa	Tumor of any size with lymph node metastases of the lateral compartment (N1b) *or* with gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a) with/without lymph node metastases		Absence of distant metastases (M0)	IVa	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (T4b)	Any lymph node status	Absence of distant metastases (M0)
IVb	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (T4b)	Any lymph node status	Absence of distant metastases (M0)	IVb	Any tumor size	Any lymph node status	Presence of distant metastases (M1)
IVc	Any tumor size	Any lymph node status	Presence of distant metastases (M1)	–	–	–	–

cohort rose from 40% (698/1765) with the AJCC-7 to 65% (1150/1765) with the AJCC-8, but in both cases, the proportion of patients with distant metastases (i.e., those classified as stage II) was identically low (2%). Given the overall increase in the age of the 'younger' stage II patients, their estimated disease-specific survival at 10 years (DSS-10) drops from 95–99% to 85–95% (Kim *et al.* 2017*b*, Tuttle *et al.* 2017*a*,*b*).

Among the 615 patients classified by both the AJCC-7 and the AJCC-8 as 'older' (Fig. 1B), 193 (31%) originally classified as stage III or IVa were re-classified as stage II, raising the proportion of patients with stages I–II DTC from 64% to 94%. Over half of the downstagings (112/193, 58%) involved patients whose previous T3 classification had been based solely on the presence of microscopic ETE, which has no effect on the T category or overall disease stage in the AJCC-8 (Tuttle *et al.* 2017*b*). In the remaining patients, the AJCC-7 classification as stage III or IV had been based on the presence of regional metastases alone (45/193, 23%), which no longer necessitates assignment

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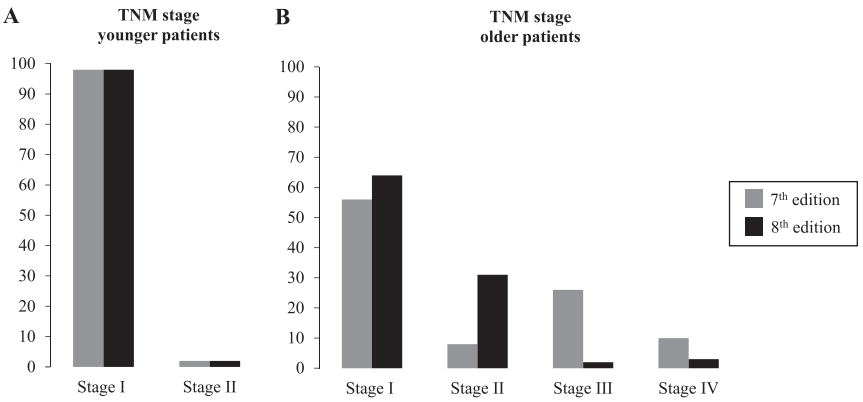

Figure 1
DTC stage distributions in the ITCO cohort based on the 7th and 8th editions of the AJCC system. (A) The younger subcohorts defined by the AJCC-7 and AJCC-8 comprised 698 patients aged <45 years and 1150 patients <55 years, respectively. In both subcohorts, 98% of the patients were classified as stage I. (B) The older subcohorts defined by the AJCC-7 and AJCC-8 comprised 1067 patients aged >45 years and 615 patients >55 years, respectively. Restaging with the AJCC-8 increased the percentages of patients with stage I (from 56 to 64%) or II (from 8 to 31%) disease.

to stage III (Tuttle *et al*. 2017*b*), or regional metastases plus microscopic ETE (18/193, 9%). It should be noted that, differently from the AJCC-7, the ITCO database has always classified level VII lymph node metastases as central neck node lesions. This reflects the well-known difficulties in distinguishing levels VI and VII and is consistent with the revised definitions adopted in the AJCC-8 (Tuttle *et al*. 2017*b*). Since the same classification was also used for our AJCC-7 staging, some cases that met the criteria for AJCC-7 stage IVa may have been erroneously reported herein as stage III. As for the entire cohort, application of the AJCC-8 criteria downstaged 477 (27%) of the 1765 DTC patients. As a result, the estimated risk for 10-year disease-specific mortality was <15% for almost all the patients. Higher estimated risks (>40%) were restricted to 2% (31/1765) of the patients who were 55 or older and had gross ETE (T4), with or without distant metastases (stages III and IV). Importantly, the mortality risk was not always paralleled by the likelihood of recurrence. The risk of recurrence, as defined by the American Thyroid Association, was rated intermediate in 25% of AJCC-8 stage I patients and 90% of AJCC-8 stage II patients aged ≥55, and high risks of recurrence were found in 3% and 4% of these groups, respectively, owing to the presence of unfavorable histologic findings (i.e., widely invasive follicular and Hürthle cell cancer with foci of vascular invasion).

The AJCC-8 stage distribution for our DTC cohort resembles those reported for retrospectively analyzed cohorts (Kim *et al*. 2017*a*,*b*), where the downstaging affected an even larger subset of patients (38%). Compared with the ITCO cohort, the Korean cohorts included higher percentages of patients with regional metastasis or microscopic ETE (56% and 32–40%, respectively), which might reflect a referral-center-selection bias. Microscopic ETE reporting can be unreliable as it is often variable even between skilled pathologists (Su *et al*. 2016). However, a far better agreement was found for the presence of gross ETE with invasion of perithyroidal muscles compared with invasion of perithyroidal fat only. The extensive downstaging effect of the AJCC-8 was intentional: the TNM staging system assesses the risk of DTC-related death, which has proved to be very low for most patients. Indeed, the results of retrospective cohort analyses confirm that the AJCC-8 provides more accurate estimates of DTC patients' DSS (Kim *et al*. 2017*a*,*b*, Pontius *et al*. 2017, Tuttle *et al*. 2017*a*). From a practical standpoint, application of the AJCC-8 criteria can be expected to simplify the staging process for most DTC patients, who will now be classified as 'younger'. It will also markedly reduce the number of patients with a substantial mortality risk (those with stages III–IV disease, where the DSS-10 is <50–70%). This new tool, together with the risk of recurrence stratification tools, should facilitate clinicians' attempts to provide more cost-effective management of DTCs, and this improvement should also have benefits in terms of their patients' quality of life.

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