

1 **8th edition of AJCC/TNM staging system of thyroid cancer: what to expect**

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44 **Summary**

45 The 8th edition of AJCC/TNM staging system for differentiated thyroid cancer (DTC) has recently been
46 published.

47 The aim of this study was to compare AJCC/TNM staging 7th and 8th edition in terms of tumor stage
48 distribution in a multicenter, consecutive and prospective cohort of newly diagnosed DTC collected in a
49 web-based observational database. Additional information concerning the extent of minimal extrathyroidal
50 extension was collected.

51 A cohort of 1765 DTC patients (76% females, median age 48 years, 94% papillary histotype) was analyzed.
52 Younger patients (<45 years or <55 years according to 7th and 8th edition, respectively) were in stage II
53 (presence of distant metastases) in 2% of the cases with both classifications. According to TNM 7th edition in
54 patients aged ≥ 45 years (N=1067), stage distribution was: stage I 595 (56%), stage II 85 (8%), stage III 283
55 (26%), and stage IV 104 (10%). According to TNM 8th edition in patients aged ≥ 55 years (N=615) was:
56 stage I 391 (64%), II 193 (31%), III 15 (2%) and IV 16 (3%). The 27% of the patients were downstaged with
57 TNM 8th edition.

58 The majority of newly diagnosed DTC patients are in low-risk stages. An important downstaging is observed
59 applying TNM 8th edition.

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62 Dear Editor:

63 Differentiated thyroid cancer (DTC) has become one of the most frequently diagnosed malignancies,
64 especially among women and young adults (Davies and Welch 2014). The outcomes are generally very
65 good: disease recurrence rates are low (Durante, et al. 2013), and survival rates are excellent (Tuttle et al.
66 2017a). Evidence-based management is crucial to avoid overtreatment of these low-risk tumors, which can
67 reduce quality of life, and yet to identify accurately those requiring more aggressive therapy. Several staging
68 systems have been created to inform DTC management. One of the most widely used is the tumor–node–
69 metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), which
70 allows to predict the risk of cancer-related death. The 8th edition of the AJCC staging system for thyroid
71 cancer (AJCC-8) was recently published (Tuttle et al. 2017b) and is scheduled to be implemented on 1
72 January 2018. Revision of the system was undertaken to address several specific limitations identified in the
73 7th edition (AJCC-7), which has been in use since 2009 (Tuttle et al. 2017a; Tuttle, et al. 2017b). The main
74 changes (described in detail below and summarized in **Table 1**) are: 1) an increase in the age threshold for
75 defining high risk of thyroid cancer-related death and 2) a decrease in the unfavorable prognostic
76 significance attributed to certain findings (i.e., cervical lymph node metastases and microscopic
77 extrathyroidal extension [ETE], which has been re-defined to include only invasion of the perithyroidal
78 muscle).

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

88 The selected cohort analyzed included 1765 patients, 76% of whom were females. The median age at
89 diagnosis was 48 years (range: 10 - 87). Total thyroidectomy (or lobectomy + completion thyroidectomy)
90 was performed in 1727 (98%) cases and followed by radioiodine remnant ablation in 954 (55%). Neck
91 dissection was performed in 711 (40%) of the 1765 patients. Most of the tumors (n=1657, 94%) were
92 papillary thyroid cancers; the remaining 108 (6%) were follicular or Hürthle cell carcinomas. Estimated risks
93 of recurrence calculated according to the criteria recommended in 2015 by the American Thyroid
94 Association were low in 1046 (59%), intermediate in 612 (35%), and high in 107 (6%) of the cases.
95 Microscopic ETE was found in 410 (23%), but only 40 (2%) of these patients had gross invasion of the strap
96 muscles (sternohyoid, sternothyroid, thyroidhyoid, and/or omohyoid muscles). Lymph node status for the
97 711 patients who underwent lymph node dissection was as follows: pN0 (no metastasis) in 338 (19%); pN1a
98 (central compartment metastases) in 221 (12%); and pN1b (lateral compartment metastases) 152 (9%).
99 Distant metastases were found in 32 (1.8%) patients.

100 As noted above, in the AJCC-8, the age threshold for high-risk of disease-specific mortality was
101 raised from 45 years—the median age at diagnosis in several published series—to 55 years (Nixon, et al.
102 2016). This change increases the proportion of relatively young patients whose mortality risk can be defined
103 solely on the basis of the absence or presence of distant metastases (stages I and II, respectively) (**Table 1**).
104 As shown in **Figure 1A**, the percentage of patients classified as “younger” in our cohort rose from 40%
105 (698/1765) with the AJCC-7 to 65% (1150/1765) with the AJCC-8, but in both cases, the proportion of
106 patients with distant metastases (i.e., those classified as stage II) was identically low (2%). Given the overall
107 increase in the age of the “younger” stage II patients, their estimated disease-specific survival at 10 years
108 (DSS-10) drops from 95-99% to 85-95% (Tuttle, et al. 2017a; Tuttle, et al. 2017b; Kim, et al. 2017b).

109 Among the 615 patients classified by both the AJCC-7 and AJCC-8 as “older” (**Figure 1B**), 193
110 (31%) originally classified as stage III or IVa were re-classified as stage II, raising the proportion of patients
111 with stage I-II DTC from 64% to 94%. Over half the downstagings (112/193, 58%) involved patients whose
112 previous T3 classification had been based solely on the presence of *microscopic* ETE, which has no effect on
113 the T category or overall disease stage in the AJCC-8 (Tuttle et al. 2017b). In the remaining patients, the
114 AJCC-7 classification as stage III or IV had been based on the presence of regional metastases alone
115 (45/193, 23%), which no longer necessitates assignment to stage III (Tuttle et al. 2017b), or regional

116 metastases plus microscopic ETE (18/193, 9%). It should be noted that, differently from the AJCC-7, the
117 ITCO database has always classified level VII lymph node metastases as central neck node lesions. This
118 reflects the well-known difficulties in distinguishing levels VI and VII and is consistent with the revised
119 definitions adopted in the AJCC-8 (Tuttle et al. 2017b). Since this same classification was also used for our
120 AJCC-7 staging, some cases that met the criteria for AJCC-7 stage IVa may have been erroneously reported
121 herein as stage III. As for the entire cohort, application of the AJCC-8 criteria downstaged 477 (27%) of the
122 1765 DTC patients. As a result, the estimated risk for 10-year disease-specific mortality was <15% for
123 almost all the patients. Higher estimated risks (>40%) were restricted to 2% (31/1765) of patients who were
124 55 or older and had gross ETE (T4), with or without distant metastases (stage III and IV). Importantly, the
125 mortality risk was not always paralleled by the likelihood of recurrence. The risk of recurrence, as defined by
126 the American Thyroid Association) was rated intermediate in 25% of AJCC-8 stage I patients and 90% of
127 AJCC-8 stage II patients aged ≥ 55 , and high risks of recurrence were found in 3% and 4% of these groups,
128 respectively, owing to the presence of unfavorable histologic findings (i.e., widely invasive follicular and
129 Hürthle cell cancer with foci of vascular invasion).

130 The AJCC-8 stage distribution for our DTC cohort resembles those reported for retrospectively
131 analyzed cohorts (Kim, et al. 2017a; Kim, et al. 2017b), where the downstaging affected an even larger
132 subset of patients (38%). Compared with the ITCO cohort, the Korean cohorts included higher percentages
133 of patients with regional metastasis or microscopic ETE (56% and 32-40% respectively), which might reflect
134 a referral-center-selection bias. Microscopic ETE reporting can be unreliable as it is often variable even
135 between skilled pathologists (Su et al, 2016). However, a far better agreement was found for the presence of
136 gross ETE with invasion of perithyroidal muscles compared with invasion of perithyroidal fat only. The
137 extensive downstaging effect of the AJCC-8 was intentional: the TNM staging system assesses the risk of
138 DTC-related death, which has proved to be very low for most patients. Indeed, the results of retrospective
139 cohort analyses confirm that the AJCC-8 provides more accurate estimates of DTC patients' DSS (Kim et al.
140 2017a; Kim et al. 2017b; Pontius et al. 2017; Tuttle et al. 2017a). From a practical standpoint, application of
141 the AJCC-8 criteria can be expected to simplify the staging process for most DTC patients, who will now be
142 classified as "younger". It will also markedly reduce the number of patients with a substantial mortality risk
143 (those with stage III-IV disease, where the DSS-10 is <50-70%). This new tool, together with risk of

144 recurrence stratification tools, should facilitate clinicians' attempts to provide more cost-effective
145 management of DTCs, and this improvement should also have benefits in terms of their patients' quality of
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147

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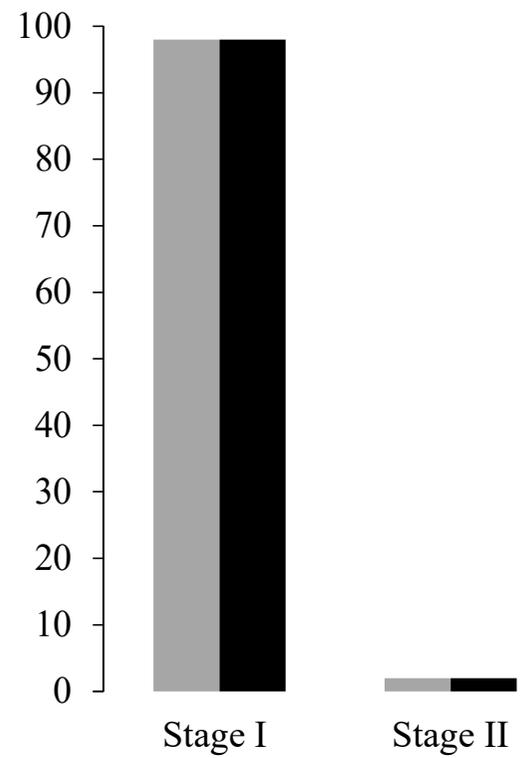
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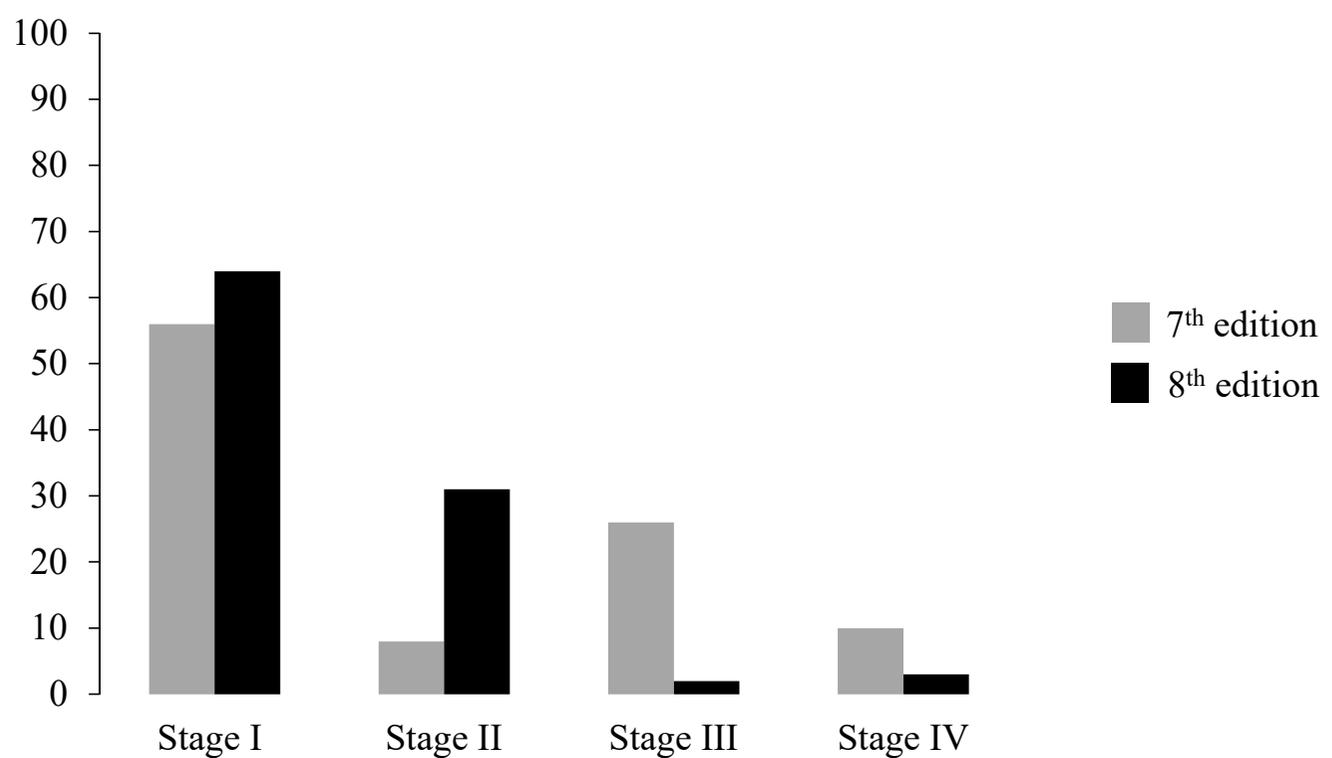
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Figure 1. DTC stage distributions in the ITCO cohort based on the 7th and 8th editions of the AJCC system. (A) The younger subcohorts defined by the AJCC-7 and AJCC-8 comprised 698 patients aged < 45 years and 1150 patients < 55 years, respectively. 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 \geq 45 years and 615 patients \geq 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.

A TNM stage younger patients



B TNM stage older patients



7th edition
8th edition

Table 1. AJCC TNM Staging: 7 th and 8 th edition							
7 th Edition	Age <45 years			8 th 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)
7 th Edition	Age ≥45 years			8 th Edition	Age ≥55 years		
I	Tumor of ≤2cm limited to the thyroid (T1)	Absence of lymph node metastases (Nx/N0)	Absence of distant metastases (M0)	I	Tumor of ≤4cm limited to the thyroid (T2)	Absence of lymph node metastases (Nx/N0)	Absence of distant metastases (M0)
II	Tumor of ≤4cm 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) <i>or</i> 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) <i>or</i> 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)		Absence of distant metastases (M0)	Iva	Gross extrathyroidal extension invading prevertebral fascia or	Any lymph node status	Absence of distant metastases (M0)

	<p><i>or</i></p> <p>with gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a) with/without lymph node metastases</p>				encasing the carotid artery or mediastinal vessels (T4b)		
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)	--	--	--	--