DOI: 10.5350/SEMB.20171224115721

What has Changed About the Eight Edition of the Differentiated Thyroid Carcinomas TNM Classification System? How will it Effect the Clinical Practice?

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ABSTRACT:

What has changed about the eight edition of the differentiated thyroid carcinomas TNM classification system? How will it effect the clinical practice?

The eighth edition of the TNM classification system was announced. Thyroid cancers were included in the fourth edition of the TNM classification system which was published in 1987. Each version of the TNM system which is updated based on evidence in the literature, includes some important differences from the previous version for the differentiated thyroid carcinomas (DTCs), like other cancers. Seventeen different classification systems for thyroid cancer have been developed until today. Some of these systems are quite complex and are difficult to use in practice. It has been shown that the TNM system with the new regaulations is the most consistent and applicable staging system for DTC in different patient groups, and the TNM system is now the most commonly used classification system in thyroid cancer, as in other cancer types.

The most important update of the eighth version is that the age as prognostic factor is regulated as younger and older than 55 years, which has been divided as younger/older than 45 years of age in prior editions. Furthermore, the change in the definition of T3 in the T stage is remarkable. In the seventh edition, the definition of minimally invasive extrathyroidal extension and the definition of perithyroidal soft tissue included in its example have been abolished. Macroscopic extension into any of the strap muscles was moved to the T3 category in the eighth edition. In N staging in the 7th edition, the upper mediastinal lymph node involvement which took place in N1b was moved to the N1a category. In the eighth edition, it is observed that generally in patients over 55 years old have a stage downgrade in all stages compared to the seventh edition.

In the eighth edition, the appropriate tumor stage can easily be determined. In patients under the age of 55 years, patients with distant metastases were defined as stage II, and without as stage I. Patients with distant metastasis over the age of 55 years are defined as stage IVB. The stages of patients without distant metastases over the age of 55 years can be defined by other clinical features (intrathyroidal tumor, macroscopic extrathyroidal extension, lymph node metastasis and distant metastasis). If there is no lymph node metastasis in patients with intrathyroidal tumors smaller than 4 cm (T1,T2), it is called stage 1, and stage II, if lymph node metastasis is present. Patients with intrathyroidal tumors greater than 4 cm (T3) are placed in stage II, regardless of lymph node status (N0 or N1). In tumors with macroscopic extrathyroidal extension; irrespective of the lymph node metastasis, the tumor is in stage II if only invasive into the strap muscles, and stage III if extended to subcutaneous tissue, larynx, trachea, recurrent laryngeal nerve and esophagus, and stage IVA if extended to the prevertebral fascia, mediastinal vessels or if surrounded carotid artery.

TNM classification is a staging system that reliably predicts disease-specific survival in the DTC. The eighth edition of TNM compared to the previous editions classifies a large proportion of patients with DTC in low-risk groups in terms of mortality, and initial evaluations show that it may be more suitable in predicting disease-specific survival.

Keywords: Differentiated thyroid carcinomas, TNM classification system, TNM eighth version

ÖZET:

Diferansiye tiroit kanserlerinde TNM evreleme sisteminin 8. sürümünde neler değişti? Klinik pratiği nasıl etkileyecek?

TNM evreleme sisteminin son olarak sekizinci sürümü (edisyonu) yayınlandı. Tiroit kanserleri TNM evreleme sisteminin 1987 yılında yayınlanan 4. sürümünde yer aldı. Literatürdeki kanıtlara dayalı olarak güncellenen TNM sisteminin her sürümü diğer kanserler gibi diferansiye tiroit kanserleri (DTC) için de bir önceki sürümüne göre önemli bazı farklılıklar içerir. Tiroit kanserleri için günümüze kadar 17 ayrı evreleme sistemi geliştirilmiştir. Bu sistemlerden bir kısmı oldukça karmaşıktır ve pratikte kullanılmaları zordur. Günümüze kadar TNM sisteminde yapılan yeni düzenlemelerle birlikte bu sistemin DTC için farklı hasta gruplarında en tutarlı, uygulanabilir evreleme sitemi olduğu ortaya koyulmuş ve diğer kanser tiplerinde olduğu gibi tiroit kanserlerinde de TNM sistemi günümüzde en sık kullanılan evreleme sistemi olma özelliğini kazanmıştır.

Sekizinci sürümün en önemli değişikliği bugüne kadarki sürümlerde prognostik faktör olarak 45 yaş üstü ve altı olarak ayrılan yaşın 55 yaş altı ve üstü olarak düzenlenmesidir. Ayrıca T evrelemesinde T3 tanımında değişiklik dikkati çekmektedir. Yedinci sürümde minimal invaziv ekstratiroidal yayılım tanımı ve bunun örneğinde yer alan peritiroidal yumuşak doku tanımı kaldırılmıştır. Sekizinci sürümde strep kaslarından herhangi birine makroskopik invazyon T3 kategorisine alınmıştır. N evrelemesinde 7. sürümde N1b içinde yer alan üst mediasten lenf düğümü tutulumu N1a kategorisine alınmıştır. Sekizinci sürümde 55 yaş üstündeki hastalarda genel olarak yedinci sürüme göre tüm evrelerde bir evre düşmesi olduğu görülmektedir.

Sekizinci sürümde uygun tümör evresi kolayca belirlenebilir. Ellibeş yaşın altındaki hastalarda uzak metaztazı olanlar evre II, uzak metastazı olmayanlar evre I olarak tanımlanmıştır. Ellibeş yaşın üstündeki uzak metastazlı hastalar evre IVB olarak tanımlanmıştır. Ellibeş yaşın üstündeki uzak metastazı olmayan hastaların diğer klinik özelliklere (intratiroidal tümör, makroskopik ekstratiroidal yayılım, lenf nodu metastazı ve uzak metastaz) göre evresi belirlenebilir. Dört cm'den küçük intratiroidal tümörlü (T1, T2) hastalarda lenf düğümü metastazı yoksa evre I, lenf düğümü metastazı varsa evre II olarak tanımlanır. Dört cm'den büyük intratiroidal tümörlü (T3) hastalar lenf düğümü durumuna bakılmaksızın (N0 veya N1) evre II'de yer alır. Makroskopik ekstratiroidal yayılımlı tümörlerde; lenf düğümü metastazı durumuna bakılmaksızın tümör sadece strep kaslarına invaze ise evre II, tümör cilaltı, larinks, trakea, reküren laringeal sinir ve özefagusa yayılmışsa evre III, prevertebral fasya, mediastinal damarlara yayılmş veya karotis arteri sarmışsa evre IVA'da yer alır.

TNM evrelemesi DTC'de hastalığa özgün sağkalımı güvenilir olarak öngörebilen bir evreleme sistemidir. Bir önceki sürüme göre TNM'nin sekizinci sürümü DTC'li hastaların büyük bölümünü mortalite açısından düşük riskli gruba evreleme olup, ilk değerlendirmelerde hastalık spesifik surviyi öngörmede daha uygun olabileceği görülmektedir.

Anahtar kelimeler: Diferansiye tiroit kanserleri, TNM evreleme sistemi, TNM sekizinci sürümü

Ş.E.E.A.H. Tıp Bülteni 2017;51(4):255-65

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Date of receipt / Geliş tarihi:
December 24, 2017 / 24 Aralık 2017

Date of acceptance / Kabul tarihi:
December 25, 2017 / 25 Aralık 2017

INTRODUCTION

As known, Differentiated thyroid cancers (DTC) arising from thyroid follicular epithelial cells constitute more than 95% of thyroid cancers and its incidence has increased worldwide, particularly due to the more frequent use of diagnostic methods (1). Although its prognosis is very good, even at low rates, DTC recurrence and DTC-related mortality can occur after treatment.

As with other cancers, different classification and related staging systems are used for DTC (2,3). Sherman et al. (4) emphasized the 3 main purposes of classification in DTC. These are; planning the patient's treatment and estimating the prognosis of the disease, facilitating communication between doctors and institutions using common identifiers about individual patients or patient groups, and creating a suitable environment for retrospective clinical trials and analysis and planning of clinical trials.

Seventeen different classification systems for thyroid cancer have been developed. In general, many of the systems except TNM are based on a multivariate analysis of the characteristics that centers have applied to their own data. However, it is also proposed that a system developed in this way may reduce the prognostic prediction value, when applied to different patient groups (5). In addition, some of these systems are rather complex and are difficult to use in practice. However, in a study involving more than 500 cases using a special formula for cancer-specific survival (CSS) prediction, 14 different classification systems were compared, and all systems were found to have significant predictive value ($p<0.001$) (6). In this study, MACIS (Table-1), AJCC/UICC-TNM (6th edition) and EORTC (Table-2) systems have been indicated to have the best predictive value respectively and MACIS system could be a very good choice (6). Later, with the new regulations in the TNM system, it has been shown that this system is the most consistent and applicable staging system for different patient groups for the DTC and the TNM system has become the most commonly used classification system in thyroid cancer as it is in other types of cancer.

Table-1: MACIS Classification. CSS[1]: Cancer specific survival

Macis (Mayo) Classification		
Variables		**Score**
Age	<39	3.1
	>40	0.08 X age
Size (Diameter of tumor)		0.3 X greatest diameter
Invasion (Extrathyroidal extension)		1
Completeness of resection		1
Distant metastasis		3
Risk Groups	**Total Score**	**CSS[1] (10 years) %**
I	0-5.99	99
II	6-6.99	89
III	7-7.99	56
IV	>/= 8	24

History of TNM Classification System

The TNM system is a classification system that evaluates the size and extent of the tumor (T), extent of regional lymph node metastases (N), and distant metastasis (M). The TNM system was developed by Pierre Denoix in 1943-1952 with the aim of grading malignant tumors. Later, in 1958, the International Union Against Cancer (UICC) proposed recommendations for the clinical staging of breast and laryngeal cancers, and as a result of various meetings between 1960 and 1967, they published

Table-2: EORTC (European Organization for Research and Treatment of Cancer) Classification. FTC[1]: Follicular thyroid carcinoma, CSS[2]: Cancer specific survival

EORTC Prognostic Index		
For All Types of Thyroid Cancers		
Variables		**Score**
Age		In years
Male patient		+12
Medullary or poorly differentiated FTC[1]		+10
Invasion in the Thyroid capsule		+10
If cells type is anaplastic		+45
One distant metastasis		+15
Multiple distant metastasis		+15
Risk Groups	**Total Score**	**CSS[2] (5 years)%**
I	<50	>95
II	50-65	80
III	66-83	51
IV	84-108	33
V	>109	5

TNM staging system for 23 body regions as 9 brochures (7). In 1968 these were assembled and published as the manual for cancer (The Livre de Poche), the first edition of the TNM classification (8).

The American Joint Committee on Cancer (AJCC) was originally established in 1959 to develop a clinical cancer staging system and decided to use the TNM classification system. Although their views and methods are different, UICC and AJCC, working in parallel to each other and for the same purposes, held a joint meeting in Toronto in 1969. As a result of this meeting, each of the two groups agreed to perform consultation together before releasing a staging scheme (9). UICC released the second edition of the TNM classification system in 1974, and third edition in 1982 (10,11). Extended and revised third edition of UICC was released in 1982. AJCC published its own classification system as 1st edition in 1977 with the name "manual for cancer" (12). As a result of the meetings held in the following years, AJCC and UICC agreed to develop a uniform TNM system in 1982 (7), and in 1987, consensus has been reached on the 4th edition of TNM (13). After this date, even though both groups published booklets individually, they both included a uniform TNM definition. In this context, until 1997, the number of TNM editions of UICC and AJCC were different, and in general the numbers of the editions of UICC were being considered. UICC and AJCC edition numbers were equalized in the 5th edition published in 1997, and the system was started to be named as UICC/AJCC TNM classification. After that, 6th edition of the TNM system was released in 2002, 7th edition in 2010, and 8th edition in 2017 (15-19). Each version of the TNM system updated based on evidence in the literature has some significant differences for also the DTCs, compared to the previous editions. TNM classification is a staging system commonly used today for research or epidemiological studies and for determining mortality risk. In this context, ETA (European Thyroid Association) and ATA (American Thyroid Association) recommend the TNM system to determine the risk of mortality. However, although the TNM system reliably predicts disease-specific survival, it is less likely to predict disease recurrence (20-22). For this reason, separate risk classifications have been proposed by ATA and ETA to predict risk of recurrence (23-25). As a result, the TNM classification system is currently maintained by UICC and AJCC. The TNM classification system is the only staging system that is periodically updated according to the level of evidence in the literature (14).

Thyroid in TNM Classification System

Unlike other tumors, the TNM classification for thyroid cancers has been described in the 4th edition of the TNM classification system, which was published by the UICC in 1987 after the agreement of AJCC and UICC. However, the first definitions of the T, N, M categories in thyroid cancer were made in the first edition of the manual for cancer published by AJCC in 1977 (Table-3). In this edition, there were no staging proposals, although the T, N, M categories have been defined (12). Although it is different from the currently used staging systems, in the second edition of the manual of cancer of AJCC published in 1983, TNM classification was also done. It is noteworthy that the age variable, which is the most important prognostic factor in DTC, entered the staging system at this time and that the groups below and over 45 years of age were staged separately (9). In common editions of TNM published after 1987, again, age was included as a significant variable in the classficiation. In all editions of TNM until the 8th, the patients are divided into two groups as younger or older than 45 years old. Patients without distant metastases in the group below 45 years of age are classified as stage I, and patients with distant metastasis are classified as stage II. Patients over forty-five years of age are evaluated at four different stages (Table-4).

Each version of the 5 TNM versions published over the 30-year period since 1987 to date includes some important differences from the previous version. There is no difference between the fourth and fifth editions. In these two editions, T1 was defined as smaller than 1 cm and intrathyroidal, T2 as between 1-4 cm and intrathyroidal, and T3 as tumors larger than 4 cm, intrathyroidal. T4 is defined as any size of tumor that has extended beyond the thyroid capsule. Both local advanced tumor invasive to the surrounding

Table-3: First edition of TNM classification by AJCC. 1: In addition to classification the following characteristics of the primary tumor should be noted; size, multicentricity, blood vessel invasion, and invasion through thyroid capsule (equivalent to clinical fixation. 2: Pulmonary, osseous, hepatic, brain, lymph nodes (LYM), bone marrow, pleura, skin, eye, other. 3: Each major type may need tobe staged separately because of the great variations in biologic behavior. PTC[4]: Papillary thyroid cancer, FTC[5]: Folliculary thyroid cancer, MTC[6]: Medullary thyroid cancer.

Primary Tumor (T)[1]			
Tx		Tumor cannot be assessed by rules	
T0		No available information on primary tumor	
T1	Mobile tumor	T1a	</=4 cm in greatest diameter
		T1b	>4 cm in greatest diameter
T2	Fixed tumor Any size, With or without neurologic involvement	T2a	Lateral position
		T2b	Midline position
T3		Fixed tumor Any size, With or without neurologic involvement	
Nodal Invoivement (N)			
Nx	Nodes cannot be assessed		
N0	No palpabl nodes		
N1	Palpabl mobile node(s)	N1a	Homolateral only
		N1b	Contralateral only
		N1c	Bilateral and/or midline
N2	Any palpabl fixed node		
Distant Metastasis (M)			
Mx	Not assessed		
M0	No (known) distant metastasis		
M1	Distant metastasis present	Specify[2] (location of metastasis)	
Postsurgical Treatment Residual Tumor (R)			
R0	No redidual tumor		
R1	Microscopic residual tumor		
R2	Macroscopic residual tumor	Specify	
Stage Grouping (S)			
No stage grouping for thyroid cancer is recommended at this time			
Histopatology[3]			
The WHO classification of thyroid cancer should be adopted using at least the four major types		PTC[4]	With or without follicular foci
		FTC[5]	Note extend of invasion of tumor capsule
		MTC[6]	
		Undifferentiated (anaplastic)	
		Unclassified	
Tumor Grade (G)			
G1	Well-differentiated		
G2	Moderately well-differentiated		
G3-4	Poorly or very poorlydifferentiated		

tissues and microscopic extrathyroidal extension is also present in this group (13,15,16). In the sixth edition, tumors with a tumor size of less than 2 cm and limited in thyroid were classified as T1. According to previous editions, the T-phase of 1-2 cm tumors regressed from T2 to T1. In addition, tumors below 1 cm were defined as T1a, and 1-2 cm tumors as T1b. All extrathyroidal extensions which appeared in T4 in the fifth edition were rearranged in the sixth edition. According to this; minimal extrathyroidal extension (sternotyroid muscle or perithyroidal soft tissue) is defined as T3, while T4 is divided into T4a and T4b. T4a is defined as any size of tumor that extended to subcutaneous soft tissue, larynx, trachea, esophagus or recurrent laryngeal nerve, T4b is defined as extension to the prevertebral fascia, or surrounding of carotid artery or mediastinal vessels (17) (Table-4).

In the seventh edition, there is not much change compared to the sixth edition. Tumors below 1cm that were indicated in the annexes in the sixth edition appeared as T1a, between 1-2 cm as T1b in the main table in seventh edition. Furthermore, the multifocality which was previously reported to be able to be indicated by the number of foci alongside its T-stage was shown as a subgroup in the 7th edition. Accordingly, in all grades, a change has been done and subgroups have been formed, as “s” indicating the solitary tumor, and “m” as the multifocal tumor (Table-5).

In the fourth and fifth editions, the same side lymph node metastasis has been defined as N1a; bilateral, midline, or contralateral side or mediastinal lymph node metastasis have been defined as N1b. In the sixth edition, central lymph node metastasis has been defined as N1a; unilateral lateral, bilateral lateral, contralateral lateral or mediastinal lymph node metastases have been defined as N1b, as they reflected the tumor biology better. There was not much change in N evaluation in the seventh edition, compared to the sixth. While the N staging in the sixth edition was maintained as it is, in the seventh edition, retropharyngeal lymph node metastasis was added to N1b (18) (Table-5).

In the fourth and fifth editions, over 45 years of age, tumors with no lymph node and distant metastasis

Table-4: Comparison of 4th & 5th editions with 6th edition of TNM system. ETE[2]: Extrathyroidal extension, GD[1]: Greatest dimension, RLN[3]: Recurrent laryngeal nerve. CLN[4]: Cervical lymph node, LN[5]: Lymph node
In 5th & 6th editions, it is stated that if tumor is solitary it can be shown as T(a), if tumor is multifocal it can be shown as T(b). In multifocal tumors, greatest dimension of focus determines the T state in 6th edition.

<table>
<tr><th colspan="10">Primary Tumor (T)</th></tr>
<tr><th></th><th colspan="3">4 and 5. Edition</th><th colspan="6">6. Edition</th></tr>
<tr><td>Tx</td><td colspan="3">Primary tumor cannot be assessed</td><td>Tx</td><td colspan="5">Tumor cannot be assessed</td></tr>
<tr><td>T0</td><td colspan="3">No evidence of primary tumor</td><td>T0</td><td colspan="5">No evidence of primary tumor</td></tr>
<tr><td>T1</td><td>Tumor </=1 cm in GD[1]</td><td colspan="2">Limited to thyroid</td><td>T1</td><td colspan="3">Tumor </=2 cm in GD[1]</td><td>Limited to thyroid</td></tr>
<tr><td>T2</td><td>>1 cm - </=4 cm</td><td colspan="2">Limited to thyroid</td><td>T2</td><td colspan="3">>2 cm - </=4 cm in GD[1]</td><td>Limited to thyroid</td></tr>
<tr><td rowspan="2">T3</td><td rowspan="2">Tümör >4 cm</td><td rowspan="2" colspan="2">Limited to thyroid</td><td rowspan="2">T3</td><td colspan="3">>4 cm in GD[1]</td><td>Limited to thyroid</td></tr>
<tr><td colspan="3">Tumor any size in GD[1]
Minimal ETE[2]</td><td>Perithyroid soft tissue
Strap muscles</td></tr>
<tr><td rowspan="2">T4</td><td rowspan="2">Tumor any size in GD[1]</td><td rowspan="2" colspan="2">ETE[2]</td><td rowspan="2">T4</td><td>T4a</td><td>Tumor any size in GD[1]
ETE[2]</td><td colspan="2">Subcutaneous tissue
Larynx, trachea
RLN[3]
Esophagus</td></tr>
<tr><td>T4b</td><td>Tumor any size in GD[1]
ETE[2]</td><td colspan="2">Prevertebral fascia
Carotid artery
Mediastinal vessels</td></tr>
<tr><th colspan="10">Regional Lymph Node (N)</th></tr>
<tr><th colspan="4">4 and 5. Edition</th><th colspan="6">6. Edition</th></tr>
<tr><td>Nx</td><td colspan="3">Regional lymph nodes cannot beassessed</td><td>Nx</td><td colspan="5">Regional lymph nodes cannot be assessed</td></tr>
<tr><td>N0</td><td colspan="3">No regional lymph nodes metastasis</td><td>N0</td><td colspan="5">No regional lymph nodes metastasis</td></tr>
<tr><td rowspan="3">N1</td><td>N1a</td><td>İpsilateral</td><td>CLN[4] metastasis</td><td rowspan="3">N1</td><td>N1a</td><td>Central neck</td><td></td><td colspan="2">Grup VI</td></tr>
<tr><td rowspan="2">N1b</td><td>Bilateral
Midline
Contralateral</td><td>CLN[4] metastasis</td><td rowspan="2">N1b</td><td>Ipsilateral
Contralateral
Bilateral</td><td>lateral neck metastasis</td><td colspan="2">Grup II, III, IV, V
Grup II, III, IV, V
Grup II, III, IV, V</td></tr>
<tr><td colspan="2">Upper mediastinal LN[5] metastasis</td><td colspan="3">Upper mediastinal lymph node metastasis</td></tr>
<tr><th colspan="10">Metastasis (M)</th></tr>
<tr><th colspan="4">4 and 5. Edition</th><th colspan="6">6. Edition</th></tr>
<tr><td>Mx</td><td colspan="3">Distant metastasis cannot be assessed</td><td>MX</td><td colspan="5">Distant metastasis cannot be assessed</td></tr>
<tr><td>M0</td><td colspan="3">No distant metastasis</td><td>M0</td><td colspan="5">No distant metastasis</td></tr>
<tr><td>M1</td><td colspan="3">Distant metastasis</td><td>M1</td><td colspan="5">Distant metastasis</td></tr>
<tr><th colspan="10">TNM Stage Grouping (S)</th></tr>
<tr><th colspan="4">4 and 5. Edition</th><th colspan="6">6. Edition</th></tr>
<tr><th></th><th>Under 45 years</th><th colspan="2">45 years and older</th><th></th><th colspan="3">Under 45 years</th><th colspan="2">45 years and older</th></tr>
<tr><td>S I</td><td>Any T& N, M0</td><td colspan="2">T1, N0, M0</td><td>S I</td><td colspan="3">Any T& N, M0</td><td colspan="2">T1, N0, M0</td></tr>
<tr><td>S II</td><td>Any T& N, M1</td><td colspan="2">T2, N0, M0
T3, N0, M0</td><td>S II</td><td colspan="3">Any T& N, M1</td><td colspan="2">T2, N0, M0</td></tr>
<tr><td>S III</td><td></td><td colspan="2">T4, N0, M0
Any T, N1, M0</td><td>S III</td><td colspan="3"></td><td colspan="2">T1, N1a, M0
T2, N1a, M0
T3, N0, M0
T3, N1a, M0</td></tr>
<tr><td rowspan="8">S IV</td><td rowspan="8"></td><td rowspan="8" colspan="2">Any T& N, M1</td><td rowspan="6">S IVA</td><td colspan="3" rowspan="6"></td><td colspan="2">T1, N1b, M0</td></tr>
<tr><td colspan="2">T2, N1b, M0</td></tr>
<tr><td colspan="2">T3, N1b, M0</td></tr>
<tr><td colspan="2">T4a, N0, M0</td></tr>
<tr><td colspan="2">T4a, N1a, M0</td></tr>
<tr><td colspan="2">T4a, N1b, M0</td></tr>
<tr><td>S IVB</td><td colspan="3"></td><td colspan="2">T4b, Any N, M0</td></tr>
<tr><td>S IVC</td><td colspan="3"></td><td colspan="2">Any T& N, M1</td></tr>
</table>

Table-5: Comparison of TNM 7th and 8th editions. 1: In greatest dimension, ETE[2]: Extrathyroidal extension, MAD[3]: Moderately advanced disease, VAD4: Very advanced disease. MMI[5]: Macroscopic muscle invasion, RLN[6]: Recurrent laryngeal nerve. L[7]:Level In 7. edition, It is stated that if tumor is solitary it can be shown as T(s), if tumor is multifocal it can be shown as T(m). In multifocal tumors, greatest dimension of focus determines the T state.

Primary Tumor (T)

7. Edition					8. Edition				
Tx		Primary tumor cannot be assessed			Tx		Primary tumor cannot be assessed		
T0		No evidence of primary tumor			T0		No evidence of primary tumor		
T1	T1a	</=1 cm[1]		Limited to thyroid	T1	T1a	</=1 cm[1]		Limited to thyroid
	T1b	>1 cm - </=2 cm[1]		Limited to thyroid		T1b	>1 cm - </=2 cm[1]		Limited to thyroid
T2		>2 cm - </=4cm[1]		Limited to thyroid	T2		>2 cm - </=4cm[1]		Limited to thyroid
T3		>4 cm[1]		Limited to thyroid	T3	T3a	>4 cm[1]		Limited to thyroid
		Any T	Minimal ETE[2]	Perithyroid soft tissue Sternothyroid muscle		T3b	Any T	ETE[2] (MMI[5])	Sternotiroit Sternohiyoid Omohiyoid
T4	T4a	Any T	ETE[2] (MAD)[3]	Subcutaneous Larynx, trachea RLN[6] Esophagus	T4	T4a	Any T	ETE[2]	Subcutaneous Larynx, trachea RLN[6] Esophagus
	T4b	Any T	ETE[2] (VAD)[4]	Prevertebral fascia Mediastinal vessel Carotid artery		T4b	Any T	ETE[2]	Prevertebral fascia Mediastinal vessels Carotid artery

Regional Lymph Node (N)

7. Edition				8. Edition			
Nx		Regional lymph nodes cannot be assesed		Nx		Regional lymph nodes cannot be assesed	
N0		No regional lymph nodes metastasis		N0		No regional lymph nodes metastasis	
N1	N1a	Central neck	L[7] VI	N1	N1a	Central neck	L[7] VI
	N1b	Ipsilateral neck	L[7] I, II, III, IV, V			Upper mediastinal	L[7] VII
		Contralateral neck			N1b	İpsilateral neck	L[7] I, II, III, IV, V
		Bilateral neck				Contralateral neck	
		Upper mediastinal	L[7] VII			Bilateral neck	
		Retropharyngeal				Retropharyngeal	

Metastasis (M)

7. Edition		8.Edition	
Mx	Distant metastasis cannot be assessed	Mx	Distant metastasis cannot be assessed
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis

TNM Stage Grouping (S)

7. Edition			8. Edition		
	Under 45 years	45 years and older		Under 55 years	55 years and older
S I	Any T& N, M0	T1a, N0, M0 T1b, N0, M0	S I	Any T& N, M0	T1a, N0, M0 T1b, N0, M0 T2, N0, M0
S II	Any T& N, M1	T2, N0, M0	S II	Any T& N, M1	T1, N1, M0 T2, N1, M0 T3, N0, M0 T3, N1, M0
S III		T1, N1a, M0 T2, N1a, M0 T3, N0, M0 T3, N1a, M0	S III		T4a, Any N, M0
S IVA		T1, N1b, M0 T2, N1b, M0 T3, N1b, M0 T4a, N0, M0 T4a, N1, M0	S IVA		T4b, Any N, M0
S IVB		T4b, Any N, M0	S IVB		Any T&N, M1
S IVC		Any T&N, M1			

and up to 1 cm intrathyroidal (T1) were in stage I, tumors over 1 cm were in stage II. Tumors without any lymph node and distant metastasis but with extrathyroidal extension (T4) and tumors of any size with lymph node metastasis were in stage III, patients with distant metastases were in stage IV. The T3N0M0 group in stage II in the fifth edition was transferred to stage III in the sixth edition. In addition, the presence of central metastasis accompanying T1-3 was also included in stage III. Stage IV in the 5th edition was divided into 3 subgroups as stage IVA, IVB, IVC in the 6th edition. Stage IVA includes the patients of T4a (with or without lymph node metastasis) or N1b with T1,2,3,4a. Stage IVB includes the patients with T4b (with or without lymph node metastases) and stage IVC includes the patients with distant metastases (18). There was no change in staging in the 7th edition, compared to the sixth edition.

Differences Between Seventh and Eighth Editions

The most important change in the eighth edition is that the age, which has been divided as below or above 45 years in the previous editions as a prognostic factor, has been updated as below or above 55 years (Table 5). Furthermore, the change in the definition of T3 in T-staging is remarkable. In the seventh edition, the definition of minimally invasive extrathyroidal extension and the perithyroidal soft tissue definition as an example of this have been removed. In the eighth edition, macroscopic invasion of any of the strap muscles was moved to the T3 category. In the N staging, the upper mediastinal lymph node involvement which appears in N1b in the 7th edition has been moved to N1a (Table-5).

Over the age of 55 years, significant changes are remarkable in the TNM classification. T2N0M0 which appears in stage II in the seventh edition was moved to stage I. Namely, all intrathyroidal tumors without lymph node metastasis of up to 4 cm are located in stage I. In the seventh edition, T3N0M0, T1-3N1aM0 in stage III, and T4aN0-1M0, T1-3N1bM0 in stage IVA existed. In the eighth edition, T3N0M0 and T1-3N1M0 are defined in stage II. That is, despite the fact that the lymph nodes were defined seperately as N1a and b in the eighth edition, the regional distinction of N was removed in the staging and the N staging was defined as one level. T3N0-1M0 and T1-2N1M0 tumors were defined as stage II. T4a, any N,M0 is defined as stage III. A significant section in stage III and stage IVA in the seventh edition was degraded to stage II, and T4a tumors in stage IVA were degraded to stage III. In the eighth edition, stage IVB and stage IVC in the seventh version were defined as stage IVA and stage IVB, respectively, and stage IVC has been removed from the staging. In the eighth edition, it is generally seen that there is a degradation in all stages (Table-5).

DISCUSSION

Since the DTC entered the TNM classification system, there have been significant changes in the editions until today. One of the most noticeable changes in the eighth edition is the age limit to be 55, which was 45 years (19). It is not clear why the age of 45 years has been selected as the prognostic threshold until today (26). Recent studies have questioned the 45-year-old threshold (25). The first noteworthy study to address this issue was the study of 3572 patient data from the records of the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) which was established in America (27). Jonklaas et al. (27) found that the overall disease-specific survival (DSS) in the series was generally similar for males and females. In multivariate analysis, DSS was found to be better in female patients than in male patients diagnosed under 55 years of age and found to be similar between female and male patients diagnosed after 55 years of age. The authors noted that these data raise the question of whether the existing staging system could be improved if the age threshold is furtherly increased (27). Ganly et al. (26) assessed the cancer patients of Memorial Sloan Kettering cancer center (MSCCC) from 1985 to 2010 by dividing them into 5 categories. They found that mortality increased linearly with increasing age and mortality increased by up to 37 times in groups, from with less than 40 years old of age, to with larger than 70 years of age, but they could not determine a certain threshold value in risk determination (26). In another study performed by the same center; it was

stated that the selection of a threshold age of 55 years instead of 45 for the DSS is a stronger threshold for the appropriateness of the TNM system (28).

In addition, in the multi-center study with 9484 patients, it was also determined that withdrawal of the age limit to 55 increased the statistical validity of the TNM classification compared to 45 years (29). Kim et al. (30) in a study with 6333 patients in South Korea, detected that the optimal threshold value to predict DSS as 55.4 years of age with the ROC analysis. After these studies, the age limit was set at 55 years in the eighth edition.

In the TNM classification, the age to be updated to 55 years showed a transition to a lower stage by 12% in a USA multicenter series, and by 20% in a South Korea series (29,30). The 10-year DSS was found to be 98% in the USA group with stage degradation. However, a stage IV patient with distant metastatis aged between 45-54 years was degraded to stage II, but in this group, 10-year DSS was detected as 68% (29). However, this small group with high risk and stage degradation is suggested to have minimal long-term effect on DSS (31).

Minimal extrathyroidal extension was found to not to affect recurrence and DSS (32,33). Nixon et al. (34) found that microscopic extrathryoidal extension did not significantly affect recurrence and mortality in DTC below 4 cm, and the extent of thyroidectomy and radioactive iodine (RAI) treatment on 10-year survival and recurrence in patients with microscopic extrathyroidal extension were found to have no significant effect. Ito et al. (35) in parallel to these findings, reported that the microscopic extrathyroidal extension in patients with papillary thyroid cancer (PTC) over the age of 45 years did not significantly affect the recurrence. After these studies questioning the place of minimal extrathyroidal extension in the T-staging (32-35), the minimal extrathyroidal extension was removed from the eighth edition.

Microscopic metastasis in only one lymph node in the central region or extranodal metastasis in multiple lymph nodes in seventh and eighth edition of the TNM system is located within the same N category (N1a). In the presence of lateral region metastasis, again, the presence of microscopic metastasis in only one lymph node or extranodal metastases in multiple lymph nodes is considered within the same N category. In a study published by the thyroid cancer nodal surgery study group of ATA (36) in 2012, they evaluated the prognostic significance of lymph node metastasis in PTC. According to this; in patients with clinically positive lymph node metastases and/or when the number of metastatic lymph nodes is increased, compared to those with microscopic metastases, the risk of recurrence is significantly increased. In addition, if there is extranodal extension in lymph node metastases, both the risk of recurrence increases and the disease-free survival decreases. In this context, the evaluation and staging of lymph node metastasis in PTC in the TNM classification system is suggested to be rearranged according to the metastatic lymph node diameter, number and extranodal extension (36). The expectation that the evaluation of lymph node metastasis could change according to this data in the next edition of TNM after this study was high. But the eighth edition evaluated the lymph node metastasis staging in a single category. Although features such as the number of involved lymph nodes, the diameter of the largest metastatic lymph node, the diameter of the metastatic focus in the lymph node, and the presence of extranodal extension are not included in this classification, it is expected that some of these features may enter into the TNM classification system in future editions (31).

After TNM classification has been updated, some studies compared edition 7 and 8. From these studies, the widest one which included the data of 64342 patients from the USA SEER (Surveillance, Epidemiology and End Results) and of 179698 patients from the National Cancer Database (NCDB) between 2004-2012 made an evaluation. 23% of the patients in the SEER database, and 24% in the NCDB database had stage degradation. Ratios and rate shifts were similar in stages of both databases. In the SEER database, the patients were classified as stage I, II, III, IV by the ratio of 75.9%, 6.8%, 11.7%, 5.7% in the seventh edition, and of 89.8%, 8.2%, 1%, 1% in the eighth edition, respectively; and in the NCDBD database, of 75.4%, 7.2%, 11.9%, 5.5% in the seventh edition, and of 89.3%, 8.8%,

1.3% and 0.6% in the eighth version, respectively. DSS and total life span were associated with the stage at the time of diagnosis at both 7th and 8th editions. In the 8th edition, the prognosis was worse in stage III and stage IV patients than in the seventh edition. The researchers have determined with this broad assessment that the eighth edition is better in predicting the life expectancy (37). In addition, in three trials in which the clinical series were re-staged, the eighth edition was found to be more appropriate than the seventh edition to predict DSS (38-40). In these studies, approximately 40% of the patients are noted to have a stage degradation in the eighth edition (38,40). The ratio of patients with advanced stage (III/IV) appears to be declining significantly (38). Kim et al. (38) found that in the eighth edition compared to the seventh, the rate of stage I patients increased from 61.9% to 81% and the rate of stage II patients increased from 1.7% to 16%. They determined that the stage III patient ratio reduced from 27.6% to 2.3% and the ratio of patients in stage IVB (stage IVC in seventh edition) from 0.8% to 0.5%. The 10-year DSS in this study was detected as 99.1%, 92.5%, 97.5% and 91.1% in stage I, II, II and IVA, respectively in the seventh edition. Mortality rate in stage III is higher than in stage I, and lower than in stage II. In the eighth edition, the 10-year DSS was changed to 99%, 94%, 80.4%, 66.7% in stages I, II, II, IVA, respectively. In stage III, the DSS declined, the Kaplan-Meier life curve did not cross over and was below stage II.

In the final guideline of the American Thyroid Association (ATA); it is indicated that initial treatment in patients with DTC should increase the overall and disease-specific life expactancy, reduce the risk of persistence and recurrent disease and associated morbidity, facilitate disease staging and risk classification, minimize the morbidity related to treatment and unnecessary treatment (25).

With the eighth edition to be launched in January 2018 to be used clinically, this edition will affect the stage of a significant number of patients and cause them to be at a lower stage than the past. Pontius et al. (37) suggest that patients who will be in lower stages from now on will be considered as low-risk patients, which may lead to more limited use of adjuvant radioactive iodine therapy, thus reducing over-treatment, with this edition.

Tuttle et al. (31) stated that the eighth edition can easily be adapted to clinical practice and that the appropriate tumor stage can be easily detected according to important clinical features (age, macroscopic extrathyroidal extension and distant metastasis). If the classification is to be repeated briefly;

- In patients under the age of 55 years, patients with distant metastases were defined as stage II, patients without distant metastases as stage I.

- Patients with distant metastasis over the age of 55 years are defined as stage IVB.

- Patients without distant metastasis over at the age of 55 years can be classified according to other clinical features. Stage I is defined as no lymph node metastasis in patients with intrathyroidal tumors smaller than 4 cm (T1, T2), and stage II as with lymph node metastasis. Regardless of lymph node status (N0 or N1), patients with intrathyroidal tumors (T3) greater than 4 cm are in stage II. In tumors with macroscopic extrathyroidal extension; irrespective of lymph node metastasis, if the tumor is extended to only to strap muscles, it is stage II, if extended to subcutaneous tissues, larynx, trachea, recurrent laryngeal nerve and esophagus, it is stage III, and if extended to the prevertebral fascia, mediastinal vessels, or surrounded the carotid artery, then it is stage IVA.

The eighth edition of TNM, according to the previous edition, is staging a major proportion of patients with DTC in a low-risk group for mortality. TNM classification is a useful method for predicting mortality in DTC. However, the course of mortality and recurrence are not parallel to each other. Therefore, the patient should also be assessed for recurrence risk in addition to TNM staging, as suggested by the ATA guideline (25,31).

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