World Journal of Surgery

Published Online: 1 February 2007

World J Surg (2007) 31: 879–887
DOI: 10.1007/s00268-006-0864-0

TNM Classification of Thyroid Carcinoma

Ashok R. Shaha, MD, FACS[1,2]

[1]*Head and Neck Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA*
[2]*Cornell University Medical Center, New York, NY, USA*

Abstract

Background: The understanding of biology of well-differentiated thyroid cancer has improved in the last two decades with the detailed understanding of prognostic factors and risk group stratification. The risk groups are crucial in the management of thyroid cancer and overall prognosis.

TNM Staging System: The TNM staging system has been used in all human cancers, and it adheres to the biology of tumors. The data in thyroid cancer comes from retrospective studies, as there are no prospective randomized trials. The most recent TNM staging system was revised and published (6th edition) in 2002. The major attributes of the staging system include: age as the most important prognostic factor, and age is included in the staging system, below and above the age of 45; T1 tumors are considered to be those below 2 cm; T3 tumors include minor extra-thyroidal extension invading the strap muscles; T4 tumors includes T4a and T4b, T4a being operable tumors; all anaplastic cancers are T4, although operable anaplastic thyroid cancers are considered to be T4a.

Conclusion: These changes in the TNM system are consistent with our current philosophy in the overall management of thyroid cancer and adjuvant therapy. The N staging system includes N1a and N1b—N1a being level VI lymph nodes, while N1b includes level IV and superior mediastinal and contralateral neck nodes. The TNM staging system helps reporting our data and comparing results in different parts of the world. However, there is no level I evidence in thyroid cancer.

The TNM staging system (tumor, node, metastasis) was developed approximately 65 years back in 1940 by Pierre Denoix.[1] The UICC (International Union Against Cancer) adopted the TNM staging system and published the 1st edition of the TNM staging system in 1968 for approximately 23 body sites.[2] This has been traditionally the clinical staging system of the primary tumor, as well as lymph node metastasis and distant metastasis. Extensive revisions have been made in the TNM staging system over the years.[3] As the technology advanced, imaging studies were included in the TNM staging system. As the revisions were made, evidence-based information was added, and the committee made every effort to use level I evidence. Unfortunately, in many human cancers, level I evidence is not available. An example of this would be thyroid cancer, where the bulk of evidence is level III.

The head and neck tumors generally include multiple sites, with a variety of histologies and different clinical behavior and outcomes. Since there is no level I evidence in thyroid tumors, generally the changes in the TNM staging are mainly based on retrospective large cohorts of published series. Unfortunately, the decisions in thyroid cancer management are based mainly on the institutional policies, direct involvement of the surgeons, nuclear physicians, and endocrinologists. However, the thyroid cancer staging system does address some of the important prognostic factors, such as age of the patient

Correspondence to: Ashok R. Shaha, e-mail: shahaa@mskcc.org

and stage of the tumor. Patients with Stage IV universally behave poorly. The clinical staging system in thyroid cancer may change after the surgical procedure, especially if the final pathology report reveals extrathyroidal extension or disease extending outside the thyroid gland.

The purpose of the cancer staging system is to divide patients into groups to categorize prognosis and define treatment. For every malignant problem, a variety of staging systems are available worldwide. These staging systems are based on studies from individual institutions or countries using analysis of retrospective data to determine prognostic factors.

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer Committee (UICC) have formulated a standardized staging system for every malignant tumor, known as the TNM staging system. The 'T' stands for tumor, 'N' for nodal metastasis, and 'M' for distant metastasis. Tumor progression occurs from the T stage to the N stage, and subsequently to the M stage. This system has been recognized in most tumors as standard progression of the disease, and has been utilized worldwide.

The TNM staging system is in a process of evolution, with the latest version adopted in the 6th edition of the AJCC/UICC Staging Manual published in 2002.[4] The Committee on the Staging System meets periodically to review the data and correct deficiencies in the previous staging system. Thyroid cancer staging has similarly evolved over time. The 6th edition of the AJCC Staging Manual reveals several changes in the staging system for papillary/follicular thyroid carcinoma. It is important for the reader to understand these changes. An attempt has been made in this article to compare the new staging system with that of the 5th edition, and to analyze the differences. The committee generally reviews the latest publications on any individual subject along with recommendations made by members. Even with, or perhaps due to, the timely re-evaluation of standards, the TNM staging system remains the global standard.

The staging system is based on clinical evaluation at the time of initial examination. However, the results of imaging studies, such as CT scan and MRI, have also been included in the recent versions. The PET scan, though commonly used in the evaluation of malignant tumors, is not currently included as a standard procedure in the staging system. The clinical TNM staging system is converted into TNMp after the pathology report has been made available following a surgical procedure.

UNIQUE FEATURES OF THYROID STAGING

The staging of thyroid tumors generates considerable confusion since various histologies have different staging systems. These histologies are grouped into papillary follicular, medullary, and anaplastic variants. The staging system is quite different for medullary and anaplastic thyroid carcinomas, since a majority of patients with anaplastic carcinoma have Stage IV disease.

Another important aspect of the thyroid staging system is the inclusion of age. This is the only human cancer with such a distinction, and patients are divided into groups below or above the age of 45. There are only two stages for patients below the age of 45, Stages I and II for papillary and follicular carcinoma. Regional lymph node metastasis has no major impact on patients with thyroid cancer, especially those with well-differentiated thyroid cancer. However, in older patients, nodal metastasis does have some impact, and these are Stage III patients.[5–7] The lymph nodes commonly involved in metastatic disease are the Delphian nodes and lymph nodes in the tracheoesophageal or paratracheal areas. These are level VI nodal groups. These are the lymph nodes commonly removed in patients undergoing total thyroidectomy with central compartment clearance.

One of the main purposes of the staging system is to guide the treating physician in the treatment of the primary tumor, nodal disease, and the management of distant metastasis. The staging system also influences the role of primary treatment and adjuvant therapy. However, the presence of distant metastasis may not become apparent in well-differentiated thyroid carcinoma unless the patient has undergone radioactive iodine ablation. Radioactive iodine ablation cannot be performed effectively unless the patient has undergone total thyroidectomy. Decisions regarding the definitive treatment in thyroid carcinoma are therefore somewhat difficult to categorize based on the staging system.

Unfortunately, there are no prospective randomized trials in well-differentiated thyroid carcinoma based on a variety of surgical treatments, mainly total versus less-than-total thyroidectomy. As there is hardly any survival difference between the groups, such a study would require a large number of patients to be followed for an extended period of time. Studies of this kind are unlikely to be undertaken, and there would likely not be any major statistical difference in the long-term follow-up to suggest which treatment modality is superior.

A majority of the data in thyroid cancer comes from retrospective studies.[8–29] There is inevitably bias in these

Table 1.
Prognostic factors in thyroid cancer: AMES (age, distant metastases, extent, size)

Low risk	High risk	Survival by AMES risk groups (20 years)
Younger patients (men = 40, women = 50) with no metastases	All patients with distant metastases	Low risk = 99%
Older patients (intrathyroid papillary, minor capsular invasion for follicular lesions)	Extra-thyroid papillary, major capsular invasion follicular	High risk = 61%
Primary cancers <5.0 cm	Primary cancers = 5.0 cm in older patients (men > 40, women > 50	
No distant metastases		

Based on Lahey Clinic data.

Table 2.
Prognostic factors in thyroid cancer: AGES (age, grade, extent, size)

Prognostic score = 0.05 × age	Survival by AGES score (20 years)
+1 (if grade 2)	<3.99 = 99%
+3 (if grade 3 or 4)	4–4.99 = 80%
+1 (if extra-thyroid)	5–5.99 = 67%
+3 (if distant spread)	>6.00 = 13%
+0.2 × tumor size (cm maximum diameter)	

Based on Mayo Clinic data.

Table 3.
Prognostic factors in thyroid cancer: MACIS (metastasis, age, completeness of resection, invasion, and size)

Score = 3.1 (if age <40 years) or 0.08 × age [if age = 40 years])	Survival by MACIS score (20 years)
+0.3 × tumor size (cm maximum diameter)	<6 = 99%
+1 (if incompletely resected)	6–6.99 = 89%
+1 (if locally invasive)	7–7.99 = 56%
+3 (if distant spread)	>8.00 = 24%

Based on Mayo Clinic data.

Table 4.
Risk groups in thyroid cancer

Group	Type
Low risk	Low risk patient/low risk tumor
Intermediate risk	Low risk patient/high risk tumor High risk patient/low risk tumor
High risk	High risk patient/high risk tumor
Patient factors	Age, gender
Tumors factors	Grade, size, extra-thyroidal extension, distant metastasis

Based on Memorial Sloan-Kettering Cancer Center data.

studies based on the philosophy of individual institutions in managing these patients, and strong influence in relation to postoperative adjuvant therapy, such as radioactive iodine ablation. Due to the lack of appropriate evidence-based studies, there is considerable debate on the management of thyroid cancer, especially in relation to the extent of thyroidectomy and the role of radioactive iodine ablation. The majority of patients in the low risk thyroid cancer group invariably get over-treatment.[17] Whether this over-treatment will result in any long-term survival difference will likely remain the subject of debate.

Histologic variations in well-differentiated thyroid carcinoma are not included in the staging system. However, it must be remembered that this differentiation is crucial in relation to outcome, extrathyroidal extension, and overall prognosis.[30–33] Hopefully, future editions of the Staging Manual will include histological variants to aid standardization.

RISK GROUP ANALYSIS FOR DIFFERENTIATED CARCINOMA

The subject of thyroid carcinoma and the extent of thyroidectomy generates considerable controversy. At the majority of institutions where radioactive iodine treatment is routinely used, patients undergo total thyroidectomy so that radioactive ablation can be facilitated. This is generally quite dependent on institutional and individual practices, rather than adherence to the staging system or prognostic factors.

In the last two decades, many institutions have defined prognostic factors and risk groups in thyroid carcinoma.[8–29] Various scoring systems have been developed, including EORTC, AGES, and MACIS, with many similarities.[9,10,12,13] These risk group analyses and scoring systems have divided the patients into low and high risk groups (Tables 1–4).

Table 5.
Risk groups definitions in differentiated carcinoma of the thyroid

	Low risk	Intermediate risk	Intermediate risk	High risk
Age (years)	<45	<45	>45	>45
Distant metastasis	M0	M+	M0	M+
Tumor size	T1, T2 (<4 cm)	T3, T4 (>4 cm)	T1, T2 (<4 cm)	T3, T4 (>4 cm)
Histology and grade	Papillary	Follicular and/or high grade	Papillary	Follicular and/or high grade
5-year survival (%)	100	96	96	72
20-year survival (%)	99	85	85	57

Based on Memorial Sloan-Kettering Cancer Center data.

Overall survival in the low risk group exceeds 98%.[9,10,13,19] However, the survival in the high risk group drops to almost 57%. Clearly, thyroid carcinoma is a serious disease for patients belonging to the high risk group. This risk group analysis is crucial in the management of thyroid carcinoma and understanding the biology and prognosis of patients with well-differentiated thyroid carcinoma. Most studies include prognostic factors of age, tumor grade, extrathyroidal extension, tumor size, and presence of distant metastasis. These prognostic factors have been considered to be important, while gender, multicentricity, and nodal metastasis are considered unimportant. Nodal metastasis may have some impact in older individuals in whom there is a high incidence of regional recurrence, though a minor impact on overall outcome.[5,6,21]

Unfortunately, the lack of randomized studies means there are no good evidence-based type I, II or III data in the management of well-differentiated thyroid cancer. Most studies are type IV or V, with no strong evidence base. However, an understanding of the prognostic factors and risk group analyses is quite helpful in directing the staging system. Even though studies from the Mayo Clinic and the Lahey Clinic divided patients into low and high risk groups, the detailed analysis of the large number of patients from Memorial Sloan-Kettering Cancer Center divided prognostic factors into patient-related and tumor-related groups.[7,22]

Patient-related prognostic factors include age of the patient and gender, while tumor-related prognostic factors include size of the tumor, grade of the tumor, extrathyroidal extension, and distant metastasis. Based on these prognostic factors, patients were divided into low, intermediate, and high risk groups. The low risk group includes patients below the age of 45 with low risk tumors, while the high risk group included patients above the age of 45 with high risk tumors. The analysis also included an intermediate risk group, which included again, two groups—a young patient with aggressive thyroid cancer or an older patient with a small thyroid cancer.

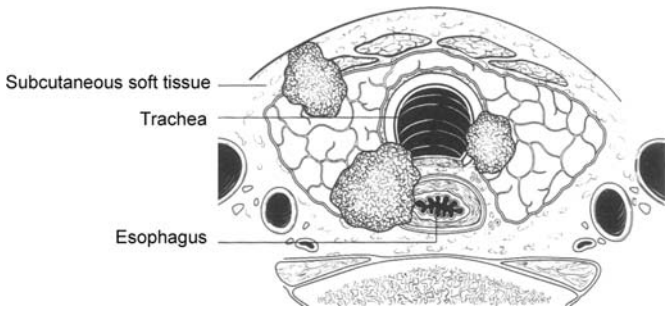

Figure 1. Schematic presentation of operable extrathyroidal extension (T4a). Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002), Springer, New York (www.springeronline.com).

The division of patients into low, intermediate, and high risk groups is important for making treatment decisions based on the long-term follow-up and survival differences. Survival in the low risk group was 99%,[7,22,19] while the survival in the intermediate and high risk groups were 87% and 57% respectively (Table 5).

SUMMARY OF THE SIXTH EDITION STAGING SYSTEM FOR THYROID CANCER

Primary site: T Staging

T staging in the 6th edition has been revised. T1 is considered to be a tumor 2 cm or less in its greatest dimension, limited to the thyroid gland, while T2 includes tumors between 2 and 4 cm. T3 tumors are more than 4 cm in their greatest dimension, limited to the thyroid, or any tumor with minimal extrathyroidal extension (extension to the sternothyroid muscle or perithyroid soft tissue). T4 has been divided into T4a and T4b. T4a includes tumor of any size, extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve, while T4b

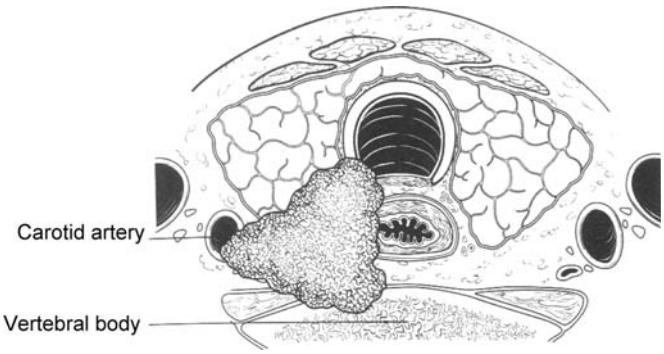

Figure 2. Schematic presentation of inoperable extrathyroidal extension (T4b). Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002), Springer, New York (www.springeronline.com).

includes tumor-invading prevertebral fascia or encasing carotid artery or mediastinal vessels. Generally T4b is considered to be an inoperable situation (Figs. 1, 2; Tables 6, 7).

Regional Lymph Nodes

Nodal metastasis is considered to be of less prognostic significance in patients with well-differentiated papillary or follicular thyroid carcinoma, while it is an important prognostic factor in patients with medullary thyroid carcinoma. The first echelon of nodal metastases is in the tracheoesophageal group or pretracheal and prelaryngeal lymph nodes. These are generally grouped as level VI. Metastases to the jugular chain or supraclavicular region are less common. Lymph node metastasis in the neck is grouped according to classification of squamous cell carcinoma: level I being submandibular; level II, III, and IV along the jugular vein, high, mid, and low jugular lymph nodes respectively; while level V is the lymph nodes in the posterior triangle of the neck. Level VI includes lymph nodes in the central compartment of the neck or paratracheal lymph nodes, while level VII includes upper mediastinal lymph nodes.

This lymph node categorization is important and is based on the patterns of lymph node metastasis. The majority of patients with nodal metastasis generally have disease at level VI. Disease at level I is quite rare, and usually submandibular and nodal dissection is not necessary in patients with well-differentiated thyroid carcinoma. Similarly, nodal metastasis at level Va is very uncommon in well-differentiated thyroid carcinoma. N1a is nodal metastasis at level VI, (pretracheal, paratracheal, prelaryngeal, and Delphian lymph nodes), while N1b is metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes. Even though medullary thyroid cancer patients follow a similar pattern of spread, nodal metastasis has a much worse impact on overall prognosis. The current AJCC staging system has elaborated on the histological examination of selective neck dissection, including 6 or more lymph nodes, where histological examination of the modified radical neck dissection ordinarily would include 10 or more lymph nodes.

Distant Metastasis

The most common organ sites for distant metastasis are lungs, bones, or brain. However, pulmonary metastases may not be recognized on routine chest X-ray or CT scan, and are best evaluated with radioactive iodine ablation. Distant metastases from medullary carcinoma to the liver are best evaluated with laparoscopy and laparoscopic liver biopsy, as these metastatic lesions are generally very small and located on the surface of the liver, and are difficult to detect with routine imaging studies.

Staging for Medullary Thyroid Carcinoma

Staging for medullary thyroid carcinoma is essentially the same as papillary follicular carcinoma; however, it does not include age as a differentiating factor. Anaplastic thyroid carcinoma is generally a Stage IV tumor; however, in the recent revision, tumors are divided into Stage IVa as T4a, while Stage IVb is considered to be T4b, and stage IVc is any patient with anaplastic thyroid carcinoma and distant metastasis. This classification has important practical implications, as patients with T4a tumors may undergo surgical resection.

Important Changes in the Fifth and Sixth Editions of Thyroid Cancer Staging

1. Tumor stage has been revised and categories have been re-defined:

a) T1 now includes tumors less than 2 cm. This is in keeping with other head and neck staging systems
b) T3 includes tumors more than 4 cm in their greatest dimension that are limited to the thyroid, or any tumor with minimal extrathyroidal extension (for example, extension to sternothyroid muscle, or perithyroid soft tissue)

Table 6.
Definition of TNM

Category	Definition
Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in its greatest dimension, limited to the thyroid
T2	Tumor more than 2 cm, but not more than 4 cm in its greatest dimension, limited to the thyroid
T3	Tumor more than 4 cm in its greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a[b]	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b[b]	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Regional lymph nodes (N)[c]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

[a]All categories may be subdivided: (I) solitary tumor, (ii) multifocal tumor (the largest determines the classification).
[b]All anaplastic carcinoma are considered T4 tumors: T4a—intrathyroidal anaplastic carcinoma (surgically resectable); T4b—extrathyroidal anaplastic carcinoma (surgically unresectable).
[c]Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

c) T4 includes T4a and T4b.

2. Nodal staging has been revised:

a) N0
b) N1 has been divided in to N1a and N1b, N1a being paratracheal and level VI nodal disease, while N1b includes unilateral, bilateral, or contralateral cervical or superior mediastinal (level VII lymph nodes).

3. For well-differentiated papillary and follicular thyroid carcinoma, the stage grouping for patients older than 45 has been revised.
4. Stage III now includes tumors with minimal extrathyroidal extension (T3).
5. Stage IVa includes tumors of any size extending beyond the thyroid capsule to invade subcutaneous soft tissue, larynx, trachea, esophagus, and recurrent laryngeal nerve, while Stage IVb includes tumors that invade prevertebral fascia, carotid artery, or mediastinal vessels. Stage IVc includes advanced tumors with distant metastasis.
6. All anaplastic carcinomas are now considered to be T4. The T staging in anaplastic thyroid carcinoma has been divided into T4a (intrathyroidal anaplastic carcinoma—surgically resectable) and T4b (extrathyroidal anaplastic carcinoma—surgically unresectable).

EVIDENCE BASE FOR TNM STAGING

Well-differentiated thyroid cancer continues to be an indolent disease. The overall survival exceeds 95%. Unfortunately, no randomized trials have been performed in well-differentiated thyroid cancer, and are unlikely to be undertaken due to the need for a large number of patients and long-term follow-up. The American College of Surgeons Oncology Group (ACOSOG) and the Endocrine Committee discussed extensively on the subject of randomized prospective trials in relation to lobectomy versus total thyroidectomy and postoperative radiation therapy. Unfortunately, these trials are difficult to undertake, and the committee decided against such randomized trials. Most of the information available in the management of thyroid cancer comes from large series, such as Mayo Clinic, Lahey Clinic, Memorial Sloan-Kettering Cancer Center, National Cancer Database, and SEER data.

Table 7.
Stage grouping: separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated carcinoma)

Staging	T	N	M
Papillary or follicular under 45 years			
Stage I	Any T	Any N	M0
Stage II	AnyT	Any N	M1
Papillary or follicular 45 years and older			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Medullary carcinoma			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Anaplastic carcinoma[a]			
Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

[a]Any anaplastic carcinomas are considered Stage IV

There is no level I or II evidence in the management of thyroid cancer. Most of the information available in the literature is level III evidence. The decisions regarding total thyroidectomy, postoperative thyroid suppression, and radioactive iodine treatment are generally based on institutional practices, the philosophy of the treating physicians, and patient preferences.

The change in the T-staging system is a valuable addition to the staging system to distinguish operable and inoperable thyroid cancer. The 6th edition changed the T-staging, T1 being less than 2 cm, rather than the previous staging system of less than 1 cm. Clearly, this has generated some debate recently. Traditionally, microcarcinoma was considered to be less than 1 or 1.5 cm. The general impression continues that the majority of patients with tumors less than 2 cm will do remarkably well, and the overall outcome exceeds 98%–99%. Since the new staging system was published, there have been two interesting publications on size of the tumor, overall outcome, and the issue related to T1 tumors being less than 2 cm. Passler *et al.*[34] reviewed their experience with papillary and follicular thyroid cancer in relation to the size of the tumor.[34] They divided their patients with papillary thyroid carcinoma into 3 groups according to the size of the tumor: 1–10 mm, 11–20 mm, and 21–40 mm. They concluded that there was significant difference in cancer-specific survival between tumors less than 10 mm and those 11–20 mm. Their group does not appear to support the T1 classification up to 20 mm. Machens *et al.*[35] reviewed the prognostic value of primary tumor size in papillary and follicular thyroid carcinoma.[35] They concluded that there was increased risk of distant metastases in tumor size more than 20 mm. However, there was no difference in the outcome in tumors below 20 mm. They concluded that earlier intervention is warranted to keep the nodules under suspicion from growing more than 20 mm. Even though these 2 studies have contradictory conclusions, it appears that most of the patients with tumors below the size of 2 cm do extremely well and in most of the series the outcome has been excellent with no major outcome difference for tumors smaller than 20 mm.

The understanding of extrathyroidal extension is crucial in the management of thyroid cancer, especially to reduce the incidence of local recurrence. The identification of distant metastasis continues to be an issue, since the majority of imaging studies will not show distant metastasis, unless the patient has undergone radioactive iodine ablation. The incidence of distant metastasis continues to be high in younger individuals, especially children with bulky nodal metastasis. However, the overall outcome in this group is excellent.

One of the major deficiencies in the staging system is the inability to include grade as an important prognostic factor. The grade of the tumor, especially identification of tall cell, insular, and poorly differentiated thyroid cancer is one of the most important prognostic factors, even though this is commonly seen in older individuals, mainly with extrathyroidal extension, in young individuals, the presence of poorly differentiated thyroid carcinoma is always a poor prognostic factor. Hopefully, in future staging systems,

grade may be included. Capsular invasion divided into minor and major is crucial, along with vascular invasion.

The molecular markers are not included in the staging system at this time. The future in thyroid surgery will be to identify one or two important molecular markers, which can be performed on the needle biopsy specimen and be used as a major prognostic factor prior to definitive treatment. These can then be included in the staging system. Unfortunately, a variety of molecular markers have been studied, but no single molecular marker has yet been used in clinical practice routinely.

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