



Published in final edited form as:

CA Cancer J Clin. 2018 January ; 68(1): 55–63. doi:10.3322/caac.21439.

Differentiated and Anaplastic Thyroid Carcinoma: Major Changes in the American Joint Committee on Cancer Cancer Staging Manual Eighth Edition

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Abstract

This is a review of the major changes in the American Joint Committee on Cancer staging manual eighth edition for differentiated and anaplastic thyroid carcinoma. All patients younger than 55 years have stage I disease unless they have distant metastases, in which case their disease is stage II. In patients aged 55 years or older, the presence of distant metastases confers stage IVB, while cases without distant metastases are further categorized based on the presence/absence of gross extrathyroidal extension, tumor size and lymph node status. Patients aged 55 years or older whose tumor is ≤4 cm (T1-2) and confined to the thyroid (N0, NX) have stage I disease and those whose tumor is >4 cm and confined to the thyroid (T3a) have stage II disease regardless of lymph node status. Patients aged 55 years or older whose tumor is confined to the thyroid and ≤4 cm (T1-2) with any lymph node metastases present (N1a or N1b) have stage II disease; those who demonstrate gross extrathyroidal extension, the disease is considered stage II if only the strap muscles are grossly invaded (T3b); stage III if there is gross invasion of the subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a); or stage IVA if there is gross invasion of the prevertebral fascia or tumor encasing the carotid artery or internal jugular vein (T4b). The same T definitions will be used for both differentiated and anaplastic thyroid cancer but the basic premise of the anatomic stage groups will remain the same.

Keywords

differentiated thyroid cancer; staging; AJCC; anaplastic; oncology

Introduction

In October 2016, the American Joint Committee on Cancer (AJCC; www.cancerstaging.org) published the eighth edition of the AJCC/TNM cancer staging system, replacing the seventh

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Conflict of interest disclosure: No Conflicts

Author contributions: Manuscript preparation, editing and review: NDP, JB, RMT
Principal anatomic site or discipline representing the topic of the paper- Oncology

edition, which has been in use since 2009.¹ The official implementation date of the eighth edition is January 1, 2018, to allow time for the cancer care community to evaluate and understand the changes in the update and to make the infrastructure changes necessary for data collection and implementation². During this transition period, however, clinicians are encouraged to use the scientific content of the eighth edition to improve patient care and continue the drive toward more individualized management recommendations.

While maintaining and emphasizing the critical prognostic importance of the anatomic extent of the disease for staging, based on the tumor, lymph node, metastasis (TNM) concept, the eighth edition allows for integration of biologic and molecular markers in an effort to create a more contemporary personalized approach in addition to a robust classification system for population-based analyses^{1,2}. The increasing appreciation of the importance of factors beyond T, N, and M variables can be seen in the naming of the stage groups (stages I-IV), which has evolved from “anatomic stage” groups in the first six editions to “anatomic stage and prognostic groups” in the seventh edition to “prognostic stage groups” in the eighth edition. Thus, appropriate staging according to the eighth edition will require integration of a wide variety of information based on patient history and physical examination findings supplemented by imaging, intraoperative findings, and pathologic data. This will clearly present a challenge to tumor registries and will require a renewed commitment to both the documentation of important clinical variables as well as widespread dissemination of this information among all members of the clinical management team and personnel responsible for documenting prognostic stage for cancer registries and other reporting obligations.

Using an evidence-based medicine approach, the eighth edition staging system for differentiated and anaplastic thyroid cancer was produced by a multidisciplinary team. Through a series of conference calls and ongoing interactions via web and email, this team carefully evaluated the seventh edition staging system and identified areas that should be evaluated for possible modification and improvement. After careful literature review (which is detailed in the chapter on differentiated and anaplastic thyroid cancer in the eighth edition), modifications to the prognostic staging system were made and initially evaluated by testing on a dataset provided by Memorial Sloan Kettering Cancer Center³. Re-evaluation of the staging for medullary carcinoma of the thyroid is reported in a separate chapter of the staging manual. (www.cancerstaging.org)

Eighth edition staging for differentiated and anaplastic thyroid cancer

While retaining the same basic reliance on T, N, and M variables as the seventh edition, the eighth edition for differentiated thyroid cancer does make substantial changes with regard to (1) the age cutoff that differentiates low risk from high risk, (2) the critical importance of the difference between minor extrathyroidal extension detected only histologically and gross extrathyroidal extension identified on imaging or clinical evaluation, and (3) the lack of prognostic importance of small volume lymph node metastasis on mortality in thyroid cancer (See Table 1 from Tuttle et al editorial Thyroid 2017)^{3,4}. As discussed in detail below, the age cutoff for differentiated thyroid cancer staged groups was raised from 45 to 55 years, and neither minor extrathyroidal extension nor lymph node metastasis will stage a

patient to T3 or stage III, respectively, in the eighth edition system. Finally, to be more anatomically consistent, level VII cervical lymph nodes (high mediastinal nodes) will be classified as N1a disease (central neck) rather than lateral neck disease (N1b).

T category definitions for differentiated and anaplastic thyroid cancer

For consistency, staging for differentiated and anaplastic thyroid cancer in the 8th edition will utilize the same definitions for T, N, and M categories (Table 2)^{3,4}. The TX, T0, T1a, T1b, and T2 category definitions are unchanged from the 7th edition. Likewise, the definitions of T4a and T4b are also unchanged in content, although the precise wording of the definitions have been edited for clarity. The major change in the T category relates to the definition of the T3 category, which has changed substantially from the seventh edition.

The T3 category in the seventh edition included any tumor more than 4 cm in greatest dimension limited to the thyroid or tumors of any size with minimal extrathyroidal extension defined as extension to sternothyroid muscle or perithyroid soft tissue⁴. This definition resulted in many patients older than 45 years being classified as having stage III disease based solely on the presence of microscopic minimal extrathyroidal extension. As already noted, the T3 category has been divided into two subgroups in the 8th edition: T3a is defined as tumors greater than 4 cm limited to the thyroid, and T3b is defined as a tumor of any size demonstrating gross extrathyroidal extension invading only a strap muscle (i.e., the sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscle). Because of this change, minor extrathyroidal extension identified only on histologic examination is no longer a variable in determining the T category. Obviously, appropriate designation of the T3 category will depend upon appropriate integration of the clinical findings of gross extrathyroidal extension documented on imaging studies or physical examination with the histologic confirmation of tumor invasion into the strap muscles.

This major change to the definition of T3 category was prompted by multiple studies showing that while the identification of gross extrathyroidal extension was clearly associated with an increased risk of recurrence and poorer survival, the presence of minor, microscopic extrathyroidal extension identified only on histologic examination carried far less independent prognostic importance⁵⁻⁹. It was the sixth edition of the AJCC staging manual in 2002 that first recognized this important distinction by downstaging minor extrathyroidal extension to T3 disease while leaving gross extrathyroidal extension as T4 disease. Part of the difficulty in assigning the clinical significance of minor extrathyroidal extension relates to the fact that the thyroid gland has an incomplete capsule and may contain adipose tissue and skeletal muscle under normal circumstances; therefore, an interface between tumor and fat or muscle may not indicate an aggressive biological feature^{5,10,11}. Several single-institution retrospective studies have demonstrated that disease-free survival rate does not differ significantly between patients demonstrating only minor extrathyroidal extension and those with a completely intrathyroidal tumor^{5-9,12}. Since publication of the 8th edition, a retrospective analysis of 241,118 patients with differentiated thyroid cancer in the SEER database demonstrated that minimal extrathyroidal extension (which was accompanied by cervical lymph node metastases in 67% of cases) was associated with a statistically significant, although minor, decrease in 5-year survival rate (96% with no extrathyroidal

extension, 94% with minimal extrathyroidal extension, and 88% with extensive extrathyroidal extension; hazard ratio 1.13, 95% confidence interval 1.05–1.22, $P < 0.01$ for the comparison of minimal extrathyroidal extension with no extrathyroidal extension)¹³.

The status of the margin can be considered very similar in a way to extrathyroidal extension. There appears to be no clinically significant difference in outcomes when comparing tumors with microscopically negative margins (R0) and those with microscopically positive margins (R1)^{7,14}. However grossly positive margins associated with an incomplete resection (R2) certainly carries higher risks of recurrence and disease-specific mortality^{7,14}.

While minimal extrathyroidal extension can be considered a minor risk factor for recurrence, there are insufficient data to warrant upstaging tumors 4 cm to T3 based on this factor. Furthermore, as described in the section on prognostic staging groups, tumors with extrathyroidal extension will be staged as prognostic stage II in nearly two thirds of older patients on the basis of coexisting lymph node metastasis. In addition, the 8th edition includes clear objective descriptors that allow for the distinction of disease invading only strap muscles (T3b) from that invading subcutaneous tissue or other surrounding structures, such as the recurrent laryngeal nerve or trachea (T4a), and from gross invasion into the prevertebral fascia or the carotid or internal jugular vein (T4b).

N category definitions for differentiated and anaplastic thyroid cancer

In the seventh edition, regional lymph nodes were classified as N0 (no regional lymph node metastasis), N1a (metastasis to level VI, which included pretracheal, paratracheal, prelaryngeal, and Delphian lymph nodes), or N1b (metastasis to unilateral, bilateral, or contralateral lymph nodes at cervical lymph node levels I, II, III, IV, or V, or retropharyngeal, or level VII superior mediastinal lymph nodes)⁴.

The eighth edition provides more detail with regard to the N0 category by introducing subgroups N0a (one or more lymph nodes confirmed as disease free via cytologic or histologic examination) and N0b (no radiologic or clinical evidence of local-regional lymph node metastasis)^{3,4}. The eighth edition also makes clear that pathologic confirmation of lymph node status is not required for staging purposes. This can be seen readily in the staging tables, where clinical N0 is equivalent to pathologic NX. This is primarily because subclinical (cN0), small volume pathologic N1 disease (pN1) carries little prognostic significance and is associated with essentially the same survival outcomes as pathologically confirmed N0 disease^{3,4}. For clarity, identification of a psammoma body (a form of dystrophic calcification commonly seen in papillary carcinoma) in a cervical lymph, even in the absence of associated malignant cells, meets the definition of pathologic N1 disease.

The definitions for the N1a and N1b categories remain largely unchanged in the 8th edition, except that the upper mediastinal lymph nodes (cervical level VII) have been reassigned to the N1a (central neck) category, whereas they were classified with the lateral neck and retropharyngeal lymph nodes in the seventh edition. This change acknowledges the anatomic continuum between the low cervical neck and the upper mediastinum and the lack of data differentiating the prognostic importance of upper mediastinal nodes from lower cervical

central neck nodes. This change will improve the reporting accuracy of central and lateral neck disease. Including both levels VI and VII nodes in N1a eliminates reporting inaccuracies due to uncertainty in distinguishing between low level VI and high level VII disease. The N1b subtype will include all disease in the lateral neck, undisputedly and anatomically defined as lateral or posterior to the internal carotid artery.

M category definitions for differentiated and anaplastic thyroid cancer

The definitions for the M category are the same in the 8th edition as in previous editions. Patients with no evidence of distant metastasis are classified as having M0 disease, whereas the presence of distant metastasis merits classification as M1.

Prognostic stage definitions for differentiated thyroid cancer

As can be seen in Table 3, the eighth edition prognostic stage groups in differentiated thyroid cancer differ significantly from those used in the seventh edition. The changes can be summarized as follows: (1) The age cutoff was raised from 45 years to 55 years. (2) The presence of minor extrathyroidal extension or of lymph node metastasis no longer defines an older patient as having stage III disease. (3) For patients aged 55 years or older, stage III now requires gross invasion into subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a) with or without lymph node metastasis. (4) N1b involvement in the absence of gross extrathyroidal extension no longer defines a patient as having stage IVA disease. (5) Stage IVA disease now requires the presence of extrathyroidal extension invading the prevertebral fascia or encasing the carotid artery or mediastinal vessels (T4b) regardless of tumor size or lymph node status in the absence of distant metastasis. (6) Older patients with M1 disease are now classified as having prognostic stage IVB disease; stage IVC no longer exists^{3,4}. Table 4 compares the seventh and eighth edition staging systems and the expected 10-year disease-specific survival rates based on our review of the published literature.

In thyroid cancer, complete staging information may not be available at the time of surgical resection of the thyroid. Therefore, the 8th edition makes it clear that any information obtained within the first 4 months after thyroid surgery should be used to refine the N and M status. Furthermore, appropriate staging will require careful assessment of clinical data, which must be used to augment the basic T, N, and M status for each patient.

Reevaluating the impact of age at diagnosis on disease-specific survival

Age at diagnosis of differentiated thyroid cancer, unlike most malignancies, has consistently been shown to be an independent predictor of disease-specific survival in multiple retrospective staging systems¹⁵. The age 45 years has been used as the cutoff in the AJCC TNM staging system since the second edition³, and other staging systems have used an age cutoff between 40 and 50 years. Multiple authors have recently endorsed an age cutoff of 55 years as the optimal single time point for prognostic models^{16–20}. One of the primary difficulties in identifying a single age cutoff is multiple studies confirming that mortality in papillary thyroid cancer increases progressively with advancing age, beginning at about age 35 years^{15,21,22}. For example, in a retrospective review of 31,802 papillary thyroid cancer

patients from the SEER database, the 10-year cause-specific survival rate exceeded 99.5% for all decades up to age 49 years, declined to 98.1% for ages 50 through 59, 94.8% for ages 60 to 69, 91.5% for ages 70 to 79, and 79.2% for ages 80 to 89, while demonstrating a linear association between age and disease-specific survival rate without an obvious age group cutpoint²¹. Furthermore, when evaluating various age cut points, an international multicenter study found 10-year disease-specific survival rates of 99.3% versus 95.6% using an age cutoff of 30 years, 99.3% versus 93.1% using an age cutoff of 45 years, 99.1% versus 89.2% using an age cutoff of 55 years, and 98.4% versus 81% using an age cutoff of 65 years; each of these differences was statistically significant in multivariate analysis adjusted for sex, pathology (papillary, follicular, Hurthle cell carcinoma), and T, N, and M groups²². Therefore, no single cut point is going to provide an optimal separation between patients at low risk and high risk of dying from thyroid cancer. To more accurately address this issue, some authors have recommended using nomograms^{22,23}, mathematical models^{24,25}, or multiple age categories^{22,26} to better reflect the continuous nature of the relationship between age at diagnosis and disease-specific mortality.

A recent international multicenter retrospective study demonstrated that by moving the age cutoff from 45 to 55 years, 17% of the patient population was downstaged to a lower risk category without significant impact on the survival curves in the lower risk categories^{22,27}. Therefore, while this increase in age cutoff from 45 to 55 years will appropriately downstage a significant number of patients, it will also move some patients with relatively high-risk disease to stage I in the absence of distant metastasis and to stage II if distant metastasis are present. However, the number of these relatively high-risk patients that will be downstaged into the lower stages is expected to be small. For example, only 0.3% of the entire cohort of 9,484 patients transitioned from seventh edition stage IV to eighth edition stage II in the international multicenter study^{22,27}. Therefore, it is unlikely that raising the age cutoff will have a significant impact on the expected survival for the stage I and stage II prognostic groups but will require increased vigilance for patients who have been downstaged but whose disease has potentially higher risk features (Table 4).

Reevaluating the impact of cervical and upper mediastinal lymph node metastases on overall survival

In the seventh edition, the presence of lymph node metastasis in patients aged 45 years or older resulted in classification as stage III disease if the involved lymph nodes were in the central neck and stage IV disease if they were in the lateral neck. In patients younger than 45 years, neither the T category nor the N category affected stage, since all were classified as prognostic stage I in the absence of distant metastases. In the eighth edition, lymph node status does not affect staging in patients younger than 55 years (consistent with the seventh edition approach) but, in patients aged 55 years or older, any lymph node involvement in either the central or lateral neck defines a patient as stage group II (in the absence of gross extrathyroidal extension or distant metastases)^{3,4}.

In the eighth edition, various lymph node characteristics (such as location, size, number of lymph nodes involved, percentage of lymph nodes involved, and extranodal extension) do not have an impact on stage group classification. While each of these features may play a

significant role in determining the risk of recurrent or persistent disease, the data on any of these individual characteristics were inadequate to warrant changing a patient's disease stage to a higher prognostic stage group. Furthermore, even studies that examined the prognostic significance based on the location of cervical lymph node metastases (N1a vs. N1b) were confounded by the influence of the size and number of involved lymph nodes, since prophylactic lateral neck dissection is not performed in papillary thyroid carcinoma and thus patients having N1b lymph nodes sampled and evaluated as part of their initial therapy would be heavily weighted toward a larger volume and higher number of lymph node metastases. Conversely, since prophylactic neck dissection is performed more frequently in the central neck, many patients with lymph nodes sampled from N1a would preferentially have very small volume disease.

An additional major difficulty in assigning clinical significance to lymph node metastasis in retrospective studies is the effect that high-resolution imaging, prophylactic neck dissection, and meticulous histologic examination of surgical specimens has had on the identification of very small volume lymph node metastases. It is now widely appreciated that up to 80% of papillary microcarcinomas likely harbor cervical lymph node metastasis in the central or lateral neck and yet have exceedingly high disease-specific survival rates at all ages. Furthermore, while the presence of lymph node metastasis can be shown to be associated with a statistically significant decrease in survival rate, the magnitude of this decrease is very small in young patients and only moderate in older patients^{28,29}. Therefore, younger patients with lymph node metastasis will continue to be defined as having stage I disease, while older patients with lymph node metastasis will be classified to prognostic stage group II. As can be seen in Table 4, older patients with lymph node metastasis or gross extrathyroidal extension into strap muscles are expected to have a 10-year disease-specific survival rate of 85–95%, which is lower than that of older patients with stage I disease, which is anticipated to be 98–100%. Further studies are needed to determine whether these other lymph node characteristics have sufficient prognostic importance that they should be used to alter stage group classification; until then, data are insufficient to stage N1a disease differently than N1b disease.

Prognostic stage definitions for anaplastic thyroid cancer

As in the seventh edition staging system, all anaplastic carcinomas are considered to be prognostic stage IV in the eighth edition (Table 3). For consistency, rather than using the seventh edition T designations for intrathyroidal anaplastic carcinoma (T4a) or for anaplastic carcinoma with gross extrathyroidal extension (T4b), the eighth edition will use the same T definitions for both differentiated thyroid cancer and anaplastic thyroid cancer^{3,4}. However, the basic premise of the anatomic stage groups will remain the same, with intrathyroidal anaplastic tumors classified as IVA disease, and the presence of lymph node involvement or gross extrathyroidal extension without distant metastasis will be classified as stage IVB, while the presence of distant metastasis merits a designation of stage IVC disease.

Other risk factors not required for 8th edition staging

The 8th edition provides a list of additional clinical factors that, while not required for TNM/AJCC staging, should be recorded in pathology reports and other medical records and collected by the tumor registrars for possible incorporation into future refinements of the staging system, and considered by clinicians to further refine initial risk stratification and assessment of response to therapy^{3,4}. These include features such as microscopic extrathyroidal extension, location of the involved lymph nodes (N1a vs. N1b), number of involved lymph nodes, number of lymph nodes sampled, size of the largest involved lymph node, size of the largest metastatic focus within a lymph node, presence/absence of extranodal extension, presence/absence of vascular invasion, postoperative serum thyroglobulin level, completeness of surgical resection (R stage), and specific histologic subtypes. Likewise, while the specific molecular profile of the primary thyroid cancer may provide prognostic information, it is unclear at this point how much the molecular characterization will improve risk stratification beyond that encompassed in traditional anatomic staging (T, N, M status). It is likely that some of these additional features may be proven to augment the 8th edition risk predictions and would be considered for inclusion in a subsequent edition.

Conclusions

Using an evidenced-based medicine approach, a multidisciplinary committee of thyroid cancer experts made several substantial modifications to the 7th edition TNM/AJCC staging system that are embodied in the new 8th edition staging system. The net effect of most of these changes will be the downstaging of many cases to more accurately reflect the excellent survival outcomes in patients with relatively low-risk disease. We have no doubt that the 8th edition will be further refined in the years to come as additional data are published linking clinicopathologic and molecular features to disease-specific survival. Nonetheless, the 8th edition is a major step forward in integrating clinical information and anatomic pathology information into a carefully defined and reproducible staging system that can be used to guide initial therapy and follow-up recommendations for patients with thyroid cancer.

Overview of key changes in the 8th edition

All patients younger than 55 years have stage I disease (regardless of tumor size, lymph node status, histologic subtype, or the presence/absence of extrathyroidal extension) unless they have distant metastases, in which case their disease is stage II.

In patients aged 55 years or older, the presence of distant metastases confers stage IVB, while cases without distant metastases are further categorized based on the presence/absence of gross extrathyroidal extension and on tumor size and lymph node status.

All patients aged 55 years or older whose tumor is ≤ 4 cm (T1-2) and confined to the thyroid (N0, NX) have stage I disease.

All patients aged 55 years or older whose tumor is confined to the thyroid and ≤ 4 cm (T1-2) with any lymph node metastases present (N1a or N1b) have stage II disease.

All patients aged 55 years or older whose tumor is >4 cm and confined to the thyroid (T3a) have stage II disease regardless of lymph node status.

In patients aged 55 years or older who demonstrate gross extrathyroidal extension, the disease is considered stage II if only the strap muscles are grossly invaded (T3b); stage III if there is gross invasion of the subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a); or stage IVA if there is gross invasion of the prevertebral fascia or tumor encasing the carotid artery or internal jugular vein (T4b).

Acknowledgments

Funding: This research was funded in part by the NIH/NCI Cancer Center Support Grant P30 CA008748 (Craig Thompson, PI).

References

1. AJCC Cancer Staging Manual. New York: Springer; 2017.
2. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin.* 2017; 67:93–99. Epub 22017 Jan 21317. DOI: 10.3322/caac.21388 [PubMed: 28094848]
3. Tuttle, M., Morris, LF., Haugen, B., et al. Thyroid-Differentiated and Anaplastic Carcinoma (Chapter 73). In: Amin, MB.Edge, SB.Greene, F., et al., editors. *AJCC Cancer Staging Manual.* 8th. New York City: Springer International Publishing; 2017.
4. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? *Thyroid.* 2017; 27:751–756. doi: 710.1089/thy.2017.0102. Epub 2017 May 1019. [PubMed: 28463585]
5. Arora N, Turbendian HK, Scognamiglio T, et al. Extrathyroidal extension is not all equal: Implications of macroscopic versus microscopic extent in papillary thyroid carcinoma. *Surgery.* 2008; 144:942–947. discussion 947-948. [PubMed: 19041001]
6. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab.* 2005; 90:5723–5729. [PubMed: 16030160]
7. Radowsky JS, Howard RS, Burch HB, Stojadinovic A. Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. *Thyroid.* 2014; 24:241–244. [PubMed: 23713855]
8. Shin JH, Ha TK, Park HK, et al. Implication of minimal extrathyroidal extension as a prognostic factor in papillary thyroid carcinoma. *Int J Surg.* 2013; 11:944–947. [PubMed: 23820062]
9. Woo CG, Sung CO, Choi YM, et al. Clinicopathological Significance of Minimal Extrathyroid Extension in Solitary Papillary Thyroid Carcinomas. *Ann Surg Oncol.* 2015
10. Ghossein R. Problems and controversies in the histopathology of thyroid carcinomas of follicular cell origin. *Arch Pathol Lab Med.* 2009; 133:683–691. [PubMed: 19415942]
11. Mete O, Rotstein L, Asa SL. Controversies in thyroid pathology: thyroid capsule invasion and extrathyroidal extension. *Ann Surg Oncol.* 2010; 17:386–391. [PubMed: 19949881]
12. Nixon IJ, Ganly I, Patel S, et al. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery.* 2011; 150:1242–1249. [PubMed: 22136847]
13. Youngwirth LM, Adam MA, Scheri RP, et al. Extrathyroidal Extension Is Associated with Compromised Survival in Patients with Thyroid Cancer. *Thyroid.* 2017; 27:626–631. doi: 610.1089/thy.2016.0132. Epub 2016 Oct 1085. [PubMed: 27597378]

14. Wang LY, Ghossein R, Palmer FL, et al. Microscopic Positive Margins in Differentiated Thyroid Cancer Is Not an Independent Predictor of Local Failure. *Thyroid*. 2015; 25:993–998. [PubMed: 26122000]
15. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. *Endocrinol Metab Clin North Am*. 2014; 43:401–421. [PubMed: 24891169]
16. Hendrickson-Rebizant J, Sigvaldason H, Nason RW, Pathak KA. Identifying the most appropriate age threshold for TNM stage grouping of well-differentiated thyroid cancer. *Eur J Surg Oncol*. 2015; 41:1028–1032. [PubMed: 25986855]
17. Ito Y, Fukushima M, Tomoda C, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. *Endocr J*. 2009; 56:759–766. [PubMed: 19506324]
18. Ito Y, Ichihara K, Masuoka H, et al. Establishment of an intraoperative staging system (iStage) by improving UICC TNM classification system for papillary thyroid carcinoma. *World J Surg*. 2010; 34:2570–2580. [PubMed: 20625728]
19. Kim SJ, Myong JP, Suh H, et al. Optimal Cutoff Age for Predicting Mortality Associated with Differentiated Thyroid Cancer. *PLoS One*. 2015; 10:e0130848. [PubMed: 26102084]
20. Mazurat A, Torroni A, Hendrickson-Rebizant J, et al. The age factor in survival of a population cohort of well-differentiated thyroid cancer. *Endocr Connect*. 2013; 2:154–160. [PubMed: 24008393]
21. Adam MA, Thomas S, Hyslop T, et al. Exploring the Relationship Between Patient Age and Cancer-Specific Survival in Papillary Thyroid Cancer: Rethinking Current Staging Systems. *J Clin Oncol*. 2016; 34:4415–4420. Epub 2016 Oct 4428. [PubMed: 27998233]
22. Ganly I, Nixon IJ, Wang LY, et al. Survival from Differentiated Thyroid Cancer: What Has Age Got to Do with It? *Thyroid*. 2015; 25:1106–1114. [PubMed: 26148759]
23. Pathak KA, Mazurat A, Lambert P, et al. Prognostic nomograms to predict oncological outcome of thyroid cancers. *J Clin Endocrinol Metab*. 2013; 98:4768–4775. [PubMed: 24152685]
24. Gimm O, Ukkat J, Dralle H. Determinative factors of biochemical cure after primary and reoperative surgery for sporadic medullary thyroid carcinoma. *World J Surg*. 1998; 22:562–567. discussion 567–568. [PubMed: 9597929]
25. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993; 114:1050–1057. discussion 1057–1058. [PubMed: 8256208]
26. Jonklaas J, Noguera-Gonzalez G, Munsell M, et al. The impact of age and gender on papillary thyroid cancer survival. *J Clin Endocrinol Metab*. 2012; 97:E878–887. [PubMed: 22496497]
27. Nixon IJ, Wang LY, Migliacci JC, et al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. *Thyroid*. 2016; 26:373–380. doi: 310.1089/thy.2015.0315. Epub 2016 Feb 1025. [PubMed: 26914539]
28. Adam MA, Pura J, Goffredo P, et al. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. *J Clin Oncol*. 2015; 33:2370–2375. [PubMed: 26077238]
29. Tran Cao HS, Johnston LE, Chang DC, Bouvet M. A critical analysis of the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid carcinoma in young patients on the basis of the Surveillance, Epidemiology, and End Results (SEER) registry. *Surgery*. 2012; 152:145–151. [PubMed: 22503316]

Table 1**Major Changes to the AJCC/TNM Staging of Differentiated and Anaplastic Thyroid Cancers in the Eighth Edition**

Differentiated	
1	The age cutoff used for staging was increased from 45 to 55 years of age at diagnosis.
2	Minor extrathyroidal extension detected only on histological examination was removed from the definition of T3 disease and therefore has no impact on either T category or overall stage
3	N1 disease no longer upstages a patient to stage III. If <55 years of age at diagnosis, N1 disease is stage I. If ≥ 55 years of age, N1 disease is stage II.
4	T3a is a new category for tumors >4 cm confined to the thyroid gland.
5	T3b is a new category for tumors of any size demonstrating gross extrathyroidal extension into strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles).
6	Level VII lymph nodes, previously classified as lateral neck lymph nodes (N1b), were reclassified as central neck lymph nodes (N1a) to be more anatomically consistent and because level VII presented significant coding difficulties for tumor registrars, clinicians, and researchers.
7	In differentiated thyroid cancer, the presence of distant metastases in older patients is classified as stage IVB disease rather than stage IVC disease. Distant metastasis in anaplastic thyroid cancer continues to be classified as stage IVC disease.
Anaplastic	
1	Unlike previous editions where all anaplastic thyroid cancers were classified as T4 disease, anaplastic cancers will now use the same T definitions as differentiated thyroid cancer.
2	Intrathyroidal disease is stage IVA, gross extrathyroidal extension or cervical lymph node metastases is stage IVB, and distant metastases is stage IVC.

AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis.

Table 2

TNM Definitions

Definition of Primary Tumor (T)	
<i>For Papillary, Follicular, Poorly Differentiated, Hurthle Cell, and Anaplastic Thyroid Carcinomas</i>	
<i>T Category</i>	<i>T Criteria</i>
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid
T2	Tumor >2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a*	Tumor >4 cm limited to the thyroid
T3b*	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
<i>Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification).</i>	

Definition of Regional Lymph Node (N)	
<i>N Category</i>	<i>N Criteria</i>
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0a*	One or more cytological or histologically confirmed benign lymph node
N0b*	No radiologic or clinical evidence of locoregional lymph node metastasis
N1*	Metastasis to regional nodes
N1a*	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
N1b*	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (Levels I, II, III, IV, or V) or retropharyngeal lymph nodes

Definition of Distant Metastasis (M)	
<i>M Category</i>	<i>M Criteria</i>
M0	No distant metastasis
M1	Distant metastasis

Table 3

Staging Guide

<i>Differentiated thyroid cancer</i>				
<i>When age at diagnosis is...</i>	<i>And T is...</i>	<i>And N is...</i>	<i>And M is...</i>	<i>Then the stage group is...</i>
<55 years	Any T	Any N	M0	I
	Any T	Any N	M1	II
55 years	T1	N0/NX	M0	I
	T1	N1	M0	II
	T2	N0/NX	M0	I
	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

<i>Anaplastic thyroid cancer</i>			
<i>T is...</i>	<i>And N is...</i>	<i>And M is...</i>	<i>Then the stage group is...</i>
T1-T3a	N0/NX	M0	IVA
T1-T3a	N1	M0	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

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Table 4

Comparison of the AJCC 7th and 8th edition staging system.

Stage	7 th Edition Description	7 th Edition 10-yr DSS	8 th Edition Description	8 th Edition Expected 10-yr DSS
Younger patients	I Age <45 years All patients without distant metastases regardless of tumor size, lymph node status, or extrathyroidal extension	97–100%	Age <55 years All patients without distant metastases regardless of tumor size, lymph node status, or extrathyroidal extension	98–100%
	II Age <45 years Distant metastases	95–99%	Age <55 years Distant metastases	85–95%
Older patients	I Age 45 years 2 cm tumor Confined to thyroid	97–100%	Age 55 years 4 cm tumor Confined to thyroid	98–100%
	II Age 45 years 2–4 cm tumor Confined to thyroid	97–100%	Age 55 years Tumor >4 cm Or tumor of any size with central or lateral neck lymph nodes or gross extrathyroidal extension into strap muscles	85–95%
	III Age 45 years >4 cm tumor Or minimal extrathyroidal extension or central neck lymph node metastasis	88–95%	Age 55 years Tumor of any size with gross extrathyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve	60–70%
	IV Age 45 years Gross extrathyroidal extension, or lateral neck lymph node metastasis, or distant metastasis	50–75%	Age 55 years Tumor of any size or lymph node status with gross extrathyroidal extension into prevertebral fascia, encasing major vessels Or distant metastasis	< 50%

DSS, disease-specific survival.