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Thyroid

Stage migration with the new American Joint Committee on Cancer (AJCC) staging system (8th edition) for differentiated thyroid cancer ☆

Ashok R. Shaha, MD [a,*], Jocelyn C. Migliacci, MS [a], Iain J. Nixon, MD [a], Laura Y. Wang, MD [a], Richard J. Wong, MD [a], Luc G.T. Morris, MD [a], Snehal G. Patel, MD [a], Jatin P. Shah, MD [a], R. Michael Tuttle, MD [b], Ian Ganly, MD [a]

[a] Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[b] Endocrinology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

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ABSTRACT

Background: Tumor, node, and metastasis staging in thyroid carcinoma is important for assessing prognosis. However, patients with stage III or IV disease have an overall survival rate of 90%. The change to 55 years of age as the cutoff will create stage migration and many patients will be downstaged.
Methods: We reviewed our database of 3,650 patients to analyze the impact of the new American Joint Committee on Cancer staging system. There were 994 men (27%) and 2,656 women (73%). The median age was 46 years. Patients were staged using both 7th and 8th editions, with a cutoff of 55 years of age and new definitions of T3 and T4, and nodal staging.
Results: Of 3,650 patients, 1,057 (29%) were downstaged. There were 104 (10%) who went from stage IV to I, 109 (10%) who went from stage IV to stage II, and 68 (6%) who went to stage III. There were 218 (21%) who went from stage III to I, 347 (33%) who went from stage III to stage II, and 211 (20%) who went from stage II to I. The overall disease-specific and relapse-free survival was analyzed and showed better stratification with the new staging system.
Conclusion: The new staging system reflects more appropriately the biology of thyroid cancer and will have significant impact on the management of thyroid cancer.

Introduction

The incidence of thyroid cancer is rapidly rising. Over the last 25 years, the annual incidence of thyroid cancer has almost quadrupled in the United States, increasing from approximately 8,000 patients to 54,000 patients.[1] Interestingly, the majority of the rise is directly related to microcarcinomas. However, the mortality in thyroid cancer has remained relatively stable over the past 20 years.[2] Thyroid cancer continues to be a unique human neoplasm, where selection of therapy and the outcomes are dependent on prognostic factors and risk group analysis, which are very critical in the evaluation and management of thyroid cancer and include age, histology, extrathyroidal extension, size of the tumor, and distant metastases. These prognostic factors are repeatedly shown to be the same in separate data sets reported from the Mayo Clinic,[3] Lahey Clinic,[4] European Organisation for Research and Treatment of Cancer,[5] and Memorial Sloan Kettering Cancer Center (MSK).[6] Each of these institutions analyzed their large number of patients with thyroid cancer and defined various prognostic factors, which have helped us to divide patients into low, intermediate, and high-risk groups. The 10-year disease-specific survival (DSS) in the low-risk group is over 99%, in the intermediate risk group it is 96% to 97%, and in the high-risk group, it drops to 78%.[6]

Staging of thyroid cancer

Staging is very important in evaluation of thyroid cancer. There are a variety of staging systems. However, all around the world, the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) system has become very popular and is essentially an initial clinical staging system, labeled as cTNM. There are a variety of other staging systems, including pathological staging, recurrence staging, and others. The goals of a staging system are to define the prognostic groups and to develop treatment philosophies based on stage groupings. Traditionally, 4 stages have been described in all human cancers. These staging systems are used

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* Corresponding author: Memorial Sloan Kettering Cancer Center, Head and Neck Service, 1275 York Avenue, New York, New York 10065.
E-mail address: shahaa@mskcc.org (A.R. Shaha).

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Table 1
Major changes between 7th and 8th edition of staging systems.

- The cutoff age increased from 45 to 55.
- Minor extrathyroidal extension removed from definition of T3.
- N1 disease does not upstage the tumor to stage III .
- Tumors more than 4cm confined to thyroid—T3a.
- T3b—any size tumor demonstrating gross extrathyroidal extension into strap muscles.
- Level VII nodes (N1b) are not considered to be stage IV.
- Distant metastases are considered as stage IVB and not stage IVC.

to compare data and develop treatment philosophies. Most of the time, the stage I and stage II cancers are treated with unimodal treatment because they are considered to be early cancers with excellent outcome. However, stage III and stage IV cancers have a drop in survival by almost 40% to 50%, frequently requiring multimodal therapy. In individual tumor types, the staging system is different.

The staging system for thyroid cancer is unique. It is interesting that age has been considered as an important prognostic factor; this is the only human cancer where age at diagnosis is an independent prognostic factor. In the previous staging systems, the age of 45 was used as a cutoff. There was data available from European Organisation for Research and Treatment of Cancer,[5] Mayo Clinic,[3] Lahey Clinic,[4] and MSK,[6] where the age of 45 was used as a cutoff and divided into low- and high-risk groups, along with other factors. There was no stage III or stage IV for patients below the age of 45 because the mortality was low in this group. Over a period of time, data from all around the world has accumulated, and Nixon et al. reviewed the data from MSK and validated it in a multiinstitutional study, defining age 55 as a better cutoff than age 45.[7] These data led to the change to age 55 in the 8th edition staging for thyroid cancer. More recently, there have been further analyses that show age as a continuum may be a more appropriate prognostic variable.[8] However, at the present time, it is not possible to design a staging system that employs age as a continuous variable; therefore, using the age cutoff of 55 years appears to be more appropriate for the new staging system.

Materials and methods

With institutional review board approval, we retrospectively reviewed our large database, which was prospectively collected, to analyze the impact of the new staging system on stage groupings. Our database included 3,650 patients, with detailed information on prognostic factors and treatment outcomes. There were 994 men (27%) and 2,656 women (73%). The median age was 46 years (age range 4–94 years). The interquartile age range was from 25 to 58 years. We staged these patients based on both the 7th and 8th edition to determine the major reclassification changes with the use of 55 years as a new cutoff age and new definitions of T3 and T4 primary tumors and nodal staging. The changes in staging system are defined in Table 1. We had robust data with detailed follow-up of these patients over the past 30 years. Some of the prognostic factors and risk groups were published before by our institution.[6] We were interested in reviewing our staging groups and analyzed the percentage of downstaging, as per the 8th edition.

Results

Of 3,650 patients, 1,057 (29%) were downstaged. Of 281 patients with stage IV disease, 104 (10%) were downstaged to stage I, 109 (10%) to stage II, and 68 (6%) from stage IV to stage III. Of 565 patients with stage III disease, 218 (21%) were downstaged to stage I, and 347 (37%) to stage II. There were 211 (20%) patients with stage II disease who were downstaged to stage I. Overall, there was downstaging of 29% of patients (Fig. 1 and Table 2). We also

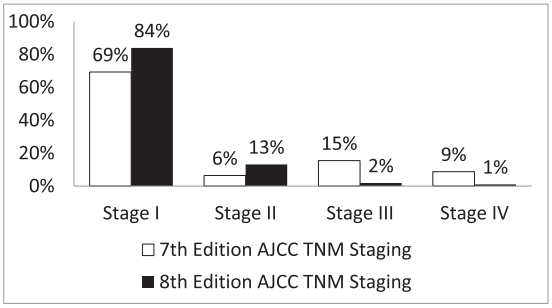

Fig. 1. Stage grouping based on 7th and 8th editions of thyroid cancer staging.

Table 2
Stage migration; AJCC stage (8th edition).

	I	II	III	IV	Total
AJCC stage 1	2,531	0	0	0	2,531
2	211	24	0	0	235
3	218	347	0	0	565
4	104	109	68	38	319
Total	3,064	480	68	38	3,650

- 1,057/3,650 (29%) of patients were downstaged
- 104/1,057 patients (10%) went from stage IV to I
- 109/1,057 patients (10%) went from stage IV to II
- 68/1,057 patients (6%) went from stage IV to III
- 218/1,057 patients (21%) went from stage III to I
- 347/1,057 patients (33%) went from stage III to II
- 211/1,057 patients (20%) went from stage II to I

wanted to study whether this will have a direct impact on their long-term survival and on the need for and the results of adjuvant therapy. The overall disease-specific and relapse-free survival was analyzed by both staging systems. Kaplan–Meier plots for cancer-specific survival (Fig. 2), overall survival (Fig. 3), and recurrence-free survival (Fig. 4) showed a more appropriate correlation and stratification with the 8th edition staging system. The data reveals that the new staging system more accurately reelected the biology of the disease with a better spread of survival curves between stages I, II, III, and IV, unlike the previous staging system, which lumped stages I, II, and III together, with the survival difference shown in only stage IV. Fig. 5 demonstrates the stage migration in our data, based on alluvial flow diagram.

Discussion

The decisions about extent of thyroidectomy and adjuvant treatment are primarily based on the risk group stratification. Recently, the American Thyroid Association has also emphasized the need for risk group stratification based on the tumor and patient factors. However, they have emphasized stratification for the risk of recurrence rather than long-term survival.[9]

The phenomenon of multifocal microscopic thyroid cancer is well known, but it has little impact on outcomes. Similarly, occult microcarcinomas are present in 6% to 10% of the population in the United States, with these individuals living unimpacted because their microcarcinoma have not become clinically evident

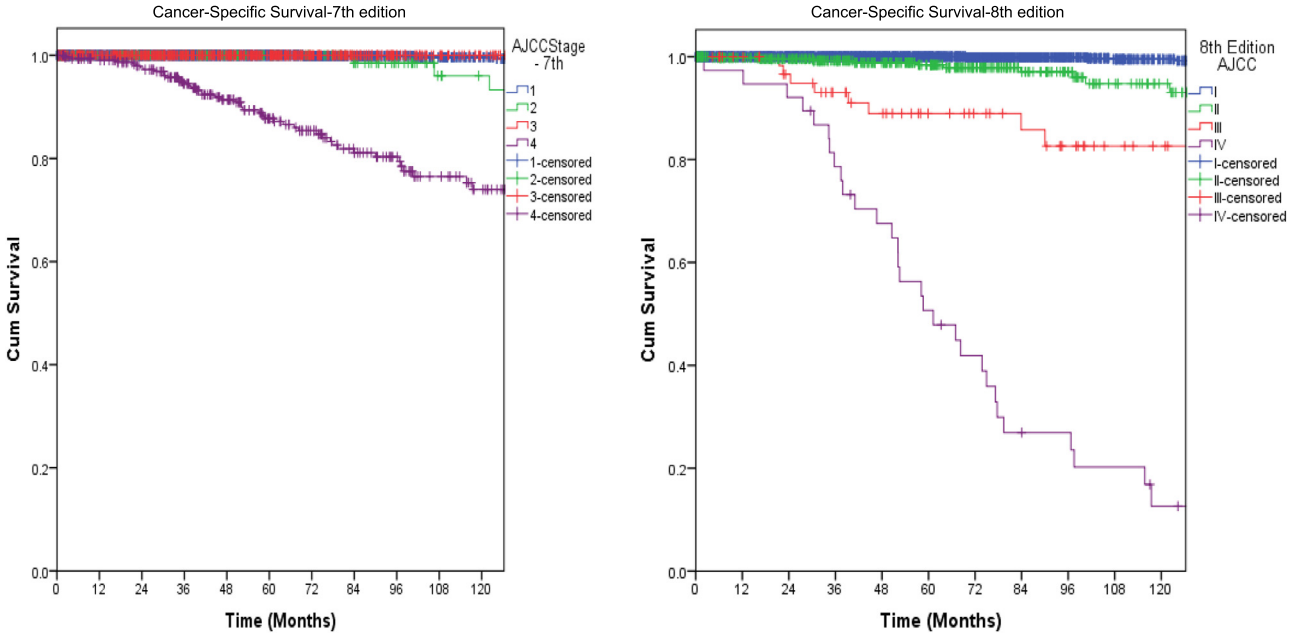

Fig. 2. Cancer-specific survival based on 7th and 8th editions.

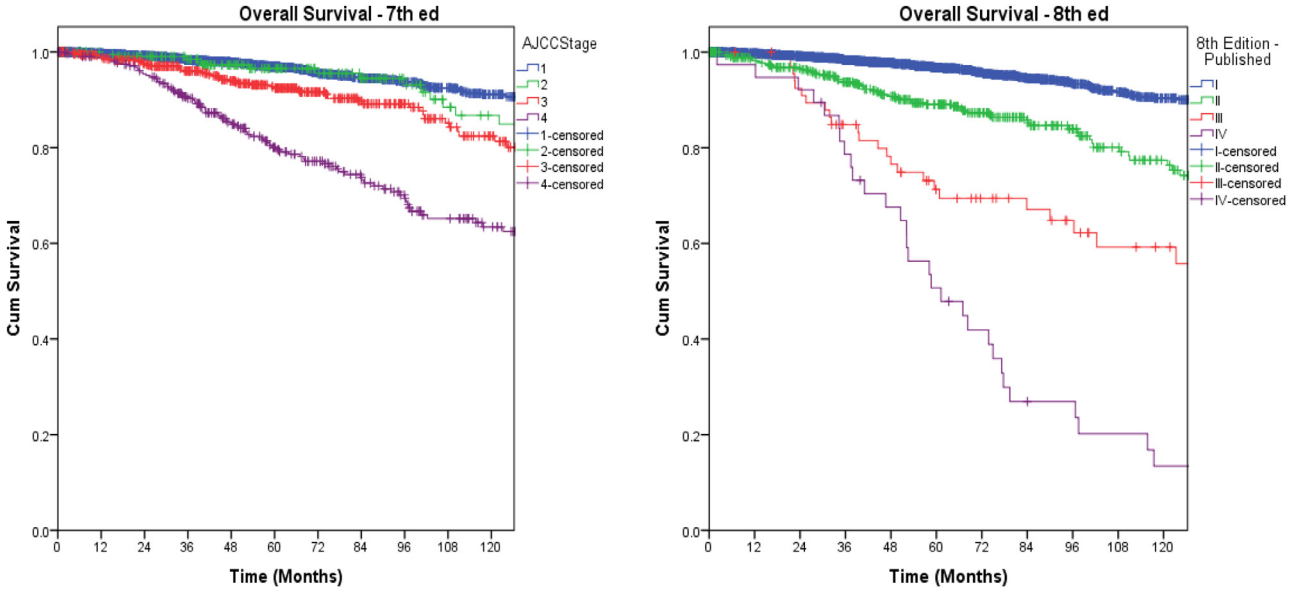

Fig. 3. Overall survival based on 7th and 8th editions.

during life. The other important factor is the presence of nodal metastasis, which has no major impact on long-term outcomes in patients who fall into the low-risk category. The only negative impact of nodal metastases is observed in the high-risk group of patients. These are usually older patients with large and poorly differentiated cancers.[10,11] This is a unique biological phenomenon of thyroid cancer, which is very important in the understanding and management of thyroid cancer.

Staging of cancer is important to evaluate the extent of the disease and overall prognosis and decisions regarding treatment selection. It also helps us to standardize the evaluation of cancer and compare results from different parts of the world. The history of the staging system dates back to the early part of the last century from attempts made by Steinthal from Germany and Halsted from the United States.[12] Pierre Denoix reported on the TNM factors to develop a staging system in 1945. These were adopted by the Union for International Cancer Control (UICC) in 1954, and subsequently, the AJCC and UICC worked together to develop the staging system for cancers. The first edition of the staging system was published in 1977, and it was well received around the world. Clinicians and cancer registrars used this staging system routinely. The clinical staging system was defined by TNM factors. In general, patients were divided into 4 groups: stages I, II, III, and IV. The overall survival declined from stage I to stage IV. The staging system for thyroid cancer has also evolved over the past 50 years, with several changes noted in the 6th, 7th, and the most recent edition. The 8th edition of the staging system more accurately reflects the biology of well-differentiated thyroid cancer. The staging manual was published in October 2016 and was implemented in January 2018.

In the past, age 45 was used as a stage grouping cutoff. This was revised to age 55, largely based on the international collaborative study reported by Nixon et al., indicating that age 55 is a better cutoff. This was endorsed by many other institutions around

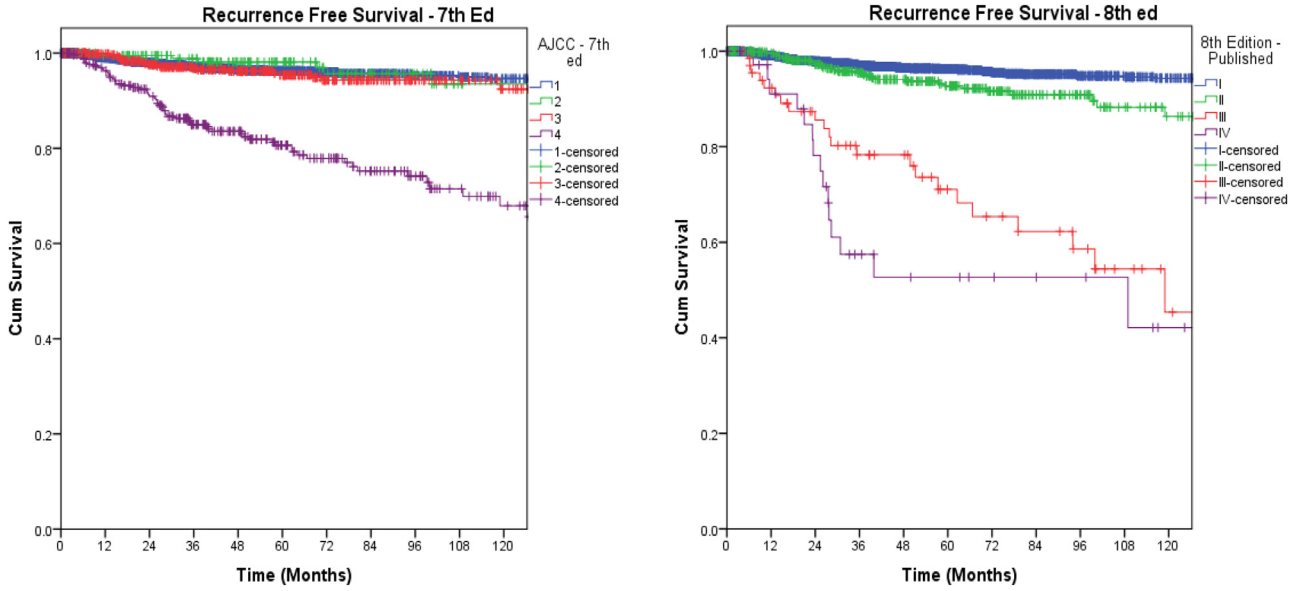

Fig. 4. Recurrence-free survival based on 7th and 8th editions.

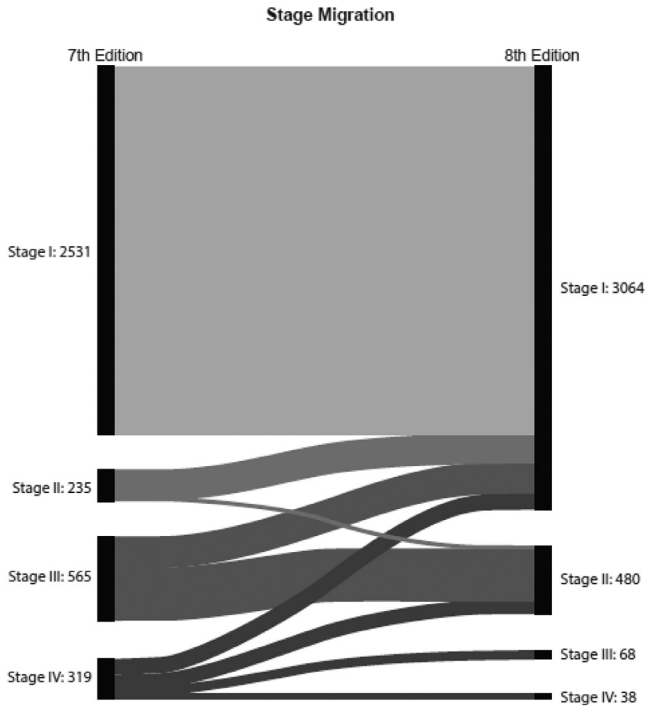

Fig. 5. Alluvial flow diagram based on stage migration in the 7th and 8th editions.

the world.[7] More recent studies by Adama and Nixon have reported that thyroid-specific mortality steadily increases with increasing age, proving that age as a continuum is a more appropriate prognostic variable.[10,13] However, the TNM staging system only allows for categorical variables; therefore the age of 55 years has been deemed the most appropriate age cutoff at present. It is possible this may change in future staging systems with the use of nomograms.

The T staging was also revised. Because microscopic extrathyroidal extension had no impact on outcomes, it is no longer used to upstage the tumor to T3. According to the new revisions, T3a is a tumor larger than 4cm, and T3b is a tumor with gross extrathyroidal extension involving the strap muscles or perithyroid soft tissues. The definition for T4 remains unchanged.[13] The N staging was also revised. N1 disease does not upstage the tumor to stage III, and level VII nodes [N1B] are not considered to be stage IV.

Since its publication, there have been several studies revisiting the staging of thyroid cancer and updating the individual institutional data. There were 3 major publications published: 2 from Korea and a study from the National Cancer Database (NCDB), all of which showed downstaging of thyroid cancer in approximately 27% to 30% of patients.[14–16] The previous staging system (7th edition) showed no major survival difference between stages I, II, and III. The new staging system (8th edition) shows a more appropriate difference between all 4 stages; however, stage I and stage II are still almost parallel to each other. The nodal metastasis and the stage grouping are also important. In 7th edition staging system, presence of nodal metastasis in patients above the age of 45 was considered stage III. Biologically, this was not stage III, as most of the patients had cancers that behaved as stage I or stage II. This downstaging will help individualize the adjuvant treatment and overall discussion regarding prognosis in patients with thyroid cancer.

The analysis of our large database has shown the new staging system to be more appropriate and biologically sound, with outcome differences between stages I–II and III–IV. This will help us understand the overall prognosis of patients with thyroid cancer and, more importantly, make critical decisions about adjuvant treatment, such as radioactive iodine. Kim et al. from South Korea retrospectively analyzed 3,176 patients with differentiated thyroid cancer from 1996 to 2005.[16] Upon reclassification, 37.6% of the patients were downstaged. As a result of this, stage I and II tumors increased from 61.9% to 81.1% and from 1.7% to 16%, respectively. Stages III and IVB decreased from 27.6% to 2.3% and 0.8% to 0.5%, respectively.

Pontius et al. compared the 7th and 8th edition staging on outcomes from the Surveillance, Epidemiology, and End Results database and NCDB.[14] They reported that 23% of the patients were downstaged from the 7th to 8th edition in Surveillance, Epidemiology, and End Results and 24% in NCDB. They concluded that the 8th edition staging was superior for predicting survival.

Mijin Kim et al. from Assan Medical Center in South Korea reported application of both staging systems to 1,613 patients with

differentiated thyroid cancer.[16] Their median follow-up was 11 years. With the application of the 8th edition staging system, 63% of T3 patients were downgraded to T1/T2; 38% were downstaged. They reported 10-year DSS in TNM/7 stages I, II, III, and IV as 99.7%, 98.2%, 98.8%, and 83.2%, respectively. As per the 8th edition, they reported DSS in stages I, II, III, and IV as 99.6%, 95.4%, 72.3%, and 46.6%, respectively. They concluded that applying the 8th edition of the TNM staging system could improve the accuracy for predicting DSS in patients with differentiated thyroid cancer. Nixon et al. reviewed databases from 10 institutions, with a total of 9,484 patients.[13] They reported using age 45 as the cutoff, 10-year DSS, rates for stages I to IV as 99.7%, 97.3%, 96.6%, and 76.3%, respectively. Using age 55 as the cutoff, they reported 10-year DSS as 99.5%, 94.7%, 94.1%, and 67.6%, for stages I to IV, respectively. This change resulted in 12% of patients being downstaged, and the downstaged group had a 10-year DSS of 97.6%. They concluded that the age cutoff of 55 years would improve the statistical validity of the model, and such a change would be clinically relevant for a large number of patients worldwide by preventing overstaging of patients with low-risk disease while providing a more realistic estimation of prognosis for high-risk patients. It is interesting that the new staging system downstages many of the tumors, unlike those reported by Feinstein et al. as Will Rogers phenomenon in stage migration in lung cancer.[17]

Shaha commented on Kim et al.'s paper as paradigm shifts in staging of thyroid cancer.[18] He concluded that the 8th edition was based on the biology of thyroid cancer, and also commented on the new American Thyroid Association guidelines as a major advance in the evaluation and management of thyroid cancer.[19] The new staging system is quite effective in stage grouping and relates to the overall prognosis. We are sure this new staging system will be most appreciated around the world.

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Conflicts of interest

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Discussion

Dr Gerard M Doherty (Boston, MA): As you know, the AJCC system is set up to predict survival, not recurrences or other kinds of risks that we should consider. I think what we have done now with the system is reflecting a change in the disease that we have seen over the last 30 years as more and more of the tumors that we treat have been detected by imaging and not palpation. So in some ways, our treatment and staging systems have been set up for palpable disease, and now we largely treat image-only disease.

My question for you is whether you expect a change in our treatment to follow the change in our staging, as we are still seeing large numbers of patients treated by total thyroidectomy, radioiodine, and so on.

Dr Ashok R Shaha: I think if you look at the old TNM system, it was based on only clinical information, and now we are measuring the primary tumor and we are monitoring for recurrence.

Would it change the philosophy of management? Yes, I think so. I think whenever you find disease, let's say a 5- or 7-millimeter node with a positive needle biopsy, you are going to be forced to do something about it.

A lot of what is going to change is that we'll probably put a number of patients in the group for observation because they had a primary below 1 centimeter or small recurrent disease. I think that is just understanding the biology of the disease. Whether that will be agreed upon by all the patients, I don't know. But, yes, it will have some impact.

Dr Dough Evans (Milwaukee, WI): Great presentation. To follow up on Jerry's question, since there's now general appreciation that the vast minority of patients with differentiated thyroid cancer died of the disease over the last couple of decades, it's become evident that recurrence is really the clinically relevant endpoint.

As someone who manages a huge database and works with Mike Tuttle and others on that, how do you ensure that you are actually capturing all the patients that recur, especially when people come to you from all over the world? Should there be a standardization of technique and observation, especially with this particular disease, to ensure that recurrence rates over 10, 15, sometimes even more years, are actually captured?

Dr Ashok R Shaha: That's a great point. This is a weakness for many of the human cancers during follow-up. Do we follow all the patients? Do we follow them clinically? Some of them by e-mails, letters? Some of them by other doctors. I think that's always going to be a problem.

We need to be on the lookout. We need to have a database, a tumor registry, where the tumor registrars will make phone calls and get all the information.

Memorial has done that, and I think many major institutions have done that in the United States.

We need to be on the lookout for high-risk thyroid cancer in particular. I think we need to spend more energy on those who are at a high risk for recurrence.

Dr Doug Evans (Milwaukee, WI): But I mean just for the database. You actually have FTEs that call these patients? You call every patient on that list? How often?

Dr Ashok R Shaha: Yes, absolutely. At least once a year.

I think our database is very robust, and the number of patients that we lose or we miss is very small—only those who have left the country or moved and we don't have their address. But our registry data people are very good with that.

Julie Ann Sosa (San Francisco, CA): Great presentation. I wholeheartedly agree with your findings, and thank Nancy Perrier and the whole group at AJCC for advancing the position.

I would question whether all of this is actually completely outmoded in 2018 and whether staging systems going forward should not really just be limited to demographic, clinical, and pathologic characteristics of patients, but rather should be integrating the mutational profile of patients, and whether we should have synergy between those mutational genotypic profiles and the phenotypic profiles of the patient to better prognosticate.

Dr Ashok R Shaha: I think you are absolutely right. There is a lot of talk about this.

I don't think we have enough data or follow-up today regarding the mutational analysis. There is a lot of interest in this for other head and neck cancers. So I completely agree with you. We need more data. We need to understand more prognostic factors, both clinical and nonclinical. The one other point that would be included eventually in the new staging system would be the patient comorbidities. They may not be very important for thyroid cancers, but for other head and neck cancers, I think they can be very important.

Dr Nancy Perrier (Houston, TX): I stand up to congratulate you on your work and also to give a plug for the AJCC. In the 8th edition, there are clinical variables that are recommended, and the migration has been exactly as Julie Ann, Doug, and you all mentioned. We need to follow these patients longer and understand it's not just TNM. Those variables that are accrued by the registrars are actually included in the AJCC 8th edition. So all of you should make sure you have your registrars at home document and use those variables. They are not absolutes, but they are suggested. There is room for looking at ultrasound characteristics and looking at mutational status because the hope is that in the 9th edition we will be able to better prognosticate, and this will serve as a database in the sense that we can answer questions about recurrence, not just survival.

Dr Ashok R Shaha: Thank you very much. Nancy is the new chair, so I am sure we'll see many more advances in the staging system.