Editorial Commentary



# Thyroid cancer staging and genomics

**Ashok R. Shaha[1], R. Michael Tuttle[2]**

[1]Department of Surgery, Head and Neck Service, [2]Department of Medicine, Endocrine Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

*Correspondence to:* Ashok R. Shaha, MD. Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA. Email: shahaa@mskcc.org.

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Kim *et al.* have published a very interesting article in *World Journal of Surgery* about staging of thyroid cancer and implications of genomic analysis based on patients' age (1). The authors compared overall survival and recurrence-free survival with different age cutoff values, and they investigated the appropriateness of the new staging system at a genomic level. They studied 505 patients for the clinical information (low- to intermediate-risk papillary thyroid cancers with 28 recurrences and 14 deaths) and The Cancer Genome Atlas (TCGA) data. They were able to show significant values using 55 years as a cutoff for relapse-free survival. Signaling pathway analysis revealed that patients above age 55 had differing genetic pathways associated with aggressiveness of thyroid cancer.

The authors also compared gene expression data, altered canonical pathways, copy number alteration, and somatic mutation profiles according to patient's age distributions to investigate differences in the new staging system on a genomic level. Ingenuity Pathways Analysis showed that patients above age 55 had alterations in Sirtuin signaling pathway, MSP-RON signaling pathway, ATM signaling, and FXR/RXR activation pathway, and TGF-beta pathway. They were not able to show a difference in copy number alteration or somatic mutation patterns between various age groups. They were also not able to show statistically significant frequency differences of somatic mutation or copy number alteration. In their multi-platform analysis, they reported that 14 age specific genes below the age of 45 and no age specific genes in the age group from 45 to 54 (age specific genes identified by multiple *t*-testing with $P<0.001$ and >1.5 difference). Compared to patients below age 55, the total number of age specific genes was 103 for patients above the age of 55.

This study is one of its kind to use the TCGA data to integrate clinical and genomic evidence in the evaluation of a genomic basis for the age cutoff point of 55 years. Despite having a relatively small number of recurrences and deaths, their data supported the proposition that the American Joint Committee on Cancer/ Union for International Cancer Control (AJCC/UICC) 8$^{th}$ edition can more accurately predict recurrence and survival data compared to the 7$^{th}$ edition (1-3). Additional studies using larger data sets with more aggressive histological phenotypes followed for longer periods of time will be needed to more completely explore possible differences in the genomic and transcriptomic landscape across the full spectrum of follicular cell derived thyroid cancer.

The incidence of thyroid carcinoma is rapidly rising around the world. Whether this is related to a true increase in the incidence of thyroid cancer or identification of incidental thyroid tumors remains unclear. The majority of the increase is directly related to identification of micro carcinomas. Davies *et al.* showed that most of the increase is seen in tumors below 2 cm and the mortality from thyroid cancer has not changed (4). The incidence of thyroid cancer has increased four-fold in the United States over the past 20 years. Interestingly, this increase is almost 15-fold in South Korea, where ultrasound of the thyroid was considered for routine cancer evaluation.

The incidence of thyroidectomies rose more than 10-fold in the last 15 years in South Korea. Interestingly, in 2014 the physician coalition group elected not to use

ultrasound as a routine evaluation of the thyroid and cancer diagnosis. This decreased the incidence of thyroidectomies in Korea almost by 50% suggesting that most of these micro carcinomas have no major clinical implication. Several advances have been made in the evaluation and management of thyroid cancer worldwide. The American Thyroid Association (ATA) and its committee on thyroid cancer have developed many guidelines in the management of thyroid cancer. The first guidelines were published in 2006 (5), subsequent ones in 2009 (6), and the most recent guidelines were published in 2015 (7). Clearly, there is an evolution in these guidelines suggesting understanding of the biology of the disease and analysis of large databases. Interestingly, Singer *et al.* had previously published the management choices in well-differentiated thyroid cancer in 1996, way before the first ATA guidelines were published in 2006 (8). These guidelines have helped us to standardize the management of thyroid cancer, and are commonly referred to by endocrinologists, thyroid surgeons, and by patients. The prognostic factors are well-defined in thyroid cancer. Several publications have shown following prognostic factors as a determinant of outcome, including age, grade of tumor, extrathyroidal extension, size of tumor, and distant metastases. Based on these prognostic factors, several staging systems have been developed, and the tumor-node-metastasis (TNM) staging system is considered to be the best for its practical clinical application. Based on the prognostic factors and staging systems, thyroid cancer can be divided into low-, intermediate- and high-risk groups (good, bad, and ugly).

The understanding of this risk stratification is extremely critical both in evaluation and management of thyroid cancer based on the extent of thyroidectomy and adjuvant therapy. The majority of the low-risk thyroid cancer patients do remarkably well with surgery alone and rarely require adjuvant therapy.

It is very important to analyze the risk stratification in well-differentiated thyroid cancer to avoid over treatment and treatment related medical and surgical complications. The complications in thyroid surgery are directly proportional to the degree of thyroidectomy performed and inversely proportional to operating surgeon's experience in performing the procedure. The overall survival in low-risk group exceeds 99%. In the intermediate and high-risk groups, overall survival drops to 87% and 57%, respectively. It is our responsibility to be more aggressive in the high-risk group, where the mortality is substantial, and risk of recurrence and distant metastases are also very high. In the intermediate-risk group, it would be important to develop a treatment strategy based on individual risk analysis.

From the beginning of the staging system popularized as TNM by the AJCC and UICC (3,9); both organizations have worked together to develop revised staging system for all organs. The most recent revision was published in 2016 and implemented in January of 2017 (2). The most recent staging system has made several important changes based on the prognostic factors, risk group analysis, and understanding of the biology of thyroid cancer. The most important change is related to age cutoff. Only thyroid cancer includes age in its staging system. Up until recently, age 45 was considered as a cutoff, and there were only two stages below age 45, stage I and II. The studies by Nixon *et al.* and multi-institutional cooperative studies revealed age 55 as a better cutoff (10,11).

The 8$^{th}$ edition staging system includes age 55 as a cutoff, and minimal extrathyroidal extension is not considered as a stage III tumor. The change in age cutoff has downstaged approximately 35% of patients from stage IV and stage III to either stage I or II. This is a major change in the staging system of thyroid cancer, which is now utilized all around the world. Several publications have strongly endorsed age 55 as a better cutoff. Our own data published recently in *Surgery* showed downstaging of approximately 35% of the patients (12). This downstaging is quite helpful to decide both extent of thyroidectomy and the role of adjuvant treatment. The authors of this manuscript in *World Journal of Surgery* have strongly endorsed the age cutoff of 55, and they have used interestingly the genomic analysis along with the standard staging systems by AJCC and UICC (1-3,9). Genomic analysis has become quite popular in various human cancers such as prostate, pancreas, and melanoma. Generally, these are aggressive cancers, and genomic analysis is of help to differentiate good from bad. The authors have reported 143 gene analyses in the group of patients from age 45 to age 55. The authors have looked at the genomic analysis in the group of patients below age 45, 45–55 (the change in staging system), and above age 55. They have shown a statistical difference in relapse-free survival based on the new age cutoff of age 55. This information is quite interesting, and not only endorses the change in the age cutoff but distinguishes the biology of thyroid cancer below and above age 55. Clearly, there will be some patients who will belong to intermediate and risk groups from ages of 45 to 55 (13). These patients will require in-depth analysis of their prognostic factors and treatment individualization.

Even though we have made major progress in genomic analysis of several human cancers, it appears that we are still in the early stages of our experience. Several new publications are reported in an expedited fashion as the technology is improving in genomic analysis. This forms the molecular basis of human cancer—a major advance, which has better implications in predicting long-term outcomes and treatment decisions, especially in relation to targeted therapies. What remains unclear is whether these clinical findings such as age, grade of tumor, extrathyroidal extension, size, and distant metastases, are parallel with genomic analysis.

Thyroid cancer is a unique human tumor, with peculiar biological behavior. This is the only tumor where age is an important prognostic factor. Nodal metastases are frequent in papillary cancer. However, it does not have major implication in the long-term outcomes. The authors have used their genomic analysis to support clinical prognostic parameters of age cutoff at 55 (1). We complement Kim *et al.* for their innovative study that begins a better integration of molecular abnormalities with clinical staging to further the understanding of the biology of thyroid cancer.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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