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EDITORS' COMMENTS

This is the tenth 2010 issue of *Clinical Thyroidology*.

EDITORS' CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

SEARCH FOR PREVIOUS ISSUES OF *Clinical Thyroidology* Many of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as Hyperthyroidism, Thyroid cancer, or other terms pertaining to thyroidology. You will find this by simply clicking the following URL: http://thyroid.org/professionals/publications/clinthy/index.html.

FIGURES The articles in *Clinical Thyroidology* contain figures with the ATA logo and a CT citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW On the last page of the journal, in addition to the section HOT ARTICLES AND REVIEWS, we have added CURRENT GUIDELINES that have relevance to thyroidologists, endocrinologists, surgeons, oncologists, students, and others who read this journal. We hope you will find this useful.

We welcome your feedback and suggestions.

Ernest L. Mazzaferri, MD, MACP
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Exposure to dental x-rays, particularly multiple exposures, may be associated with an increased risk for thyroid cancer

Memon A, Godward S, Williams D, Siddique I, Al-Saleh K. Dental x-rays and the risk of thyroid cancer: a case–control study. Acta Oncol 2010;49:447-53.

SUMMARY

BACKGROUND

Exposure of the thyroid gland to high-dose ionizing radiation is the only widely accepted environmental cause of thyroid cancer, which may occur from a number of sources, such as diagnostic radioiodine scans and computed tomography, radiation fallout, as occurred in Chernobyl, or stratospheric environmental contamination, as occurred during the 1950s from the testing of nuclear weapons in Nevada. One of the not-so-obvious sources of exposure, however, is dental radiography—a common source of low-dose diagnostic radiation that is not commonly thought to be a cause of thyroid cancer. This source has not been fully studied and thus might be associated with thyroid cancer more often than is generally appreciated. Still, an increased risk for thyroid cancer has been reported in dentists and dental assistants and x-ray workers, and dental radiation has been associated with an increased risk for meningiomas, brain tumors, and salivary tumors. The aim of this study was to examine whether exposure to dental x-rays is associated with a risk for thyroid cancer. This is a population-based case–control interview study of 313 patients with thyroid cancer and a similar number of individually matched control subjects in Kuwait. The study was designed to assess the hypothesis that dental radiography is associated with thyroid cancer.

SUBJECTS AND METHODS

Kuwait has a population of approximately 2.8 million; it has a government-funded national health service for all residents, including dental services. There are a number of specialty hospitals, including the Kuwait Cancer Control Center (KCCC), which provides cancer treatment and follow-up services for the entire population. Every week, a special follow-up clinic is held at the center for patients with thyroid cancer. A population-based cancer registry (the Kuwait Cancer Registry) has been available at the center since 1979; it regularly contributes data to the Cancer Incidence in Five Continents database compiled by the International Agency for Research on Cancer.

For this study, residents of Kuwait who were living and ≤70 years of age and had primary thyroid cancer were identified from the records of the Kuwait Cancer Registry using the International Classification of Diseases for Oncology topography codes. In addition to selecting patients with thyroid cancer, control subjects were selected from local primary health care clinics, in which a wide range of services is offered; all of these subjects had equal opportunity to visit their local clinic. A control subject was matched with each patient with thyroid cancer, based on year of birth (±3 years), sex, nationality, and district of residence in Kuwait. Individuals were eligible to serve as controls if they were visiting the primary care clinic for minor symptoms or were visiting the clinic for other purposes, such as vaccinations.

Study Subjects and Controls

The study subjects comprised 313 patients and 313 matched controls. A bilingual interviewer proficient in Arabic and English who was unaware of the diagnosis of thyroid cancer obtained information from all the participants. The data were recorded in a structured questionnaire that integrated a broad group of information, including sociodemographic characteristics, gynecologic and reproductive history, medical history, and exposure to diagnostic and other x-rays of the head, neck, and chest, radiotherapy, and exposure to and the number of dental x-rays. Also elicited were a family history of thyroid disease and cancer and other clinical and histopathologic information from KCCC.

Validity of Self-Reported Dental X-Rays

The consistency of self-reported dental x-ray exposure was assessed in a validation study using telephone interviews that included a random sample of 49 cases and 42 controls. The participants in the validation study were also questioned about their age (<20 years or ≥20 years) and first exposure to dental x-rays.

For each control, a “pseudo-diagnosis“ date—the date on which the subject was the same age as his or her matching subject was at the time of diagnosis—was determined. The analysis of data on exposure to radiation was confined to events before the diagnosis of thyroid cancer (cases) or matching study case date (controls).

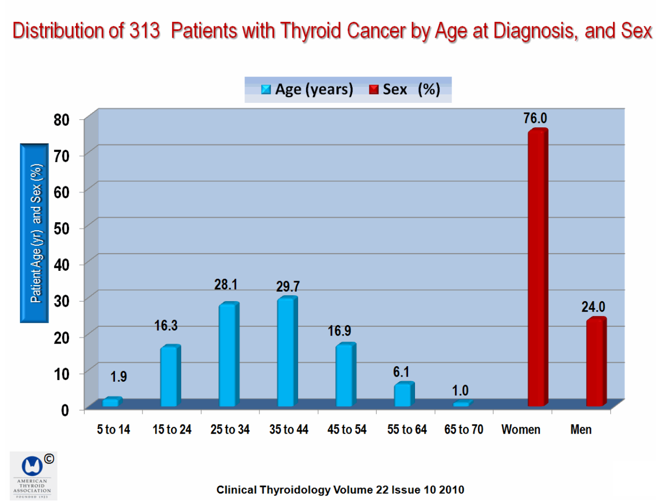

Figure 1. This figure shows the distribution of 313 patients with thyroid cancer by age at the time of diagnosis and by sex. The peak age at which thyroid cancer occurred from dental x-rays was 35 through 44 years, with a low range of 5 to 14 years to a high range of 64 to 70 years. The data for this figure and Figures 2 and 3 are derived from Table 1 of Memon et al.

A conditional logistic-regression analysis was used to assess the association between exposure to dental x-rays and the risk for thyroid cancer (odds ratio with 95% confidence intervals adjusted for confounding variables as necessary). Also examined was the dose-response pattern according to the number of exposures to dental x-rays. Subgroup analyses were performed to determine the risk of thyroid cancer according to age at the time of diagnosis, sex, nationality, level of education, parity, and histology.

RESULTS

The Demographic Features of the Patient Cohort (Figures 1 and 2)

Of the 313 patients with thyroid cancer, 238 (76%) were women, and 75 (24%) were men *(Figure 1)*. A total of 172 (55%) were Kuwaiti nationals and the remainder were non-Kuwaitis, among which the majority (70%) were from Arab countries, 26% were from Southeast Asia, and 4% were other nationalities *(Figure 2)*. Most of the thyroid cancers (74%) were diagnosed at a young age (range, 15 to 24 years). The average age (±SD) at the time of diagnosis in women was 34.7±11.0 years, (range, 10 to 65), and in men was 39.0±13.4 years (range, 6 to 69). The median age at diagnosis was 35 and 38 years in women and men, respectively; however, there was no difference in mean age at diagnosis between Kuwaiti and non-Kuwaiti patients.

The Incidence of Thyroid Cancer (Figures 3 to 6)

Papillary carcinoma was the most common histopathologic tumor, comprising 83% of all cases of thyroid cancer *(Figure 3)*. There was approximately a twofold increased risk for thyroid cancer among individuals who were exposed to dental x-rays (odds ratio, 2.1, 95% confidence interval, 1.4 to 3.1, P = 0.001) *(Figure 4)*. There also was a statistically significant dose-response pattern, which revealed an increasing trend in risk with the increasing number of dental x-rays (P for trend <0.0001) *(Figure 5)*. The association between dental x-rays and the risk for thyroid cancer was observed across all investigated subgroups, including age at the time of diagnosis, sex, nationality, level of education, parity, and histology *(Figure 6)*. The histologic subtypes were essentially papillary thyroid cancers, including cases classified as mixed papillary/follicular variant thyroid cancer.

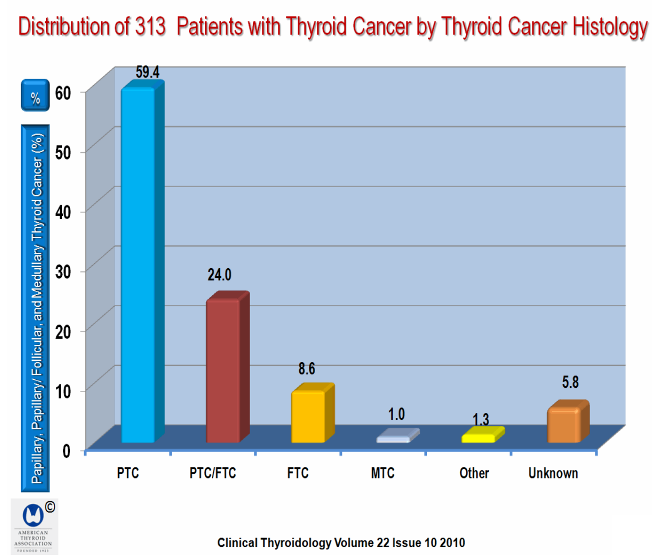

Figure 3. This figure shows the histology of patients in whom cancer was caused by dental x-rays. FTC = follicular thyroid cancer; MTC = medullary thyroid cancer; PTC = papillary thyroid cancer; PTC/FTC = papillary/follicular variant thyroid cancer. PTC comprises the majority (59%) of thyroid cancers.

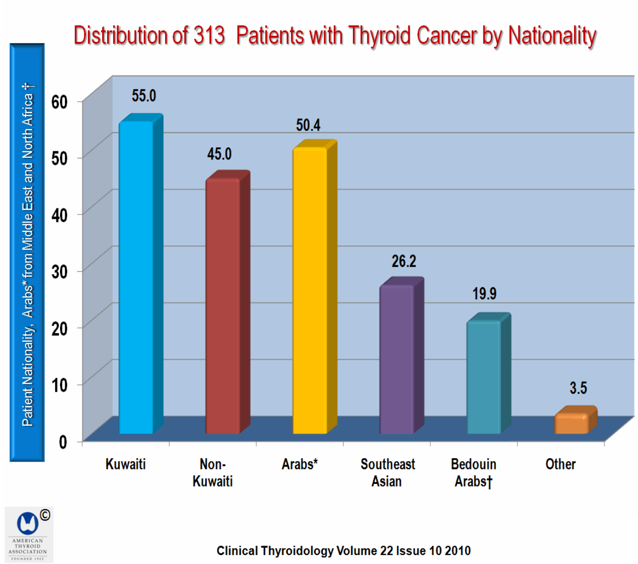

Figure 2. This figure shows the distribution of 313 patients by nationality, the majority of whom were from Kuwait. Arabs* = Arabs from Middle East and North Africa; Bedouin Arabs† = "stateless" Arabs resident in Kuwait.

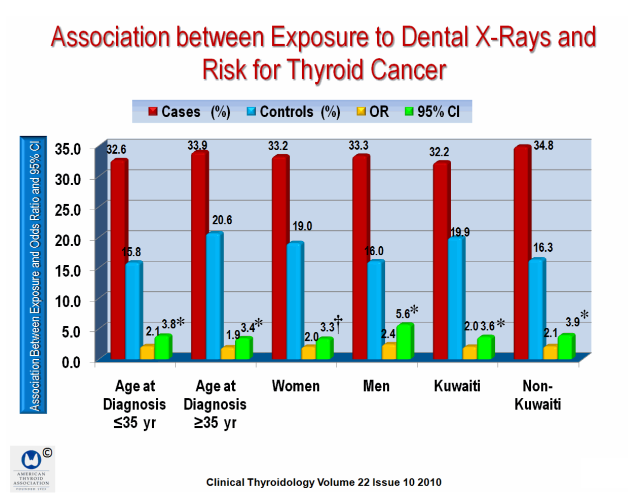

Figure 4. This figure shows the association between exposure to dental x-rays and the risk for thyroid cancer. The figure shows the logistic-regression analysis with results adjusted for upper-body (head, neck, and chest) x-rays.(*P for trend = 0.001, comparing patients with thyroid cancer and controls) Odds ratios [OR} and 95% confidence intervals [CI] for patients with and without thyroid cancer are shown. This figure shows the difference between controls with no dental x-rays and patients with thyroid cancer who received dental x-rays. The data for this figure and Figure 5 are derived from Table 2 of Memon et al.

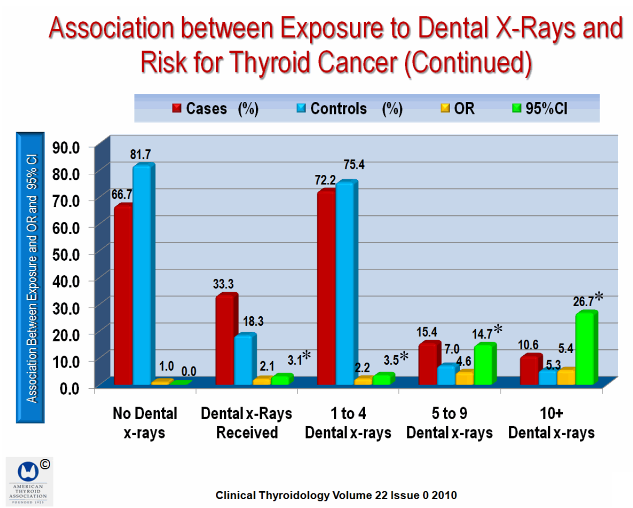

Figure 5. This is a continuation of Figure 4, which shows the risk for thyroid cancer with exposure to dental x-rays as compared with no x-rays. There is a significant difference of (odds ratio [OR], 2.1) for patients with thyroid cancer who were exposed to dental x-rays as compared with an OR of 1 in those who had no dental x-rays. The figure shows that the number of dental x-rays significantly altered the rate of thyroid cancers, ranging from 1 to 4 dental x-rays (OR, 2.2) to ≥10 dental x-rays (OR, 5.4).

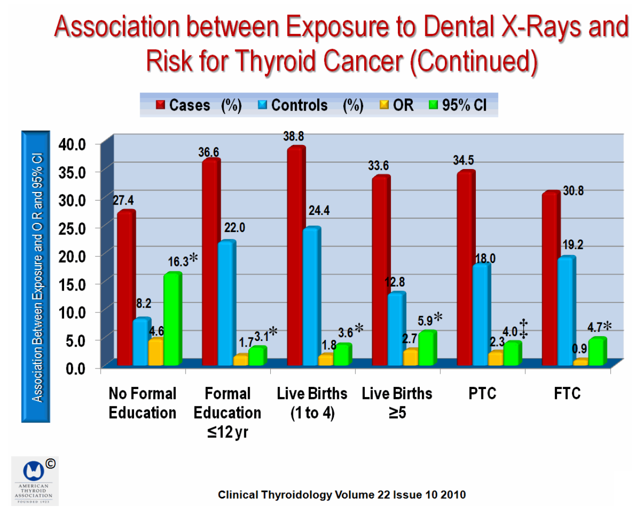

Figure 6. This is a continuation of Figure 5. The figure shows the association between exposure to dental x-rays and the risk for thyroid cancer by age at diagnosis, sex, nationality, level of education, and parity. Patients with no formal education had a lower exposure to dental x-rays as compared with patients with 12 years or more of formal education. Subjects with 1 to 4 live births were at significantly higher risk from those with ≥5 births (*P<0.05). Sex appears to influence the use of dental x-rays (P = 0.002 for papillary thyroid carcinoma [PTC] as compared with follicular thyroid carcinoma [FTC]; P<0.01) for women as compared with men with regard to the age at the time of diagnosis and other forms of thyroid cancer as compared with PTC (P not significant for FTC). ǂP = 0.002.

CONCLUSION

The authors of this study concluded that self-reported dental x-rays provide support for the hypothesis that exposure to dental x-rays, particularly multiple exposures, may be associated with an increased risk for thyroid cancer, the majority of which are papillary thyroid cancer.

COMMENTARY

The thyroid gland is very sensitive to radiation carcinogenesis, and exposure to high-dose ionizing radiation is especially harmful, particularly during childhood and adolescence. There is a long history of the damaging effects of ionizing radiation in children who were exposed to radiation in the form of x-ray treatment for benign conditions such as enlarged tonsils, ringworm of the scalp (tinea capitis) hemangioma, skin disorders, and spondylosis of the cervical spine (1-3).

The study by Memon et al. shows that the risk for thyroid cancer is associated with exposure to dental x-rays. There was an approximately twofold increased risk for thyroid cancer in individuals exposed to dental x-rays (OR, 2.1; 95% CI, 1.4 to 3.1; P = 0.001). The study also demonstrates a dose-response pattern of an increasing trend in risk for thyroid cancer with an increasing number of dental x-rays (P for trend <0.0001). The association of dental x-rays with thyroid cancer was observed across all the investigated subgroups, including age at the time of diagnosis, sex, nationality, level of education, and parity. The authors of this study point out that the literature on high-dose radiation and thyroid cancer shows a substantial age-related sensitivity, with the patients who are youngest at the time of exposure being the most sensitive; in this study, patients with thyroid cancer were more likely to be exposed to dental x-rays at younger ages as compared with normal controls. Among the patients with thyroid cancer who were <25 years of age at the time of diagnosis, approximately 27% were exposed to dental radiation, as compared with only 18% of the controls; among patients <20 years of age, about 22% were exposed to dental radiation, as compared with none of the controls. Also, the median age for women with thyroid cancer was 35 years; the younger patients at the time of diagnosis had a slightly higher risk for thyroid cancer as compared with older patients. Lastly, a greater proportion of patients exposed to dental radiation (57%) reported that their first dental x-ray exposure occurred before the age of 20 years. Moreover, a similar risk for dental x-rays had a similar association with thyroid cancer across multiple categories such as patient sex, nationality, ethnic background, level of education, type of dental x-ray exposure, and age at diagnosis, suggesting that recall bias or case–

control bias are unlikely to account wholly for the significant dose response .

The authors point to two similar studies (4;5), which concluded that interview data alone may be used for case–control comparisons of dental x-ray exposure and would, because of unbiased misclassification, tend to underestimate the relative risks.

Dental radiography has been implicated in the development of other tumors. One group of studies (4-6) found that age <20 years to full-mouth dental x-ray series was related to thyroid cancer (OR, 4.0; P<0.01). Similar studies of glioma (7) and brain cancer (8) also showed similar findings concerning dental x-rays. However, the association of diagnostic x-rays with meningioma was not confirmed in one study (9) of dental x-rays but also have been associated with benign and malignant tumors of the parotid gland. Also, an increased risk for thyroid cancer has been reported in dentists and dental assistants (10;11).

In 2003, The American Dental Association recommended that the National Council on Radiation Protection and Measurements update its recommendations on radiation protection in dentistry. The council concluded that dentists should be aware of, and comply with, applicable federal and state regulations and recommended that dentists should weigh the benefits of dental radiography against the consequences of increasing a patient's exposure to radiation and should implement appropriate radiation control procedures. Recent recommendations by the American Dental Association stress the need for shielding the thyroid (12).

There is little question that this is not a settled problem, but based on the conflicting studies, the recent American Dental Association recommendations are appropriate and should be carefully followed, considering the implications of the study by Memon et al. and other studies of this problem.

— Ernest L. Mazzaferri, MD, MACP

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There is a possible molecular basis for the difference in the extent of thyroid cancer at the time of presentation and the difference in outcomes observed in adolescents and young adults as compared with older adults

Vriens MR, Moses W, Weng J, Peng M, Griffin A, Bleyer A, Pollock BH, Indelicato DJ, Hwang J, Kebebew E. Clinical and molecular features of papillary thyroid cancer in adolescents and young adults. Cancer 2010. 10.1002/cncr.25369 [doi]

SUMMARY

BACKGROUND

Thyroid cancer in adolescents and young adults (AYAs) is underreported, and similarly to thyroid cancer in adults, the incidence has doubled over the past 30 years. In this study, the molecular and clinical features of papillary thyroid cancer (PTC) in AYAs are compared with the same features among older patients. The disparity in the incidence and outcome in AYAs typically appears as more advanced disease with a higher prevalence of lymph-node and distant metastases as compared with adults, but nonetheless usually has a favorable outcome with therapy. In 2006, the National Cancer Institute (NCI) initiated a Progress Review Group on AYA to investigate the biologic basis of age-related differences in the outcome for AYAs with thyroid cancer.

MATERIALS AND METHODS

The data for the subjects of this study were derived from medical records of 1011 patients who had their initial therapy for conventional and follicular variant PTC that was initially treated at the University of California at San Francisco (UCSF) from January 1983 through December 2003 and had follow-up at UCSF for ≥5 years. The study variables were age, sex, tumor–node–metastasis (TNM) classification, type of surgery, radioiodine ^{131}I treatment, and clinical disease-free and overall survival. The patients were subdivided into two age groups: 15 to 39 years (AYA group) and ≥40 years using data in the Surveillance, Epidemiology, and End Results (SEER) program from 1973 through 2006 (n = 46,680). The National Cancer Institute SEER Program at the time of this study represented approximately 26% of all cancer cases in the U.S. population.

Genotyping for Somatic Mutations

Primary PTC tumor samples from 245 patients (AYA group, n = 109; ≥40 years group, n = 145) were genotyped for common activating mutations that occur in PTC, including the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) valine to glutamine substitution at amino acid 600 (V600E) point mutation; the ret proto-oncogene/papillary thyroid cancer 1 (*RET/PTC1*), *RET/PTC3*, and neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) rearrangements; and hotspot point mutations in v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and neuroblastoma *RAS* viral (v-ras) oncogene homolog (*NRAS*). Point mutations in *BRAF* V600E, *KRAS*, and *NRAS* were detected by polymerase chain reaction (PCR) and direct sequencing. *RET/PTC1*, *RET/PC3*, and *NTRK1* were detected by using nested PCR. The number and type of mutation in the AYA group was compared with those in the ≥40 years group.

Analysis of Pathway-Specific Array Genes

Previous studies by the authors identified 39 genes in pathway-specific array analyses, which are genes involved in the cell cycle, angiogenesis, extracellular matrix, and cell adhesion, that had significantly different expression in thyroid cancer. The expression of these genes were compared between the AYA group (n = 16) and the ≥40 years group (n = 22) in the available samples. Also compared were the expression levels of genes that the authors associated previously with the extent of disease in thyroid cancer (epidermal growth factor receptor [*EGFR*], extracellular matrix protein 1 [*ECM1*], ephrin-B2 [*EFNB2*], and minichromosome maintenance complex component 7 [*MCM7*]) between the AYA group (n = 106) and the ≥40 years group (n = 151).

Genomewide Gene Expression Analysis

The authors used the Affymetrix Gene Chip (U133 Plus 2.0) array probe set, including 38,500 well-characterized human genes (Affymetrix), to identify differences in gene expression between the two age groups in 96 available PTC samples (AYA group, n = 46; ≥ 40 years group, n = 50). RNA samples were hybridized using the Human Genome U133 Plus 2.0 Chip (Affymetrix). The criteria used for differential gene expression between the two age groups were: (1) twofold higher or lower gene expression

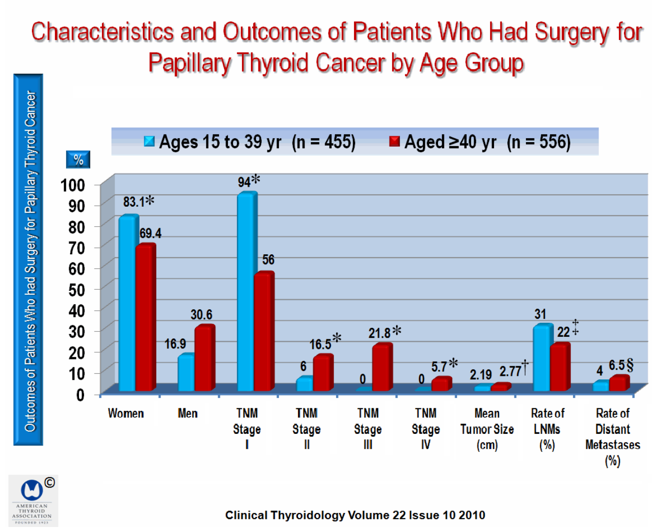

Figure 1. This figure shows the characteristics and outcomes of patients who had surgery for papillary thyroid cancer by age group. *P<0.001. †P = 075. ‡P<0.08. §P = 0.08. All comparisons are between the AYA group and the ≥40 years group. LNM = lymph-node metastases; TNM = tumor–node–metastasis. The data for this figure and Figures 2 and 3 are derived from Table 2 of Vriens et al.

levels, and (2) P value <0.5, determined by t-test. The study also used gene set enrichment analysis to determine any differences in biologic pathways between the two age groups.

RESULTS

Study Subjects (Figure 1)

DEMOGRAPHICS OF STUDY SUBJECTS (FIGURE 1)

Of the 1011 patients who had been treated for PTC over 20 years at UCSF, 455 (45%) were in the AYA group (15 to 39 years) and 556 (55%) were in the older group (≥40 years) *(Figure 1)*. There were significantly more women in the AYA group (83.1%) as compared with the ≥40 years group (69.4%; (P<0.001) *(Figure 1)*. Also, a greater proportion of patients in the AYA group had TNM stage I disease as compared with the ≥40 years group (94% vs. 56%), respectively (P<0.001), which turned out this way because age is included in the TNM staging system (P<0.01) *(Figure 1)*.

Mean tumor size was smaller in the AYA group as compared with the ≥40 years group,(2.19 cm vs. 2.77 cm, P = 0.075) *(Figure 1)*. The incidence of lymph-node metastases was significantly greater in the AYA group versus the ≥40 years group (31% vs. 22%, P = 0.008) *(Figure 1)*. In addition, the rate of distant metastases was lower in the AYA group as compared with the ≥40 years group (4% vs. 6.5%; P = 0.08) *(Figure 1)*.

Initial Surgery (Figure 2)

Surgery was lobectomy in 6.8% of AYAs and 16.7% of adults ≥40 years of age (P< 0.001), and subtotal or near-total thyroidectomy was performed in 16.5% and 16.4%, respectively (P not significant). Total thyroidectomy was performed in 74.3% and 63.3%, respectively (P<0.001) *(Figure 2)*.

Duration of Disease-free and Overall Survival (Figures 2 and 3)

A total of 64.5% of the AYA group and 57.1% of the ≥40 years group had no recurrences or were free of disease (0.017%); 7.1% of the AYA group had a recurrence, as compared with 6.1% of the ≥40 years group *(Figure 2)*. Death occurred in 2.4% of the AYA group and 21.8% of the ≥40 years group (P<0.001) *(Figure 2)*.

Mean (±SD) disease-free survival rates were 597.68±15.2 weeks in the AYA group and 531.11±15 weeks in the ≥40 years group (P = 0.126) *(Figure 3)*.

Median disease-free survival for the AYA group was 568 (95% confidence interval [CI], 493.1 to 623), and 497.57±15 for the ≥40 years group *(Figure 3)*.

Mean overall survival rates were 615.30±14.1 weeks for the AYA group and 532.08±13.1 weeks for the ≥40 years group (P = 0.0013) *(Figure 3)*.

Median overall survival rates were significantly higher in the AYA group (580.29; 95% CI, 525.3 to 641.0; P = 0.013), as compared with the ≥40 years group (476.29; 95% CI, 436.3 to 522.4; P = 0.0013).

When SEER data were subdivided into the two age groups (15 to 39 years, n = 16,983; ≥40 years, n = 29,697), there was a significant difference in the sex distribution between the AYA and the ≥40 years group (P<0.001); and as in the California study group, more AYA patients were women (80%, vs. 71% in the ≥40 years group *(Figure 3)*.

SEER Database

In the SEER data the mean tumor size was comparable to that in the California study group (2.05 cm for the AYA group vs. 2.16 cm for the ≥40 years group, P not significant). The number of lymph-node metastases was comparable for both groups (33% for AYAs vs. 34% for those ≥40 years), as was the number of distant metastases (6% for both groups). Similar to the California group, the SEER data showed a median overall survival in the AYA group that was significantly higher than that in the group ≥40 years of age (588 weeks vs. 296 weeks); however, disease-free survival data were not available in the SEER database.

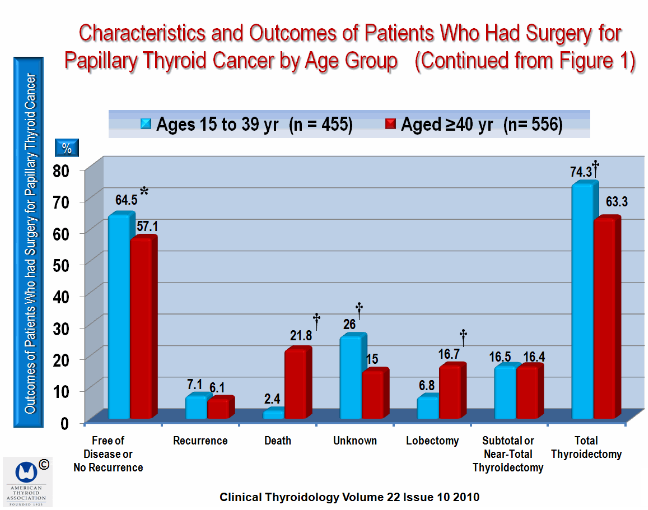

Figure 2. This is a continuation of Figure 1.*P = 0.017 and †P<0.001, comparing the two age groups.

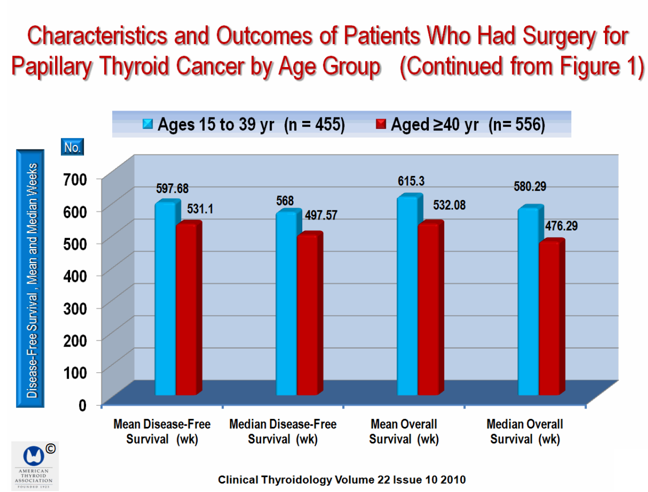

Figure 3. This is a continuation of Figure 1.*P = 0.0126, †P =0.0013, comparing the two age groups.

Genotype in Adolescent and Young Adult Papillary Thyroid Cancer

The authors underscore that previous studies of age with differentiated thyroid cancer mainly addressed the finding that older age (>45 years) was associated with a worse prognosis, increasing the recurrence and mortality rates of the disease. The present study takes a significantly different approach to this disease.

Analysis of the most common somatic mutations revealed that the number and type of somatic mutations detected in PTCs among AYAs as compared with adults age ≥40 years were similar. A total of 39% of patients in the AYA group had no mutation, as compared with 44% of the patients in group ≥40 years of age. A cutoff of 40 years was chosen to divide patients into two groups, because it is the official definition of the upper end of the AYA age range according to the NCI Progress Review Group on AYA Oncology. In the current study, the mortality rate was significantly higher in the group ≥40 years of age, and disease-free survival was significantly lower than that in the AYA group. The difference in the survival rate in the current study was concordant with the SEER database, perhaps because of confounding factors such as different stage, rage/ethnicity distribution, or differences in treatment and care.

A greater number of the AYA group had multiple somatic mutations (18% vs. 10%; P = 0.06). The prevalence of *BRAF* mutations alone was not significantly different between the two groups (42% in the AYA group vs. 35% in the ≥40 years group) *(Figure 4)*. A matched analysis between the AYA group and the ≥40 years group found that according to the extent of disease at the time of diagnosis (tumor size, ±2 cm), lymph-node status, and distant metastasis status had no significant difference in the type and number of mutations that existed between the two groups *(Figure 4)*.

Gene Expression Differences in Pathway-Specific Array Genes

Of the 39 genes analyzed, 3 (ECM1, v-erb-2 erythroblastic leukemia viral oncogene homolog 2 [ERBB2], and urinary plasminogen activator [UPA]) had expression levels that differed significantly between the AYA group and the ≥40 years group. The mean delta-Ct expression of ECM1 was significantly lower for patients in the AYA group (5.47±3.41 vs. 6.69±3.09; P = 0.0031).The same was true for ERBB2 (71.9±60.2 vs. 95.83±39.2; P = 0.01), and for UPA (0 vs. 0.031±0.078; P = 0.025). A matched analysis between the AYA group and the group ≥40 years of age according to the extent of disease at presentation (tumor size, ±2 cm, lymph-node status, and distant metastasis status) found that only ECM1 had significant differential expression (P = 0.02) *(Figure 5)*.

Genomewide Gene Expression Analysis

A cluster analysis of the gene expression profile found no distinct clustering in 96 PTC samples according to patient age (AYA group, n = 46; ≥40 years group, n = 50). The 12 most differentially expressed genes between the two age groups found that none of the genes had significantly differential expression *(Figure 5)*. There were no differentially expressed gene sets or pathways in a gene set enrichment analysis using a false discovery rate of ≥25%. For a nominal P value <1%, however, 10 gene sets were expressed differently in both groups (1 gene set was up-regulated in the AYA group, and 9 gene sets were down-regulated in the AYA group). Leading-edge analysis of these gene sets found that 1 gene, carbonic anhydrase II (CA2), was the most common in 3 of these 10 gene sets, and CA2 was down-regulated in the AYA group.

CONCLUSION

There is a possible molecular basis for the difference in the extent of disease at the time of presentation and the difference in outcomes observed in adolescents and young adults as compared with older adults

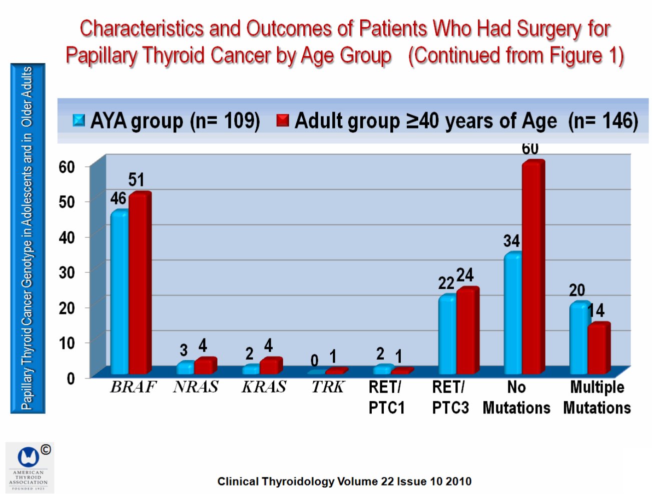

Figure 4. This figure shows papillary thyroid cancer genotypes in adolescents and young adults (AYAs, n = 109) and the group ≥40 years of age (n = 145). The number of genotypes are shown for each age group. This figure is derived from Table 3 of Vriens et al.

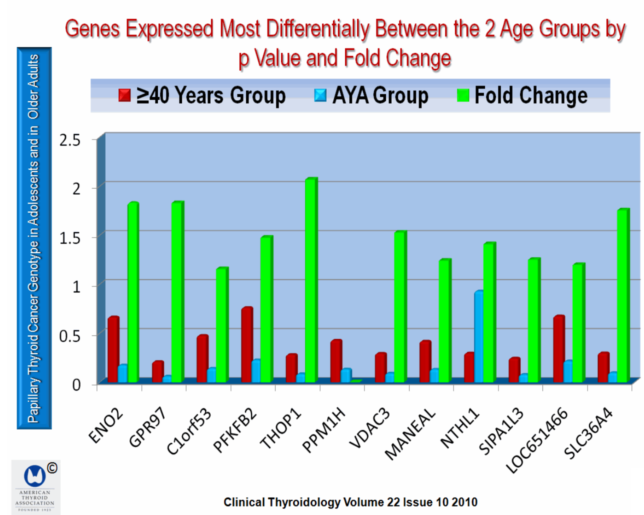

Figure 5. This figure shows the genes expressed most differentially between the two age groups.

COMMENTARY

This study found that AYA patients with PTC have a different scope of disease at presentation and have better outcomes as compared with outcomes in older patients. No significant differences were found in the type or number of somatic mutations that occurred in PTC between the AYA group and the ≥40 years group. However, the study identified several genes that were expressed differentially between the AYA group and the ≥40 years group (*ECM1*, *ERBB2*, *UPA*, *PFKFKB2*, and *MEIs2*). However, only *ECM1* had differential expression when a matched analysis was performed. These findings thus suggest a possible molecular basis for the difference in the extent of disease at the time of presentation and the difference in outcome observed in the AYA group. The authors note that the function of *ECM1*, an extracellular matrix protein, has not been characterized completely in carcinogenesis.

In a serial analysis of gene expression in both benign and malignant thyroid tumors, *ECM1* expression was higher in malignant tissue samples (1;2). Moreover, the level of *ECM1* expression was higher in older patients who had differentiated thyroid cancer of follicular-cell origin. The authors suggest that the findings that aggressive tumors are capable of growth without interactions between the cell surface and the extracellular matrix for survival and cell-cycle progression suggests that the decreased expression of *ECM1* in more aggressive differentiated thyroid cancers might reflect cell anchorage-independent tumor growth (3;4).

This study thus found that AYA patients with PTC had a different extent of disease at the time of diagnosis and had better outcomes as compared with older patients. The analysis suggested several candidate genes (*ECM1*, *ERBB2*, *UPA*, *PFKFB2*, *MEIS2*, and *CA2*) might account for the differences in outcomes in younger patients as compared with older patients.

This is a superb study. The authors suggest that such studies may provide new screening, diagnostic, and therapeutic options for the evaluation and treatment of common cancers in the AYA population that has been under study. I have no doubt that the authors are correct in this prediction.

— Ernest L. Mazzaferri, MD, MACP

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CLINICAL THYROIDOLOGY

Primary tumor diameter is related to the histologic tumor type, extrathyroidal extension, and lymph-node metastases in patients with differentiated thyroid cancer without initial distant metastases

Krämer JA, Schmid KW, Dralle H, Dietlein M, Schicha H, Lerch H, Gerss J, Frankewitsch T, Schober O, Riemann B. Primary tumour size is a prognostic parameter in patients suffering from differentiated thyroid carcinoma with extrathyroidal growth: results of the MSDS trial. Eur J Endocrinol 2010;163:637-44. EJE-10-0116 [pii];10.1530/EJE-10-0116 [doi]

SUMMARY

BACKGROUND

The Multicenter Study Differentiated Thyroid Cancer (MSDS) collective is a well-defined group of patients with thyroid carcinomas with extrathyroidal extension. The aim of this study was to evaluate the relationship of the primary tumor size with clinicopathologic features and the outcome of patients with minimum and extensive extrathyroidal tumor growth. The delineation between low-risk and high-risk tumor size is not well defined, with tumor sizes ranging from 1 cm to 4 cm. Accordingly, it is unclear whether the diameter of the tumor is prognostically relevant for tumors with perithyroidal infiltration (pT3b and pT4a, according to the former 6th edition of the International Union against Cancer tumor–node–metastasis (UICC TNM) classification 2002/2003.

METHODS

The MSDS trial is a prospective, randomized study that was conducted in Germany, Austria, and Switzerland that was performed in order to determine the benefit of adjuvant radiotherapy in patients with differentiated thyroid cancer growth (pT4; UICC 1997) with or without lymph-node metastases and without known distant metastases. The criteria for entry into the study were age from 18 to 70 years at the time of initial surgery, completion of primary surgical therapy with R0 resection (complete removal of all tumor with microscopic examination of margins showing no tumor cells) or R1 resection, (the margins of the resected tumor show tumor cells when viewed microscopically), and Karnofsky index ≥70% (normal activity with effort; some signs or symptoms of disease), without distant metastases at the time of initial radioiodine therapy. Excluded from the study were poorly differentiated (insular) thyroid carcinoma, secondary cancer, and R2-resection (complete resection with residual macroscopic tumor). A reference pathologist reclassified the tumors, if necessary.

Patients who agreed to participate in the study were randomly assigned to two treatment group A (external-beam radiotherapy) or B (no external-beam radiotherapy) at the time of the first ^{131}I scintigraphy 3 to 4 months after initial radioiodine therapy. The MSDS treatment protocol comprised total thyroidectomy with central lymphadenectomy, radioiodine (^{131}I) therapy to ablate the thyroid remnant, and thyrotropin (TSH)-suppressive therapy with levothyroxine suppression of TSH (<0.1 mIU/L). Preparation for remnant ablation was achieved by thyroid hormone withdrawal for 4 weeks followed by standard activities of 3 to 4 GBq (81 to 108 mCi), with a posttherapy whole-body scintigraphy study. If ^{131}I uptake was visible in the thyroid remnant with TSH withdrawal 3 to 4 months after ^{131}I therapy with TSH stimulation, a second treatment of ^{131}I was administered. At the time of each whole-body scan, serum TSH thyroglobulin (Tg), Tg recovery, anti-Tg antibodies (TgAb), blood-cell count, and neck ultrasonography were performed.

For patients in group A, external-beam radiotherapy (EBRT) was initiated after complete elimination of documented cervical ^{131}I uptake in a diagnostic whole-body scan (DxWBS). EBRT included the thyroid bed, with doses of 59.4 Gy after R0 resection and 66.6 Gy after R1 dissection, and the regional lymph nodes of the neck and upper mediastinum including the posterior cervical chain from the mandible and mastoid process to the tracheal bifurcation, with doses of 50.4 Gy in pN0 and 54.0 Gy in pN1.

^{131}I DxWBS, cervical ultrasonography and serum Tg under endogenous TSH stimulation or recombinant TSH stimulation were performed 3 months and 1 year after the last ^{131}I ablation and thereafter at 2-year intervals. Outpatient follow-up visits were then scheduled at 6-month intervals. As a consequence of a deficit of patient recruitment for EBRT, randomization was closed in 2003 and the trial was continued as a prospective multicenter study.

All patients with thyroid cancer identified before January 2003 were staged according to the 5th edition of the TNM classification. For the purposes of this study, these patients were retrospectively restaged or reclassified according to the 6th edition of the TNM classification, which was used until the end of the study in 2009. A total of 307 patients (94.8%) were assigned to stage pT3b, 17 (5.2%) to stage pT4a, and 137 (4.2.3%) to stage 1 (pT3b-patients <45 years of age, 173 (53.4%) to stage III and 14 (4.3%) to stage IVA, and there were no patients with pT4b tumors. Median follow-up was 6.2 years.

The association between primary tumor size and the following clinicopathologic data were investigated: age, sex, histologic tumor type, and TNM classification; in addition, the correlation between the primary tumor size and event-free and overall survival were assessed. Lastly, the patients were arbitrarily subdivided into three groups according to their primary tumor size, as follows: group 1 (≤1.0 cm, n = 85), group 2 (>1.0 to ≤2 cm, n = 136), and group 3 (>2 cm, n = 103). In the analysis, an event was defined as a local recurrence, metastatic lymph-node recurrence, distant metastases, or death after the achievement of a total clinical tumor-free status.

Remission Was Designated as Follows:

Complete remission was defined as no evidence of disease, comprising negative tumor parameters, serum Tg measurement, DxWBS, and sonographic or radiologic examinations.

Partial remission was defined as a reduction in tumor parameters without reaching complete remission under therapy.

Stable disease was defined as an absence of change in tumor parameters.

Progressive disease was defined as an increase in tumor parameters without a therapeutic response.

Multivariate analysis of prognostic factors was performed using Cox regression. The variables were dichotomized as follows: age <45 vs. ≥45 years, sex, histology (follicular thyroid cancer [FTC] versus papillary thyroid cancer [PTC], tumor diameter ≤2 vs. >2 cm, and TNM classification (6th edition) of pT3b vs. pT4a and pN1 vs. pN0/X.

RESULTS

Distribution of Tumor Size (Figures 1 and 2)

A total of 351 patients were included in the MSDS trial. Complete primary surgical therapy was achieved by one operation in 35% of the patients, by two operations in 59%, and by three operations in 7% of the patients, and systematic lymphadenectomy was performed in 72% of the patients. Patients were treated with a mean cumulative radioiodine activity of 6.5±5.0 GBq (176±135 mCi), and 26 additional patients were treated EBRT.

Initial Follow-up Data (Figures 1 and 2)

Follow-up data were available in 347 of 351 patients (99%). The exact tumor diameter was documented in 324 (92.3%) of the patients, 244 of whom were women and 80 men, with a mean (±SD) age of 47.7±12 years (range, 20.1 to 69.8). A total of 302 patients (93.2%) had PTC, and 22 (6.8%) had FTC. Tumor size was significantly larger in patients with FTC as compared with patients with PTC (3.46 vs. 1.84 cm, P<0.001). In addition, there was a significant difference between tumor size in pT3b and pT4a tumor categories. Patients with minimal extrathyroidal extension (pT3b) had significantly smaller primary tumor diameter as compared with those who had extensive extrathyroidal tumor extension (1.9 vs. 3.0 cm). Patient age was not significantly related to primary tumor size and sex. PT4a tumors were relatively small, with a diameter of at least 1.2 cm. In contrast, patients with initial lymph-node metastases had significantly larger primary tumors as compared with those without lymph-node spread (2.2 vs. 1.8 cm, P<0.001) .

Follow-up During a Median of 6.2 Years

During a median follow-up of 6.2 years, complete remission was achieved by 303 patients (93.5%); 5 (1.5%) had partial remission; 3 (0.9%) had stable disease; and 13 (4%) had progressive disease. After achieving complete remission, 22 patients (6.8%) had a recurrence. The median delay between primary treatment and recurrence in this group was 1.3 years. There were 17 recurrences (77.3%) in patients with PTC and 5 (22.7%) in patients with FTC. Eighteen patients (5.6%) had locoregional tumor recurrence, 7 (2.2%) had recurrence in more than one location, and 11 (3.4%) were found to have distant metastases during follow-up, all of whom had tumors >2 cm (group 3). *(Figure 1)*

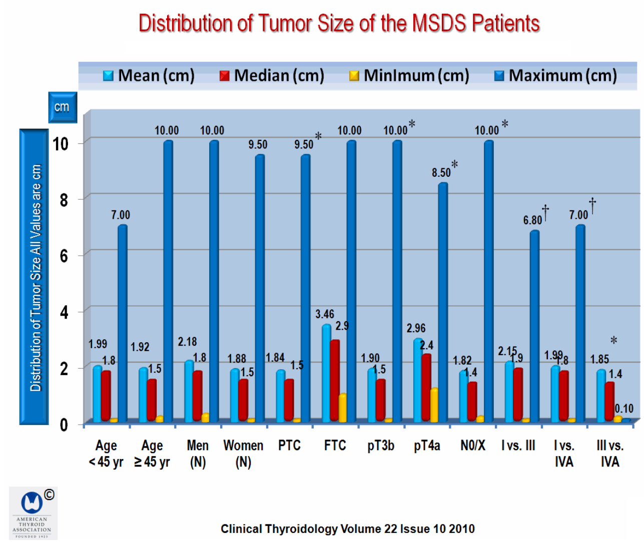

Figure 1. This figure shows the distribution of tumor size of the MSDS patients. The variables were dichotomized as follows: age <45 vs. ≥ 45 years; women vs. men, histology, follicular thyroid carcinoma (FTC) vs. papillary thyroid c (PTC); tumor category PT3b and pT4a; lympnode category, pN1 vs. pN0/X; tumor stages. *P<0.001 comparing PTC and FTC; and pT3b vs. pT4a. †P<0.01 and stages II vs. III, I vs. IVA (P<0.05) and III vs. IVA P<0.01.

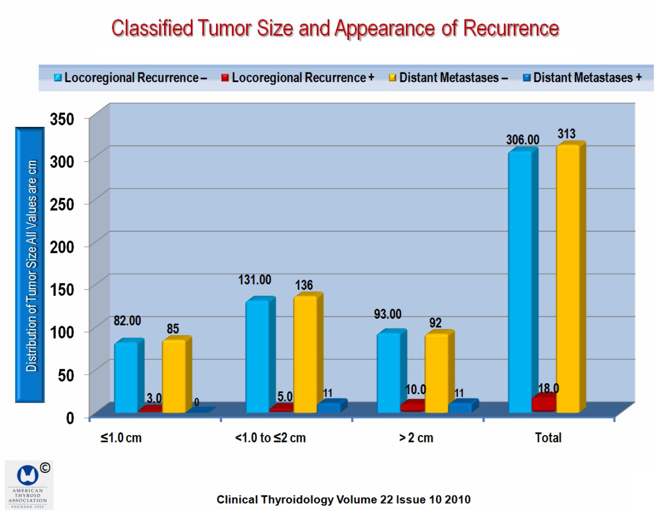

Figure 2. This figure shows the classified tumor size and appearance of recurrence. P<0.01 for locoregional recurrences, and P<0.001 for distant metastases.

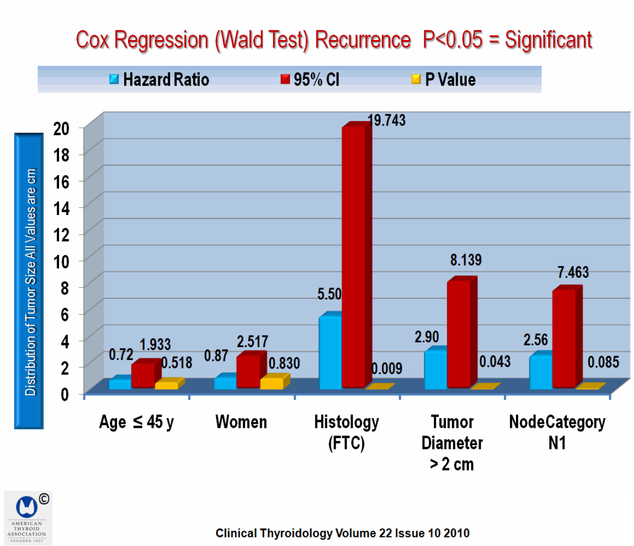

Figure 3. This figure shows the prognostic factors identified by Cox regression, for age, sex, histology (FTC), tumor diameter >2 cm, and tumor category (pT4a) and node category (N1). The P values are shown in the figure.

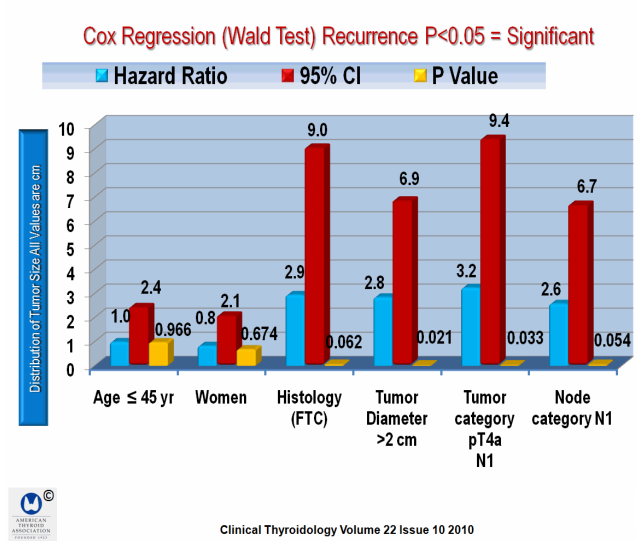

Figure 4. This figure shows the prognostic factors calculated by Cox regression. The hazard ratios and 95% confidence intervals (CIs) are shown in the figure.

Tumor Size and Event-free Survival (Figures 3 and 4)
Event-free survival was significantly correlated with tumor size. Patients with tumors ≤2 cm (groups 1 and 2) had significantly fewer events as compared with patients who had tumors >2 cm (group 3) ($P<0.01$). As a consequence, a significant threshold tumor diameter of 2 cm was also associated with event-free survival of patients with American Joint Committee on Cancer stage III tumors ($P<0.001$).

Multivariate analysis showed that a tumor diameter >2 cm and a pT4a category were both independent predictors of event-free survival. However, because of the small number of patients with pT4a tumors, factors associated with recurrences were also studied in the large subgroup of pT3b patients. Still, tumor size remained a significant predictor of tumor recurrence using multivariate analysis. Also, histology was a prognostic factor for event-free survival ($P< 0.01$) *(Figures 3 and 4)*.

Overall survival in this study cohort was excellent. Only 3 patients (0.9%) had fatal tumor progression, and 1 other patient died in an auto accident. Tumor size was significantly correlated with overall survival ($P<0.05$) and still was significant if the patient with an auto accident was excluded from the analysis. EBRT had no significant impact on the correlation between primary tumor size and event-free or overall survival. Only one patient treated with EBRT showed a local recurrence and pulmonary metastases.

CONCLUSION

Primary tumor diameter is related to the histologic tumor type, extrathyroidal extension, and lymph-node metastases in patients with differentiated thyroid cancer without initial distant metastases. Whether this holds for patients with distant metastases has not been determined.

COMMENTARY

The MSDS trial represents one of the larger prospective multi institutional cohort studies of high-risk patients with differentiated thyroid cancer. This study was conducted in Germany, Austria, and Switzerland in order to determine the benefit of adjuvant radiotherapy in patients with differentiated thyroid cancer showing extrathyroidal growth (pT4) with or without lymph-node metastases, in which patients who agreed to participate were randomly assigned to either external-beam radiotherapy (EBRT) or no EBRT. In addition, patients were treated with ^{131}I for remnant ablation. On average, patients with lymph-node metastases had significantly larger primary tumors than patients without documented lymph-node spread. The study found that patients with tumors >2 cm (group 3) had significantly higher recurrence rates as compared with those with tumors ≤2 cm. About 5.6% of the patients had locoregional tumor recurrences, and 3.4% presented with distant metastases. The authors point out that <4 cm has been generally accepted as a significant predictor of a high-risk situation, which, according to the authors, should be applied with caution in view of the poorer prognosis with tumors >2 cm if extrathyroidal extension is present. Specifically, the lack of division of pT3 tumors into those with and without extrathyroidal extension in the TNM classification should be reconsidered in view of the present finding in this study. The authors opine that using this large prospective multicenter study database allows for retrospective scientific analysis of a multitude of parameters collected during a follow-up period of up to 9 years.

According to the authors, the MSDS trial represents the largest multiinstitutional study of high-risk patients with differentiated thyroid cancer worldwide, second only to the North American National Thyroid Cancer Treatment Cooperative study (1). Not mentioned is the study by Bilimoria et al. (2) of a U.S. database of 52,173 patients with PTC, in which recurrence rates are shown to be closely related to initial tumor size, beginning with <1 cm, in which 10-year recurrence rates are approximately 5%, increasing incrementally to recurrence rates of approximately 25% with primary tumors >8 cm. In addition, 10-year cancer-specific mortality rates ranged from 2% for tumors <1 cm, which incrementally increased to 19% for tumors >8 mm. This seems to support the hypothesis that PTC outcome is related to the initial tumor size, increasing progressively with increasingly larger tumors. Limiting the cutoff to 2 cm seems to ignore the well-recognized effect of initial primary tumors ranging to over 8 mm in diameter.

While tumor diameter is surely an independent predictor of overall survival and mortality, it seems that increasingly larger tumors have a progressive effect on recurrence, survival, and mortality rates, with or without extrathyroidal extension.

— Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.

Call for Proposals – American Thyroid Association (ATA) Research Grants
Deadline: January 31, 2011

Electronic Submission: Proposals should be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, clinical thyroidology, thyroid autoimmunity, thyroid and the brain, thyroid hormone action and metabolism, and thyroid cell biology. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH).

Eligibility of Applicant and Use of Funds Guidelines:

1. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
2. Faculty members (MD and PhD) are eligible.
3. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position. Students working towards a PhD are not eligible.
4. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible. In general, investigators who have achieved the rank of associate professor or higher are not eligible.
5. Applications are limited to one per individual researcher.
6. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
7. Recipients of ATA grants should be ATA members or must apply to become ATA members. For new members, membership dues for the first year will be waived.

Proposal Requirements: Interested investigators should submit a brief description of the proposed research by January 31, 2010. Each proposal must include the following:

1. Name and affiliation of applicant with complete work and home contact information
2. Title of proposed study
3. Short proposal that should be no longer than 900 words or three double-spaced pages in 12 point type. These space requirements are absolute and nonconformance will preclude review. This short proposal should include:
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - References (selected)
4. An NIH-style CV (no longer than two pages) including evidence that the applicant is a new investigator (see above), namely date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2011 and invited to submit a complete grant application.

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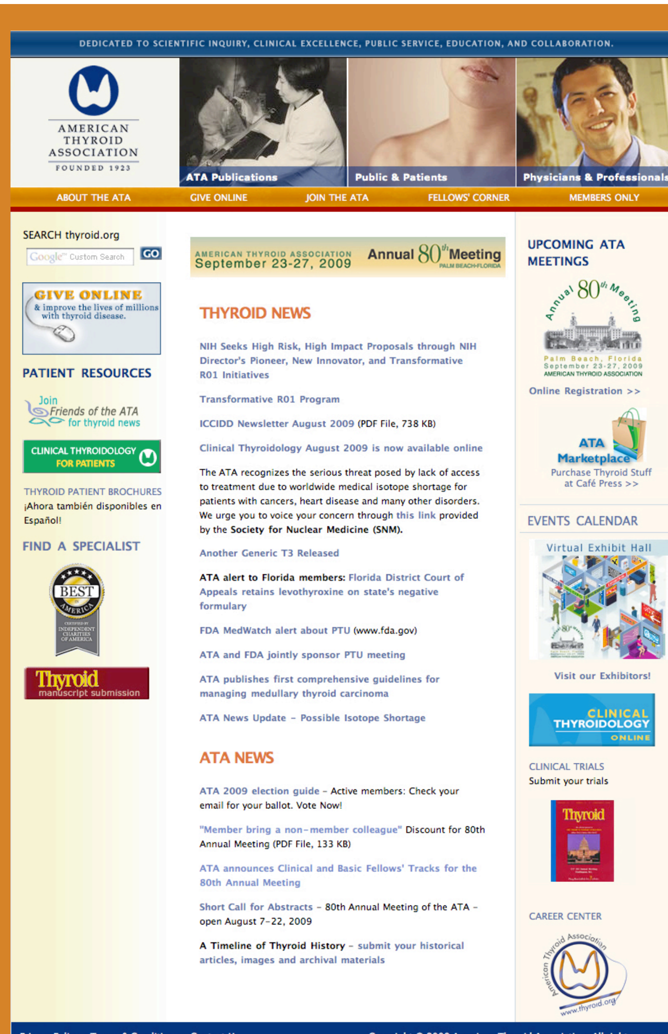

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