The incidence of pediatric thyroid cancer is increasing and is higher in girls than in boys and may have an adverse outcome

Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res 2009;156:167-72.

SUMMARY

BACKGROUND Thyroid cancer is the most common endocrine malignancy in children. The principal thyroid malignancies in children are of the same histology as those afflicting adults, including papillary, follicular, and medullary thyroid cancer. However, children tend to present with more advanced disease, with a greater frequency of lymph-node metastases and distant metastases at the time of diagnosis and high rates of recurrence during the first decade of life. Most studies are relatively small or are from single institutions, which may not fully reflect the features of this disease, including the extent of tumor at the time of diagnosis and the long-term response to therapy. The latter is particularly important, since healthy children have a long life expectancy that may not be achieved in children with thyroid cancer, even with aggressive therapy. The aim of this study was to examine outcomes and predictors of survival for pediatric patients with thyroid cancer.

METHODS This study was performed on the latest records from the Surveillance, Epidemiology, and End Results (SEER) registry from 1973 through 2004 for all patients with thyroid cancer who were younger than 20 years of age. Tumor histology was identified using morphology codes from the International Classification of Disease for Oncology, 3rd edition. There were no duplicate cases, and patients with missing data were excluded from univariate and multivariate analyses. The SEER staging criteria, which were used in this analysis, are different from the TNM (tumor–node–metastases) staging system. In the SEER staging system, "local" denotes disease confined to the thyroid and "regional" tumor extension into adjacent organs, regional lymph nodes, or both.

RESULTS

Study Subjects and Tumor Features (Figures 1 to 3)

A total of 1753 pediatric patients with thyroid cancer were identified during the study period. The annual incidence of thyroid cancer in 2004 was 0.54 cases per 100,000, and was categorized by sex, race, age group, and histology (Figure 1). The mean age at the time of diagnosis in this cohort was 15.9 years (range, <1 to 19). Girls outnumbered boys more than

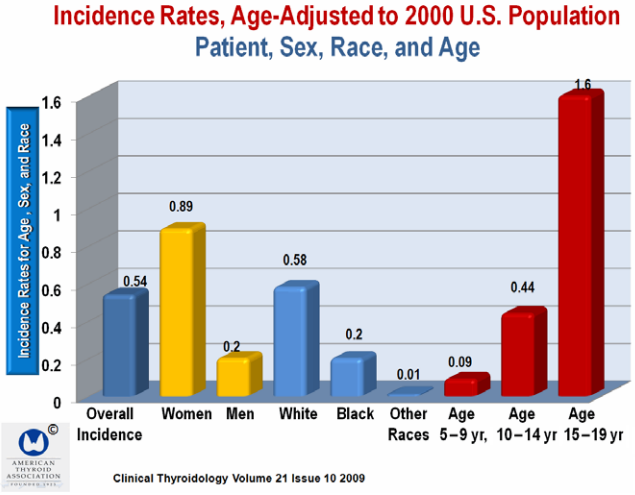

Figure 1. This figure shows the annual incidence rate per 100,000 pediatric population for thyroid cancer in 2004 and the age and race of patients at the time of diagnosis. The age-adjusted incidence was 0.89 cases per 100,000 girls and 0.2 cases per 100,000 boys.

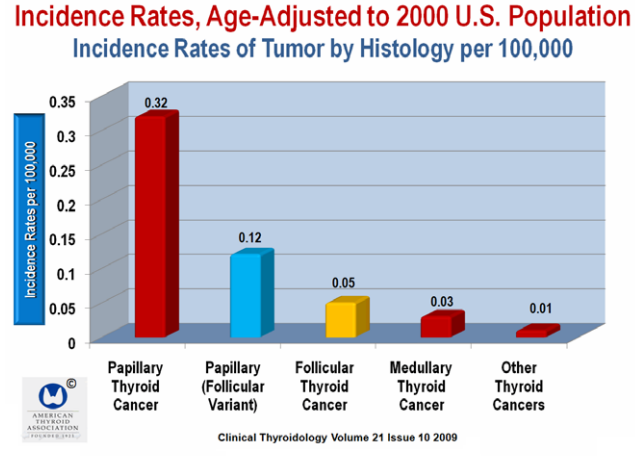

Figure 2. This figure shows the incidence rates per 100,000 age-adjusted to the 2000 U.S. standard population.

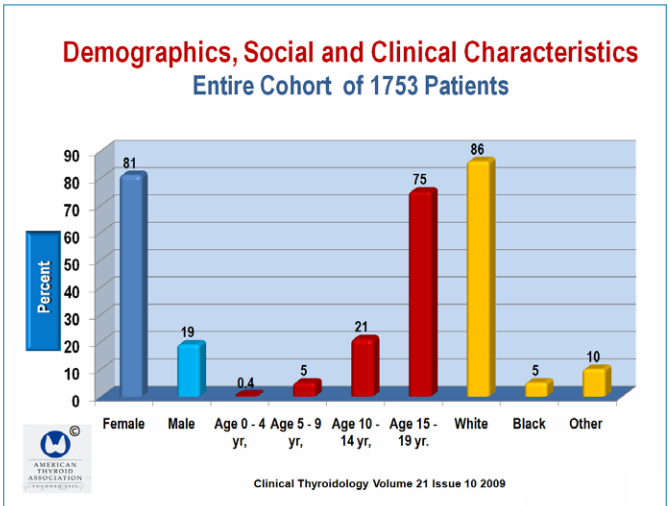

Figure 3. This figure shows that girls outnumber boys more than 4 to 1, and that overall, 95% of the patients with thyroid cancer (1658 patients) with thyroid cancer were older than 10 years of age, and 74% were between the ages of 15 and 19. The figure is derived from data in Table 1 and the text in Hogan et al.

4 to 1 (1424 vs. 329). A total of 1658 patients (95%) were more than 10 years of age, and 1298 (74%) ranged in age from 15 through 19 years (Figure 1). Tumor histology was papillary thyroid cancer (PTC) in 1044 patients (60%), follicular variant papillary cancer (FVPC) in 398 (23%), and medullary thyroid cancer in 87 (7.6%) (Figure 2). Distant metastases were found in 133 (7.6%) of the patients at the time of diagnosis and were most commonly found in the lung and rarely in the bone or liver. Regional lymph-node metastases were found in 814 patients (46%), and disease confined to the thyroid gland was found in 741 (42%). Here and elsewhere, percentages are rounded to the nearest integer.

Initial Surgical and Medical Therapy (Figure 4)

Surgery was performed on 1695 patients (97%), but the extent of surgery was known in only 901 patients. In this group, total thyroidectomy was performed on 744 patients (86%) and lobectomy was performed on the remaining 157 (18%). Half of the patients received some form of radiation therapy.

Outcome (Figures 5 and 6)

For the entire cohort, the overall mean survival time was 30.5 years, and the mean disease-specific survival was 31.5 years. Overall mean survival was longer in female patients as compared with male patients (40 vs. 20 years, P = 0.0001). However, there were significant differences in survival in patients with tumors of different histology.

Five-, 15- and 30-year survival rates for patients with papillary thyroid cancer were, 98%, 87%, and 91%, respectively, and

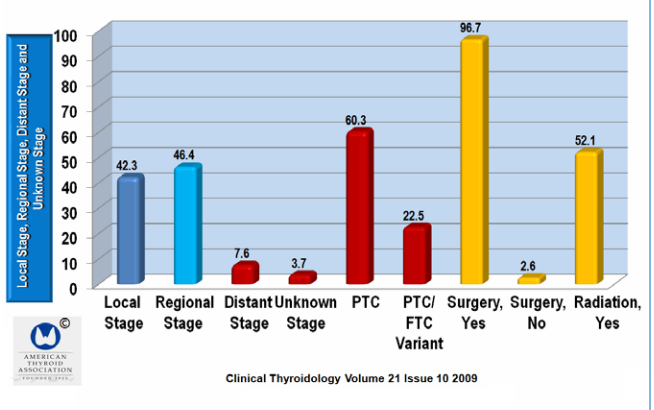

Figure 4. This figure shows the stage, histology, surgery, and radiation features of the entire cohort. PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma. The data are derived from Table 2 in Hogan et al.

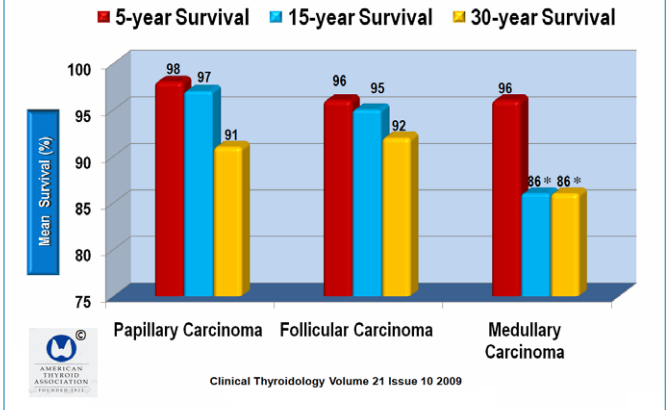

Figure 6. This figure shows the 5-, 15-, and 30-year survival rates for papillary follicular and medullary thyroid carcinoma *P = 0.006.

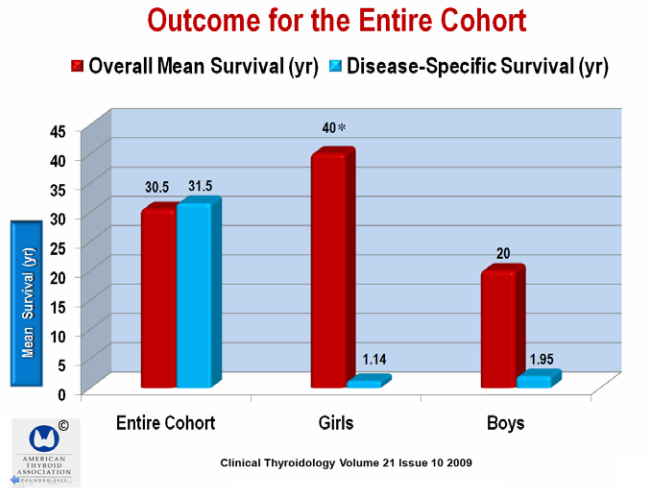

Figure 5. This figure shows that the mean overall survival for the entire cohort was 30.5 years and the mean disease-specific survival was 31.5 years. Mean disease-specific survival of girls was twofold that of boys. *P = 0.0001.

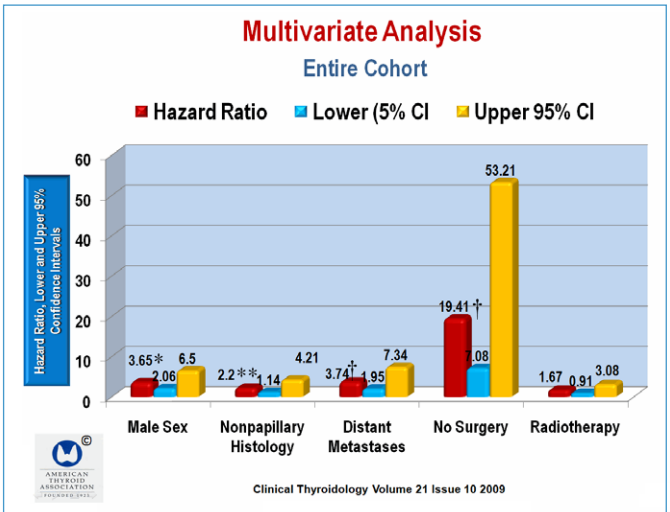

Figure 7. This figure shows the five independent variables found on multivariate analysis to be associated with a poor outcome: male sex, nonpapillary histology, distant metastases, no surgery, and radiotherapy. *P<0.002. **P= 0.018. CI = confidence interval. The data are derived from Table 3 in Hogan et al.

were similar with follicular thyroid cancer, being 96%, 95%, and 92%, but were lower in patients with medullary thyroid cancer, being 96%, 86%, and 15%, respectively. The mean survival of patients with medullary thyroid cancer was 28.3 years as compared with 30.7 years for patients with papillary thyroid cancer (P = 0.006).

Patients who had metastases at the time of initial diagnosis had significantly worse outcome as compared with patients who presented with regional disease (tumor in adjacent organs, regional lymph nodes, or both, P<0.0001).

Survival in patients who had surgery, regardless of the extent, had significantly longer survival as compared with patients who did not have surgery (P = 0.007).

Multivariate Analyses (Figure 7)
Multivariate analysis of the entire cohort revealed that the following were independent variables predicting a poor outcome—male sex: hazard ratio (HR), 3.65 (95% confidence interval [CI], 2.06 to 6.50], P<0.001; nonpapillary histology: HR, 2.20 (95% CI. 1.14 to 4.21), P = 0.018; distant metastases: HR, 3.78 (95% CI, 1.95 to 7.34), P<0.001; no surgery: HR, 19.41 (95% CI, 7.08 to 53.21), P<0.001; and radiotherapy: HR, 1.67 (95% CI, 0.91 to3.08), P not specific.

Multivariate analysis for medullary thyroid cancer found that the following were independent variables predicting a poor outcome: medullary thyroid cancer: HR, 14.82 (95% CI, 3.71 to 59.13), P<0.001; distant metastases: HR, 13.33 (95% CI, 4.24 to 41.84), P<0.001; no surgery: HR, 29.03 (95% CI, 3.09 to 242.81), P = 0.003; radiotherapy: HR, 5.79 (95% CI,) 1.44 to 23.26, P = 0.013.

CONCLUSION The incidence of thyroid cancer in children and adolescents is increasing. The incidence is higher in girls than in boys. Although papillary thyroid cancer has an excellent survival rate in the majority of patients, male sex, nonpapillary tumor, distant metastases, and nonsurgical treatment are predictors for an adverse outcome.

COMMENTARY

This is a study of 1753 patients that was performed on the latest records from the Surveillance, Epidemiology, and End Results (SEER) registry from 1973 through 2004 for all patients with thyroid cancer who were younger than 20 years of age. This is clearly one of the most important studies on pediatric thyroid cancer that has been published to date.

Although thyroid cancer is an uncommon disease in the pediatric population, the incidence of this disease in children and adolescents has been increasing since 2004, when the overall incidence of thyroid cancer was slightly more than 1 per 200,000 children and adolescents. Hogan et al. found that the annual incidence of thyroid cancer in this cohort has been increasing 1.1% per year over a 31-year period. The authors suggest that a possible explanation for this increase may be the use of radiotherapy for childhood malignancies (1). Winship and Rosvoll (2) reported that the latency period between radiation therapy and the development of thyroid cancer averaged 8.5 years. This was further substantiated by analysis of the Chernobyl accident (3). In the Hogan cohort of 1753 patients, 2.4% were treated for an earlier malignancy.

The increased incidence of differentiated thyroid cancer in women is a well-recognized phenomenon (4) that has been attributed to estrogen (5). The first to demonstrate this effect was Imai et al. (5), who found that endogenous estradiol was located in thyroid cancers more frequently in women than in men and that there was estrogen-binding activity in the cells of not only thyroid cancers, but also in normal and benign thyroid tissues. Still, the survival rates in women with differentiated thyroid cancer are considerably higher than the survival rates in men (4). In the study by Hogan et al., female patients outnumbered male patients by more than 4 to 1, and the overall mean survival times were 30.5years, 40 years for girls and 20.4 years for boys. In this study, thyroid cancers were classified as papillary in 60%, follicular variant papillary in 23%, follicular in 10%, and medullary in 5%, a distribution of tumors that closely follows the pattern in adults (6). Patients with medullary thyroid cancer had significantly shorter mean survival than those with papillary cancer (P = 0.006). Of great importance, surgical treatment significantly improved outcome. Multivariate analysis found that the following four variables were independent factors that portended a worse outcome: male sex, nonpapillary histology, distant metastases, and no surgery.

The authors conclude that the incidence of pediatric thyroid cancer is increasing and that girls have a higher incidence of thyroid cancer than boys, but had a more favorable outcome than did boys. The scope of this analysis is wide and the depth of the conclusions is deep and will help physicians manage this disease in children and adolescents.

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