The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Population-Based Outcomes for Pediatric Thyroid Carcinoma

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Objectives/Hypothesis: **The objective was to determine clinical features and clinical outcomes for pediatric thyroid carcinoma.** ***Study Design:*** **Cross-sectional analysis of national cancer database.** ***Methods:*** **The Surveillance, Epidemiology, and End Results database (1988–2000) was surveyed, extracting all cases of pediatric thyroid carcinoma. Clinical features including age, gender, tumor type, tumor size, nodal disease, treatment modality, and survival variables were retrieved. Kaplan-Meier survival analysis was conducted to determine actuarial survival according to histological type. Cox regression analysis was conducted to determine prognostic factors affecting survival in pediatric carcinoma.** ***Results:*** **In all, 566 cases of thyroid carcinoma were extracted for the time period. Mean patient age at presentation was 16.0 years, with a female predominance (84.8%). There were 378 cases of papillary carcinoma, 137 cases of follicular variant of papillary carcinoma, and 51 cases of follicular carcinoma. The average tumor size was 2.6 cm, and 37.1% of patients presented with positive nodal disease. Overall survival was excellent with mean survivals greater than 145 months for each histological type. Follicular carcinoma exhibited a slightly poorer survival that was statistically significant (P = .017)** ***Conclusion:*** **Pediatric thyroid carcinoma primarily affects girls. Clinical features of tumor presentation are similar to those of adults with thyroid carcinoma. However, overall survival for pediatric thyroid carcinoma is excellent, with few patients dying of disease.** ***Key Words:*** **Outcomes, pediatric outcomes, thyroid carcinoma.**

Laryngoscope, **115:337–340, 2005**

INTRODUCTION

Thyroid carcinoma is the third most common solid malignancy in children.[1,2] This tumor shares several characteristics with its adult counterpart, including the following: 1) The most common histological subtypes are papillary, follicular and medullary; 2) the female-to-male ratio is approximately 6:1; and 3) cervical nodal disease can be observed at the time of presentation in 30% to 60% of cases in both papillary and follicular variants.[3,4]

Although the long-term survival of pediatric thyroid carcinoma is purportedly excellent, there have been few large studies identifying clinical outcomes of pediatric thyroid malignancies. Several small studies have been composed of single-institution reviews. Other studies have included multiple institutions in an effort to create a larger database but may be limited by institutional or regional bias.[1,5] The sample size limitations, coupled with the need for long-term follow-up of a disease with a slow rate of recidivism, have resulted in difficulties in assessing prognostic factors in this disease. For these reasons, we examined the Surveillance, Epidemiology, and End Results (SEER) database over a 12-year period in an effort to better understand long-term clinical outcomes of this indolent, although occasionally fatal, disease in the pediatric population.[6]

PATIENTS AND METHODS

From the SEER database we extracted all pediatric patients with thyroid carcinoma according to the following criteria: 1) age at diagnosis ranging from birth to 18 years, 2) primary occurrence of a malignant thyroid tumor, 3) well-differentiated thyroid carcinoma (papillary or follicular), and 4) year of diagnosis between 1988 and 2000.[6] Patients with alternative tumor types such as anaplastic or medullary carcinoma were excluded. Clinical and tumor-specific data extracted from the database included age at diagnosis, gender, tumor histological type, tumor size, extent of primary-site disease, extent of nodal disease, treatment with surgery and/or radioactive iodine, and survival statistics.

Data were tabulated and imported into SPSS, version 10.0 (Chicago, IL). From the disease variables, the extent of primary-site disease was staged as previously reported[3] (Table I). Nodal disease was recorded as presence or absence of cervical nodes at the time of initial diagnosis. The extent of primary-site surgical therapy was classified as biopsy only, lobectomy, subtotal thyroidectomy, or total thyroidectomy.

Standard descriptive statistics were calculated for the demographic and clinical variables. Kaplan-Meier survival analysis was conducted for the entire cohort according to histological tumor subtype. The survival data were then analyzed with the Cox proportional hazards model using a backward likelihood ratio model with probabilities for inclusion and exclusion of P = .05

Presented at the Annual Meeting of the American Society of Pediatric Otolaryngology, Phoenix, AZ, May 2, 2004.

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Editor's Note: This Manuscript was accepted for publication August 30, 2004.

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DOI: 10.1097.01.mlg.0000154743.71184.09

TABLE I.
Classification and Extent of Disease at Primary (Thyroid Gland) Site.

Degree of Local Extension	Description	N (%)
Intrathyroidal disease	Tumor does not extend outside capsule of thyroid gland; may be multifocal within gland.	420 (74.2)
Minor local extension	Tumor invades soft/connective tissue of thyroid gland, parathyroid glands, strap musculature or recurrent laryngeal nerve.	71 (12.5)
Major local extension	Tumor extends into carotid sheath, sternocleidomastoid muscle, esophagus, or thyroid/cricoid cartilages.	15 (2.7)
Extravisceral extension	Tumor invades trachea, paraspinal musculature, or vertebral bone.	16 (2.8)
Unspecified		44 (7.8)

and $P = .10$, respectively. The multivariate model included the following potential predictor variables: histological tumor type, age, gender, extent of primary-site disease, presence or absence of nodal disease, extent of thyroidectomy, and the use of radioactive iodine ablation. Clinically and statistically appropriate variables based on the univariate analysis were included in the Cox regression analysis. Hazard ratios and their 90% confidence intervals were computed for statistically significant predictor variables of survival in the Cox model.

RESULTS

In all, 566 cases of pediatric thyroid carcinomas were identified for the time period under consideration. The mean age at presentation was 16.0 years, with a female predominance (84.8%). With respect to histological type, there were 378 (66.8%) papillary carcinomas, 137 (24.2%) papillary carcinomas with follicular variant, and 51 (9.0%) follicular carcinomas. Overall, the average tumor size at presentation was 2.6 cm. With regard to primary disease site, the majority of patients (74.2%) had intrathyroidal disease alone. A small group had minor local extension (12.5%), and a few patients had major or extravisceral extension (5.4%) (Table I). Positive nodal disease in the neck was present in 37.1% of patients at initial diagnosis. Most patients were treated with total thyroidectomy (72.8%), followed by subtotal thyroidectomy (13.4%) and by simple lobectomy (7.2%). Radioactive iodine treatment was administered to 51.4% of patients.

The overall survival for the entire cohort was 153.8 months, limited to 155 months of maximum follow-up. Figure 1 presents Kaplan-Meier survival curves for papillary and follicular carcinoma cohorts. Papillary carcinomas (mean survival, 155.3 mo) fared better than follicular carcinomas (mean survival, 146.9 mo) (log rank test, $P = .0054$).

Table II presents the results of the Cox proportional hazards analysis. Among the potential clinical predictor variables, male gender, increasing extent of disease at the primary site, and follicular carcinoma histological type all negatively influenced prognosis. Patient age, presence of positive cervical nodes, extent of surgery, and use of radioactive iodine therapy did not significantly influence overall survival.

DISCUSSION

Analysis of the natural history of differentiated thyroid carcinoma requires a large population and lengthy follow-up periods.[3] Such an analysis can be difficult at a single institution or even multiple institutions. Although thyroid carcinoma has an excellent long-term prognosis, a small subset of children die of this disease. Given the relatively small fraction of the patient population with poor outcomes, it is difficult to identify prognostic factors for increased mortality.

The SEER database is a large, government-funded database that has previously been highly useful in studying clinical outcomes in other head and neck tumors.[3] It has also been used to examine a multitude of cancer types in adolescents and young adults.[2] This database surmounts some of the obstacles inherent in studying long-term results in disease processes that may remain idle for years, by rigorously collating data from large numbers of patients from across the United States. Evaluating a pediatric population from this database allowed us to identify both significant and nonsignificant risk factors on clinical presentation and to determine the relative value of treatment options for differentiated pediatric thyroid carcinoma.

In agreement with other studies, we found that pediatric thyroid carcinoma presents most commonly in the

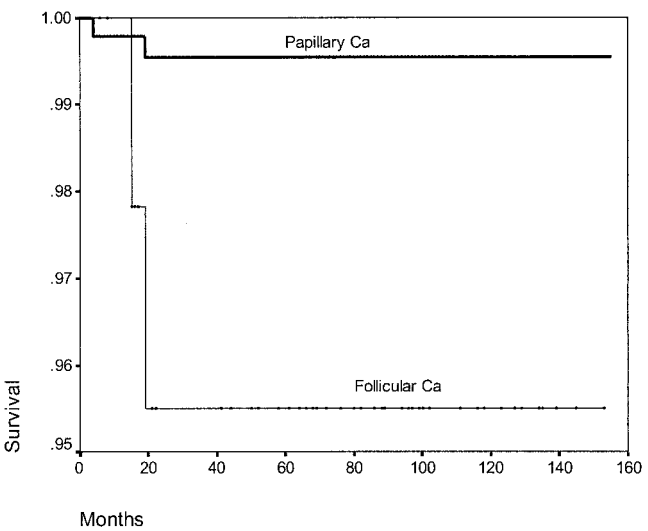

Fig. 1. Kaplan-Meier survival analysis for pediatric thyroid carcinoma according to histological appearance of tumor.

TABLE II.
Results of Cox Proportional Hazards Model.

Clinical Variable	Significance	Hazard	95% CI
Age	0.699	NS	
Gender	0.014	17.3	2.5–117.5
Primary site extent	0.029	2.7	1.3–5.6
Positive nodal disease	0.522	NS	
Extent of surgery	0.187	NS	
Radioactive iodine	0.846	NS	
Tumor histological appearance	0.009	16.3	2.8–95.8

CI = confidence interval; NS = not significant.

teenage years, and primarily in girls.[4] As in the adult population, papillary carcinoma predominates. The distribution of nodal disease at presentation (37.1%) was also similar to that seen in prior studies.[3,4,7] Our data revealed that, although treatment of the primary tumor ranged from simple lobectomy to total thyroidectomy, the extent of surgical intervention did not significantly influence survival outcomes. This finding differs from several prior reports that described superior outcomes in patients undergoing more radical resection such as subtotal or total thyroidectomy.[1,8–10] Age at diagnosis, nodal status, and the addition of radioactive iodine therapy also had no significant influence on survival in pediatric patients. Some of these discrepancies may be due to the cross-sectional nature of this analysis, which does not account for post-treatment morbidities or salvage therapy. In keeping with prior reports, male gender, increasing primary disease site extension, and follicular subtype all had negative prognostic influence on overall survival. Surprisingly, extent of surgical therapy and the use of postoperative radioactive iodine therapy did not alter the survival outcome, regardless of tumor type.

Follicular carcinoma has been reported to demonstrate more aggressive characteristics and a poorer prognosis than papillary carcinoma. This is probably due to propensity of follicular carcinoma for vascular invasion as opposed to propensity of papillary carcinoma for regional metastases.[11] In children with follicular carcinoma, the current data identified a statistically significantly poorer mean survival than those with papillary carcinoma, although clinically the percentage differences in survival were relatively small.

The presentation and clinical behavior of thyroid carcinoma differ significantly between children and adults. Among children, the average age at diagnosis is 11 to 19 years,[8–10,12,13] and younger patients have been shown to have a poorer prognosis than those diagnosed later in childhood or adolescence.[4,5,7,14] Moreover, although treatment guidelines for adults are fairly well accepted, evaluation and treatment recommendations for pediatric thyroid carcinoma vary in the literature.[15] Surgical management may include subtotal or total thyroidectomy with or without selective neck dissection.[1,5,8] Postoperatively, iodine 131 (I-131) therapy and thyroid hormone suppression are usually given, but because of the relative youthful age of the patients, many groups have reported that maximal doses of both adjuvant therapies can be limiting.[8–10] However, a recent report from the National Institute of Child Health and Human Development has recommended near-total or total thyroidectomy followed by I-131 ablation and long-term thyroid hormone suppression therapy.[8]

The impact of positive cervical nodal disease at the time of diagnosis has been controversial with respect to impact on long-term outcomes in both adults and children.[12] Several studies have reported that cervical nodal disease at the time of surgery has a negative impact on long-term outcomes in children.[4,7] Our study, as well as a study by Bhattacharyya[3] in the adult population, found no increased risk of poor outcomes when cervical nodes were present.

Overall survival outcomes in our pediatric population were similar to those found in other small studies. Feinmesser et al.[1] reported a 12- to 33 –year survival in 527 of 540 subjects (97.6%) in a nine-center review. The Tumor Registry of the Duke Comprehensive Cancer Center reported 100% 25-year survival in 56 patients.[4] Similarly, Arici et al.[9] reported a 100% 57-month survival in 15 patients. In a multi-institutional cohort of 329 patients, two disease-related deaths (99.4% survival) over a 10-year period were described.[5]

As previously detailed, the SEER database is an excellent resource to evaluate clinical outcomes for relatively rare malignancies by potentially limiting institutional or regional biases in management. However, one of the main drawbacks of this database is that there are no data on comorbidity, recurrence of local disease, or subsequent distant metastases during the course of cancer surveillance. In a population with potential for 60- to 70-year post-treatment survival, these data would be valuable in determining overall morbidity and disease burden for these patients.

CONCLUSION

Overall survival for pediatric thyroid carcinoma is excellent. Male gender, increasing primary site extension, and follicular histological type are associated with poorer prognosis, whereas cervical nodal involvement is not. Further study is required to determine optimal treatment strategies, including extent of surgery and use of postoperative radioactive ablation for children with differentiated thyroid carcinoma.

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