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Differentiated Thyroid Cancer: Determinants of Disease Progression in Patients <21 Years of Age at Diagnosis

A Report from the Surgical Discipline Committee of the Children's Cancer Group

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Objective
This study was done to define the extent of disease and evaluate the effect of staging and treatment variables on progression-free survival in patients with differentiated thyroid carcinoma who were less than 21 years of age at diagnosis.

Summary Background Data
Differentiated thyroid cancer in young patients is associated with early regional lymph node involvement and distant parenchymal metastases. Despite this, the overall long-term survival rate is greater than 90%, which suggests that biologic rather than treatment factors have a greater effect on outcome.

Methods
Variables analyzed for their impact on progression-free survival in a multi-institutional cohort of 329 patients included age, antecedent thyroid irradiation, extrathyroidal tumor extension, size, nodal involvement, distant metastases, technique of thyroid surgery and lymphatic dissection, initial treatment with ^{131} Iodine, residual cervical disease, and histopathologic subtype. Surgical complications were correlated with the specific procedures completed on the thyroid gland or cervical lymphatics.

Results
The overall progression-free survival rate was 67% (95%, CI: 61%–73%) at 10 years with 2 disease-related deaths. Regional lymph node and distant metastases were present in 74% and 25% of patients, respectively. Progression-free survival was less in younger patients ($p = 0.009$) and those with residual cervical disease after thyroid surgery ($p = 0.001$). Permanent hypocalcemia was more frequent after total or subtotal thyroidectomy ($p = 0.001$) while wound complications increased after radical neck dissections ($p < 0.00001$).

Conclusions
The progression-free survival rate was better after a complete resection and in older patients. Progression-free survival rate was the same after lobectomy or more extensive thyroid procedures, but comparison was confounded by the increased use of total or subtotal thyroidectomy in patients with advanced disease. The risk of permanent hypocalcemia increased when total or subtotal thyroidectomy was done. Thyroid lobectomy alone may be appropriate for patients with small localized lesions while total or subtotal thyroidectomy should be considered for more extensive tumors.

A paradox exists with respect to the clinical course of children with differentiated thyroid carcinomas: although thyroid cancer often presents with extensive disease, it is rarely fatal. This fact has generated enduring controversy over the optimal surgical management of children with thyroid tumors. This controversy also exists in adult patients where the value of extensive thyroid surgery without regard to staging parameters has been questioned.[1–10] Some arti-

cles have favored an aggressive surgical approach for children, utilizing total or near total thyroidectomy, because of the propensity of differentiated thyroid cancer to disseminate to lymph nodes or distant sites in this age group.[11,12] Conversely, other investigators have advocated a more conservative surgical management technique employing thyroid lobectomy. This is based on the observation that the mortality rate for differentiated thyroid cancer in children is remarkably low,[13–16] whereas serious operative complications are reduced with less extensive surgery.[17–21]

The following multi-institutional analysis was completed to: 1) develop a clinical profile of patients in this age group who had differentiated thyroid cancer, 2) define variables predictive of progression-free survival, and 3) correlate the techniques of thyroid and lymphatic surgery with complications.

MATERIALS AND METHODS

Patients

This analysis includes patients from the institutions listed in Appendix 1. Patient lists were obtained by individual institutional review of hospital archives, registries, and databases in an attempt to capture consecutively treated differentiated patients with thyroid cancer at each institution. Patients included in this study were diagnosed from January 1, 1946 through August 8, 1991, but there was some variation in intervals between different participating centers. Data were obtained from the cancer registries, hospital charts, operative reports, and office notes from each contributing center. Pathologic review was carried out at each participating institution and cases of medullary and anaplastic carcinomas were excluded from analysis. The 15 participating centers are comprised chiefly of children's hospitals and cancer centers (Appendix 1) and all are members of the Children's Cancer Group (CCG). All patients had at least a 1-year follow-up from initial treatment (median = 11.3 years). The project was coordinated by the Surgical Discipline Committee of the CCG. Data were entered on a standardized questionnaire by a surgeon at each institution. The questionnaire was three and one-half pages in length, and it was filled out by the institutional CCG surgeon. It contained entries for demographic data, history of radiation exposure, staging data, treatment, complications, ^{131}Iodine treatment, and patient status. In addition, specific categories were included to specify disease progression and time of progression. Staging variables included primary tumor size, extrathyroidal extension, regional nodal involvement, and distant metastases. Data concerning tumor size were usually taken from the pathology report, although a clinical measurement taken before or at the time of surgery was used if the pathologic measurement was not available. Distant metastases were identified most commonly by preoperative plain chest radiographs. These questionnaires were collected, computerized, and analyzed. A cohort of 365 patients, 21 years of age or younger at the time of diagnosis, with histologically confirmed differentiated thyroid carcinomas was identified. Of this group, 329 (90%) patients had sufficient data and follow-up (>1 year) for statistical analysis, and these patients are the basis of this report.

Variables

Because there were few deaths, the endpoint of analysis was disease progression. Disease progression was chosen because many patients, (25%) had metastatic disease at diagnosis. Because lung abnormalities can persist for a long period of time and may not represent a persistent tumor, the time of complete response in these patients could not be determined accurately. Consequently, disease progression was used as the dependent variable in analysis. Disease progression included clinically recognized local recurrence within the thyroid bed or regional lymph nodes after complete removal, progression in the thyroid bed or regional nodes after incomplete surgical resection, and the development or progression of metastatic disease (lung, bone, etc.). Independent variables assessed for their influence on disease progression included age, antecedent thyroid irradiation, the presence of extrathyroidal extension of the primary tumor into surrounding tissues, primary tumor size, regional lymph node involvement, presence of distant metastases at diagnosis, the technique of initial thyroid surgery, the technique of lymph node dissection, the existence of positive gross or microscopic margins, the use of ^{131} I in initial treatment of the thyroid bed, and histopathologic subtype. Extrathyroidal extension was defined by local infiltration of the primary thyroid tumor beyond the glandular capsule and included all cases of local invasion of surrounding muscles, esophagus, or trachea. Usually this was based on the pathology report, but surgical assessment also was included if the findings were obvious. Regional lymph node involvement included nodal metastases to the jugulodigastric and recurrent laryngeal (peritracheal) chains in the neck or anterior-superior mediastinal nodes. Nodal involvement was determined by histologic examination of resected lymph nodes. Lymph node dissections were completed when involvement was documented by biopsy or strongly suspected clinically and not as a prophylactic procedure. Distant metastases included parenchymal metastases to the lung in the vast majority of cases. Metastases to the brain, bone or other sites were seen in only a few patients. Metastatic disease was most commonly diagnosed by radiographic imaging studies. Usually, pulmonary metastases were identified by

Contributing Children's Cancer Group Investigators and Institutions are listed in the Appendix. Grant support from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services (CA 13539).

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Table 1. PATIENT CHARACTERISTICS

Variable	Positive (%)	Negative (%)	Inevaluable (%)
Histopathology			
Papillary	149 (45)	na	0
Papillary-Follicular	148 (45)	na	0
Follicular	32 (10)	na	0
Regional lymph nodes	243 (74)	82 (25)	4 (1)
Extrathyroidal extension	105 (32)	209 (64)	15 (4)
Distant metastases at Dx	83 (25)	243 (74)	3 (1)
Residual disease	43 (13)[22micro;21gross]	279 (85)	7 (2)
I^{131} as initial treatment	143 (43)	181 (55)	5 (2)
History of radiation to the head and neck	43 (13)	250 (76)	36 (11)
Family history of cancer	21 (6)	265 (81)	43 (13)

Table I lists numbers of patients positive and negative for staging variables, along with percentages. The last column, inevaluable, gives the number of patients for whom the status of that particular variable could not be accurately determined.

plain chest radiographs or computerized tomography, and biopsies were not done.

Initial thyroid surgery was divided into four groups: a) total thyroidectomy, b) subtotal thyroidectomy, c) lobectomy, and d) lesser procedures, such as a biopsy. Nodal dissection also was divided into four categories: a) radical neck dissection, b) modified neck dissection, c) multiple local excisions (berry picking), and d) no lymphatic surgery or single lymph node biopsy. Determination of a residual tumor in the neck after primary surgery was based on the operative note and pathology reports.

The treatment morbidity rate was assessed by determining the association of significant wound complications, permanent recurrent nerve paralysis, permanent hypocalcemia with the extent of thyroid surgery or nodal dissection. Wound complications included: serious hemorrhage or hematoma (requiring reexploration), infection, pneumothorax, and requirement for tracheostomy. Nonrecurrent nerve injuries like accessory or facial nerve dysfunction, or Horner's syndrome first noted after surgery also were included under wound complication. Permanent hypoparathyroidism was presumed if there was a postoperative need for calcium supplements and/or vitamin D replacement for 6 months after surgery and was continued until the last follow-up. Permanent recurrent nerve paralysis was defined by change in voice and/or indirect laryngoscopic evidence of vocal cord paralysis that lasted at least 6 months after the primary thyroid surgery. This included cases of operative sacrifice of the recurrent nerve. Temporary recurrent nerve injury or hypoparathyroidism resolved within 6 months of surgery.

Statistical Methods

This was an exploratory analysis, and observations drawn from this study are intended to be hypothesis generating. The probability estimates of time to progression were obtained from the product-limit (Kaplan-Meier) method, and differences between progression patterns within a covariate were evaluated by the log-rank statistic.[22] Multiple factors were evaluated using the stratified log-rank statistic. Fisher's exact test was used to assess the association between surgical technique and the morbidity rate.

RESULTS

Patient Characteristics

The median age at diagnosis was 15.2 years (range: 0.4–20.8; mean, 14.6 ± 3.9 years). The male:female ratio was 80:249 (76% female). The median follow-up time was 11.3 years (range: 1–41 years). Two-hundred forty-five (74.5%) patients were followed for 5 years or more. More than 90% of the patients were white.

Staging and Histology

Table 1 lists pertinent staging variables and shows the number of patients inevaluable for each parameter. The distribution by histologic subtype was 148 papillary-follicular (45%), 149 papillary (45%), and 32 follicular (10%). The median maximal diameter of the primary tumor in the thyroid gland was 2.5 cm (range: 0.4 cm–11 cm; mean= 2.9 cm ± 1.7 cm). Of the 83 patients who had distant metastases, 77 (93%) had dissemination to lungs alone, 4 to lung and bone (5%), and 2 patients had brain metastases (2%).

Treatment

Total thyroidectomy, subtotal thyroidectomy, thyroid lobectomy, and lesser procedures were done in 178 (54%), 55 (17%), 82 (25%), and 14 (4%) of patients, respectively, in this study (Table 2). Radical neck dissection, modified neck dissection, multiple nodal excisions (berry picking), and no

Table 2. TREATMENT, EXTENT OF DISEASE, AND OUTCOME

Thyroid Surgery	N	Hx RTX Neck (%)	Histology*	Nodes (%)	Size/Range	Mets at Dx (%)	Number Progressing Local:Distant (%)
Biopsy	14	6 (43)	5/5/4	7 (50)	2.0 (0.4–11)	6 (43)	7:3 (71)
Lobectomy	82	7 (9)	35/35/12	48 (59)	2.5 (1.0–6.0)	2 (2)	22:5 (33)
Subtotal thyroidectomy	55	4 (7)	34/18/3	44 (80)	2.5 (0.4–6.0)	20 (36)	4:7 (20)
Total thyroidectomy	178	26 (15)	75/90/13	144 (81)	2.5 (0.5–11.0)	55 (31)	24:34 (33)

Table 2 correlates rates of disease progression with the type of primary thyroid surgery done and history of prior neck irradiation, histopathologic type, regional lymph node involvement, primary tumor size, and distant metastases at diagnosis.
* Papillary/papillary-follicular/follicular.
HxRTX, prior history of head and neck irradiation.

lymphatic surgery or simple biopsies were completed on 70 (21%), 115 (35%), 70 (21%), and 74 (22%) patients. A complete primary resection was performed in 279 (85%) patients, while gross residual disease was left in 21 patients (6%). Microscopic margins were positive in 22 patients (7%). ^{131}Iodine was administered as part of *the initial treatment* in 143 (43%) patients. I^{131} was administered to treat the thyroid bed alone in 60 (18%) patients, both distant metastases and the thyroid bed in 74 (22%) patients, and to treat distant metastases alone in nine (3%) patients.

Complications

One hundred thirty-six patients developed postoperative hypocalcemia which was temporary in 97 (29%) and permanent in 39 patients (12%) (Table 3). The greatest incidence of hypocalcemia was observed with total thyroidectomy. Postoperative recurrent nerve dysfunctions were reported in 46 cases. This was temporary in 39 patients (12%) and permanent in 7 patients (2%). There were 56 additional surgical complications of which 33 were considered major. These major complications included 15 tracheostomies, 6 cases of extensive wound necrosis or severe infection, 3 cases of Horner's syndrome, 2 cases of spinal accessory nerve injuries, 2 cases of facial nerve injuries (marginal mandibular branch), 2 cases of postoperative pneumothorax, and 1 case each of severe postoperative hemorrhage requiring reexploration, vagus nerve, and superior laryngeal nerve injury. The 23 minor wound complications included 9 cases of hypertrophic scarring, 7 patients with significant postoperative seromas or serous wound drainage, 2 cases of temporary dysphagia, 2 cases of significant facial edema, and 1 case each of serous otitis media, delayed wound healing (minor), and significant wound erythema. Major and minor complications, along with the technique of primary thyroid surgery, are listed in Table 3.

Permanent ($p = 0.001$) hypocalcemia was correlated with the use of either subtotal or total thyroidectomy, while major wound complications were associated with the use of radical neck dissections ($p < 0.00001$) but not the type of thyroid surgery. The technique of primary thyroid surgery or lymphatic dissection did not correlate with permanent recurrent nerve dysfunction.

Survival and Progression-free Survival

Disease progression is correlated with the primary thyroid procedure and other variables of interest in Table 2. Disease progression, including local recurrence in patients with an initial complete resection, occurred in 106 (32%) patients, and the overall progression-free survival rate is

Table 3. TECHNIQUE OF THYROID RESECTION AND COMPLICATIONS

Complications	Primary Thyroid Surgery			
	Biopsy (%)	Lobectomy (%)	STT (%)	TT (%)
N	14	82	55	178
Recurrent n. palsy (temporary)	0	10 (12)	9 (16)	20 (11)
Recurrent n. palsy (permanent)	0	3 (4)	1 (2)	3 (2)
Hypocalcemia (temporary)	0	6 (7)	10 (18)	81 (46)
Hypocalcemia (permanent)	0	3 (4)	6 (11)	30 (17)
Minor wound complications	0	12 (15)	3 (5)	8 (4)
Major wound complications	1 (7)	13 (16)	3 (5)	16 (9)

Table 3 lists the extent of thyroid surgery with specific complications. Percentages were obtained by dividing each number in a column by the total number (N) for that column.
STT, subtotal thyroidectomy; TT, total thyroidectomy.

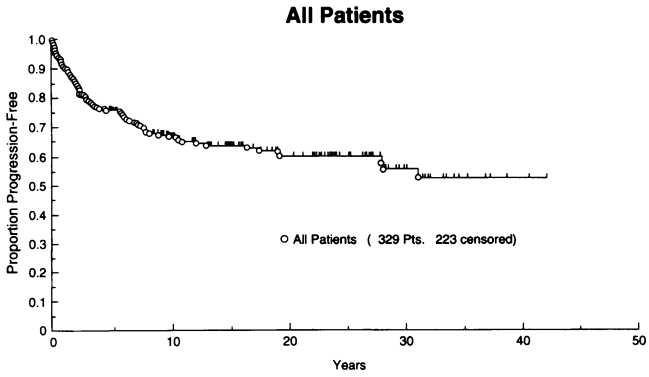

Figure 1. Figure 1 is a Kaplan-Meier curve of overall progression-free survival for patients in this study.

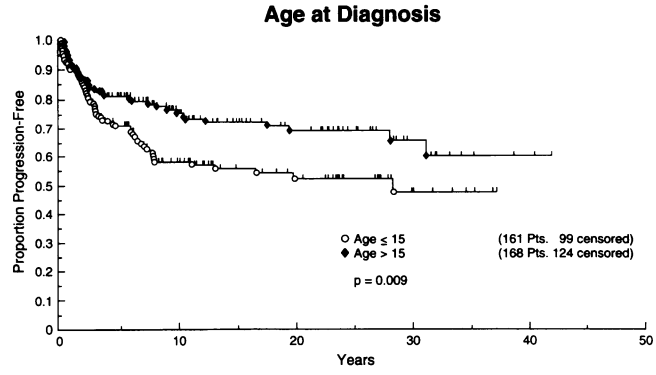

Figure 2. Figure 2 shows an association between progression-free survival and age at diagnosis for patients in this study. Younger patients were more likely to develop disease progression.

depicted in Figure 1. Overall progression-free survival was 67% (95%; CI: 61%–73%) at 10 years after diagnosis and 60% (95%; CI:54%–76%) at 20 years after diagnosis. The anatomic sites of disease progression were cervical lymph nodes in 71 patients, lungs in 16 (6 of these also had progression in cervical nodes), the contralateral thyroid lobe or thyroid bed in 13, bone (tibia, skull, and costochondral junction) in 4, and the spinal cord and base of tongue in 1 each.

In 60 patients without distant metastases, ^{131}Iodine was administered as part of initial therapy. In this group, 49 were treated after complete resections of the primary tumor with no residual disease, whereas 11 had residual thyroid cancer in the primary site after a resection. There were 18 instances of disease progression in this group (30%). Fourteen of these consisted of relapse in the cervical and two in the mediastinal lymph nodes. The other two patients recurred in lungs and the contralateral thyroid lobe, respectively. Of the 49 patients treated with ^{131}I after complete resection, 12 patients relapsed. Of the 11 patients who were administered ^{131}Iodine with residual cervical disease after surgery, 6 developed disease progression.

Predictors of Progression-free Survival

An increased risk of disease progression was observed in younger patients (p = 0.009) (Figure 2) and those with residual cervical disease after definitive thyroidectomy (p = 0.001) (Fig. 3). Unfortunately, younger patients also were more likely to have residual cervical disease precluding determination of an independent effect of either variable on progression-free survival.

In contrast, primary tumor size, extrathyroidal extension of tumor, regional node involvement, distant metastases (Figure 4), type of thyroid surgery (Figure 5) or type of lymphatic dissection, use of ^{131}Iodine in initial therapy, and history of antecedent thyroid irradiation were not determinants of progression-free survival (Table 4). In summary, after controlling for either age or residual disease no other factor was predictive of progression-free survival.

We found that more intensively treated patients also had more extensive disease. There were strong correlations between the use of total and subtotal thyroidectomy and the presence of extrathyroidal extension, and regional or distant metastases as summarized in Table 5.

Disease-Related Deaths

There were 8 deaths out of a total of 329 patients of which 2 were disease related. One of these patients was a girl diagnosed at 11 years of age who had a 6-month history of a stable, asymptomatic mass in the right neck. A maternal aunt suffered from an unknown thyroid problem, and there was no history of antecedent cervical irradiation. A total thyroidectomy and bilateral modified neck dissections were performed. After surgery, a tracheostomy was required because of cervical swelling, but the patient was subsequently discharged in good condition. Histologic analysis revealed a papillary thyroid carcinoma with involvement of cervical nodes, and ^{131}I treatments were given as part of initial therapy. Radioiodine scans performed 4 and 5 years after the initial treatment showed no evidence of metastases or local recurrence. However, repeat ^{131}I treatments were required because of pulmonary metastases 6 years after initial

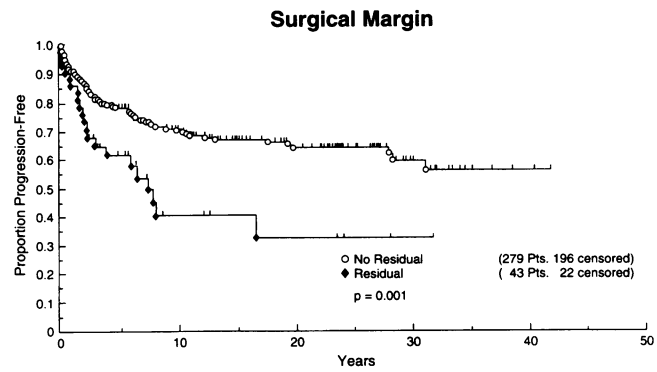

Figure 3. Figure 3 compares progression-free survival for patients with and without residual cervical disease after the primary procedure on the thyroid gland.

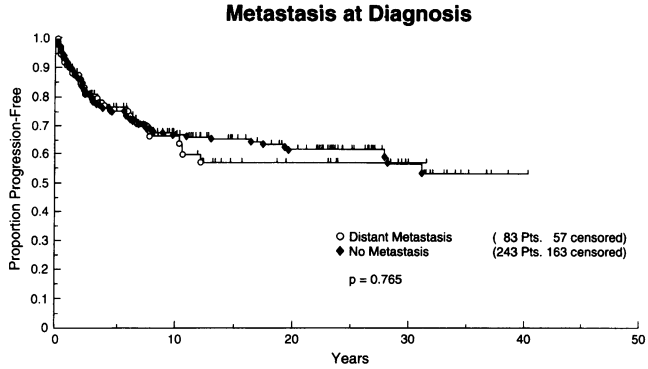

Figure 4. Figure 4 compares progression-free survival in patients with and without distant metastases at diagnosis. Outcomes did not differ although treatment was more intensive in patients with metastatic disease.

Table 4. RESULTS OF STATISTICAL ANALYSIS

Variable	p =
Age at diagnosis	0.009
Positive surgical margin	0.001
Tumor size	0.44
Extrathyroidal extension	0.92
Regional nodes+	0.18
Technique of lymphatic surgery	0.20
Metastases at diagnosis	0.77
Type of thyroid resection	0.75
Initial ^{131}Iodine treatment	0.58
Pathologic subtype	0.09
History of cervical irradiation	0.85

Table 4 lists the results of univariate analysis. Each variable was analyzed for its effect on progression-free survival.

therapy. A total of 300 mCi were administered during the patient's life because of persistent pulmonary disease. Eighteen years after diagnosis the patient died of pulmonary failure and had active disease.

The second patient was 15 years of age and had a 6-month history of a neck mass and swelling. She had no history of neck irradiation, and the only significant family history was a grandmother with goiter. On examination, a 5-centimeter subdigastric mass along with multiple smaller neck nodules bilaterally was found. Bone scan and chest x-ray showed no evidence of metastatic disease. A total thyroidectomy and right radical neck dissection were done and histologic examination revealed papillary-follicular carcinoma with six metastatic nodes. She was maintained on thyroid replacement. One year after the primary surgery, 750 cGy of external beam radiation was administered to treat keloid formation in the cervical wound. A recurrent papillary-follicular carcinoma was noted on a biopsy of enlarged supraclavicular lymph nodes, while a chest x-ray showed bilateral pulmonary metastases 2 years after the primary surgery. She received 150 mCi of ^{131}Iodine and had improvement in the lung metastases. However, an additional 200 mCi was required 2 years later because of radiographic evidence of progression of the lung disease. Sixteen years after diagnosis, she had skull metastases that progressed despite treatment with another 150 mCi of ^{131}I, and external beam radiotherapy (3500cGy) was required for control. She subsequently developed bony metastases in multiple sites and died with persistent pulmonary and skeletal metastases 21 years after diagnosis.

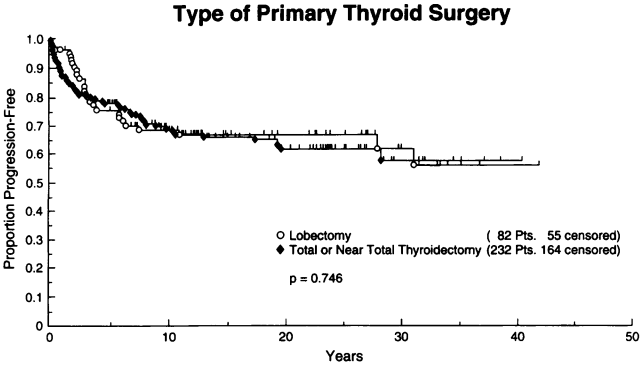

Figure 5. Compares progression-free survival in patients undergoing biopsy or thyroid lobectomy to those treated by total or subtotal thyroidectomy. Patients with more extensive tumors were more frequently treated by total or subtotal thyroidectomy.

DISCUSSION

Our aim with this study was to develop a profile of differentiated thyroid carcinoma in this age group and to identify determinants of disease progression. We used progression-free survival as an endpoint because the survival rate was almost 100% as reported in the literature. [23–33] Because patients with distant metastases (e.g., pulmonary) may have abnormalities on imaging studies for long periods of time after treatment, the date of complete response, and the time of recurrence is uncertain. Using disease progression rather than recurrence allowed patients with metastases to be included in the analysis.

It is apparent from Tables 1 and 2 that differentiated thyroid cancer in this age group is an aggressive tumor as measured by its ability to penetrate the thyroid capsule and metastasize to regional lymph nodes or distant sites. The observed proportion of patients with lymphatic involvement or distant metastases at diagnosis, 74% and 25% respectively, is consistent with other reports. It is tempting to assume that this increased biologic virulence requires more radical surgery or aggressive administration of ^{131}I.

Table 3 correlates the number of patients suffering a surgical complication with the technique of primary thyroid surgery. There was a strong correlation between use of total or subtotal thyroidectomy and the development of permanent hypocalcemia. Not shown is a similar correlation with the use of radical neck dissection and the occurrence of

Table 5. CORRELATION OF TREATMENT WITH EXTENT OF DISEASE

Extent of Disease	Proportion Treated with Subtotal or Total Thyroidectomy	Proportion Treated with ^{131}I
Extrathyroidal extension	84/105;80%	62/105; 59%
Regional nodes positive	188/243;77%	122/243; 50%
Distant metastases at diagnosis	75/83;90%	83/83;100%

Table 5 shows the association between extent of disease at diagnosis and type of treatment. Patients with more extensive disease were more likely to be treated by total or subtotal thyroidectomy and to receive ^{131}Iodine.

major wound complications. These findings are consistent with reported complication rates from other childhood series of differentiated thyroid cancer. Presently, radical neck dissection should not be used in treatment of this disease except under unusual circumstances. Also, our initial inclination to use total or subtotal thyroidectomy must be tempered because of its association with an increased risk of permanent hypocalcemia.

Age at diagnosis and the presence of residual gross or microscopic disease in the neck were the only determinants of progression-free survival (Table 4). We did not find a difference in progression-free survival between patients with and without extracapsular extension, lymph node involvement, and distant metastases. Unfortunately, the use of more extensive thyroid surgeries, and therapeutic radioiodine was correlated with the extent of disease at diagnosis, as listed in Table 5. Of patients initially treated with thyroid lobectomy, 59% had regional nodal involvement whereas 2% had distant metastases. In contrast, 80% of the patients who were treated by subtotal or total thyroidectomy had involved regional lymph nodes. More than 30% of the 50% of these patients had distant metastases. Also, there was strong correlation between the use of initial ^{131}I therapy and the presence of extrathyroidal extension, and lymph node or distant metastases at diagnosis. Thus, patients with more extensive thyroid tumors, heavier involvement of cervical lymphatics, or those with distant metastases had an increased likelihood of being treated with total or subtotal thyroidectomy. This finding confounds a direct comparative analysis of thyroid lobectomy with total or subtotal thyroidectomy.

It is possible that progression-free survival in patients with extensive disease is the same as for those with more localized tumors because of the greater use of total or subtotal thyroidectomy or addition of radioiodine therapy. Alternatively, unknown factors in the basic biology of differentiated thyroid carcinoma arising in this age group might determine the outcome despite treatment. This latter explanation has been supported based on 1) the mortality rate from disease was almost zero despite greater rates of regional node involvement and distant metastases; 2) there are reports from the literature of prolonged quiescence of pulmonary metastases without treatment; and 3) some authors note an improved outcome in younger patients who had metastases compared with older ones that develop them later.[34–36] It is possible that unknown biological factors and not therapy, are the final determinant of outcome in this age group. The problem of identifying the "best therapy" is not wholly academic, because we have already noted an increased complication rate with total and subtotal thyroidectomy. Also, there are reports of early complications and possible late effects from radioiodine therapy.

Despite limitations, our analysis suggests some guidelines for the treatment of differentiated thyroid cancer patients in this age group. First, staging each pediatric and adolescent patient with suspected thyroid cancer is crucially important. This involves a thorough head and neck examination that ideally includes indirect laryngoscopy to learn vocal cord function before surgery. Attention should be directed to determination of the size and location of the thyroid nodule, clinical evidence of fixation, and a careful mapping of abnormal lymph nodes. A preoperative chest x-ray or computerized axial tomography of the chest also should be performed. Multifocal thyroid nodules should be recorded. At exploration, the surgeon should inspect and palpate both thyroid lobes and inspect the lymph nodes in the jugulodigastric chain and the packet of nodes running along the recurrent laryngeal nerve in the tracheoesophageal groove. Complete surgical removal of cervical disease should be done. This might require lobectomy for small and isolated lesions or total thyroidectomy for a multifocal large and invasive carcinoma. Total or subtotal thyroidectomy should be done if adjuvant radioiodine treatments are planned. Patients with distant metastases, extensive lymph node involvement, or invasive tumors in whom radioiodine therapy is presently a standard adjuvant treatment should undergo complete thyroid removal. Routine use of total or subtotal thyroidectomy did not improve outcome in patients with localized tumors and is associated with an increased risk of complications. In summary, small lesions completely resected by lobectomy may be best treated by simple post update observation and thyroid suppression. More extensive lesions may require a combination of total or subtotal thyroidectomy.

Finally, the underlying biologic mechanisms that predict advanced stage at presentation, coupled with a greater relapse but paradoxically a low mortality rate, remain obscure. In a cytogenetic analysis, Hermann et al.[37] suggested that 10q abnormalities are more common in papillary tumors, whereas abnormalities of chromosome three were

more frequently noted in follicular cancer. Another study identified expression of the p21 ras protein as a prognostic factor in papillary cancer.[38] Recently, mutations in the ret protooncogene have been implicated in the development of thyroid tumors, including medullary and papillary thyroid carcinomas. Germ line mutations of the ret protooncogene were identified in multiple endocrine neoplasia (men) types 2a and 2b that share the clinical feature of medullary thyroid carcinoma and pheochromocytoma. Also, somatic rearrangements of the ret protooncogene frequently were detected in the papillary thyroid carcinomas in adult Europeans, and the same rearrangements were observed in approximately 60% of papillary carcinomas from children inhabiting areas contaminated by the Chernobyl accident. This suggests that ret rearrangements may be induced by radiation exposure.[39–41] These varied observations represent a beginning in our understanding of the pathogenesis of thyroid cancer. Establishment of a centralized thyroid tumor bank would facilitate similar investigations and might translate into better treatments.

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APPENDIX 1

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Charles Sklar, MD - Memorial Sloan-Kettering Cancer Center, New York, NY

Mark Smith, MD - Anderson Cancer Center, Houston, TX

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