Initial near-total or total thyroidectomy and central compartment lymph-node metastases has the greatest impact on recurrence in children with papillary thyroid cancer treated at the Mayo Clinic

Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg 2010; January 20. [Epub ahead of print].

SUMMARY

BACKGROUND

Thyroid cancer is a relatively uncommon disorder in children, making it difficult to perform meaningful studies because the cohorts are usually very small and follow-up is generally short. As a consequence, there is considerable debate concerning the most effective treatment of children and young adults with differentiated thyroid cancer. This study of children and young adults with papillary thyroid cancer reports the efficacy of therapy in one institution. One of the objectives of the study was to determine the efficacy of surgical therapy and radioactive remnant ablation (RRA) in this group of patients.

METHODS

This is a retrospective study of 215 patients younger than age 21 years who had surgery for papillary thyroid carcinoma (PTC) at the Mayo Clinic during a 68-year period from January 1, 1940, through December 31, 2008. The data concerning this cohort were retrieved from the hospital database, from which details of the patient's initial presentation, treatment, and pathology records were reviewed, and for this study, the histologic diagnosis was reconfirmed by the pathology department. Follow-up information was obtained by a review of death certificates in 22 patients and by reexamination or correspondence with the patients, family, or attending physicians in the other 193 patients, who were alive, up to June 2009.

RESULTS

The study subjects were 215 patients, 152 of whom were women (70%) with a median age of 16 years at the time of initial diagnosis. Thirty-six patients had a history of head or neck irradiation, which occurred during 1936 through 1957. Mean tumor size was 2.65 cm (median, 2.20; range, 1 to 9.5). Of the 190 reexamined histologic specimens, 55 (29%) were multifocal and 39 (6%) were locally invasive.

Initial Surgery (Figure 1)

Of the 215 patients who had thyroid surgery, bilateral lobar resection (BLR) was performed in 188 (87%). The most frequently performed primary surgical procedure was near-total thyroidectomy (NTT) in 96 patients (45%); total thyroidectomy (TT) was performed in 82 patients (38%). Bilateral subtotal thyroidectomy (BST) was performed in 10 patients (5%). Unilateral lobectomy (UL) was performed in 25 patients (12%). Lesser procedures were performed in the remaining 1% of patients. A total of 11 patients (5%) had incomplete initial tumor resection, 185 patients (86%) had lymph nodes removed at the time of initial surgery, and 168 (78%) had lymph-node metastases. In addition, 11 patients (5%) had incomplete tumor excision, and 192 (89%) had complete thyroid resection with no distant metastases at the time of initial examination or within 30 days of the operation.

Complications of Surgery (Figure 2)

Permanent unilateral recurrent laryngeal-nerve damage occurred

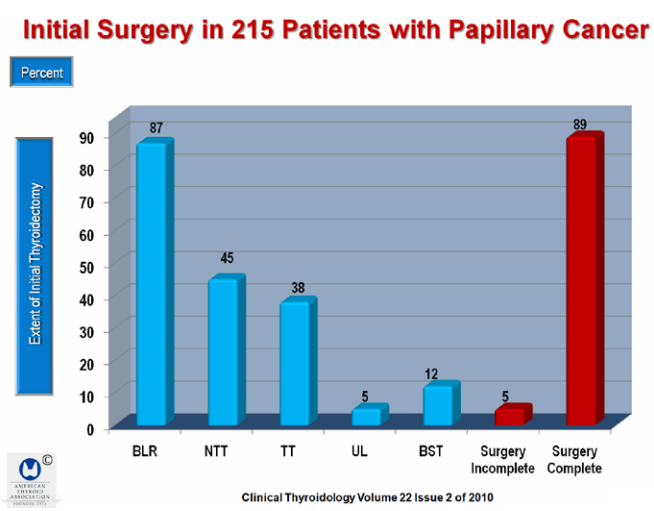

Figure 1. This figure shows the extent of initial surgery in the study cohort of 215 patients. BLR = bilateral thyroid lobar resection; BST = bilateral subtotal thyroidectomy; NTT = near-total thyroidectomy, TT = total thyroidectomy, UL = unilateral lobar resection.

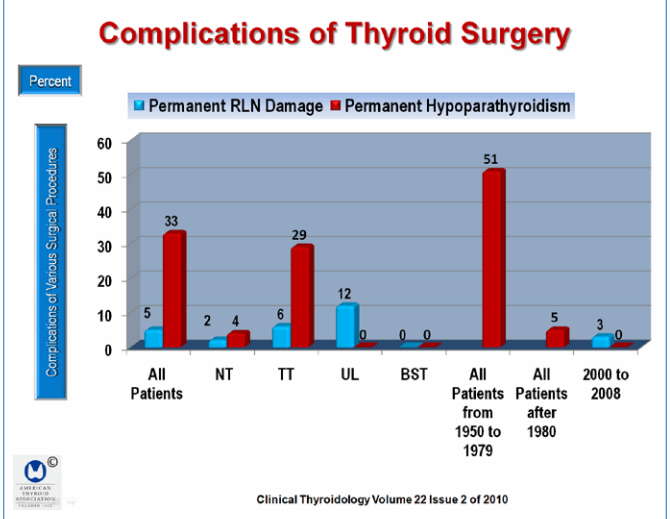

Figure 2. This figure shows the extent of complications of thyroid surgery. RLN = recurrent laryngeal nerve. See Figure 1 for definitions of other abbreviations.

in 10 patients (5%): in 3 (12%) after UL, in 5 (6%) after TT, and in 2 (2%) after NTT.

Permanent hypoparathyroidism requiring long-term calcium and vitamin D therapy occurred in none of the 35 patients treated with either BST or UL. However, permanent hypothyroidism occurred in 9 patients (4%) after NT and in 28 after TT (29%), but in no patients who underwent UL or BST.

During 1950 through 1979, permanent hypoparathyroidism developed in 22 of 43 patients who had TT (51%) but since 1980, only 2 of 30 patients (5%) have had permanent hypoparathyroidism. However, during 2000 through 2008 there have been no cases of permanent hypoparathyroidism and only 1 case of permanent unilateral recurrent laryngeal-nerve damage.

Neck Lymph-Node Surgery (Figure 3)

A total of 185 of the 215 patients (86%) had cervical lymph-node surgery as part of the initial surgery. In the early decades, "node-picking" in the central lymph-node compartment (CLNC) was performed unilaterally in 51 of the 215 patients (24%) and bilaterally in 13 (6%). Only 27 patients (13%) had bilateral modified neck central neck lymph-node dissection (CLND), while 29 of 215 (13%) had unilateral CLND modified neck dissection as part of the initial surgery. A combination of "berry picking" and lateral-compartment dissection was performed in 25 patients (12%). Since 1995, CLND was performed routinely with BLR in 40 of the 215 patients (19%)

Postoperative Thyroid RRA (Figures 4 and 5)

A total of 192 of the 215 patients (89%) had tumor that was confined to the neck and completely resected. Only the 192 patients with no evidence of residual thyroid tissue were deemed eligible to receive RRA. Of this group, 68 (35%) were treated with ^{131}I RRA; 54 (79%) received one ^{131}I treatment, 9 had two treatments (13%), 4 had 3 (6%) and 1 had 4 (6%). The cumulative ^{131}I activity varied greatly, from 29 to 400 mCi, averaging 79 mCi.

There was enough information in 64 of the 68 patients (86%) to evaluate the efficacy of the ^{131}I treatment; 55 of 64 ^{131}I treatments (86%) were judged to be successful according to a diagnostic whole-body scan using ^{131}I or ^{123}I, showing no residual disease ^{131}I and no uptake higher than background ^{131}I uptake.

Figure 5 shows the trend in RRA ablation at the Mayo Clinic from 1960 to 2008, which reflects the change in surgery during this period.

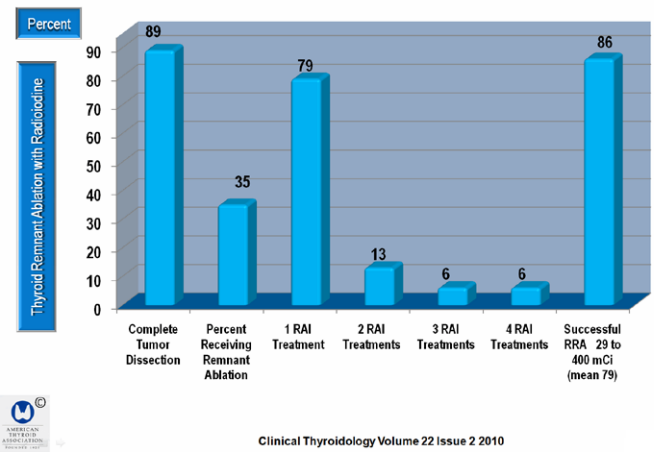

Figure 4. This figure shows the rate of successful RRA with one or more radioactive iodine (RAI) treatments. Complete dissection refers to a subset of 192 (89%) of the 215 patients who had complete thyroid resection with no distant metastases at the time of initial examination or within 30 days after the operation. The cumulative ^{131}I activity in successful RRA varied greatly, from 29 to 400 mCi, averaging 79 mCi.

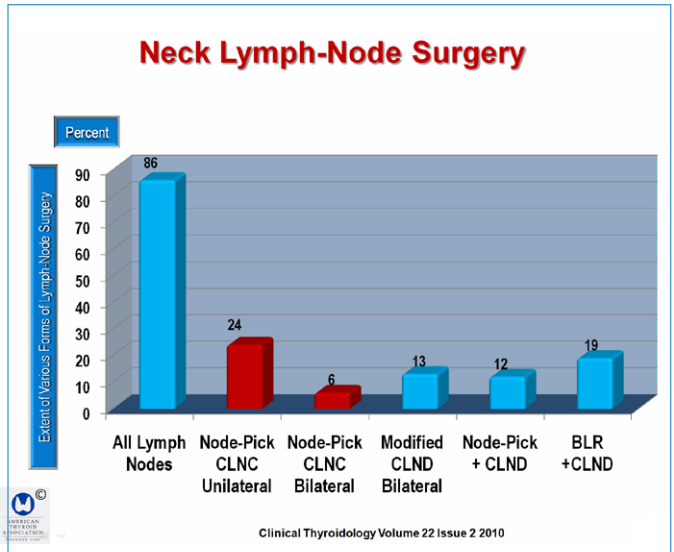

Figure 3. This figure shows the extent of lymph-node surgery. BLR = bilateral thyroid lobar resection; CLNC = central lymph-node compartments; CLND = central lymph-node compartment dissection node-pick = dissection of single lymph node metastases.

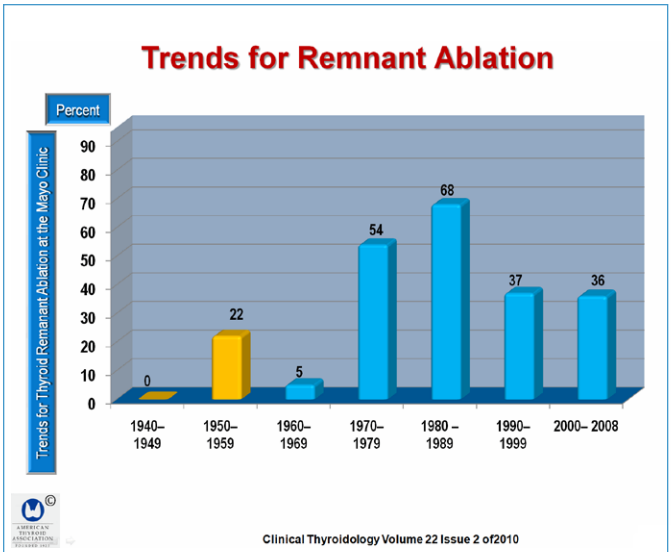

Figure 5. This figure shows the trends in RRA in the Mayo Clinic. This figure is adapted from Figure 5 of Hay et al.

Postoperative Recurrence Rates (Figures 6 and 7)

Postoperative recurrence was considered only for the 192 patients who had complete thyroid resection with no distant metastases within 30 days after the initial surgery. The recurrence rates at 5, 10, 20, and 30 years were 20, 22, 27, and 30% (Figure 6).

After 40 years of follow-up, neck or distant metastases were found in 61 patients (32%). Among the 192 patients, recurrences were found in the thyroid bed in 12 patients (6%), in regional neck metastases in 38 (20%), and in distant metastases in 13 (7%). After 5, 10, and 20 years of follow-up, the postoperative local recurrence rates were 3, 4, and 7%, respectively, and the rates of distant metastases were 4, 4, and 5% (Figure 7).

Cause-Specific Mortality

After a median follow-up of 28.7 years, there were no deaths from PTC during the first 20 years of follow-up, including 12 patients (5%) who had distant metastases at the time of initial diagnosis. After 25 years, there were two deaths from distant metastases (0.09%), both of which were associated with localized disease at the time of initial treatment that comprised bilateral lobar resection performed with curative intent. The cause-specific survival rates since 1951 were 100% at 20 years and 98% from 30 through 50 years.

Comparison of Surgical Outcome after UL or BLR (Figure 7)

During the first three decades of the study period from 1940 through 1970, UL was performed in 24 of the 25 patients who had surgery (96%). During 1940 through 1969, UL comprised 24% and BLR 73% of the primary surgeries; however, there were only two deaths during this period, making the difference between UL and BLR statistically insignificant.

After 40 years of follow-up, the rates of local recurrences were 6% with BLR and 35% with UL (P<0.001). The rates of regional recurrence were 13% after BLR and 60% after UL (P<0.0001).

From 1970 through 2008, most of the BLR surgeries (94%) were near-total (n = 59) or total (n = 51) thyroidectomy.

Outcome of Thyroid RRA

From 1950 through 2008, 169 patients had BLR surgery with the intent of curing the patient, which in 53 patients (31%) was followed by ^{131}I RRA within 6 months of surgery. There was only one death in the group without ^{131}I and no deaths in those who received ^{131}I, which was not statistically significant (P = 0.62). Lower recurrence at both local and distant sites were found in the 53 patients who had been treated with ^{131}I as compared with surgery alone, but the difference was not statistically significant (n = 116) (P = 0.018, and P = 0.013, comparing the two treatments respectively).

Using similar data from 1950 through 2008 in which 161 patients were treated with either near-total or total thyroidectomy, there were no deaths due to PTC. The differences between survival after surgery alone versus surgery plus ^{131}I was not significantly different for multiple end points, including local recurrence (P = 0.18), regional neck lymph-node metastases (P = 0.61), locoregional recurrence (P = 0.37), distant metastases (P = 20), and recurrence at all disease sites (P = 0.27).

Death from Malignancy

During 1941 through 1950, there were 24 patients with PTC treated at the Mayo Clinic, ranging in age from 7 to 20 years (average, 14). Fourteen survived and, to date, 10 of them (42%) have died from malignancy, 2 of whom died from metastatic PTC and 8 died from nonthyroidal second malignancies (NSPM). This preceded the approval of ^{131}I as a radiopharmaceutical. Of the eight who died from NSPM, seven (87%) had been treated with radium-seed application or a course of external-beam radiation and 4 of the 7 were additionally treated with ^{131}I in amounts ranging from 175 to 200 mCi. The number and sites of radiation-associated NSPM were lung (three patients) trachea (one patient) pleura (one) and liver (one) and the seventh had grade 4 adenocarcinoma, and the eighth patient, who was 7 years old

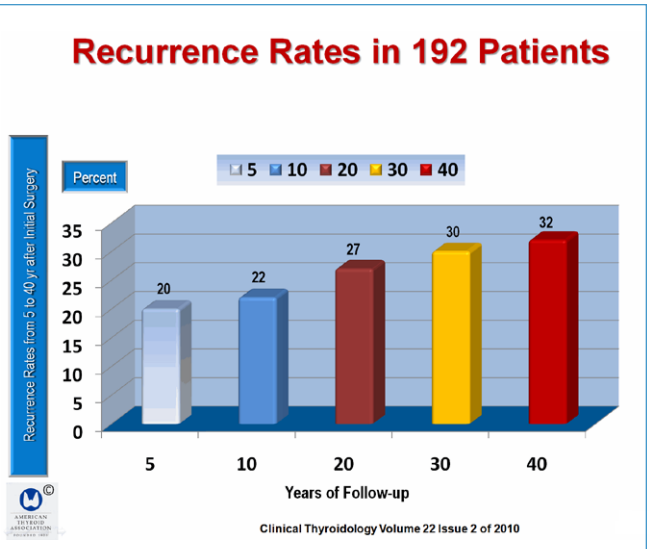

Figure 6. This figure shows the recurrence rates in 192 patients who had complete thyroid resection with no distant metastases at the time of initial examination or within 30 days after the operation

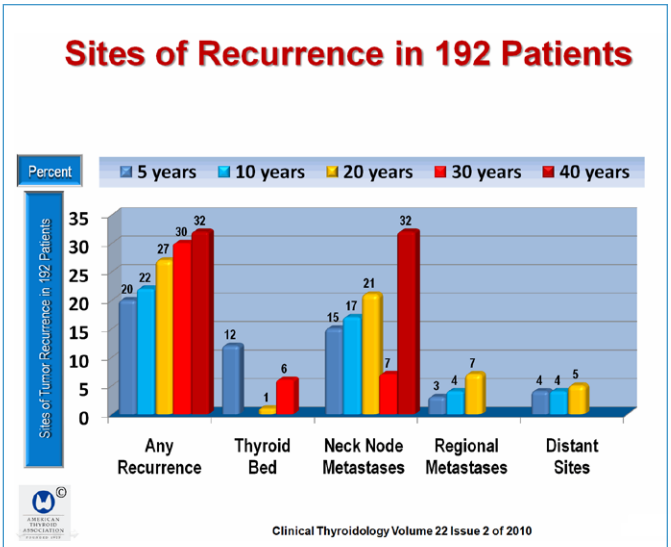

Figure 7. This figure shows the sites of tumor recurrence in the 192 patients described in Figure 6.

at diagnosis and did not receive adjunctive radiation therapy died from cervical cancer 40 years after the diagnosis of PTC.

During 1951 through 2008, 12 of the 191 patients died of causes other than PTC. Five of the seven who died of NSPM each died from one the following tumors: acute myelogenous leukemia (AML), duodenum, lung, breast, and brain, and two had adenocarcinoma of uncertain origin. The patient with AML had been treated with 95 mCi and th patient with lung cancer had received 200 mCi. Of the 15 patients who died of NSPM, 11 (73%) had received postoperative therapeutic irradiation.

Expected versus Observed Mortality Rates

A total of 22 patients died during the study period. The expected and observed death rates were not significantly different during the first 30 years; however, in the interval from 30 through 50 years of follow-up, there was an unexpected excessive death rate in the juvenile patients with PTC as compared with the control population of identical age and sex, in which 11 deaths would have been expected. This difference is highly significant (P = 0.00045). Of the 22 patients who died, 17 (77%) died from malignancy, 2 of which were PTCs and the remaining 15 (88%) were NSPMs and 5 fatalities were attributed to causes other than malignancy.

Of the 24 children ranging in age from 7 to 20 years during the period from 1941 through 1950, 10 (42%) died from malignancy, two from PTC and 8 from NSPMs. Of the eight with NSPMs seven (87%) had been treated with radium-seed application or a course of external-beam radiation and four were treated with ^{131}I in amounts ranging from 95 to 200 mCi. Of the seven who died from nonthyroidal malignancies, one died of acute myelocytic leukemia (AML), and one each died from duodenal tumor, lung cancer, breast cancer, and brain tumor, and two others died of adenocarcinoma of uncertain origin. Four of the seven patients had received ^{131}I in amounts from 95 through 200 mCi. The patient with AML had received 95 mCi, and the others were treated with of ^{131}I for RRA, a few with relatively high amounts of ^{131}I for RRA . The remaining five fatalities were unrelated to malignancy and five were attributed to cardiovascular disease.

CONCLUSION

The authors of this study suggest that initial near-total or total thyroidectomy and routine central compartment lymph-node metastases has the greatest impact on recurrence and is not further influenced by RRA.

COMMENTARY

This retrospective study from the Mayo Clinic reports their experience in the treatment of PTC in children and young adults over a span of almost seven decades. The cause-specific mortality rate was 2% and the tumor recurrence rate was 32% after a 40-year followup. The main conclusion was that the initial surgical approach has the greatest impact on recurrence and is not further influenced by ^{131}I RRA. The authors link various forms of adjuvant ionizing radiation to the occurrence of nonthyroidal second primary malignancies that appeared 30 to 50 years after the initial diagnosis. As a consequence, the authors recommend radioiodine only for high-risk patients, such as those with distant metastases or incomplete surgical resection. They reject ^{131}I RRA, which is still performed in over 30% of the patients treated at the Mayo Clinic.

Children with PTC pose a particularly difficult problem because they generally have low cause-specific mortality rates and consequently have a long life expectancy during which adverse effects of therapy may develop, including the complications of surgery, radioiodine treatment, or external-beam radiotherapy. As compared with adults, children have a greater degree of extrathyroidal tumor extension and more lymph-node and lung metastases at the time of initial diagnosis. Still, they responded to total thyroidectomy and postoperative ^{131}I RRA (1), which is particularly relevant, as up to 90% of children with PTC have lymph-node metastases (2). Yet there is evidence that the response to ^{131}I therapy is not always prompt and may require more than one ^{131}I treatment to destroy residual thyroid tissue or tumor. Also, the child's age plays an important role in outcome, which in the Hay study ranged from 7 to 20 years, with a mean of 14 years

Lazar et al. (1) found that total thyroidectomy with or without lymph-node dissection had similar effects in both prepubertal and pubertal patients, but the amount of weight-adjusted radioiodine for RRA was significantly greater in the prepubertal group as compared with the pubertal group (P = 0.004). Also, a family history of thyroid cancer was more prevalent in the prepubertal children (P = 0.037), who had a greater degree of extrathyroid tumor extension (P = 0.012), lymph-node metastases (P = 0.009), and lung metastases (P = 0.009). Still, after a median follow-up of 5 years after initial therapy with surgery and RRA, there were no significant differences in the extent of residual or recurrent tumor in prepubertal or pubertal children. The authors concluded that differentiated thyroid cancer has a more aggressive presentation in prepubertal children, but that rigorous initial surgical and ^{131}I therapy and thyrotropin suppression resulted in an outcome similar to that achieved in the pubertal group who ranged in age up to 17 years.

The Mayo Clinic patients were treated with a spectrum of different surgical procedures that changed over time, including both the extent of thyroid surgery and surgical techniques for lymph-node metastases. The study group for RRA comprised 192 patients who had tumor confined to the neck that was completely resected with a potentially curative operation with no postoperative gross residual disease. Node-picking was performed in 28% of patients who had RRA and 27% of those not treated with RRA, while compartment dissection was performed in 41% of the patients who had RRA and 40% of without RRA (chi-square P=0.48) (personal communication with Dr. Hay)

Still, over a 40-year span, 32% had a recurrence in the thyroid bed or regional neck area or had distant metastases. Of the 192 patients, only 68 (35%) were treated with RRA that was given as

one treatment in 54 patients (79%) and up to four treatments in the others, with a cumulative amount of ^{131}I ranging from 29 to 400 mCi, and a mean of 79 mCi.

The study does not provide data concerning how disease status was ascertained at the end of follow-up, including thyroglobulin measurements. Modern evaluations of the outcome of PTC require stringent analyses to identify patients with no evidence of disease. The American and European Thyroid Associations both recommend the following triad to identify patients who are free of disease: (1) no clinical evidence of tumor, (2) no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole-body scan, or, if uptake outside the thyroid bed had been present), no imaging evidence of tumor on a recent diagnostic radioiodine scan and neck ultrasound, and (3) undetectable serum Tg levels during thyrotropin (TSH) suppression and stimulation in the absence of interfering antibodies. Without this information, it is difficult to accurately assess the final outcome in this group of patients.

The authors of this study are understandably concerned about the fact that observed and expected death rates, which were not significantly different during the first 30 years of follow-up, unexpectedly increased after 30 to 50 years of follow-up. Seven (87%) had been treated with radium-seed application or a course of external-beam radiation and four were treated with ^{131}I. Four of the seven patients who died from nonthyroidal tumors had received radioiodine in amounts ranging from 95 through 200 mCi. The patient with AML had received 95 mCi, and some of the others were treated with larger amounts of ^{131}I for RRA. The authors conclude that these results strongly highlight the necessity to carefully delineate the indication for ^{131}I therapy, particularly in a population of young patients.

There is little question that second nonthyroidal malignancies are related to the cumulative amount of ^{131}I therapy. The study by Rubino et al. (3) was quoted by Hay et al. to emphasize the caveat concerning the potential risk for treating young patients with ^{131}I. The Rubino study of 6841 patients found an increased risk of both solid tumors and leukemias with the administration of larger cumulative amounts of ^{131}I. The study found an excess absolute risk of 14.4 solid cancers and of 0.8 leukemia per 1 GBq (27 mCi) of ^{131}I during 100,000 person-years follow-up. The risk for nonthyroidal malignant tumors increased with a cumulative amount of ^{131}I >400 mCi for solid tumors and ≥500 mCi for leukemia. The authors estimated that 100 mCi of ^{131}I will induce an excess of 53 solid malignant tumors and 3 leukemias in 10,000 patients during 10 years of follow-up (100,000 patient-years). The Hay study found that of after 5838 patient-years follow-up, 15 patients who died of NSPM, 11 (73%) had received postoperative therapeutic irradiation, 4 of whom had been treated with ^{131}I. The patients had been treated with 29 to 400 mCi of (mean, 79), and thus some may have been treated with amounts of ^{131}I that fall into the worrisome range described by Rubino et al.

A comprehensive review of the management of childhood thyroid cancer is the evidence-based study by Rachmiel et al. (4). The definition of the types of evidence and grading of data, which followed the recommendations of the U.S. Agency for Health Care Policy and Research, were as follows: Ia = obtained from meta-analysis of randomized, controlled trials (RCTs); Ib = obtained from at least one RCT; IIa = obtained from at least one well-designed controlled study without randomization; IIb = obtained from at least one other type of well-designed quasi-experimental study; and III = obtained from a well-designed non-experimental, descriptive study, or case controlled studies. Data were obtained from a literature search using PubMed, Cochrane databases, guidelines from various international groups, and studies pertaining to pediatric differentiated thyroid cancer (DTC) management and outcome in order to answer pertinent questions concerning the management of pediatric thyroid cancer. Several of the recommendations deserve brief mention. The first question addressed was: What is the most appropriate initial therapy?

Recommendation 1a is: It is important to diagnose and initiate therapy as early as possible, as initiation of therapy more than 1 year after the appearance of symptoms is associated with an increased mortality and is probably attributable to more diffuse and progressive disease.

Recommendation 1b is: Pediatric patients with DTC should have total or near-total thyroidectomy with selective lymph-node dissection (when involved) as the initial treatment. The goal should be to achieve complete surgical remission (Grade B, Level III). The authors identified similar guidelines in the adult population with tumors larger than 5 cm (Level IV). The recommendations in children were based on registry data, historical uncontrolled data, and retrospectively attained data in various groups of children and adolescents with DTC. They found a significant amount of evidence to support total or near-total thyroidectomy for children with DTC. Children had a high rate of local tumor recurrence, either in the thyroid bed or in regional cervical lymph nodes in 4.6 to 30% of cases (Level III). They found that children have a high rate of extrathyroidal invasion and cervical involvement at initial presentation, which have been reported as significant negative predictive factors for progression-free survival in children (Level III). They recommend initial removal of as much tumor tissue as possible and found that total thyroidectomy or near-total thyroidectomy may increase disease-free survival as compared with lobectomy (Level III). Jarzab et al. (5) found that radical surgery was the most significant factor for disease-free survival, and others have found that it may increase cancer-specific survival (6;7).

Recommendation 2a is: All pediatric patients with DTC should undergo radioiodine RRA within 4 to 6 weeks after the initial thyroidectomy (Grade B, Level III). This approach is similar to that in adults with intermediate-to-high-risk disease (Level IV [guidelines]). This was based on a report of 1510 patients (adults and children) without distant metastases at diagnosis showed ^{131}I RRA to be an independent variable that reduced relapse and disease-related mortality in patients with tumors larger than 1.5 cm (6). A meta-analysis (8) in high-risk adults and adolescents demonstrated that RRA was associated with a decrease in relative risk of 0.3 for local relapse and 3% decrease (from 4%) in the absolute risk for recurrent distant metastases

at 10 years However, the decrease in cancer-related mortality has not been a consistent finding, and the benefit of RRA was less clear in low-risk patients treated with total thyroidectomy and suppressive levothyroxine therapy (Level IIb). However, a recent multivariate analysis of predictive factors for progression-free survival in children demonstrated that RRA decreased the relative risk of relapse, but with borderline significance (Level III) (9). In still another study (10), ^{131}I RRA was associated with a decreased risk for distant metastases recurrence in two adjusted analysis, as well as the pooled unadjusted analysis (pooled risk difference, -2% for DTC). RRA was associated with a statistically significant reduction in risk of distant metastatic recurrence with a risk difference of -2% (95% confidence interval, -4 to -1) (Z = 3.49, P = .0005, pooled data from 2263 patients). Rachmiel et al. recommend ^{131}I administration according to risk stratification. A child was regarded as low risk if age was >10 years, the nodule <1.5 cm, and there was no residual disease, capsular invasion, or lymph-node metastases. If a child does not meet these criteria, he or she is deemed as high risk. Rachmiel et al. also recommend ^{131}I RRA with 30 to 50 mCi.

The risk for ^{131}I in children is an especially important issue. The risk for ^{131}I of radiation to body tissues is dependent on the serum concentration of ^{131}I. New therapy paradigms in the administration of ^{131}I for RRA show that total-body radiation can be significantly reduced (35%) when patients are prepared with recombinant human TSH, which reduces bone-marrow and other tissue radiation. Body radiation can be lowered even more by administering smaller amounts of ^{131}I, as little as 30 to 50 mCi of ^{131}I, which in prospective, randomized studies have been shown to be as effective as 100 mCi of ^{131}I (11;12).

The Hay study shows that lymph-node compartment dissection has a favorable effect on outcome; however, whether this alone with total thyroidectomy is sufficient therapy remains uncertain. Two recent studies suggest that ^{131}I is still necessary after extensive neck-compartment dissection in patients with lymph-node metastases (13;14).

Hay et al. emphasize the importance of central lymph-node metastases, although it is not clear that these are all prophylactic dissections or therapeutic dissections, or a mixture of both. Although the efficacy of prophylactic lymph node compartment dissection is currently under intense debate, it is an intriguing aspect of initial surgery that will continue to spark important debate. Whether this alone can suffice as the full extent of initial therapy remains unresolved. The studies by Schlumberger's group suggest that ^{131}I may play a selective role in treatment of patients with lymph-node compartment dissection, when lymph-node metastases and tumor invasion are discovered.

It is likely that this debate will extend for decades before consensus is reached. , Nothing short of randomized studies will quell the disparate views.

— Ernest L. Mazzaferri, MD, MACP

References

1. Lazar L, Lebenthal Y, Steinmetz A et al. Differentiated Thyroid Carcinoma in Pediatric Patients: Comparison of Presentation and Course between Pre-pubertal Children and Adolescents. J Pediatr 2009.

2. La Quaglia MP, Black T, Holcomb GW, III et al. Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the Surgical Discipline Committee of the Children's Cancer Group. J Pediatr Surg 2000;35:955-9.

3. Rubino C, De Vathaire F, Dottorini ME et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003;89:1638-44.

4. Rachmiel M, Charron M, Gupta A et al. Evidence-based review of treatment and follow up of pediatric patients with differentiated thyroid carcinoma. J Pediatr Endocrinol Metab 2006;19:1377-93.

5. Jarzab B, Handkiewicz JD, Wloch J et al. Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. Eur J Nucl Med 2000;27:833-41.

6. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.

7. Bilimoria KY, Bentrem DJ, Ko CY et al. Extent of Surgery Affects Survival for Papillary Thyroid Cancer. Ann Surg 2007;246:375-84.

8. Sawka AM, Thephamongkhol K, Brouwers M et al. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3668-76.

9. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer 2005;12:773-803.

10. Sawka AM, Brierley JD, Tsang RW et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 2008;37:457-80, x.

11. Maenpaa HO, Heikkonen J, Vaalavirta L et al. Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS ONE 2008;3:e1885.

12. Pacini F, Ladenson PW, Schlumberger M et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91:926-32.

13. Hartl DM, Al GA, Chami L et al. High rate of multifocality and occult lymph node metastases in papillary thyroid carcinoma arising in thyroglossal duct cysts. Ann Surg Oncol 2009;16:2595-601.

14. Bonnet S, Hartl D, Leboulleux S et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 2009;94:1162-7.