Lymph-node metastases at the time of initial surgery predict recurrent lymph-node metastases

Baek SK, Jung KY, Kang SM, Kwon SY, Woo JS, Cho SH, Chung EJ. Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. Thyroid 2010;20:147-52.

SUMMARY

BACKGROUND

Papillary thyroid cancer (PTC), which comprises 85% of all thyroid cancers, has a relatively low 10-year cancer-specific mortality rate of approximately 7%, yet despite this favorable survival rate, the incidence of PTC lymph-node metastases is high, varying from 15% to 50%, depending on the extent of lymph-node surgery. There is considerable controversy about routine central and lateral lymph-node compartments when preoperative studies fail to identify cervical-lymph-node metastases. There also are conflicting views about whether lymph-node surgery has a long-term impact on disease-free survival. The aim of this retrospective study was to assess the risk factors that are associated with recurrence of regional lymph-node metastases.

METHODS

The study cohort comprised 189 patients with PTC who were treated with thyroidectomy from 1992 through 2003 and had medical records sufficient for analysis and follow-up for periods longer than 2 years. Hemithyroidectomy was performed in 11 patients (6%), and the other 178 (94%) had total thyroidectomy. Central level VI lymph-node compartment dissection (CLND) was performed if metastases were suspected intraoperatively. Lateral lymph-node compartment dissection (LND) was performed if preoperative ultrasound-guided fine-needle aspiration biopsy revealed lateral-compartment lymph-node metastases. The study subjects were 33 patients (17%) with regional lymph-node recurrence and 156 (83%) who did not have cervical-lymph-node recurrence.

The mean follow-up was 81±44 months (range, 48 to 386). Patients who were treated with hemithyroidectomy were followed with serial serum thyroglobulin (Tg) levels and neck ultrasonography. The remaining patients who had total thyroidectomy and ^{131}I remnant ablation (RRA) had follow-up with serial serum Tg levels with or without thyroid-hormone suppression of thyrotropin (TSH) and had neck ultrasonography and whole-body ^{131}I scans (WBS) performed every 3 to 6 months.

Regional lymph-node recurrence was defined as positive if any of the following were present: uptake of ^{131}I on WBS, positive ultrasonography, or an increase of serial serum Tg levels with or without thyroid-hormone suppression. When these findings were positive, patients had computed tomography (CT) and preoperative ultrasonographically guided fine-needle aspiration biopsy.

RESULTS

Recurrence According to Patient Risk Factors (Figure 1)

The study group comprised 189 patients, 44.7 years of age (range, 9 to 80). Of this group, 151 were women (80%; mean age, 45.3 years; range, 9 to 80) and 38 men (20%; mean age, 45.3 years; range, 9 to 80). Regional lymph-node metastases were found in 27 of the 151 women (18%) and in 6 of the 38 men (16%). The difference in regional lymph-node metastases was not significantly different between men and women (P>0.05).

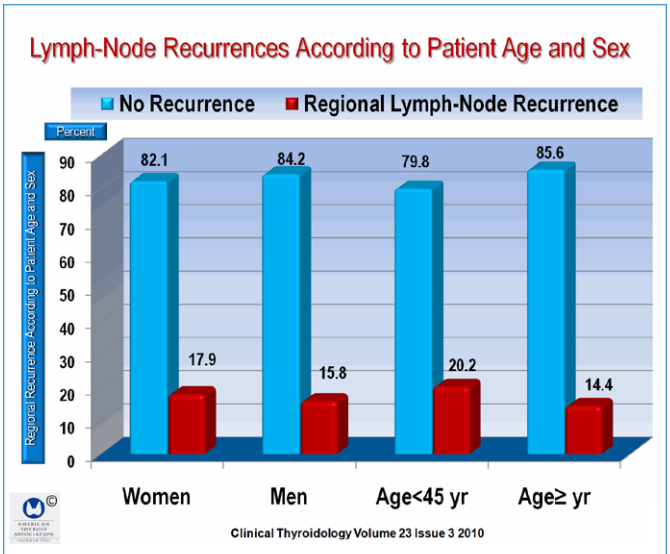

Figure 1. This figure shows the result of univariate analysis comparing recurrence of regional lymph-node metastases according to sex and age (<45 vs. ≥45 yr). There are no significant differences in patient risk factors that influence recurrence of lymph-node metastases. *P = 0.817. †P = 0.341.

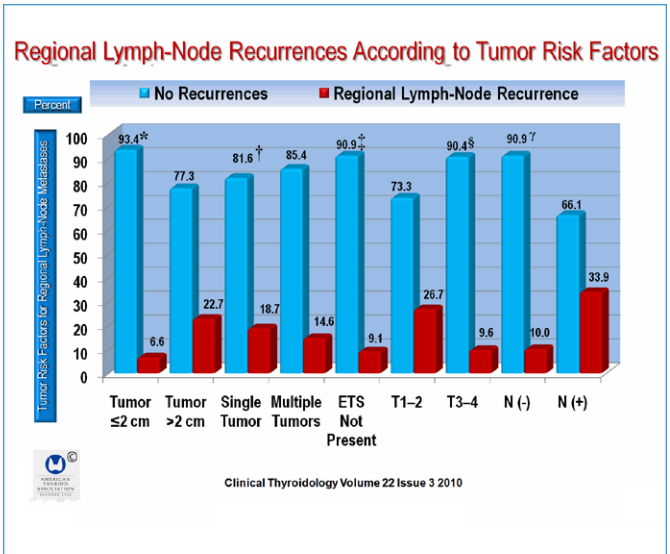

Figure 2. This figure shows the effect of tumor features on regional lymph-node recurrence. *P = 0.007 comparing <2 with ≥2 cm. †P = 0.662, comparing solitary with multiple primary tumors. ‡P = 0.002, comparing ETS with no ETS. §P = 0.007, comparing T1 to T2 with T3to T4. ɣP<0.001, comparing N stage (–) vs. N stage (+).

Likewise, there was no significant difference in age when this variable was stratified into <45 versus ≥45 years (Figure 1).

Recurrence According to Tumor Risk Factors (Figure 2)

The following were found to be risk factors for regional lymph-node metastases: tumor ≤2 cm versus >2 cm (P = 0.007); multifocality versus single tumor (P = 0.662); extrathyroidal spread of tumor (ETS) versus no ETS, (P = 0.002); higher tumor (T) stage (T1 to T2 vs. T3 to T4) (P = 0.007); and lymph-node (N) stage with (+) and without (–) lymph-node metastases (P<0.001); all of these were significantly associated with regional lymph-node recurrence (Figure 2).

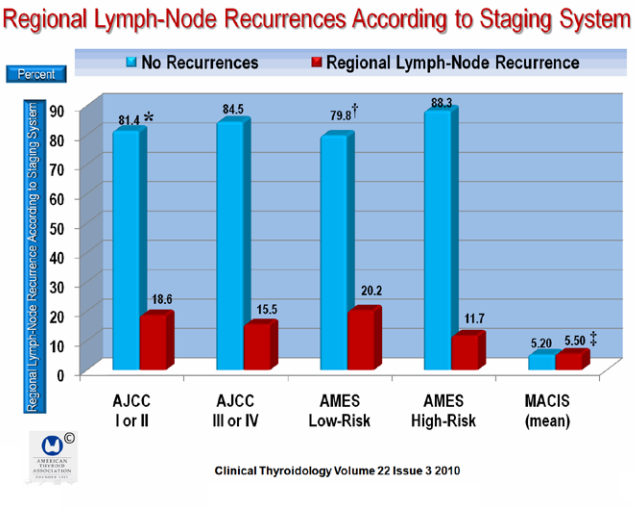

Figure 3. This figure shows that prognostic scoring systems (see text) do not predict lymph-node recurrence.*P = 0.693, comparing AJCC stage I or II with III or IV. †P = 0.261, comparing AMES low-risk with high-risk. ‡P = 0.624, as compared with MACIS mean ±SD; all comparisons refer to recurrence of lymph-node metastases.

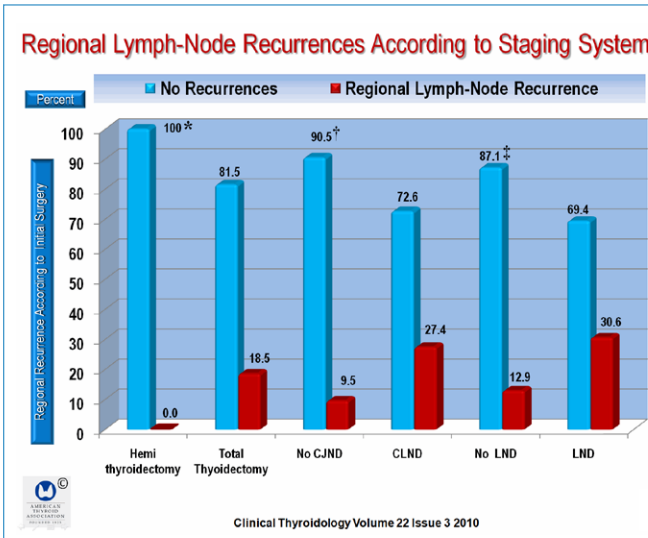

Figure 4. This figure shows the effect of initial surgical treatment on recurrent lymph-node metastases *P = 0.217, comparing total thyroidectomy with hemithyroidectomy. †P = 0.002, comparing CLND (central compartment lymph-node dissection) with no CLND. ‡P = 0.008, comparing patients with and without lateral neck-compartment dissection (LND).

Recurrence According to Prognostic Scoring Systems (Figure 3)

There were no significant differences in recurrence when risk was defined according to the American Joint Committee on Cancer (AJCC) staging system (P = 0.693), the AMES (age, distant metastases, extent, and size)scoring system (which includes patient age, distant metastases, and extent and primary tumor size) (P = 0.216, comparing low-risk vs high-risk group); and the MACIS system (which includes distant metastases, patient age, completeness of resection, local invasion, and tumor size, (P = 0.624). Thus, none of the staging systems predicted recurrence of lymph-node metastases (Figure 2).

Recurrence According to Surgical Treatment (Figure 4)

Of the 11 patients treated with hemithyroidectomy, none had regional lymph-node recurrences; however, of the 178 patients treated with total thyroidectomy, 33 of 178 (18.5%) had regional lymph-node recurrence. Still, the extent of thyroidectomy was not associated with regional lymph-node recurrence (Figure 4). A total of 84 patients had CLND and 49 had LND. The rate of regional lymph-node metastases were significantly greater in patients who had CLND as compared with LND (P<0.05).

Multivariate Analysis of the Relationship between Regional Recurrence and N Stage (Figure 5)

Multivariate analysis found that N stage was the only statistically significant variable that identified lymph-node recurrence (P<0.05). Neither CLND nor LND had an impact on regional lymph-node recurrence (Figure 5).

Multivariate Analysis of Regional Recurrence and Clinical Factors (Figure 6)

Multivariate analysis of sex, age, tumor size, T stage, N stage, and ETS, found that only N stage significantly increased the probability of regional lymph-node recurrence, by 3.474-fold (Figure 6).

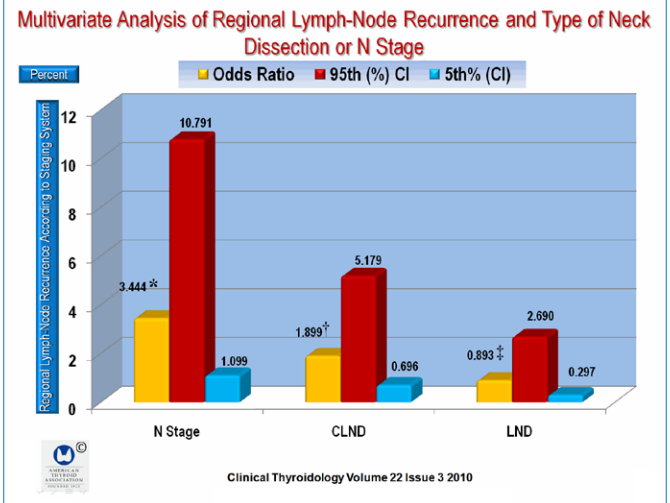

Figure 5. This figure shows the odds ratio and confidence intervals (CIs) for multivariate analysis in which only N stage significantly increased the risk for recurrence of lymph-node metastases. *P = 0.034. †P = 0.210, comparing surgery with and without CLND (central compartment lymph-node dissection). ‡P = 0.841, comparing surgery with and without LND (lateral neck-compartment dissection). Multivariate analysis found that only N stage was an independent factor in increasing the risk for lymph-node metastases.

Relationship between Disease-free Survival and Clinical Factors (Figure 7)

Univariate analysis found that disease-free survival was significantly associated with tumor >2 cm, higher T stage, lymph-node metastases, and ETS (P<0.05).

Multivariate analysis found that patients with lymph-node metastases had a 3.3-fold shorter disease-free survival period than those without lymph-node metastases (P<0.05). The 10-year disease-free survival rates were 77.8% in patients without and 57.9% in those with lymph-node metastases (P<0.05) (Figure 7).

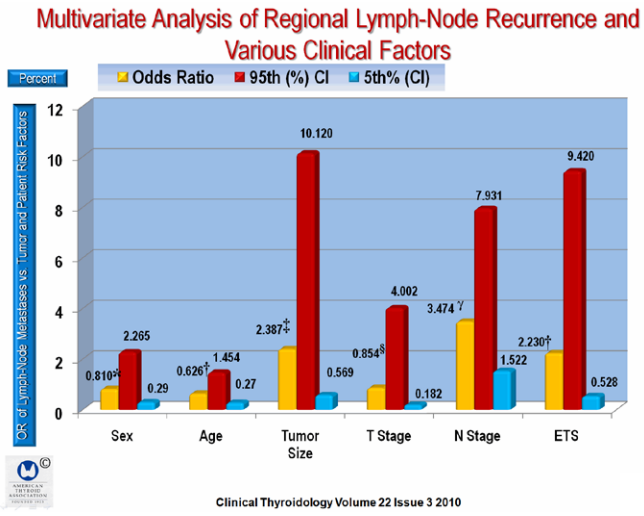

Figure 6. This figure shows the likelihood of various clinical factors increasing the risk for recurrent lymph-node metastases. The odds ratio (OR) and 95% and 5% confidence intervals (CIs) are shown. Only N stage was found to be a significant variable that was independently predictive of recurrent lymph-node metastases. *P = 0.0687, comparing women with men. †P = 0.274, comparing young with older patients. ǂP = 0.234, comparing smaller with larger primary tumors. §P = 0.841, comparing different T stages. ɣP = 0.003. ǁP = 0.275, comparing different N stages. Only N stage was an independent factor significantly increasing the risk for recurrent lymph-node metastases. ETS = extrathyroidal spread of tumor.

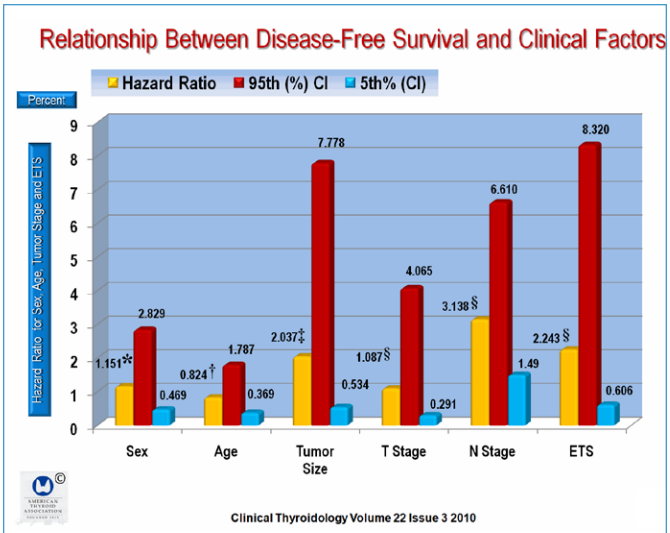

Figure 7. This figure shows the relationship between clinical factors and disease-free survival. *P = 0.739, comparing men with women. †P = 0.426, comparing young with older patients. ǂP = 0.004, comparing small and larger tumors, §P<0.001 for T stage, N stage, and extrathyroidal spread of tumor (ETS).

Clinical Characteristics of Lymph-Node Metastases (Figures 8 and 9)

Of 130 patients without lymph-node metastases at the time of initial surgery, 13 had ipsilateral neck recurrence, 1 had contralateral recurrence, and 2 had bilateral neck recurrence. Regional neck recurrence was frequent in ipsilateral neck levels II, III, and IV (Figure 8). Among 59 patients with lymph-node metastases at the time of initial surgery, 20 (33.9%) had regional recurrences. Among these patients, 14 had ipsilateral and 10 had contralateral regional neck recurrences. In the

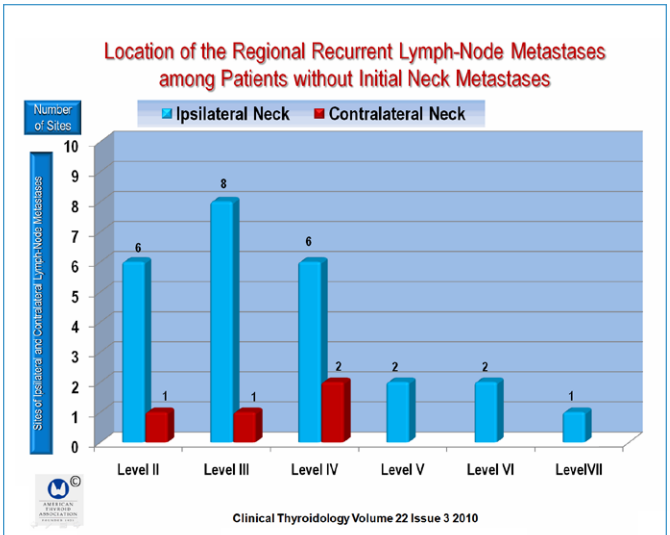

Figure 8. This figure shows the location of regional lymph-node recurrences according to ipsilateral and contralateral recurrent lymph-node metastases in patients without neck metastases at initial surgery.

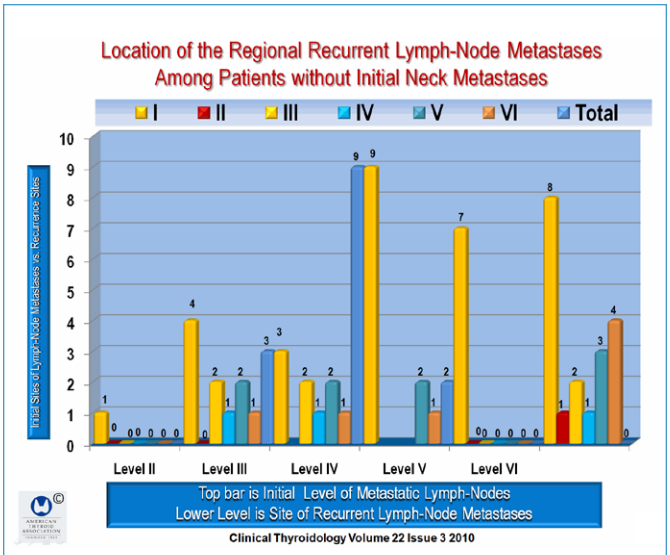

Figure 9. Regional lymph-node metastases were commonly found in ipsilateral levels II, III, and IV (Figure 8), and ipsilateral lymph-node recurrences were more frequent in levels II, III, and VI.

ipsilateral regional recurrence group, lymph-node metastases were frequently found in neck levels II, III, and VI at the initial surgery, and the regions with frequent lymph-node recurrences were in levels IV, V and VI (Figure 9).

In the contralateral regional recurrence group, the levels of lymph-node metastases in the initial surgery were in levels II, III, and VI. In the contralateral regional recurrence group, the initial levels of lymph-node metastases were in levels III, and VI, and recurrent lymph-node metastases were most common in level II. For surgical treatment of recurrent lymph-node metastases, selective neck dissection in levels II to IV and VI was performed in 18 patients and in levels I or II to V in 12 cases, and lymph-node excision in 3 cases. No patients with metastatic lymph-node recurrence died of the disease.

CONCLUSION

This study found that lymph-node metastases at the time of initial surgery were the most predictable clinical factor for disease-free survival. The authors concluded that routine prophylactic lymph-node compartment surgery in all patients is questionable, considering the low incidence (10%) of recurrent regional lymph-node metastases among patients who did not have lymph-node metastases at the time of initial surgery—the majority (79%) of patients having initial surgery.

COMMENTARY

There is considerable disagreement concerning the efficacy of routine prophylactic CLND. The foundation of this disagreement rests on the fact that relatively few studies have found that lymph-node metastases impair long-term survival (01;2;3), whereas others find no effect of lymph-node metastases on cancer-specific survival rates (4). This is not surprising considering the highly variable study subjects, the length of follow-up, and the standards that identify patients who are disease-free. Moreover, there are no prospective, randomized studies concerning the efficacy of prophylactic CLND or LND (5). Yet there are advocates who find sufficient evidence-based data to support CLND for PTC in patients under the care of experienced endocrine surgeons (5). The notion that prophylactic lymph-node dissection should be approached with caution is in accord with the American Thyroid Association guidelines (6). Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central- or lateral-neck lymph-node metastases should accompany total thyroidectomy to provide clearance of disease from the central neck (Recommendation rating: B). (b) Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central-neck lymph nodes, especially for advanced primary tumors (T_3 or T_4) (Recommendation rating: C).

(c) Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancers (Recommendation rating: C).

However, contrary to the Baek study, some have identified risk factors for cervical-lymph-node recurrence. For example, Leboulleux et al. (7) studied 148 consecutive patients with PTC who had lymph-node metastases, with or without extrathyroidal tumor extension at the time of diagnosis. After a mean follow-up of 8 years, eight patients (7%) with a normal postablation whole-body diagnostic ^{131}I scan experienced tumor recurrence. They found that significant risk factors for persistent disease were the number of lymph-node metastases (>10), the number of lymph-node metastases with ETS (>3), primary tumor size (>4 cm), and central lymph-node metastases. Likewise, for recurrent disease, the significant risk factors were number of lymph-node metastases (>10), ETS (>3), and elevated serum Tg levels after levothyroxine withdrawal 6 to 12 months after initial treatment. Leboulleux et al. found that the number of lymph-node metastases, ETS lymph-node metastases, tumor location, tumor size, and serum Tg concentrations were important prognostic risk factors for recurrence.

Baek et al. also found on univariate analysis that clinical risk factors such as tumor size, ETS, T stage, and N stage at the time of initial surgery were associated with regional lymph-node recurrence, in accord with several other studies (7;9). However, multivariate analysis found that only lymph-node metastasis at presentation was associated with a significant difference in regional recurrence, and it was the most predictable clinical factor for disease-free survival. Part of this result might be attributable to the fact that CLND was performed only in patients with preoperative or intraoperatively identified lymph-node metastases. This is a considerably different scenario as compared with prophylactic CLND or LND.

An additional concern about the therapeutic efficacy of prophylactic CLND is the complications of this surgical procedure, which have been summarized by Doherty, Steward, and Mazzaferri (8). Still, prophylactic CLND and level III LND identifies tumors that are not easily detected preoperatively by ultrasonography-guided fine-needle aspiration biopsy or during initial surgery. Leaving occult lymph-node metastases after surgery are in turn related to the use of postsurgical ^{131}I remnant ablation.

Radioiodine ablation is not generally recommended for tumors <10 mm, and its use depends on various factors for tumors between 10 and 20 mm, such as lymph-node metastases, which must be taken in the context of risk stratification.

The ATA guidelines define low-risk patients as having the following characteristics: (1) no local or distant metastases; (2) all macroscopic tumor has been resected; (3) there is no tumor invasion of locoregional tissues or structures; (4) the tumor does not have aggressive histology (e.g., tall-cell, insular, or columnar-cell carcinoma) or vascular invasion; and (5) if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first posttreatment whole-body ^{131}I scan. Intermediate-risk patients have any of the following: (1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; (2) cervical-lymph-node metastases or ^{131}I uptake outside the thyroid bed on the therapeutic whole-

body scan done after thyroid remnant ablation; or (3) tumor with aggressive histology or vascular invasion. High-risk patients have: (1) macroscopic tumor invasion; (2) incomplete tumor resection; (3) distant metastases; and possibly (4) Tg levels out of proportion to what is seen on the posttreatment scan. The problem is that central-neck-compartment metastases are generally not identified preoperatively or intraoperatively, and as many as high as 50% (Scheumann et al. 559-67;White, Gauger, and Doherty 895-904).

A retrospective study by Bonnet et al.(9) that was aimed at determining the effect of lymph-node staging on the indication for radioiodine treatment found that among 115 patients with PTC <2 cm without ultrasonographically detectable cervical-lymph-node metastases were treated with total thyroidectomy and complete selective dissection of the CLND and LND compartments. Radioiodine treatment was based on definitive histopathology, and follow-up was based on neck ultrasound and Tg levels. Lymph-node metastases were found for 42% of the patients. Radioiodine was not given to 42% of the patients with tumors <20 mm and no metastatic lymph-node metastases.

On the other hand, 58% of the patients were treated with radioiodine for lymph-node metastasis, extracapsular thyroid invasion, or unfavorable histologic subtype. The status of lymph-node metastases affected the indication for radioiodine in 30.5% of cases classified as T1: 12 patients with tumors <10 mm but with lymph-node metastases (who received radioiodine) and 13 patients with tumors between 10 and 20 mm but without lymph-node metastases (who did not receive radioiodine). Vocal-fold paralysis and hypoparathyroidism each occurred in 0.9% of cases. After 1 year of follow-up , neck ultrasonography was normal in all the patients, and recombinant human TSH-stimulated Tg was undetectable for 97% of the patients. The authors concluded that precise lymph-node staging by prophylactic neck dissection for tumors initially staged T1N0 modified the indication for radioiodine ablation for 30% of patients.

Prophylactic lymph-node compartment dissection remains a complex issue that will require further study, hopefully by prospective, randomized trials. The goal is to render patients free of disease with targeted therapy.

— Ernest L. Mazzaferri, MD, MACP

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