

Tumor multifocality and extrathyroidal tumor extension should be considered for prophylactic CLND, especially in men with papillary thyroid microcarcinoma

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SUMMARY

BACKGROUND

The frequency of subclinical lymph-node metastases (LNM) in the central cervical-lymph-node compartment may be found in up to 65% of clinically negative lymph-node metastases in papillary thyroid microcarcinomas (PTMC). However, routine prophylactic central-neck lymph-node dissection (CLND) continues to be a matter of debate, concerning both the efficacy of this surgical procedure and the possibility of parathyroid or recurrent laryngeal-nerve injury. The aim of this study was to assess the clinicopathologic factors associated with subclinical central lymph-node dissection and the recurrence rates and postoperative complications of total thyroidectomy and CLND.

PATIENTS AND METHODS

A total of 551 patients treated from 2005 through 2009 with clinically node-negative PTMC based on preoperative neck ultrasonography and fine-needle aspiration biopsy comprised the study subjects, all of whom had had total thyroidectomy and bilateral prophylactic CLND. The diagnosis of PTMC was reconfirmed by the surgical pathology findings for all patients.

RESULTS

Clinicopathologic Characteristics of the Study Patients

(Figures 1 and 2)

The clinicopathologic characteristics of these patients are shown in Figure 1. A total of 440 women (79.9%) and 111

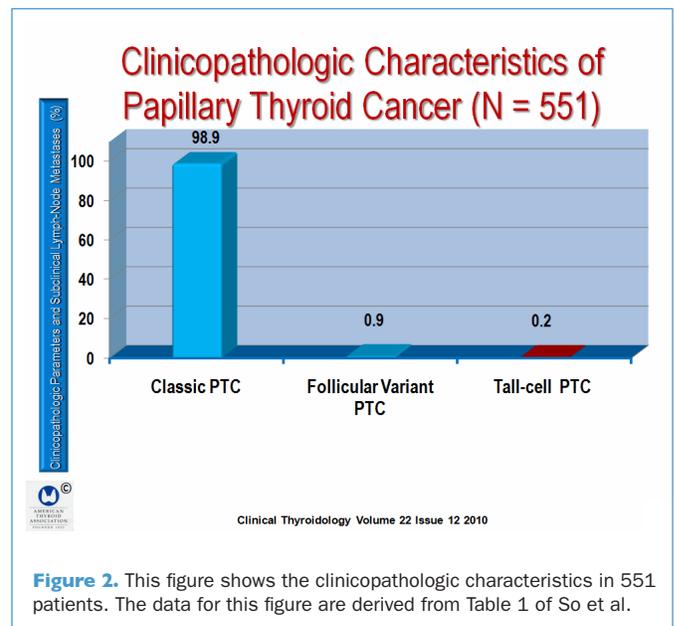
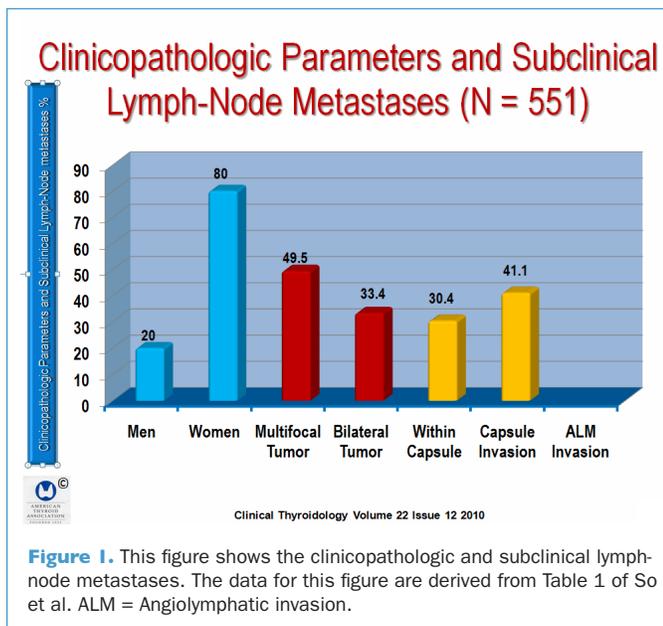
men (20.1%) comprise the study subjects, whose mean age was 50.2±9.2 years. The mean tumor size was 0.6±0.2 cm, and for multifocal tumors, the largest tumor was used in the analysis. The majority of patients (98.5%) had classic papillary thyroid cancer (Figure 2). The mean number of lymph nodes in the central compartment was 8.9 (range, 1 to 41), and the surgeon's description verified the adequacy of bilateral CLND, whereas patients who had unilateral CLND were excluded from the study. A total of 73.8% of the patients had bilateral CLND with PTMC.

Extent of Tumor (Figure 3)

The extent of tumor was classified into three categories based on the pathology results: confined within the capsule, capsule invasion (n = 11 patients, 2%), and extrathyroidal extension (n = 292, 53%). Extrathyroidal extension was mostly minimal invasion of perithyroidal soft tissue or strap muscle (pT3), which also included microscopic capsule invasion into perithyroidal tissue (Figure 3). Only 4 patients had invasion of tumor into the adjacent organs (pT4); all of which had posterior extension to the recurrent laryngeal nerve.

Postoperative Radioiodine (¹³¹I) Treatment

Patients with unfavorable pathologic characteristics, such as multifocal tumors, extrathyroidal extension, angiolymphatic invasion, or lateral LNM were treated with ¹³¹I. A total of 444 of 551 (80.6%) patients were treated with a mean and median of 42.6 and 30.0 mCi of ¹³¹I, respectively. A total of



242 patients (44.1%) had ≥ 2 ^{131}I treatments. The first ^{131}I treatment was performed within 2 to 3 months of surgery and was administered after 4 weeks of thyroid hormone withdrawal, with a TSH >30 mIU/L. Subsequent ^{131}I treatments were based on the serum Tg levels, anti-Tg antibody (TgAb), and the RxWBS. When ^{131}I was no longer required, patients had regular follow-up with ultrasonography and unstimulated serum Tg levels. Fine-needle aspiration was performed if pathologic confirmation of recurrence was necessary.

Complications

Postoperative hypocalcemia was defined as at least 1 event of hypocalcemic symptoms, including perioral numbness or hand and feet paresthesia, or at least of 1 ionized calcium level <1.0 mmol/L or a total calcium level <8.0 mg/dl.

Permanent hypocalcemia was defined as persistent symptoms or persistent biochemical hypocalcemia for more than 6 months. Postoperative vocal-cord palsy, chyle leakage, or hematoma was also investigated, and patients had monthly laryngoscopy at every follow-up regardless of corrective thyroplasty.

Central Lymph-Node Metastases

Among 551 patients with clinically node-negative PTMCs, subclinical central LNM was identified in 202 (36.7%). The mean number of metastatic lymph nodes was 2.4 ± 1.9 . The frequency of LNM was greater in men ($P = 0.002$), in patients with multifocal tumors ($P = 0.003$), and in patients with capsule invasion or extrathyroidal extension ($P = 0.001$). Tumor size >0.5 cm and angiolymphatic invasion were also associated with subclinical central LNM ($P = 0.010$ and 0.008 , respectively) (Figure 1).

Multivariate analysis showed that the following were independently predictive of subclinical central LNM (odds ratio [OR], 2.184;

$P = 0.001$), tumor multifocality, (OR, 1.582; $P = 0.015$), and extrathyroidal extension (OR, 1.893; $P = 0.001$). The probability that a woman with a solitary tumor confined within the thyroid capsule did not have central LNM was 80.6%, and the sensitivity and specificity were 38.6% and 85.6%, respectively (Figure 4).

Postoperative Complications

Transient hypocalcemia occurred in 152 patients (27.6%), in whom it resolved within 6 months. Permanent hypocalcemia developed in 6 patients (1.1%). Vocal-cord palsy developed in 28 patients, 21 of whom (3.8%) recovered within 6 months. Seven patients (1.3%) had vocal palsy that persisted for more than 1 year with permanent vocal palsy, and injection laryngoplasty was performed. Chyle leakage occurred in 3 patients (0.5%), and the rates of leakage were <100 ml/day in all cases. Leakage was controlled nonoperatively with a fat-free diet. A postoperative hematoma developed in 3 patients (0.5%) and was treated with reoperation.

Recurrence

Six patients were lost to follow-up (5.4%) and 104 had follow-up for more than 3 years after surgery. The median duration of follow-up was 40.5 months. There were no recurrences in the central cervical compartment (level VI), and only 1 patient had a recurrence outside the central cervical compartment (level IV) ipsilateral to the primary tumor 19 months after thyroidectomy. The 3-year locoregional control rate was 99.0%.

CONCLUSION

The frequency of subclinical central LNM was high in PTMC and was managed with prophylactic CLND, which did not cause permanent morbidity. PTMC multifocality and extrathyroidal tumor extension should be considered for prophylactic CLND, especially in men.

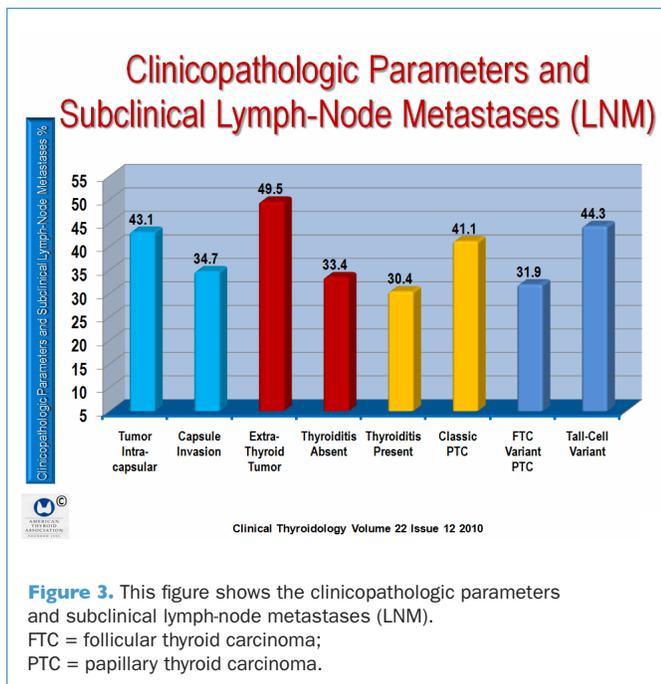


Figure 3. This figure shows the clinicopathologic parameters and subclinical lymph-node metastases (LNM). FTC = follicular thyroid carcinoma; PTC = papillary thyroid carcinoma.

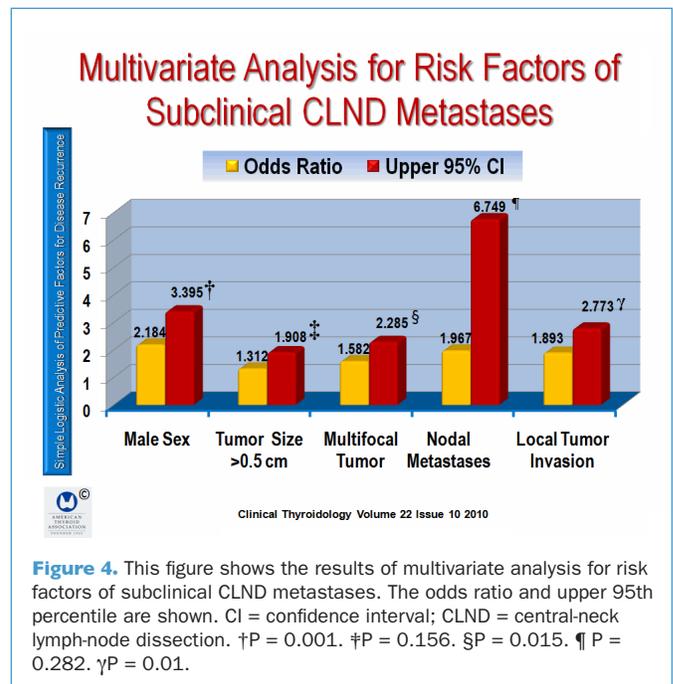


Figure 4. This figure shows the results of multivariate analysis for risk factors of subclinical CLND metastases. The odds ratio and upper 95th percentile are shown. CI = confidence interval; CLND = central-neck lymph-node dissection. [†] $P = 0.001$. [‡] $P = 0.156$. [§] $P = 0.015$. [¶] $P = 0.282$. ^γ $P = 0.01$.

COMMENTARY

The debate concerning routine prophylactic CLND for PTMC centers on studies that report little benefit for this surgery (1-3). Still, these studies report late recurrence with PTMC even with occasional distant metastases. Others recommend prophylactic CLND for patients ≥ 45 years of age, including the study by So et al. and others (4-8). For example Mercante et al. (9) reported that total thyroidectomy seems advisable in PTMC with extrathyroidal extension and neck lymph-node metastasis at the time of presentation and that capsular invasion without extrathyroidal extension may suggest aggressive tumor behavior and require radical treatment.

There are several studies that found BRAF mutations in patients with PTMC may identify patients with more aggressive tumor behavior, despite the small size of the tumor (10).

Most experts suggest that CLND be performed by high-volume surgeons who are trained for this procedure. Lastly, there is evidence that selected small PTMCs require RRA, which is facilitated by CLND (11).

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References

1. Ito Y, Tomoda C, Uruno T, et al. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. *World J Surg* 2006;30:91-9.
2. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* 2003;237:399-407.
3. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. *World J Surg* 2008;32:747-53.
4. Doherty GM. Routine central neck lymph node dissection for thyroid carcinoma. *Surgery* 2006;140:1007-8.
5. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid* 2009;19:683-9.
6. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. *World J Surg* 2007;31:895-904.
7. White ML, Doherty GM, Gauger PG. Evidence-based surgical management of substernal goiter. *World J Surg* 2008;32:1285-300.
8. White ML, Doherty GM. Level VI lymph node dissection for papillary thyroid cancer. *Minerva Chir* 2007;62:383-93.
9. Mercante G, Frasoldati A, Pedroni C, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* 2009;19:707-16.
10. Basolo F, Torregrossa L, Giannini R, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. *J Clin Endocrinol Metab* 2010;95:4197-205.
11. 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.

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