

Central neck compartment lymph-node-metastases in papillary thyroid carcinoma can be effectively managed with prophylactic CLND, without a high complication rate and with very few recurrences

So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, Chung MK. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery* 2010. doi:10.1016/j.surg.2010.01.003

SUMMARY

BACKGROUND

Initial preoperative neck ultrasonography performed in preparation for thyroidectomy ordinarily fails to identify central-compartment lymph-node metastases, especially in papillary thyroid microcarcinoma (PTMC). Lymph-node metastases are usually identified only when prophylactic central-compartment lymph-node dissection (CLND) is performed, in which case the rate of lymph-node metastases may be as high as 65%. Nonetheless, this approach has been widely debated for papillary thyroid carcinomas (PTCs) of all sizes. The ATA guidelines suggest that prophylactic CLND, ipsilateral or bilateral, may be performed in patients with PTC with clinically uninvolved central-neck lymph nodes, especially for advanced primary tumors (T3 or T4). PTMC is often treated with hemithyroidectomy alone and is almost never treated with prophylactic CLND, despite the 10-year incidence of PTMC lymph-node recurrence of 5% that has been found in large studies. The debate concerning CLND thus revolves around the balance of efficacy versus the complication rates of this surgery. The aim of this study was to assess the clinical factors associated with subclinical central compartment lymph-node metastases, in order to determine when prophylactic CLND might be performed in these small tumors.

METHODS

The study cohort comprises 551 patients treated at the University School of Medicine in Seoul, Korea, from January 2005 through March 2009. Patients selected for study were those with PTMC who had no preoperative evidence of lymph-node metastases based on clinically negative neck ultrasonography and fine-needle aspiration (FNAB). All patients had total thyroidectomy with bilateral CLND, defined as dissection of bilateral paratracheal and prelaryngeal lymph nodes. The diagnosis of PTMC was reconfirmed by histology from the surgical specimen.

Tumor classification

Adequacy of CLND was based on the surgeon's description of bilateral complete CLND. The removal of selected lymph nodes ("node picking") was not performed by this group of surgeons. Excluded from the study were patients who had unilateral CLND, leaving 73.8% of the 551 patients with bilateral CLND for the study. The extent of tumor was stratified into three categories according to pathology results: confined within the thyroid capsule, capsular invasion, and extrathyroidal extension, including microscopic capsular breach with extension into perithyroidal tissues.

Postoperative radioiodine treatment and follow-up

Postoperative radioiodine (¹³¹I) was administered to patients with unfavorable pathologic characteristics such as multifocal

tumors, extrathyroidal extension, angiolymphatic invasion, and lymph-node metastases. As a consequence, 444 of the 551 patients (80.6%) were treated with ¹³¹I within 2 to 3 months after thyroidectomy. Patients were prepared with a 4-week cessation of levothyroxine to increase TSH to >30 mIU/L. The mean initial ¹³¹I treatment was 42.6 mCi (median, 30.0; range, 30 to 150). A total of 242 patients had two or more ¹³¹I treatments. Subsequent ¹³¹I treatments were assessed by serum thyroglobulin (Tg) levels, anti-Tg antibody (TgAb), and the findings on post-¹³¹I-treatment scans. Follow-up studies with unstimulated serum Tg levels were performed every 6 months, during which recurrences were identified with ¹³¹I whole-body scans, ultrasonography, and FNAB.

Postoperative complications

Hypocalcemia was defined as at least one event in which symptoms of hypocalcemia such as perioral numbness, or paresthesia of hands and feet, or at least one event of hypocalcemia with an ionized blood calcium level <1.0 mmol/L or a total calcium level <8.0 mg/dl that was assessed at every follow-up until the calcium returned to normal. Permanent hypocalcemia was defined as persistent symptoms or hypocalcemia lasting more than 6 months. Patients were evaluated for other complications, including postoperative vocal-cord palsy, chyle leakage, and hematoma. Laryngoscopy was performed at every follow-up, regardless of corrective laryngoplasty.

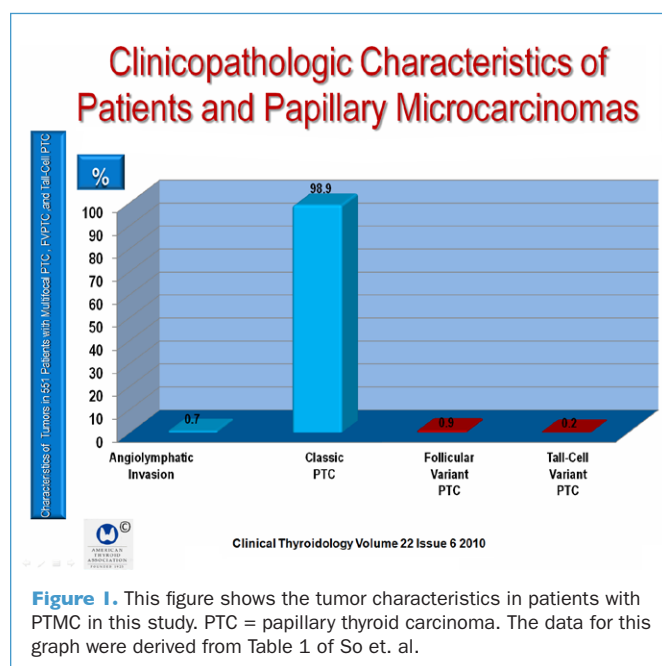


Figure 1. This figure shows the tumor characteristics in patients with PTMC in this study. PTC = papillary thyroid carcinoma. The data for this graph were derived from Table 1 of So et al.

RESULTS

Clinicopathologic characteristics of 551 patients (Figures 1 and 2)

The study comprised 440 women (79.9%) and 111 men (20.1%) with a mean (±SD) age of 50.2±9.2 years. The mean size of the primary tumors was 0.6±0.2 cm, and for multifocal tumors, the diameter of the largest tumor was used in the analysis. The tumors comprised classic PTC in 98.9% of the patients, follicular-variant PTC in 0.9%, and tall-cell-variant PTC in 0.2% (Figure 1). Capsular invasion was found in 11 patients (2.0%), and extrathyroidal extension was found in 292 patients (53.0%) (Figure 2). Most of the extrathyroidal extension was minimal invasion of perithyroidal soft tissue or strap muscle (pT3). Only 4 patients had invasion of adjacent organs (pT4), all of whom had posterior extension of tumor to the recurrent laryngeal nerve.

Subclinical CLND lymph-node metastases and clinicopathologic risk factors (Figure 2)

Subclinical CLND lymph-node metastases were detected in 202 of 551 patients (36.7%) who had clinically node-negative lymph-node metastases. The mean number of lymph-node metastases was 2.4±1.9 (Figure 2).

The frequency of lymph-node metastases was greater in men (49.5%) than in women (33.4%) (P = 0.02), in patients with multifocal tumors (44.3%) versus solitary tumors (31.9%) (P = 0.003), and in patients with tumors within the thyroid capsule (28.2%) versus extrathyroidal tumor extension (43.5%) (P = 0.01). Also associated with subclinical lymph-node metastases was primary tumor size >0.5 cm (P = 0.01), as compared with larger tumors, and tumors without angiolymphatic invasion (36.2%), as compared with those with angiolymphatic invasion (P = 0.008) (Figure 2).

Multivariate analysis (Figures 3 and 4)

Multivariate analysis found that the following three factors were independently predictive of subclinical CLND lymph-node metastases: men (odds ratio [OR], 2.184; P = 0.001); multifocal tumor (OR, 1.582; P = 0.015), and extrathyroidal extension (OR, 1.893; P = 0.01) (Figure 4).

The probability that a woman with a solitary tumor confined within the thyroid capsule did not have CLND lymph-node metastases was 80.6%. (Figure 4A and 4B). The sensitivity of this probability was 28.6% and the specificity 85.6%.

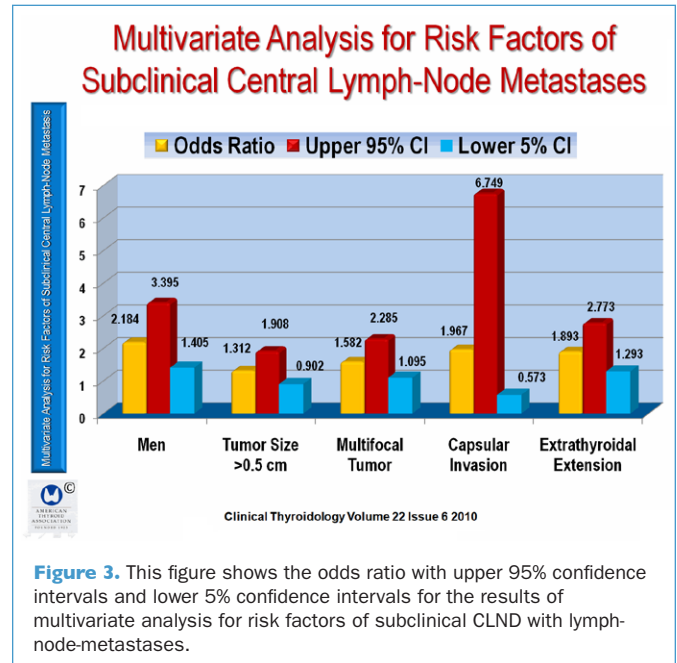


Figure 3. This figure shows the odds ratio with upper 95% confidence intervals and lower 5% confidence intervals for the results of multivariate analysis for risk factors of subclinical CLND with lymph-node-metastases.

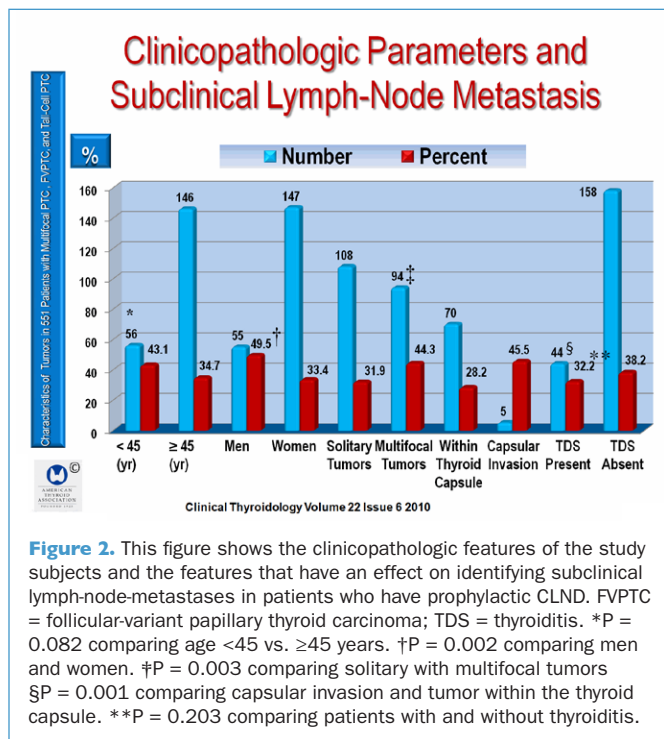


Figure 2. This figure shows the clinicopathologic features of the study subjects and the features that have an effect on identifying subclinical lymph-node-metastases in patients who have prophylactic CLND. FVPTC = follicular-variant papillary thyroid carcinoma; TDS = thyroiditis. *P = 0.082 comparing age <45 vs. ≥45 years. †P = 0.002 comparing men and women. ‡P = 0.003 comparing solitary with multifocal tumors §P = 0.001 comparing capsular invasion and tumor within the thyroid capsule. **P = 0.203 comparing patients with and without thyroiditis.

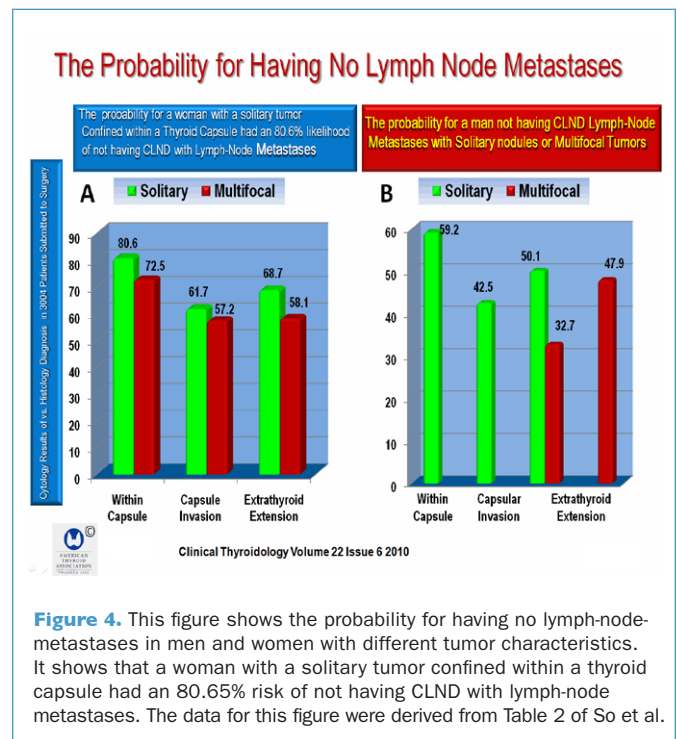


Figure 4. This figure shows the probability for having no lymph-node-metastases in men and women with different tumor characteristics. It shows that a woman with a solitary tumor confined within a thyroid capsule had an 80.65% risk of not having CLND with lymph-node metastases. The data for this figure were derived from Table 2 of So et al.

Postoperative complications (Figure 5)

Transient hypocalcemia developed in 152 of 551 patients (27.6%), which resolved within 6 months, whereas permanent hypocalcemia developed in 6 of 551 patients (1.1%).

Vocal-cord palsy developed in 28 patients (5%); 21 of these cases (3.8%) resolved within 6 months (transient vocal-cord paralysis), while 7 cases (25%) persisted for >1 year (permanent

vocal-cord paralysis) and laryngoplasty was necessary.

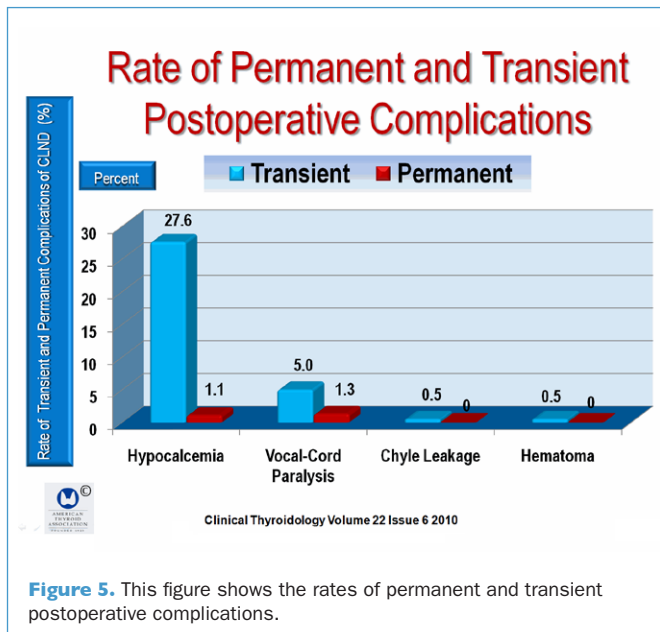
Chyle leakage occurred in 3 patients (0.5%), and the rates of leakage were <100 ml/day in all cases, which was controlled nonoperatively with a fat-free diet. Postoperative hematoma developed in 3 patients (0.5%) and was treated with reoperation (Figure 5).

RECURRENCE

Six patients (5.4%) were lost to follow-up and 104 had follow-up for more than 3 years after thyroidectomy. The median duration of follow-up was 40.5 months. During this time, there were no recurrences in the central cervical compartment (VI). At 19 months after thyroidectomy, only 1 patient had a recurrence outside the central cervical compartment ipsilateral to the primary tumor that required resection. No patient had a Tg level >2 ng/ml at 3 years after thyroidectomy; thus, the 3-year locoregional rate of no evidence of disease was 99%.

CONCLUSION

There is a high incidence of occult central-neck-compartment lymph-node-metastases that can be effectively managed with prophylactic CLND, without a high complication rate and with very few recurrences. The authors suggest that prophylactic CLND should be considered for patients with certain clinicopathologic features such as male sex, tumor multifocality, and extrathyroidal extension which may be particularly beneficial in patients with PTMC.

**COMMENTARY**

This is one of the largest studies to address the utility and safety of CLND in patients with PTMC, which explores the patient and tumor characteristics that relate to the selection of patients for prophylactic CLND and the patient and tumor features that are most likely to help identify patients with lymph-node metastases when treated with central-neck CLND. In addition, the authors address the safety of this surgery and the likelihood of complications and tumor recurrence following this surgical approach of total thyroidectomy with prophylactic CLND. This is a sound study of 551 patients, all of whom had histopathological evaluation of the resected tumors. The main results of the study were that male sex, tumor multifocality, and extrathyroidal tumor extension all were independent predictors of occult central-compartment lymph-node metastases. Although age is a significant prognostic factor in the outcome of PTC, age in this study did not predict occult central lymph-node metastases, although patients ≥ 45 years of age were slightly more likely to have lymph-node-metastases with CLND.

Primary tumor size was not an independent predictor of occult lymph-node-metastases in patients who had undergone CLND. This may be related to the size of the study cohort, despite its relatively large size. For example, a study by Bilimoria et al. of 52,173 patients with PTC found that cumulative 10-year recurrence rates for patients with primary tumors ranging in size

from <1 cm through >8 cm, found recurrence rates increased by 1-cm tumor increments from 4.6% with tumors <1 cm, to 24.8% with tumors >8 cm, a fivefold increase in recurrence rates (1).

During the 3-year follow-up in the So study, there were no recurrences in the central cervical compartment, which may be related to the CLND, but most patients also had ^{131}I remnant ablation. Nonetheless, the outcome after more than 3 years of follow-up after thyroidectomy and CLND, excluding 6 patients (5.4%) who were lost to follow-up, found that only 1 patient had a recurrence outside the central cervical compartment, and at 9 months after surgery, this recurrence was resected, and no patient had a Tg level >2 ng/ml, leaving 99% of the cohort free of disease. Still, this would have been more convincing had the serum Tg been undetectable after TSH stimulation rather than >2 cm for the cutoff to identify disease-free outcome.

The postoperative complication rates were very low, with transient hypocalcemia in 27.6%, which resolved in 6 months. Permanent hypocalcemia developed in 6 patients (1.1%). Vocal-cord palsy, which developed in 28 patients, recovered spontaneously within 6 months in 21 cases, and it remained present in 7 patients for more than 1 year (permanent vocal-cord palsy) and required therapy. Three patients had chyle leakage that resolved spontaneously with a fat-free diet, and postoperative hematoma in 3 patients (0.5%) was treated by reoperation.

This complication rate is approximately that seen in the hands of other well-trained surgeons. An article by Mazzaferri et al. (2) debated the pros and cons of prophylactic CLND and found that the mean rate of transient laryngeal-nerve injury in eight studies in which patients had total thyroidectomy and CLND was $4.5\pm 2.0\%$ for transient nerve damage and in nine studies it was $0.9\pm 1.8\%$ for permanent nerve injury. The mean (\pm SD) complication rates for transient hypoparathyroidism were $26.8\pm 11.8\%$ in five studies and $2.7\pm 22\%$ in four other studies.

The rate of lymph-node metastases may be as high as 65% in patients with PTMC who have had prophylactic CLND (3). One retrospective study by Scheumann et al. (4) found that systematic compartment-oriented dissection of cervical lymph-node metastases improved survival with PTC ($P < 0.005$) and recurrence ($P < 0.001$) especially in patients with T1 to T3 tumors. The authors concluded that lymph-node-metastases in a cohort with a significant incidence of young age and male sex had a substantial effect on survival and recurrence, especially in those with pT1 to T3 tumor, and that systematic compartment-oriented dissection of lymph-node metastases results in better survival and a lower recurrence rate; however this study had no contemporary controls, which leaves some question about this outcome as compared with patients treated without prophylactic lymph-node dissection.

Noguchi et al. (5) reported their findings in 2070 patients with PTMC ranging from 6 to 10 mm that were not treated with CLND

and in whom 14% had tumor recurrence at 35 years of follow-up, as compared with 3.3% in patients with smaller tumors (< 6 mm). Among patients older than 55 years, the recurrence rate was 40% at 30 years, with a worse prognosis in older than younger patients who had a recurrence rate of less than 10%. Extracapsular invasion by the primary tumor also had a higher rate of recurrence, the majority of which were in the neck, with some invading organs in the neck and others with distant metastases. The authors concluded that PTMC is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rate that extends for many years, justifying long surveillance after surgery.

So et al. have made important observations, especially that male sex, tumor multifocality, and extrathyroidal tumor extension all were independent predictors of occult central-compartment lymph-node metastases. Their study also raises questions about the long-term recurrence rates in patients treated with thyroidectomy alone.

The debate concerning prophylactic CLND likely will extend over several decades to produce prospective randomized studies, which hopefully will bring a solution to this dilemma. Until then, physicians should carefully inform their patients concerning the pros and cons to provide sufficient information for the patient to make a knowledgeable choice of therapy.

— Ernest L. Mazzaferri, MD, MACP

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