

Patients with papillary thyroid cancer have significantly reduced serum parathyroid hormone levels after prophylactic central neck compartment dissection

Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. *Ann Surg* 2007;245:604-10.

SUMMARY

BACKGROUND Although lymph-node metastases are common in papillary thyroid cancer, there is considerable debate concerning the use of routine prophylactic central neck dissection (CND) for all patients undergoing total thyroidectomy. The debate mainly stems from the fact that there are no robust data regarding either the benefit or the complications of prophylactic lymph-node dissection. The aim of this retrospective study was to investigate the pattern of lymph-node metastases, morbidity, and recurrence rates after bilateral CND with or without lateral neck dissection (LND).

METHODS The study subjects were 155 patients who had total thyroidectomy from 2001 through 2004 for papillary thyroid cancer at the Asian Medical Center of the University of Ulsan College of Medicine in Seoul, Korea. Patients who had prior neck surgery, unilateral lobectomy, and subtotal or completion thyroidectomy were excluded from the study. Data were collected on patient demographics, surgical procedures, the number of parathyroid glands preserved or autotransplanted, and the presence of symptoms of hypocalcemia. Devascularized parathyroid glands confirmed by frozen-section analysis were transplanted into the sternocleidomastoid muscle. Postoperatively, patients were routinely monitored for symptoms of hypocalcemia and abnormal serum calcium and parathyroid hormone (PTH) levels. CND (without microdissection methods) was performed cranially to both superior thyroid arteries and the pyramidal lobe and caudally to the innominate vein, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. The central compartment was

divided into four node sites: pretracheal, ipsilateral, contralateral paratracheal, and to the superior mediastinal area below the sternal notch. Parathyroid autotransplantation was performed as required, not routinely. Preoperative baseline blood samples were obtained on the morning of surgery for measurements of serum ionized calcium, total calcium, and intact PTH levels. Postoperative serum calcium was measured 1, 8, 24, 48, and 72 hours after surgery. Hypocalcemia was defined as a symptomatic ionized serum calcium level <1.0 mmol/L during hospitalization or at any time after discharge. Patients in whom hypocalcemia developed were treated with oral calcium, vitamin D, and if necessary, intravenous calcium gluconate.

RESULTS Of the 155 study patients, 130 (84%) were women and 25 (16%) were men; the mean age was 47 years (range, 18 to 75). Patients were divided into two groups, one with 82 patients (53%) who had total thyroidectomy and bilateral CND, and the other with 73 patients (47%) who had total thyroidectomy without CND. Sex, age, and MACIS (metastases, age, completeness of surgery, invasiveness, and size of the tumor) tumor scores were similar between the two treatment groups. The mean tumor size, the rate of tumor multifocality and extracapsular tumor invasion, and the number of patients with primary tumors ≤1 cm (papillary microcarcinoma), did not differ among the two treatment groups (Figure 1). Lymph-node metastases were found in the central neck in 51 (62%) of the CND group, and in 21 (25.6%) of the non-CND group (Figure 1). The rate of lymph-node metastases was higher in patients with tumor that extended beyond the thyroid capsule (29 of 45; 64%) than in patients with no tumor invasion (10 of

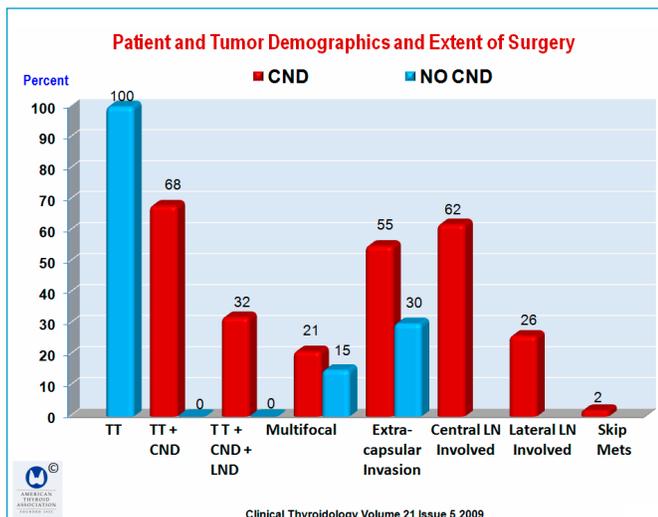


Figure 1. The tumor demographics are shown in patients who did or did not have central neck dissection (CND). TT = total thyroidectomy; LND = lateral lymph-node dissection; LN = lymph nodes; Mets = metastases. Here and elsewhere the percentages are rounded to an integer.

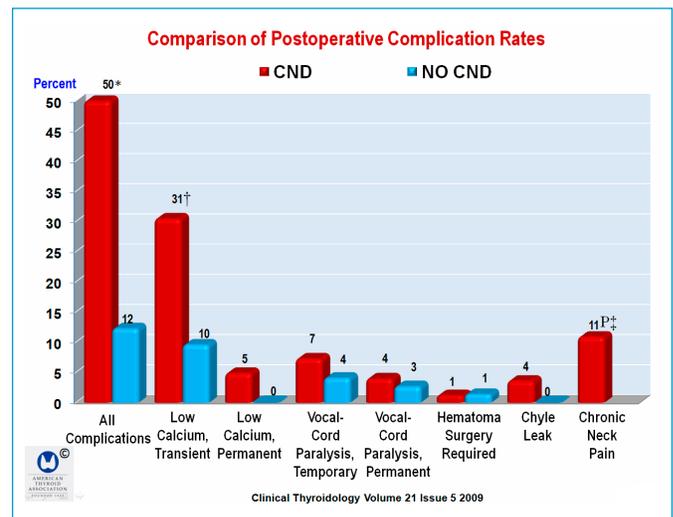


Figure 2. This figure shows the complication rates among patients who did or did not have central neck dissection (CND). *P < 0.001, †P = 0.001, ‡P = 0.004, comparing patients who did with those who did not have central neck dissection.

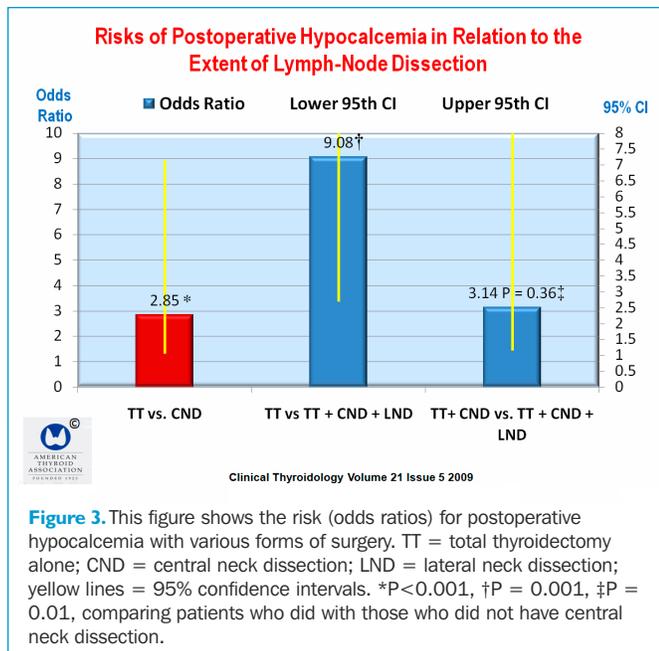


Figure 3. This figure shows the risk (odds ratios) for postoperative hypocalcemia with various forms of surgery. TT = total thyroidectomy alone; CND = central neck dissection; LND = lateral neck dissection; yellow lines = 95% confidence intervals. *P<0.001, †P = 0.001, ‡P = 0.01, comparing patients who did with those who did not have central neck dissection.

37; 27%, P = 0.001). Among 70 patients with a primary tumor located in a thyroid lobe, 47 (67%) had central compartment metastases that involved the ipsilateral paratracheal (62%), pretracheal (33%), superior mediastinal (20%), and contralateral (13%) sites. Of 12 patients with tumors originating in the thyroid isthmus, 4 (33%) had central lymph node compartment metastases that involved the pretracheal (25%), paratracheal (17%), and mediastinal (8%) sites.

Parathyroid glands were found in the thyroid or central lymph-node specimens from 16 patients (10%) who had CND; the mean number of parathyroid glands that were incidentally removed was 1.2, the frequency of which did not differ between the two treatment groups (P = 0.180). The complication rate was higher in the CND group than the no-CND group (50% vs. 12.3%, respectively; P<0.001) (Figure 2). Four patients in the CND group required calcium supplements 1 year after surgery. Vocal cord paralysis occurred in 9 (6%) patients, 5 of whom had permanent vocal-cord paralysis due to intentional resection of a

unilateral recurrent laryngeal nerve involved with tumor invasion. Other complications included postoperative bleeding that required surgery in 2 patients (1.3%), chyle leakage in 3 (3.6%), and longstanding pain in the operated lateral neck in 9 (34%), some of whom also had chronic shoulder pain (Figure 2). The risk for postoperative hypocalcemia in different surgical procedures is shown in Figure 3.

Although preoperative levels of serum calcium and PTH were similar, those who had neck lymph-node compartment dissections had a greater decline in mean serum calcium levels as compared with patients who did not have lymph-node dissections (12% vs. 7.6%; P = 0.002). Serum calcium levels were lower within 1 day after surgery for the lymph-node dissection group as compared with those who did not have lymph-node dissections. Still, for both groups, serum calcium levels were nearly normal within 3 months after surgery. The serum PTH levels decreased in most patients within an hour after surgery. The mean serum intact PTH levels declined more in the lymph-node-dissection group than in the no-lymph-node-dissection group (66% vs. 41%; P= 0.001), with PTH concentrations of 13.9 and 24.9 pg/ml in the two groups, respectively, which remained low for 7 days and slowly recovered within 6 months after surgery. The PTH concentration decreased to 24.9 pg/ml after surgery without lymph-node dissections and remained low for 7 days, recovering to preoperative levels within 1 month after surgery. For the group that had lymph-node dissections, PTH concentrations decreased

The mean (±SD) duration of follow-up was 51±25 and 53±28 months in patients who had CND and those who did not have CND, respectively (P = not significant). After a mean of 48 months, cancer recurrence developed in 4 patients (2.6%), 1 in the central neck alone and 3 in both the central and lateral neck compartments. Three patients who did not have lymph-node dissection had recurrences in the central compartment alone (n = 1) or the central and lateral compartments (n = 2), and all subsequently underwent CND or CND plus LND. Except for one patient with distant metastases, all patients became free of disease.

CONCLUSION Patients with papillary thyroid cancer who have prophylactic central neck compartment dissections have significantly reduced serum parathyroid hormone levels.

COMMENTARY

Although this is not a recent publication, it was highlighted in this issue of Clinical Thyroidology to emphasize the wide range of complications that may be associated with prophylactic lymph-node dissection. As the debate surrounding this topic increases, we must continue to consider the broad spectrum of experiences that have been reported with this surgical procedure.

This is a careful analysis of the morbidity, recurrence, and postoperative serum calcium and PTH levels in patients who had total thyroidectomy with prophylactic CND and, in some cases, LND. The study demonstrates the extent to which complications may occur with CND. Half the patients who had lymph-node dissections experienced complications, as compared with only 12% of patients who had total thyroidectomy alone. Transient hypocalcemia occurred in 32% of the CND group and only 10% of the total thyroidectomy group without CND;

the hypocalcemia was permanent in 5% and 0%, respectively. Temporary vocal-cord paralysis occurred in 7% and 4% of the two groups, and permanent paralysis in 4% and 3%, respectively. The only difference between the two treatment groups that was statistically significant occurred with transient hypocalcemia (P = 0.001). Postoperative hypocalcemia and a rapid decline in serum PTH concentrations occurred more commonly in the prophylactic lymph-node-dissection group than in those who did not have lymph-node dissections. After performing this study, the authors concluded that prophylactic central and lateral compartment lymph-node dissections should not be recommended, because of the high rate of complications.

Henry et al. (1) compared the morbidity of total thyroidectomy with prophylactic central neck dissection in 50 patients with papillary thyroid carcinoma with that in 50 patients who were treated for multinodular goiter. None of the patients in the entire study

developed permanent laryngeal-nerve paralysis, although two patients (4%) in the lymph-node-dissection group and three (6%) in the total thyroidectomy group developed transient laryngeal-nerve paralysis. Transient hypoparathyroidism occurred in 7 (14%) of the central lymph-node-dissection group and 4 (8%) of the total thyroidectomy group, which became permanent in 2 patients (4%) in the central lymph-node-dissection group. The authors concluded that it is difficult to advocate routine central neck dissection, even when taking into account the possible benefits.

Another study of 342 patients with papillary thyroid carcinoma by Scheumann et al. (2) found that systematic lymph-node dissection of cervical lymph-node metastases improved recurrence ($P < 0.001$) and survival ($P < 0.005$), especially in patients with T1 to T₃ tumors (1 to >4 cm). The authors concluded that compartment-oriented dissection of lymph-node metastases results in enhanced survival and a lower tumor-recurrence rate.

White et al. (3) performed a systematic review of the literature concerning central lymph-node dissection in patients with differentiated thyroid cancer. Using evidence-based criteria, the authors reached several important conclusions.

- Systematic compartment-oriented central lymph-node dissection may decrease the recurrence of papillary thyroid cancer and likely improves disease-specific survival (grade C recommendation).
- Limited level III data suggest survival benefit with the addition of prophylactic dissection to thyroidectomy (grade C recommendation).
- The addition of total thyroidectomy can significantly reduce levels of serum thyroglobulin and increase the rates of undetectable serum thyroglobulin levels (level IV data, no recommendation).
- There may be a higher rate of permanent hypoparathyroidism and unintentional permanent nerve injury when central lymph-node dissection is performed with total thyroidectomy than for total thyroidectomy alone (grade C recommendation).
- Reoperation in the central neck compartment for recurrent papillary thyroid carcinoma may increase the risk of hypoparathyroidism and unintentional nerve injury as compared

with total thyroidectomy with or without central lymph-node dissection (grade C recommendation), supporting a more aggressive initial operation.

The authors concluded that evidence-based recommendations support central lymph-node dissection for patients with papillary thyroid carcinoma under the care of experienced endocrine surgeons.

A recent and very important study by Bonnet et al. (4) comprised 115 patients with papillary thyroid carcinoma less than 2 cm without ultrasonographically detectable cervical lymph nodes were treated with total thyroidectomy and complete selective dissection of the central and lateral neck compartments. This was aimed at determining the effect of surgical lymph node staging on the indication for radioiodine treatment. The main finding was that precise lymph-node staging by prophylactic neck dissection of tumors initially staged T1N0 favorably modified the indication for radioiodine ablation for 30% of patients. In this study, vocal-cord paralysis and hypoparathyroidism each occurred in only 0.9% of cases.

In summary, the initial therapy for patients with papillary thyroid cancer has been gradually changing, with increasingly more emphasis on prophylactic lymph-node dissection. Whether patients will accept extensive prophylactic neck lymph-node compartment surgery for what appears to be low-risk tumor remains uncertain. Still, despite the low mortality rates with these tumors, the recurrence rates are high. It is thus unlikely that many patients will forgo both remnant ablation and prophylactic lymph-node compartment dissection if informed of the high rate of preoperatively unrecognized lymph-node metastases.

As with the learning curve that occurred with total thyroidectomy, extensive lymph-node compartment surgery must be provided by well trained and highly experienced surgeons. The Bonnet study shows a way to blend cervical lymph-node dissection with the accurate selection of patients for postoperative radioiodine therapy. Much of the predictable controversy over this issue is likely to sound similar to the decades-old arguments concerning lobectomy versus total thyroidectomy.

Ernest L. Mazzaferri, MD, MACP

References

1. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. *Langenbecks Arch Surg* 1998;383:167-9.
2. Scheumann GF, Gimm O, Wegener G, et al. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg* 1994;18:559-68.
3. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. *World J Surg* 2007;31:895-904.
4. 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.