

Preferential Use of Total Thyroidectomy without Prophylactic Central Lymph Node Dissection for Early-Stage Papillary Thyroid Cancer: Oncologic Outcomes in an Integrated Health Plan

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ABSTRACT

Context: The oncologic benefit of prophylactic central lymph node dissection (pCLND) in node-negative papillary thyroid cancer has been debated.

Objective: To determine the use of pCLND in an integrated health care system and to evaluate recurrence in the cohort.

Design: Retrospective cohort study of patients with clinically node-negative papillary thyroid cancer who underwent total thyroidectomy with or without pCLND in Kaiser Permanente Southern California Region hospitals between January 1996 and December 2008. Chart review of all patients was performed to collect demographic data, tumor features, stage, and recurrences.

Main Outcome Measures: Proportion undergoing pCLND and recurrence rate of papillary thyroid cancer.

Results: There were 864 patients identified (mean age, 46.1 years). Almost all patients had total thyroidectomy alone, and 34 (3.9%) underwent pCLND. The TNM (tumor, node, metastasis) stages for the 2 groups were not significantly different ($p = 0.18$). Overall recurrence was 24 (2.8%). There were 23 (2.8%) recurrences in the no-pCLND group and 1 (2.9%) recurrence in the pCLND group ($p = 0.95$). The rate of recurrence in the central neck compartment in those without pCLND was 1.1% and 0% in the pCLND group ($p = 0.54$). The recurrence rate in the lateral neck compartment in the no-pCLND group was 2.2%, and this rate was 2.9% in the pCLND group ($p = 0.76$). The no-pCLND group had a recurrence-free survival rate of 96.4% at 10 years vs 96.8% in the pCLND patients ($p = 0.80$).

Conclusion: Presently, routine pCLND is difficult to advocate in our medical system.

INTRODUCTION

Papillary thyroid cancer has a high propensity for metastases in the central and lateral cervical lymph nodes. However, even with regional lymph node spread, the overall prognosis remains good.¹⁻³ The presence of nodal disease confers increased risk of recurrence but has traditionally been thought to have no impact on overall survival.⁴ More recently, some larger studies have shown differences in prognosis between patients with node-positive cancer and those with node-negative cancer, but these differences have been very small, on the order of 1% to 3% survival differences

up to 20 years from treatment.^{5,6} Approximately 20% of patients present with clinically palpable nodal disease, and the need for therapeutic lymph node dissection in these patients has been well established.⁵ However, controversy remains over the benefit of a prophylactic central lymph node dissection (pCLND) at the time of thyroidectomy when the nodes are clinically negative for metastases, which occurs in about 20% to 40% of patients⁶; the primary reason for the controversy is that until recently, no randomized trial existed that answered the question of the therapeutic benefit of pCLND. Some

studies have shown a survival benefit from pCLND, some have shown reduction in locoregional recurrence, and others have shown no benefit.⁷⁻¹¹

Proponents of pCLND argue that it enhances accurate staging, removes microscopic disease, and reduces recurrence rates.^{10,12} Opponents counter that low recurrence rates exist without performing pCLND, the procedure causes increased complications, and that therapeutic central lymph node dissection in the event of central compartment recurrence can be done with low morbidity, no higher than that after an initial pCLND.^{11,13-15} A recent randomized controlled trial showed no difference in survival in those patients who had pCLND, but the sample size may have been too small to answer the question without a type II error.¹⁶

The main objective of this study was to determine the use of pCLND in our integrated medical system at the time of total thyroidectomy for papillary thyroid cancer, and secondarily to attempt to compare overall recurrence rates in patients who underwent pCLND with those who had nodal observation.

METHODS

Subjects

This study was approved by the Kaiser Permanente Southern California (KPSC) institutional review board (Study Identification Number 5830). All patients with papillary thyroid cancer who underwent total thyroidectomy with and without pCLND in KPSC Region hospitals between January 1996 and December 2008

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were identified for the study. They were identified using the International Classification of Diseases, Ninth Revision, code of 193 (malignant neoplasm of thyroid gland) and the Current Procedural Terminology Procedure Codes 60240 (total thyroidectomy) and 60252 (total thyroidectomy with limited neck dissection). An individual chart review on all patients was then conducted. Data on patient demographics, tumor size, number of lymph nodes removed, number of positive lymph nodes, and TNM (tumor, node, metastasis) classification stage were collected. There was no specific protocol or algorithm used for preoperative staging. Operative reports were examined to determine if pCLND was performed; if the surgeon mentioned that lymph nodes were removed from the anatomic boundaries of level VI or anterior compartment in the neck as previously described, the patient was placed in the pCLND group.¹⁷

Patients were excluded from the study if they had known preoperative or intraoperative regional (either central neck compartment or lateral neck compartment) or distant metastatic disease, if they were age 45 years or older and had T3 (Stage III) tumors, if they underwent less than a total thyroidectomy (hemithyroidectomy, subtotal thyroidectomy, or completion thyroidectomy), had previous thyroid surgery or any cervical lymph node dissection, if they were pregnant, or if they were KPSC members for less than 6 months. Thus, the study cohort included only patients with clinically negative (cN0) papillary thyroid cancer.

Main Outcome Measures

The main outcomes were the proportion undergoing pCLND and recurrence rates. The types of recurrences included the following: central neck recurrence (including central lymph node recurrence and recurrence in the thyroid bed), lateral neck lymph node recurrence, and distant recurrence. Recurrence was determined by clinical suspicion and examination combined with ultrasound and/or radioactive iodine scan, or elevated thyroglobulin level with abnormal results of imaging, with or without cytologic result, or with

histopathologic evidence of cancer. There was no specific protocol or algorithm used for surveillance postoperatively. Any evidence of disease after a disease-free interval of one year was categorized as a recurrence.

Statistical Analysis

Chi-squared test or Fisher exact test was used to detect the difference in proportions of categorical variables, which were described using frequencies and percentages between pCLND and

no-pCLND groups. Student *t*-test was used for comparing continuous variables between groups. We also described follow-up time, time to recurrence, and percentages of recurrence among treatment groups.

Recurrence-free survival was determined using Kaplan-Meier survival function estimations. P values less than 0.05 indicate statistical significance. All tests were 2-tailed. All statistical analyses were performed using SAS Enterprise Guide 4.3 (SAS Institute Inc, Cary, NC).

Table 1. Demographics and tumor features in patients undergoing total thyroidectomy with or without prophylactic central lymph node dissection

Feature	No prophylactic central lymph node dissection (n = 830)	With prophylactic central lymph node dissection (n = 34)	Total patients (N = 864)	p value
Age at diagnosis, years				
Mean (SD)	46.4 (14.0)	40.0 (11.4)	46.1 (14)	0.005
Median	46.0	38.0	45.0	
Range	14.0-87.0	25.0-67.0	14.0-87.0	
Sex, no. (%)				
Female	709 (85.4)	24 (70.6)	733 (84.8)	0.018
Male	121 (14.6)	10 (29.4)	131 (15.2)	
Tumor size, cm				
Number of tumors	792	33	825	0.014
Mean (SD)	1.9 (1.5)	2.7 (1.9)	2.0 (1.5)	
Median	1.6	2.2	1.6	
Range	0.1-9.0	0.1-8.0	0.1-9.0	
Number of lymph nodes removed, no. (%)				
0	774 (93.3)	1 (2.9)	775 (89.7)	< 0.0001
1	5 (0.6)	0 (0)	5 (0.6)	
2	1 (0.1)	0 (0)	1 (0.1)	
3	23 (2.8)	7 (20.6)	30 (3.5)	
4	14 (1.7)	8 (23.5)	22 (2.5)	
5	5 (0.6)	4 (11.8)	9 (1)	
6	4 (0.5)	7 (20.6)	11 (1.3)	
7	4 (0.5)	7 (20.6)	11 (1.3)	
Number of positive lymph nodes, no. (%)				
0	812 (97.8)	21 (61.8)	833 (96.4)	< 0.0001
1	7 (0.8)	4 (11.8)	11 (1.3)	
2	3 (0.4)	3 (8.8)	6 (0.7)	
3	5 (0.6)	5 (14.7)	10 (1.2)	
4	2 (0.2)	0 (0)	2 (0.2)	
6	1 (0.1)	1 (2.9)	2 (0.2)	
TNM stage, no. (%)				
1	654 (78.8)	30 (88.2)	684 (79.2)	0.184
2	176 (21.2)	4 (11.8)	180 (20.8)	
Radioactive iodine, no. (%)	52 (6.3)	4 (11.8)	56 (6.5)	0.202

SD = standard deviation; TNM = tumor, nodes, metastasis.

RESULTS

There were 864 patients who met the criteria for inclusion into the study. Mean age (\pm standard deviation) was 46.1 ± 14 years, and 85% were women. Almost all patients had total thyroidectomy without pCLND, and 34 (3.9%) of the patients underwent pCLND (Table 1). The patients in the pCLND group were somewhat younger and men were more represented compared with the no-pCLND patients. Mean tumor size was larger in the pCLND group than in the no-pCLND group (2.7 cm vs 1.93 cm, $p = 0.014$). The TNM stages for the 2 groups were not statistically significantly different ($p = 0.18$, Table 1).

Not surprisingly, the pCLND group had more lymph nodes removed. They had more positive lymph nodes compared with the no-pCLND group ($p < 0.0001$, Table 1). With increasing tumor size, there was a higher proportion of node-positive disease ($p = 0.002$, Table 2).

The mean follow-up period was 7.9 years. There were no patients lost to follow-up, and there were 36 deaths. The overall number of recurrences in the study period was 24 (2.8%), with the mean time of 4.6 years between the index operation and recurrence. Recurrence in the central neck compartment occurred in 9 patients: 4 patients had recurrence in the central neck compartment only; 4 patients had recurrence synchronously in the central and lateral compartments of the neck; and 1 patient's cancer recurred synchronously in the central neck compartment, the lateral neck compartment, and distant sites. In the remaining 15 patients, 14 had recurrence in the lateral neck compartment as the sole region of disease, and 1 patient had recurrence at distant sites only.

When stratified by pCLND, there were 23 (2.8%) recurrences in the no-pCLND group and 1 (2.9%) recurrence in the pCLND group. No patients in the pCLND group had recurrence in the central compartment of the neck, whereas 9 patients (1.1%) in the no-pCLND group had recurrence in this area ($p = 0.54$). One patient (2.9%) in the pCLND group had recurrence in the lateral neck compartment, whereas 18 patients (2.2%) in the no-pCLND group had recurrence in this region ($p = 0.76$). With Kaplan-Meier

Table 2. Tumor size and presence of positive lymph nodes in the 825 tumors

Tumor size (cm)	Positive lymph nodes ^a
< 1	2/248 (0.8)
1 - < 2	6/209 (2.9)
2 - < 3	15/185 (8.1)
3 - < 4	2/92 (2.2)
4 - < 5	0/40 (0)
≥ 5	6/51 (11.8)

^a Data are no. (%)

estimations, the no-pCLND group had a recurrence-free rate of 96.4% at 10 years compared with 96.8% in the pCLND patients ($p = 0.80$).

DISCUSSION

We found in KPSC that nearly all patients with papillary thyroid cancer were treated with total thyroidectomy without pCLND. Our findings also suggest that performing pCLND in patients with initially clinically node-negative papillary thyroid cancer may not provide additional oncologic benefit. Alternatively, if there was a benefit that was not detectable because of a small number of patients who underwent pCLND, it would appear to be a very low absolute benefit and probably clinically insignificant, with such low recurrence rates found in the study.

The KPSC patient population is ethnically diverse and is representative of the larger community. There are 14 KPSC hospitals, ranging from 154 to 464 beds, all considered general surgical and medical centers. In addition, these operations were performed by more than 100 surgeons in KPSC.

The surgeons in KPSC are predominantly low-volume thyroidectomy surgeons, performing fewer than 10 thyroidectomies per year. In a later period of 2008 to 2013, 83% of total thyroidectomies in KPSC were performed by low-volume KPSC surgeons (Christine Ferioli, personal communication, November 24, 2015³). We believe this percentage would be similar in the study period. It has been shown previously that low-volume surgeons make up the majority of surgeons doing thyroidectomies. Sosa et al¹⁸ reported on thyroid surgery in Maryland, and 79% were surgeons who performed fewer than 10 thyroidectomies per year. Similarly, Stavakis et al¹⁹ found that 65% of surgeons doing

thyroid, parathyroid, or adrenal operations in New York and Florida performed only 1 to 3 such operations per year. Thus, our findings of low recurrence rates in our population of patients who are racially mixed and who are operated on by low-volume surgeons who rarely perform pCLND, as in the rest of the country, are probably generalizable to patients undergoing total thyroidectomy with or without pCLND in many other regions or communities in the US.

Our finding that pCLND is rarely performed in KPSC is mirrored outside our medical system in the US. In a population-based study of more than 14,000 patients with papillary thyroid cancer, only 6.6% potentially received a pCLND or a therapeutic central lymph node dissection that retrieved 5 or more lymph nodes.²⁰ However, it is unclear in that study of the National Cancer Institute's Surveillance, Epidemiology, and End Results database how many patients actually underwent a formal pCLND because data on operative technique are missing; it is probable that nodes were retrieved in the total thyroidectomy specimen inadvertently without formal pCLND. Our study scrutinized each operative report, and so we believe that 4% is accurate regarding who received a formal pCLND. With the limited evidence supporting pCLND, it may be justified that such a low number of pCLND was performed in the KPSC system, and it also may be similar in other hospitals and regions in the US.

Our retrospective study has several limitations. With only a very small minority who underwent pCLND, this group may well have been selected to undergo the procedure, and so a direct comparison with the no-pCLND group could be biased. The low number in the pCLND group and the low event rate also may have contributed to a type II error, with a difference in recurrence rates that was undetectable. Furthermore, it is probable that patients were treated differently by the many physicians involved at the different Medical Centers in the KPSC Region, from initial staging to postoperative adjuvant radioactive iodine therapy to surveillance. Therefore, the outcomes in patients who had pCLND may have been confounded by any number of factors. However, we are quite certain that

those who did and did not have a formal pCLND were assigned correctly, and the absolute recurrence is very low in those who had total thyroidectomy alone, regardless of the ability to discern all other confounders.

Although a randomized clinical trial is necessary to definitively address the oncologic benefit of pCLND, only recently has such a trial been completed, and it showed no benefit; in 181 patients randomly assigned to total thyroidectomy alone or thyroidectomy with pCLND, the outcomes of biochemical and structural recurrence were similar after 5 years of follow-up.¹⁶ It may be argued that the study was not powered appropriately; an impressive sample size of nearly 6000 patients would be required for 80% power.²¹ However, the study was powered as a noninferiority trial, and so fewer patients were required, and this is assuming that total thyroidectomy with pCLND would never have higher recurrence rates than total thyroidectomy alone.¹⁶

Most of the published literature to date has been retrospective studies. In a study of 752 patients with clinically node-negative papillary thyroid cancer, 390 underwent total thyroidectomy alone and 362 underwent total thyroidectomy with pCLND, and similar incidences of locoregional recurrence were found in the 2 groups of patients.¹¹ Furthermore, those who had bilateral pCLND had greater rates of transient and permanent complications. Our findings of very low recurrence rates in the central compartment in those who did not undergo pCLND were similar to those of Nixon et al.¹⁴ In their review of 275 patients who underwent total thyroidectomy alone, the rate of structural central lymph node recurrence was even lower at 0.4%. On the other hand, Popadich et al²² reported that the rate of repeated operation in the central neck compartment was higher in those who did not undergo a pCLND compared with the group of patients who did (1.5% vs 6.1%, $p = 0.004$). They also found lower postoperative stimulated thyroglobulin levels after pCLND. Other studies have also shown decreased thyroglobulin levels with pCLND or transiently decreased levels, but it is unclear if this translates to a survival advantage.^{23,24} Finally, systematic reviews have been done on the subject, with no difference in oncologic

outcomes with pCLND, yet pCLND may be associated with increased complications, particularly with increased rates of hypoparathyroidism.^{25,26}

The American Thyroid Association in 2015 released guidelines on lymph node dissection for well-differentiated thyroid cancer.²⁷ In Recommendation 36B, the association stated that “pCLND should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy.”²⁷ The recommendation was considered weak because of low-quality evidence.²⁷ Recommendation 36C stated that “thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2), noninvasive, clinically node-negative [papillary thyroid cancer] (cN0) and for most follicular cancers”; this was considered a strong recommendation with moderate-quality evidence.²⁷ These updated guidelines have slight wording changes compared with the 2009 and the 2006 guidelines, but the general trend has changed to now accept total thyroidectomy alone for early-stage papillary thyroid cancers.^{28,29} It appears in our study that surgeons in KPSC had already opted overwhelmingly for total thyroidectomy alone in patients with these early-stage cancers.

CONCLUSION

In our study of patients with early-stage papillary thyroid cancer treated preferentially with total thyroidectomy without pCLND, there was a very low rate of recurrence. Presently, pCLND is difficult to advocate for these patients. If pCLND is ever shown to be beneficial with a large multicenter and appropriately powered randomized trial, it might be difficult to find surgeons at local hospitals who would perform the procedure. ❖

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Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Feared

Where there are several chronic diseases more destructive to life than cancer, none is more feared.

— Charles Horace Mayo, MD, 1865-1939, American medical practitioner and cofounder of the Mayo Clinic