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Prophylactic Central Neck Dissection in Papillary Thyroid Carcinoma: All Risks, No Reward

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Abstract

Background: Central neck dissection (CND) remains a controversial intervention for papillary thyroid carcinoma (PTC) patients with clinically negative nodes (cN0) in the central compartment. Proponents state that CND in cN0 patients prevents locoregional recurrence, while opponents deem that the risks of complications outweigh any potential benefit. Thus, there remains conflicting results amongst studies assessing oncologic and surgical outcomes in cN0 PTC patients who undergo CND. To provide clarity to this controversy, we sought to evaluate the efficacy, safety, and oncologic impact of CND in cN0 PTC patients at our institution.

Materials and Methods: Six hundred and ninety-five patients with PTC who underwent thyroidectomy at our institution between 1998 and 2018 were identified using an institutional cancer registry and supplemental electronic medical record queries. Patients were stratified by whether or not they underwent CND; identified as CND(+) or CND(-), respectively. Patients were also stratified by whether or not they received adjuvant radioactive iodine (RAI) therapy. Patient demographics, pathologic results, as well as surgical and oncologic outcomes were reviewed. Standard statistical analyses were performed using ANOVA and/or *t*-test and chi-squared tests as appropriate.

Results: Among the 695 patients with PTC, 492 (70.8%) had clinically and radiographically node negative disease (cN0). The mean age was 50 ± 1 years old and 368 (74.8%) were female. Of those with cN0 PTC, 61 patients (12.4%) underwent CND. CND(+) patients were found to have higher preoperative thyroid stimulating hormone (TSH) values, 2.8 ± 0.8 versus 1.5 ± 0.2 mU/L ($P = 0.028$) compared to CND(-) patients. CND did not significantly decrease disease recurrence, development of distant metastatic disease ($P = 0.105$) or persistence of disease ($P = 0.069$) at time of mean follow-up of 38 ± 3 months compared to CND(-) patients. However, surgical morbidity

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Author contributions

Herbert Chen conceived and designed the analysis. Ruth Obiarinze collected the data. Jessica Fazendin, Erin Buczek, and Brenessa Lindeman contributed data by performing patient care and charting. Jonathan Dismukes performed the analysis and wrote the paper. All authors contributed to revision of the manuscript and final submission.

Disclosure
None.

rates were significantly higher in CND(+) patients; including transient hypocalcemia (36.1% versus 14.4%; $P < 0.001$), transient recurrent laryngeal nerve (RLN) injury (19.7% versus 7.0%; $P < 0.001$), and permanent RLN injury (3.3% versus 0.7%; $P < 0.001$).

Conclusions: The majority of patients at our institution with cN0 PTC did not undergo CND. This data suggests that CND was not associated with improvements in oncologic outcomes during the short-term follow-up period and led to increased postoperative morbidity. Therefore, we conclude that CND should not be routinely performed for patients with cN0 PTC.

Keywords

Papillary thyroid carcinoma; Central neck dissection; Thyroid surgery

Introduction

Thyroid cancer is the most common endocrine malignancy and due in part to advancements in imaging techniques, the incidence has been steadily rising.¹⁻⁵ Papillary thyroid carcinoma (PTC) is almost solely responsible for the large increase in thyroid cancer incidence,⁶ currently accounting for 80% to 90% of thyroid cancer diagnoses.⁷ PTC affects women at a much higher rate than men (3:1), which remains true even as detection rates increase.⁴ PTC carries a favorable long-term prognosis, with complete clinical remission achieved in 80% of patients following total thyroidectomy and radioiodine therapy.⁸ Although most PTC patients have an indolent course with recurrences occurring 20 to 30 years after initial treatment, morbidity from metastatic disease and locoregional recurrence remains an important issue.⁸ Between 20% to 40% of patients with PTC have regional nodal involvement at time of diagnosis, most of whom have clinically occult nodal disease, most commonly in the central neck compartment, that is only identified on final pathology.⁹ There is a positive correlation between nodal disease at diagnosis and disease recurrence, but no recognized impact on survival outcomes, which is likely a factor of the very low mortality rate of PTC and further highlights the need to balance the risk of operative complications with minimal oncologic benefits.¹⁰

For patients with clinically positive central neck nodal disease (cN1) at time of diagnosis (including radiographically positive nodal disease), there is general consensus that surgical therapy should include thyroidectomy with at least ipsilateral therapeutic central neck dissection (tCND). In contrast, for patients with clinically node-negative (cN0) disease, there remains a paucity of high-quality evidence to support definitive recommendations in the surgical management of clinically negative central nodes; thus, central neck dissection (CND) has been left to the surgeon's discretion.

Those who advocate for CND in cN0 PTC argue that regional nodal basin clearance reduces the risk of locoregional recurrence, especially with the modest rate of occult nodal disease in the central neck diagnosed on surgical pathology evaluation. Ducoudray *et al* and Chen L *et al* are among the limited studies to discuss the effectiveness of this intervention.^{9,11} The contrary argument centers on the prohibitively high surgical risks and long-term complications including permanent hypocalcemia and recurrent laryngeal nerve injury, which are higher in patients who undergo CND; these risks far outweigh the oncologic

benefits of CND.¹² The purpose of this study is to review our institution's operative experience with PTC over a 20 year period to evaluate the impact of CND on rate of locoregional and metastatic disease development in patients with cN0 PTC.

Materials and methods

A retrospective review of patients who underwent thyroid surgery for PTC at a single institution between 1998 to 2018 was performed using data from an institutional thyroid cancer registry and supplemental electronic medical records. All patients who underwent thyroidectomy with PTC confirmed on surgical pathology were included. Patients were stratified by whether or not they also underwent CND at time of thyroidectomy; identified as CND(+) or CND(-), respectively. Patients were further stratified by whether or not adjuvant radioactive iodine (RAI) therapy was received as part of the initial treatment regimen.

Operative technique for CND was performed utilizing well-defined anatomic boundaries as previously described and includes level VI nodes and associated fibrofatty tissue extending from carotid laterally to trachea medially, insertion of the RLN and/or inferior thyroid artery and/or cricoid cartilage cephalad to the thoracic inlet caudally.¹³ The decision to perform CND in cN0 PTC was made at the surgeon's discretion based on standard practice, clinical evaluation, and/or intraoperative findings of extrathyroidal extension or suspicious nodal appearance or architecture. All performed CNDs were ipsilateral.

Disease recurrence was indicated by an elevated postoperative thyroglobulin level and confirmed through FNA biopsy-proven recurrence of PTC. Distant metastases were diagnosed by imaging studies and/or biopsy for histologic confirmation. Pathology was reviewed.^{14,15} Hypocalcemia was defined as serum calcium < 8.4 mg/dL. Hypocalcemia was categorized as either "transient" or "permanent" based on symptom duration of less than 6 months or greater than 6 months postoperation, respectively. Recurrent laryngeal nerve injury was defined by voice change postoperatively and confirmed by direct laryngoscopy. Injury duration was categorized as either "transient" or "permanent" based on symptom duration of less than 12 months or greater than 12 months post-operation, respectively.

Standard, two-tailed statistical analyses, including but not limited to ANOVA, *t*-test, and chi-square, were performed using Microsoft Excel PivotTable and IBM SPSS software to determine statistical significance in patient outcomes and complications based on the difference in their surgical management. Statistical significance was set at a *p* value of < 0.05. IRB approval was obtained at the University of Alabama at Birmingham, and study participants acknowledged an IRB approved waiver of consent.

Results

Patient demographics

Between 1998 and 2018, 695 patients with PTC had thyroid surgery at our institution. Of these 695 patients, 492 (70.8%) had cN0 disease. The mean age was 50 ± 1 years and the majority were female (74.8%). Table 1 summarizes patient demographics and characteristics. The majority of the patients included were Caucasian (60.9%) with African

Americans representing 15.6%, Asian 1%, and other and/or unknown 22.5%. Of the 492 patients with cN0 PTC, only 61 patients (12.4%) underwent CND. When compared to patients who did not undergo CND, CND(+) patients had significantly higher preoperative TSH levels, 2.8 ± 0.8 versus 1.5 ± 0.2 mU/L ($P = 0.028$), and on average had a lower BMI, 29 ± 0.9 versus 31 ± 0.4 ($P = 0.024$).

Staging and operations

Utilizing the AJCC, eighth edition of TNM staging system for differentiated thyroid cancer, we then compared the cancer T stage and extent of thyroidectomy performed among CND(+) and CND(-) patients. There was no difference in the distribution of different T stages between CND(+) and CND(-) groups ($P = 0.35$; Table 2) or in total length of operative time ($P = 0.072$.) The majority of all cN0 PTC patients underwent total thyroidectomy (62.2%), with only 27% undergoing thyroid lobectomy. The majority of CND(+) patients underwent total thyroidectomy (88.5%) compared to only 51% of CND(-) patients ($P < 0.001$). Table 3 summarizes the type of surgery performed and operative times.

Patient outcomes

There was no significant difference in postoperative thyroglobulin levels ($P = 0.495$), development of recurrent or distant metastases ($P = 0.105$), or persistence of disease ($P = 0.069$) at time of follow-up (mean = 38 ± 3 months) between CND(+) versus CND(-) patients. This data is summarized in Table 4.

Adjuvant RAI therapy data was recorded for 336 (68%) of the 495 cN0 PTC patients. RAI was given to 28 (60%) of the 47 CND(+) patients and 147 (51%) of the 289 CND(-) patients with RAI data. Adjuvant RAI therapy was not significantly different ($P = 0.268$) between these patient populations. For all cN0 PTC patients who underwent adjuvant RAI therapy, CND(+) patients did not see a significant difference in recurrent or distant metastasis ($P = 0.855$) or persistent disease ($P = 0.614$) in comparison to CND(-) patients. However, in those that did not undergo adjuvant RAI therapy, CND(+) patients were found to have a significantly increased risk of recurrent or distant metastasis ($P < 0.001$) and persistent disease ($P = 0.009$) in comparison to CND(-) patients. This data is summarized in Table 5.

Of note, surgery-related morbidity was significantly higher in CND(+) cN0 PTC patients. Transient hypocalcemia occurred in 36.1% of CND(+) patients compared to 14.4% of CND(-) patients ($P < 0.001$), and the rate of intravenous calcium administration mirrored these results with 18% in CND(+) patients and 5% in CND(-) patients ($P < 0.001$). Transient RLN injury occurred in nearly 20% of those who had a CND performed versus only 7.0% of patients who did not undergo CND ($P < 0.001$). Rate of permanent RLN injury was also significant higher in CND(+) patients with 3.3% affected compared to 0.7% in CND(-) patients. Table 6 summarizes this data.

Discussion

These results demonstrate that patients with cN0 PTC who underwent total thyroidectomy with CND were found to have no difference in oncologic outcomes at a mean follow-up time

of 38 months when compared to those who underwent thyroidectomy alone. Additionally, CND(+) patients had higher rates of surgery-related complications including post-operative hypocalcemia and both permanent and transient RLN injury, which is a factor of parathyroid manipulation, devascularization or inadvertent resection within the CND specimen. Due to both increased complication risk and no disease-specific benefit observed during the duration of our follow-up, we suggest that CND should not be routinely performed in cN0 PTC patients without extensive physician-patient communication and shared decision making.

Similar studies investigating the role of CND for cN0 PTC have been performed but many have criticized for high complication rates or were found to have contradictory findings. There has been one prospective, randomized controlled trial¹⁶ which concluded that patients treated with CND did not show superior oncologic outcomes than those who did not undergo CND and were at no greater risk of RLN injury. However, they found that CND resulted in higher rates of permanent hypoparathyroidism. Another study¹¹ was conducted that reviewed literature for both prospective and retrospective cohort studies involving cN0 PTC patients who underwent CND. Outcomes were measured by locoregional recurrence (LRR) and the study tracked complications similar to ours – transient and/or permanent RLN injury and transient and/or permanent hypocalcemia. The findings showed that CND resulted in lower LRR while increasing rates of transient RLN injury, transient hypocalcemia, and permanent hypocalcemia. While our study found similar complication differences between the two study groups, we did not find any significant change in patient outcomes as defined by recurrence or distant metastases and persistent disease.

Our study has several important limitations to note. This was a retrospective, non-randomized trial that only sought to explore postoperative outcomes of a single defining variable: CND. Patients were not randomized, and groups were not equal in risk; therefore, those undergoing CND might have been those that were more likely to recur provided that CND was made purely on surgeon discretion and standard practice. This can limit the generalized applicability of our data. Similarly, our study population was developed from patients treated at a single institution which increases the possibility of selection bias and limits application of our findings. Our mean follow-up was only 38 months, which is likely too short of an interval to capture the expected future recurrences given the indolent nature of PTC. Additional long-term reanalysis will be necessary to confirm these findings.

While current ATA guidelines suggest CND in cN0 patients with T3/T4 tumors,^{17,18,19} many surgeons elect to perform CND in less extensive tumors due to intraoperative findings or patient preferences which are not well defined or captured in the database and limits the development of discrete, objective decision-making guidelines. Thus, it is reasonable to assume that the increased risk of complications could be due to the possibility that undocumented, aggressive clinical features and perioperative findings influenced the decision of surgeons to perform CND in cN0 patients in a more challenging operative environment.

Concerning the further stratification of the patient population based on adjuvant RAI therapy, there is no reason to believe that RAI therapy substantially alters the initial

interpretation of the CND outcome data as there remained no significant difference in oncologic outcomes between CND(+) and CND(-) cN0 patients with adjuvant RAI therapy. Nonetheless, our study did not track complications directly related to adjuvant RAI therapy that have been documented in outside studies;²⁰ thus, we cannot discuss the impact of CND on adjuvant RAI therapy.

In this study, more cN0 patients that underwent CND had total thyroidectomy despite no difference in t-staging. However, this was not due to a change in practice based upon revised ATA guidelines (2015) regarding indication for CND in cN0 PTC. To note, 12+ surgeons performed cervical endocrine operations at our institution during the study period, and thus, surgeon volume may account for higher complication rates amongst the patient populations.

Lastly, as previously described, hypocalcemia was defined as a post-surgical value of < 8.4 mg/dL. Beginning in 2015, postoperative parathyroid hormone (PTH) measurement was standard protocol by three of the primary surgeons in group with hypoparathyroidism treated with calcium or vitamin D administration. However, due to lack of consistent protocol amongst other surgeons and operations prior to 2015, there could be an under-recognition of transient postoperative hypoparathyroidism and/or hypocalcemia.

Conclusions

In patients with cN0 PTC, CND was not associated with improvements in oncologic outcomes during the short-term follow-up period and led to increased postoperative morbidity. Therefore, we conclude that CND should not be routinely performed for patients with cN0 PTC.

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Table 1 –

Demographics of patients with cN0^a papillary thyroid carcinoma.

Demographics	CND(+) ^b	CND(-) ^b	P value
N	61	431	
Gender			0.665
Male	23.0%	25.5%	
Female	77.1%	74.5%	
Race			0.761
American Indian / Alaskan Native	0%	0%	
Asian	0%	2%	
Black / African American	11%	16%	
White / Caucasian	70%	63%	
Other / Unknown	18%	19%	
Age (years; at time of surgery)			0.619
Mean	50	51	
Std. Error of Mean	2	1	
Minimum	17	18	
Maximum	83	84	
BMI ^c (day of surgery)			0.024
Mean	29	31	
Std. Error of Mean	1	0	

^a cN0 = no clinically-evident nodal metastasis

^b CND = central neck dissection

^c BMI = body mass index

Table 2 –Disease staging of patients with cN0^a papillary thyroid carcinoma.

Disease Staging	CND(+) ^b	CND(-) ^b	P value
T-stage			0.347
T1a	36%	45%	
T1b	25%	17%	
T2	11%	10%	
T3	13%	11%	
T4a	10%	6%	
Tx (cannot be assessed)	2%	2%	

^acN0 = no clinically-evident nodal metastasis^bCND = central neck dissection

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Table 3 –

Type and duration of surgery of patients with cN0^a papillary thyroid carcinoma.

Surgical Data	CND(+) ^b	CND(-) ^b	P value
Type of Surgery			< 0.001
Total Thyroidectomy	89%	51%	
Hemithyroidectomy	5%	27%	
Isthmusectomy	2%	0%	
Tumor Debulking	0%	0%	
Other	5%	2%	
Unknown	0%	20%	
Duration of Surgery (minutes)			0.072
Mean	113	90	
Std. Error of Mean	17	4	
Minimum	48	37	
Maximum	470	458	

^a cN0 = no clinically-evident nodal metastasis

^b CND = central neck dissection

Table 4 –

Post operation data for patients with cN0^a papillary thyroid carcinoma.

Post operation Data	CND(+) ^b	CND(-) ^b	P value
Follow-up Thyroglobulin (ng/mL)			0.495
Mean	0.565	10.63	
Std. Error of Mean	0.88	76.4	
Evidence of Recurrence or Distant Metastasis	8%	4%	0.105
Evidence of Persistent Disease	8%	5%	0.069
Mortality within 30 days of Surgery	0%	0%	

^a cN0 = no clinically-evident nodal metastasis

^b CND = central neck dissection

Table 5 –

RAI^g Therapy and outcomes for patients with cN0^g papillary thyroid carcinoma.

Post operation Data	CND(+) ^c	CND(-) ^c	P value
Adjuvant RAI Therapy - Given	46%	34%	0.268
Evidence of Recurrence or Distant Metastasis	7%	8%	0.855
Evidence of Persistent Disease	7%	10%	0.614
Adjuvant RAI Therapy - Not Given	31%	33%	
Evidence of Recurrence or Distant Metastasis	16%	1%	< 0.001
Evidence of Persistent Disease	16%	2%	0.009
Adjuvant RAI Therapy - Unknown	23%	33%	

^aRAI = radioactive iodine

^bcN0 = no clinically-evident nodal metastasis

^cCND = central neck dissection

Table 6 –

Post operation complications for patients with cN0^a papillary thyroid carcinoma.

Post operation Complications	CND(+) ^b	CND(-) ^b	P value
Transient Hypocalcemia	36.07%	14.59%	< 0.001
Intravenous Calcium Administration	18.03%	5.10%	< 0.001
Recurrent Laryngeal Nerve Injury			< 0.001
Transient (< 6 months)	19.67%	6.96%	
Permanent (> 6 months)	3.28%	0.70%	

^a cN0 = no clinically-evident nodal metastasis

^b CND = central neck dissection