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Central Lymph Node Dissection In Patients With Papillary Thyroid Cancer: A Population Level Analysis Of 14257 Cases

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Central Lymph Node Dissection in Patients with Papillary Thyroid Cancer: A Population Level Analysis of 14,257 Cases

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ABSTRACT

CENTRAL LYMPH NODE DISSECTION IN PATIENTS WITH PAPILLARY THYROID CANCER: A POPULATION LEVEL ANALYSIS OF 14,257 CASES. Chineme Enyioha, Sanziana Roman and Julie Ann Sosa. Department of Surgery, Yale School of Medicine, New Haven, CT.

The role of prophylactic central lymph node dissection (CLND) in patients with differentiated thyroid cancer has been controversial. This study analyzes the impact of patient demographic factors and tumor size on surgery with CLND in patients with papillary thyroid cancer (PTC) in the U.S.

All patients ≥18 years with PTC and follicular variant-PTC, who underwent thyroidectomy with or without CLND in SEER, 2004-08, were included. Bivariate and multivariate analyses were performed to determine effects of patient demographic and clinical characteristics on the likelihood of undergoing CLND.

Of 14,257 patients in the study, 80.3% were women, 84.3% white, and the average age was 50.1 years. 79.6% had a total thyroidectomy, and 37.1% had a CLND. Bivariate analysis revealed that patients who were older, black, and from the South were less likely to undergo CLND (all p<. 001). Patients with T1 tumors were least likely to undergo CLND (36.6% compared to 57.2% of T4 tumors, p<. 01). 32.1% of patients with microPTC (≤1 cm) and 42.5% of patients with tumors 1-2 cm had CLND, of which 3.6% (microPTC) and 8.8% (tumors 1-2cm) had positive nodes compared to 34.2% of patients with T4 tumors. From 2004 to 2008, there was an 18.3% increase in overall use of

CLND. On multivariate analysis, younger age, female gender, white race, and Northeast region were independently associated with an increased likelihood of undergoing CLND. While the use of CLND has increased over time even in patients with T1 tumors, several demographic factors remain associated with lower likelihood of receiving CLND. This variation in practice suggests potential disparity in access and quality of surgical care for PTC in the U.S.

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Introduction

Thyroid cancer is known to be one of the most common malignancies in young women. It represents 1% of all cancers in the United States and it is the most common endocrine malignancy, besides ovarian cancer (1-3). The incidence of thyroid cancer has continued to increase. This trend began in the 1940s and has been observed in the United States, Canada, and some European countries, increasing from a rate of 3.6 per 100,000 in 1973 to 16.3 per 100,000 women and 5.6 per 100,000 men by 2008 (4-6). Over the last two decades, the annual incidence of thyroid cancer in the United States has doubled (7). In 2010, over 40,000 people were newly diagnosed with thyroid cancer and about 1600 deaths were recorded in the United States alone (1, 4, 6). This trend has been noted for differentiated thyroid cancer, including papillary, follicular, and hurthle cell subtypes, which together currently account for more than 90% of all thyroid cancers and papillary thyroid cancer accounting for most of the increased incidence (2, 3).

Among all differentiated thyroid cancers, papillary thyroid cancer is the most common (8, 9) and some studies suggest that its incidence varies by gender and ethnicity. Eneworld et al analyzed data from the Surveillance, Epidemiology and End Results (SEER) program and estimated that papillary thyroid cancer incidence is higher among females and non-Hispanic whites (9). Mitchell et al recorded similar findings; with a 7.8 fold increase and 6.6 fold increase in the incidence of papillary thyroid cancer reported over a two-year period in women and men respectively. There was also an increased rate of papillary thyroid cancer in whites compared to blacks (8). The reason for a higher incidence in women is unclear. High estrogen levels have been associated with increased proliferation of the thyroid gland although no study has linked high estrogen levels with thyroid cancer (10, 11). Further evaluation of incidence in the same study showed that regional variations also exist in the incidence of thyroid cancer. The northern and southern regions of the United States have a higher incidence rate while a decrease has been observed in the Midwest. Thyroid cancer incidence has remained stable in the West (3).

A higher incidence of papillary thyroid cancer has also been noted in older patients. A study by Hughes and colleagues revealed that up until 1999, the incidence of papillary thyroid carcinoma was higher in patients younger than 45 years of age especially with tumors less than 1cm. From 1999, a shift occurred with a higher incidence of micropapillary thyroid cancer in patients 45 years or older; accounting for over 61% of all cases (12). Eneworld and colleagues also showed that even though the increase in incidence occurred at a higher rate in patients between the ages of 40 and 59 years, the increase in incidence was steeper in patients between ages 60 to 79 years (9).

With regards to pathologic characteristics of thyroid cancer tumors, all ethnic groups, except for non-Hispanic white women, have a higher number of large tumors rather than small tumors (4). Older patients are more likely to have more than one primary tumor, larger tumors and present at an advanced stage of disease compared to younger patients (2).

Controversies surround proposed etiologies for this observed increasing incidence. The major risk factor for thyroid cancer is radiation exposure. Radiation was used in the past for treatment of benign head and neck conditions, especially in children, between the years 1920 and 1950 (4). Studies have shown that there is a high rate of papillary thyroid cancer among the irradiated population (13). Ronkers et al showed that in patients with other primary malignancies treated with external beam radiation, there was a 29% increased risk of thyroid cancer compared with the control group (14).

More recently, there have been suggestions that subclinical tumors are now better detected with the use of fine-needle biopsy, ultrasound and computerized tomography (CT) scan, which may lead to detection of subclinical cancers with subsequent observed increase in thyroid cancer incidence. This theory has been supported by the fact that over 80 % of thyroid cancer tumors detected are less than 2 cm in size (5,15), especially with the increased use of diagnostic imaging. For example, about 3 million CT scans were performed in the United States in 1980. In 2006, that number increased to approximately 67 million (16, 17). The recognition of incidentalomas in surgical specimens especially with the use of near or total thyroidectomy for benign thyroid disease has also been given as an explanation for the increased incidence. Since routine biopsy of nodules less than 1cm is not recommended except if there are concerning features as stated in the ATA guidelines, some microcarcinomas are only recognized during histological analysis of surgical specimens (18). Others have suggested that the increased incidence is not limited to subclinical tumors but cuts across tumors of different sizes. Infact, if the increase in incidence is solely a result of increased detection of early-stage tumors, one will expect a decline in the rate of incidence of larger and more advanced tumors but that is not the case. In a study designed to investigate the trend of thyroid cancer incidence, Chen et al concluded that the increase in incidence is not exclusively due to detection. There is a true increase in the number of tumors across sizes, including tumors greater than 4cm and tumors with metastasis (19).

The following have also been suspected as risk factors for thyroid cancer: increased body mass index (BMI), fertility drug use and changes in reproductive patterns (20-23). Thyroid stimulating hormone (TSH) regulates the thyroid gland and an increase in TSH level may be associated with excessive proliferation, and lead to a malignancy. Exposure to certain environmental chemical such as polychlorinated biphenyls (PCB) has been positively associated with elevated TSH and hence, development of cancer of the thyroid (24, 25). Some studies support high iodine diets and goitrogenic chemicals found in food materials as risk factors for thyroid nodules and thyroid cancer, while other studies have refuted these findings (26).

Thyroidectomy with or without radioactive iodine administration is considered standard of care for differentiated thyroid cancer, and together they are associated with excellent short and long-term outcomes. Still, up to 20% of patients may develop recurrent disease or distant metastases (27). Metastasis tends to occur first to central neck lymph nodes and then progress to the lateral neck lymph nodes (28). Hematologic spread to lungs, bones and liver may occur in certain types thyroid cancers. Factors associated with recurrence or worse prognosis include age over 45 years, male gender, extrathyroidal tumor extension, large tumor size, extent of lymph node metastases, and presence of distant metastases at the time of diagnosis. In particular, factors associated with central lymph node involvement include age younger than 45 years, tumor size and extrathyroidal involvement (29, 30).

The American Thyroid Association (ATA) recommends thyroidectomy with central compartment lymph node dissection (CLND) for patients with differentiated thyroid cancer and clinically positive central compartment metastatic lymph nodes, and for those patients at high risk for occult lymph node metastases, such as patients with T3 and T4 tumors. The indications for therapeutic CLND are clear and clinical involvement of central nodes can be detected by ultrasonography. The ideal ultrasound procedure should include lymph node compartments of levels II to VI. Lymph node involvement detected by ultrasound can be confirmed by ultrasound-guided fine needle aspiration (28).

The role of prophylactic CLND in patients with smaller tumors and with no clinically evident central lymph node metastasis remains controversial, as there is a paucity of evidence for overall reduced recurrence rates or improved survival. In addition, CLND has been associated with an increased risk of surgical complications such as hypoparathyroidism and recurrent laryngeal nerve injury (28, 31). For the purposes of consistency with terminology, prophylactic CLND refers to CLND in the absence of detectable nodal metastasis either clinically or by imaging while therapeutic CLND suggests CLND after detection of nodal metastasis pre-operatively, intra-operatively or by imaging.

Several studies have assessed the rates of complications and survival among patients who underwent a thyroidectomy with and without CLND (32-34). These studies have been mostly institutional series, often reporting the outcomes of high-volume and experienced thyroid surgeons. Access to high-volume surgeons is limited, especially for certain vulnerable patient populations, such as the elderly, ethnic and racial minorities, and those living in geographic areas where there are relatively few surgeons, such as in the South and rural areas (29). For these reasons, institutional studies may not be applicable to the general population. In addition, it appears unlikely that a randomized controlled trial can be performed, since the number of patients needed to have adequate statistical power to detect clinical benefit from CLND would be prohibitive (1). To our knowledge, there has been no study assessing the influence of patient demographic factors such as age, race/ethnicity, gender, and geographic region of the U.S. on the likelihood of undergoing CLND in addition to thyroidectomy for differentiated thyroid cancer.

Statement of Purpose, Specific Hypotheses, and Specific Aim

The aim of our study was to analyze the impact of patient demographic factors and tumor size on the likelihood of undergoing thyroidectomy with CLND for papillary thyroid cancer in the U.S. Due to the current controversial nature of prophylactic central neck dissection, we hypothesized that the use of CLND has increased in recent years across the United States but disparities in access to standard of care persist. Older patients, male patients and patients of minority ethnic groups are less likely to have central neck dissection. The result of this study will lead to a better understanding of factors that may influence the incorporation of central neck dissection in the treatment of patients with differentiated thyroid cancer.

Methods

Note: The author performed all data analysis described below.

Data sources and study subjects

The Surveillance, Epidemiology, and End Results (SEER) database was used to obtain data on patients with papillary thyroid cancer from 2004 to 2008. SEER is a population-based, comprehensive cancer registry that receives support from the National Cancer Institute and Centers for Disease Control and Prevention. It has been in existence since 1973 and has been used for numerous research projects on cancer of different kinds. The SEER program regularly collects information on patient demographics, primary characteristics of neoplasms such as tumor size, metastasis, course of treatment except chemotherapy, and patient survival. We conducted a retrospective, population based cohort analysis of adult patients ≥18 years diagnosed with papillary thyroid cancer (International Classification of Diseases for Oncology [ICD-O] histology codes 8050/3, 8341, 8342, 8343, 8344, and follicular variant PTC code 8340) in the SEER 17 regions. Areas that make up SEER 17 regions include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Alaska, rural Georgia, greater California, Kentucky, Louisiana and New Jersey (SEER). These regions represent approximately 26% of the total U.S. population (35).

All patients with histologically confirmed papillary thyroid cancer between 2004 and 2008 were identified and of patients identified, only those with information on central lymph node status were included. Patients with no central lymph node involvement and those with missing data on "lymph nodes examined" were excluded. Only patients actively followed by SEER were included in analyses; patients were excluded if they were diagnosed based on autopsy or death certificate.

Patient demographic variables of interest were gender, race (White, Black, Asian-Pacific Islander, and other), age at diagnosis (18-44, 45-64, 65-79, and ≥80 years), year of diagnosis (2004, 2005, 2006, 2007, and 2008), and geographic location (West, Midwest, South, and Northeast). Clinical variables included type of surgical procedure performed (lobectomy/isthmusectomy and total/near total thyroidectomy) and survival status at the end of the study period. Pathologic information included tumor size, focality (solitary or multifocal), extension (intrathyroidal vs. extrathyroidal), number of metastatic lymph nodes removed, and PTC stage at diagnosis.

SEER provides the largest dimension of the primary tumor as the tumor size. Extrathyroidal extension was defined as tumor invasion beyond the thyroid capsule. Tumor size and extension were combined and subdivided into categories that correlate with the T staging system of the 2002 American Joint Commission on Cancer's tumor, node and metastasis (TNM) system, with T1 tumors accounting for tumors 2cm of less in size and intrathyroidal. T1 was further subdivided into T1a and T1b, with T1a representing tumors limited to the thyroid and less than 1cm while T1b represents intrathyroidal tumors between 1-2 cm in size. T2 tumors represent tumors greater than 2cm but less than 4cm in size and limited to the thyroid. T3 tumors have their greatest dimension 4cm or more, and are limited to the thyroid or any tumor with minimal extrathyroidal involvement such as involvement of the perithyroid tissue and sternothyroid muscle. T4 tumors are represented by any sized tumor that extends outside of the thyroid capsule and involves the trachea, larynx, esophagus and surrounding subcutaneous tissues (36). The number of lymph nodes examined was classified as none, 1, 2-5, >5.

Statistical Analysis

Baseline characteristics of patients were described with summary statistics. Bivariate analysis of the independent variables and outcomes of interest was done with chi-square analysis. A time trend analysis of CLND utilization based on tumor stage was performed for all years under study. Multivariate logistic regression was used to adjust for patient demographic and clinical characteristics. In the multivariate analysis, the strength of association between independent variables and outcomes of interest was expressed as an odds ratio (OR) for the likelihood of undergoing a CLND, along with 95% confidence intervals (95% CIs). Statistical significance for all tests used was set at a probability (p) value of $\leq .05$. Survival time was calculated as the time (in years) from diagnosis until death, date last known to be alive, or December 31, 2008, whichever came first. Overall and cancer-specific survival rates were calculated. Data analyses and management were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL). Because SEER is a public database with no personal identifying information, this study was granted an exemption from our institutional review board.

Results

Summary Statistics

Between 2004 and 2008, a total of 14,257 adults with papillary thyroid cancer had surgery with information regarding central compartment lymph nodes, equating to an estimation of over 54000 cases in the United States over the four-year period. Most patients were white (84.3%) and female (80.3%) (Table 1). The average age was 50.1 years with 46.7% of the total population between the ages of 45 and 64 years, and 2.2 % of patients were 80 years of age or older. Patients from the West made up 48.9% of the study population and only 8.6% of patients were from the Midwest. T1 tumors represented 71.2% of tumors studied while T2, T3 and T4 were made up of 19.4%, 7.0 % and 2.4% of the tumors respectively. 87.7% of patients had only one primary tumor and 98.7% had no metastases. Majority of patients underwent total thyroidectomy (79.6%), and over a third (37.1%) underwent a CLND.

Bivariate Analysis

Although older patients were more likely than younger patients to have T4 tumors (6.1% aged ≥80 years vs. 1.5% aged 18-44 years, $p<0.001$), older patients were less likely to have CLND compared to younger ones (25.1% aged ≥80 years vs. 43.4 % aged 18-44 years, p<. 001). White patients had an increased likelihood of receiving CLND compared to blacks (38.3% vs. 21.5%, p< .001). Patients in the South were least likely to undergo a CLND based on geographic region (29.7%, p<. 001) whereas patient in the Northeast had the highest likelihood (41.8%, p <. 001). (Table 2)

Patients with more advanced stage tumors had an increased likelihood of undergoing CLND as part of their treatment compared to patients with smaller tumors (57.2% for T4 tumors vs. 36.6% for T1 tumors, p<. 001). Of the patients with microcarcinomas (tumor <1cm – T1a) and tumors 1-2 cm (T1b), 32.1% and 42.5% underwent CLND respectively; 3.6% of patients with T1a tumors and 8.8% of patients with T1b tumors had positive nodes compared to 34.2% of patients with T4 tumors. Patients who underwent a total thyroidectomy were more likely to undergo simultaneous CLND compared to patients undergoing a lobectomy (40.6% for thyroidectomy vs. 23.1% for lobectomy, p<. 001)

Time Trend of Utilization

Table 3 shows the increasing utilization of CLND by T stage over the study period. Over five years, there was an 18.3% overall increase in CLND, with the greatest increase seen in patients with T1 tumors (23.2%). Patients with microcarcinomas also were noted to have a significant increase in utilization of CLND (28.1% in 2004 vs. 34.2 % in 2008, p<. 001). Utilization of CLND increased by 5.4% and 44.1% in patients with T2 and T3 tumors respectively. Although the least increase was seen in patients with T4 tumors at 2.53%, a greater percentage of them underwent CLND across all four years compared to patients with less-advanced stages tumors.

Number of Lymph Nodes Examined

There was no difference in the total number of lymph nodes examined based on patient age, race, geographic location, or the year of their thyroid cancer diagnosis. The average total number of lymph nodes removed was four. Patients with stage T4 tumors had the largest number of lymph nodes removed, with an average of 8 lymph nodes while those with T1 tumors had an average of 4 lymph nodes removed. (Table 4)

Multivariate Analysis

Patient characteristics independently associated with an increased likelihood of undergoing CLND included youth (age 18-44 years), female gender, white race, and Northeast region. (Figure 1) Patients aged ≥ 80 years, who were black, or lived in the South had the lowest likelihood of undergoing CLND ($p < .001$).

At the end of the study period, 98.1% of patients were still alive, with thyroid cancer-specific mortality reported for only 33 patients (0.2%).

Discussion

To our knowledge, this is the first population-level study to examine the impact of patient demographic and pathologic factors on surgery with CLND in patients with papillary thyroid cancer in the U.S. The study demonstrates that patients who are younger, female, white, located in the Northeast, and who have T4 tumors have an increased likelihood of undergoing CLND. Patients who are older, male, black, and living in the South are less likely to undergo CLND for PTC.

Time trend analysis indicates an increase in utilization of CLND over time, but the revised ATA guidelines for thyroid nodules and differentiated thyroid cancer published in 2009 still do not appear to be followed consistently. Only a third of the eligible patients in our study underwent CLND despite the ATA recommendation, which states: "prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)" (37). Even with set treatment guidelines, questions about degree of adherence among surgeons continue to arise.

A recent study by Famakinwa et al, analyzed compliance with the 2006 ATA guidelines for differentiated thyroid cancer treatment, and demonstrated significant variations in practice patterns across the United States. For surgical treatment, the ATA recommendation is a near total or total thyroidectomy for most tumors except for isolated, intrathyroidal carcinomas with no metastasis, for which a thyroid lobectomy is sufficient. Famakinwa and colleagues showed that 24% of patients in the study were not treated according to guidelines, including 8% who met the criteria for surgery but received no surgical treatment. Radioactive iodide remnant ablation (RAI) was recommended by the ATA for patients with stages III and IV differentiated thyroid cancer. RAI was also recommended for patients with stage II disease and younger than 45 years of age, for most patients with stage II disease but greater than or equal to 45 years old, in addition to a few stage I disease patients such as those with nodal metastasis, multifocal disease, vascular involvement or aggressive histologies. Of over 10,000 patients who met RAI criteria, only 62% overall compliance was observed. Among patients with stage III differentiated thyroid cancer, only 61% of them received RAI and 64% of patients with stage IV disease received it.

For central neck dissection, at the time, the ATA recommended that it should be performed in patients with papillary thyroid cancer over 4 cm and Hurtle cell carcinoma. Patients with follicular cancer and patients receiving RAI could be treated with a near total or total thyroidectomy without central neck dissection. Only 71% of the population that met the treatment requirement was treated in accordance with the guidelines, with 15% receiving CLND alone and 25% receiving CLND plus RAI (38). The level of compliance with the guidelines in this study was higher than that observed in our study and it may be partly because of the inclusion of all types of differentiated thyroid cancer. The study was also done with the 2006 ATA guidelines, which is slightly different from the 2009 guidelines used in our study. There were also variations in surgical treatment and use of RAI according to age, race and geographical location, all of which will be discussed later.

Although the recommendation is clear in its statements, the extent of lymphadenectomy that qualifies as CLND remains unclear and has been somewhat controversial. More recently, clear description of the surgical anatomy of the central neck has been described. The surgical boundaries include superiorly the hyoid bone, laterally the carotid arteries; posteriorly the deep layer of the cervical fascia; and anteriorly the superficial layer of the cervical fascia. The innominate artery and vein make up the inferior border. Structures in the central neck besides the thyroid and lymph nodes include the trachea, esophagus, larynx, blood vessels of the thyroid and nerves such as the superior and recurrent laryngeal nerve, external branch of the superior laryngeal nerve and the parathyroid glands. The central lymph nodes most commonly involved in thyroid cancer are the right and left para-tracheal nodes, the pre-laryngeal and pre-tracheal nodes. The posterior retropharyngeal and retro-esophageal nodes are not usually involved.

In describing the extent of CLND, Carty and colleagues mentioned that the pre-laryngeal, pre-tracheal and not less than one para-tracheal lymph node group should be removed at the minimum. The dissection of the recurrent laryngeal nerve should be done in an atraumatic manner. Both the superior parathyroid gland and its primary blood supply should be preserved. The inferior parathyroid gland and its blood supply can be reflected. If the parathyroid glands are devascularized, auto-transplantation can take place (39).

In our study, only 6% of patients in the CLND group had more than 5 lymph nodes removed. The study demonstrates that a minority of patients likely undergoes an adequate CLND; rather, many may have isolated resection of selected lymph nodes or incidental lymph node removal from the central compartment. The excision of only clinically involved lymph nodes instead of a whole nodal group does not qualify as a CLND, and may lead to a higher risk of persistent and recurrent disease, since all pathologic lymph nodes may not be extirpated based only on their gross appearance (37). Some other studies have even suggested that level VII nodes in the superior mediastinum should be included in CLND because of the persistence of disease at this site even after central dissection (28).

The case of ipsilateral versus bilateral central neck dissection as more beneficial for papillary thyroid cancer has also been in question. Ipsilateral CLND includes the removal of one paratracheal nodal basin in addition to pretracheal and prelaryngeal nodes on the side where the tumor is located. Bilateral CLND is referred to the removal of both paratracheal nodal basins along with the removal of the pretracheal and prelaryngeal nodal groups (39). Moo and colleagues carried out a study to analyze the sufficiency of ipsilateral CLND for the detection and removal of positive lymph nodes. Patients included in the study were patients with papillary thyroid cancer who underwent either ipsilateral or bilateral CLND prophylactically. While a total of 47 out of the 104 patients who underwent bilateral CLND had positive lymph node involvement, 31% of them had tumors greater than 1 cm and contralateral lymph node involvement. Patients with tumors less than 1cm had no lymph node involvement. Their results suggest that for tumors less than 1cm in size, unilateral CLND may be sufficient but patients with tumors greater than 1 cm will benefit from bilateral CLND. Of all the parathyroid glands found in the central neck specimen, 60% of them were from the side contralateral to the tumor, suggesting that there may be a higher incidence of hypocalcemia with bilateral CLND (40).

Some studies have also looked into risk factors that may be associated with contralateral lymph node involvement in patients with papillary thyroid cancer. Koo et al conducted a prospective study to investigate the risk factors involved with occult ipsilateral and contralateral lymph node involvement in the central neck of patients with unilateral papillary thyroid cancer. A total of 111 patients were included in the study and univariate analysis showed that having a tumor with a maximum diameter greater than 1 cm was a risk factor. Tumors with lymphovascular involvement, male gender, and high-risk MACIS (metastases, age, completeness of resection, invasion, and size) score were also found to be risk factors. In multivariate analysis, tumor size was found to be an independent predictor of ipsilateral lymph node involvement which was, in turn, an independent risk factor for contralateral neck involvement (41). The results of this study support Moo's findings and support bilateral CLND as beneficial for patients with tumor sizes greater than 1cm. Other studies, however, have shown opposing results and maintain that ipsilateral CLND is sufficient regardless of tumor size (42). Our study focused more on the number of lymph nodes removed and did not distinguish between ipsilateral and bilateral CLND.

There are conflicting studies in the literature regarding the benefits and disadvantages of prophylactic CLND. With regards to the disadvantages, the close proximity of the recurrent laryngeal nerve places it at risk for injury during central neck dissection. Most importantly, the parathyroid glands share the same blood supply as some lymph nodes, and are often confused with lymph nodes, and thereby at risk for inadvertent devascularization or resection (32). CLND has been shown to increase the risk of hypoparathyroidism, both temporary and permanent, as well as the risk of recurrent laryngeal nerve palsy. While some studies have demonstrated increased risks of injury to the recurrent laryngeal nerve and postoperative hypoparathyroidism compared to thyroidectomy alone (30, 32, 43, 44), other studies have suggested that CLND in the hands of experienced surgeons does not necessarily increase the risk of complications (33). For instance, Bozec and colleagues, in a retrospective study to evaluate morbidity associated with central neck dissection, found that post-operative hypocalcemia occurred in 28% of the study population, with 13 % developing permanent hypoparathyroidism. Only 4.8% of patients without CLND developed hypocalcemia. No statistically significant association between CLND and recurrent laryngeal nerve injury was found (30). In another study, Rosenbaum et al collected data on patients from a single institution who were treated for papillary thyroid cancer. 20% of the 110 patients in the study had CLND with initial surgical therapy. Transient hypocalcemia occurred in 86% of patients who underwent CLND compared with 61% of those with thyroidectomy alone. The only patient who developed permanent hypoparathyroidism had CLND (45). On the other hand, Shindo et al conducted a retrospective study and compared complication rates in patients who underwent thyroidectomy with and without CLND. They found that the both groups had a similar incidence rate of permanent recurrent laryngeal nerve injury and similar incidence of permanent hypocalcemia. (33).

For patients who did not previously have a CLND and develop a recurrence of disease, reoperative CLND is usually done. Some argue that complication rates are higher with reoperative CLND compared with initial dissection especially with distorted neck anatomy and scarring after thyroidectomy, and therefore, initial CLND is more beneficial (46). However, Shen and colleagues carried out a study to compare complication rates between initial and reoperative CLND. 106 out of 295 cases involved in the study were reoperations. Their result showed that patients with initial CLND had a higher rate of transient hypocalcemia compared to patients with reoperation. 41% of patients with initial CLND had transient hypocalcemia while only 23.6% of the reoperative cases developed this complication. For other complications such as neck hematoma, transient and permanent hoarseness, and permanent hypoparathyroidism, both groups had similar rates. (32)

There is also controversy regarding the benefits of prophylactic CLND in terms of disease recurrence and survival benefit, with some authors maintaining that CLND reduces local recurrence rates of papillary thyroid cancer, and others showing minimal to no benefit overall (8,31,47). For example, Shen's study mentioned above showed a similar rate of papillary thyroid cancer recurrence in both patients who underwent initial CLND and those with reoperative CLND. Studies such as that done by Zuniga and colleagues support the idea that prophylactic CLND may not have significant benefit. In a cohort study by Zuniga's group, data were collected on patients who were treated for stage N0 papillary thyroid cancer. Of the 266 patients in the study, 136 of them had prophylactic neck dissection and over 90% of all patients had a follow-up time of more than two years. 82.3% of patients who underwent prophylactic CLND had lymph node metastasis. 5-year disease free survival in patients with CLND was 88.2% and 85.6 % for those who did not undergo CLND (34).

In many cases, the goal of therapy is to have an undetectable thyroglobulin level after surgery and for many patients; an elevated thyroglobulin level after thyroidectomy and radioactive iodine ablation is an indication of recurrence. Some studies have suggested that lower thyroglobulin level is associated with lymph node dissection and an inverse relationship exists between thyroglobulin levels and the extent of CLND (42,48). In addition, although cervical ultrasonography has a high specificity and positive predictive value for detecting lymph node metastasis in the central neck, the sensitivity is low (49). This allows for clinically involved lymph nodes to go undetected many times and leads to persistent disease. Hence, an indication of the possible benefit of prophylactic CLND.

Several opposing results such as those mentioned above have only heightened the controversy over prophylactic CLND. Many of these studies are retrospective in nature and this serves as a limitation to their ability to sufficiently predict clinical outcomes. To test the possibility of overcoming this limitation, Carling and colleagues analyzed the feasibility of a prospective randomized trial to compare the prophylactic CLND and an absence of the procedure in patients with cNO papillary thyroid cancer. According to that analysis, with the assumption of a 7 – year study period, a 4 –year enrollment period, a minimum and maximum follow-up of 3 and 5 years respectively, and primary outcome of persistent, recurrent or metastatic disease after CLND, over 5000 patients will be required to participate in the study to realize a statistical power of 80%. Thousands of patients will need to be enrolled for significant difference in the rates of complications to be identified especially with the low rates of morbidity associated with papillary thyroid cancer. The cost for such a study is estimated to be about $20 million. In addition, because of the large number of patients that will be needed to achieve statistically significant results, it will need to be a multi-institutional study with the participation of many surgeons and other physicians and this will be associated with several challenges, making such a study not feasible. (1)

Our study showed that vulnerable populations are less likely to undergo CLND. We found that older age was negatively associated with undergoing a CLND. This was revealed even though elderly patients tend to present with more aggressive disease secondary to less timely evaluation of their complaints or symptoms of thyroid cancer. They have been shown to have larger tumors, extra thyroidal and vascular involvement (2). Our finding is similar to that of Famakinwa et al who demonstrated a low compliance with the guidelines for lymphadenectomy and RAI in older patients. There was about a 20% difference in adherence between older and younger patients. Park et al also conducted a retrospective cohort study to assess patterns of treatment in elderly patients. The study showed that older patients with differentiated thyroid cancer receive less aggressive treatment compared with younger patients. Although patients who age 65 years or older had larger tumors and worse disease, only 74% of them had a total thyroidectomy compared with 80% of younger patients. Older patients were also less likely to have RAI treatment, with 47% of them receiving RAI compared with 54% of younger patients (2). Another study by Bilimoria et al showed that patients older than 65 years were 35% less likely to have a total thyroidectomy compared with patients younger than 45 years (18). In a similar way, a study by Sosa and colleagues showed that age is inversely proportional to getting a thyroidectomy (50). As demonstrated by these various studies, older patients are less likely to receive standard treatment of care.

Numerous other studies have shown age-related variations in treatment for other types of health concerns. For example, with breast cancer, the second leading cause of cancer death in women, treatment varies by age. In a study of stage I and II breast cancer treatment by August and colleagues, an analysis of age-related differences in treatment was carried out. Only 59 out of 77 patients who were older than or equal to 65 year of age received surgery including axillary dissection compared with 50 out of 51 patients in the younger age group. As little as 7% of older patients received chemotherapy (51). The higher rate of co-morbidity in older women was cited as a possible reason for some patients receiving sub-standard care but it was not applicable to all patients involved. Treatment variation by age has also been reported in patients with endometrial cancer, where Ahmed et al, in determining the extent of surgery in older women with endometrial cancer, found an inverse relation between age and the likelihood of receiving surgery. Only 75% of women older than 84 years received the recommended surgical treatment, while in the youngest group of ages 50-64 years, 96% of the women underwent surgery (52). No reasons were proposed for the disparity noted the study.

Earlier studies have revealed that older patients may have a significant benefit from resection of metastatic lymph nodes because disease recurrence is more common in elderly patients shortly after initial treatment (53, 54). It has been suggested also that tumor cells of older patients may harbor biological changes, which may make radioactive iodine therapy (RAI) less effective. Schlumberger and colleagues conducted a study showing that while uptake of RAI at metastatic sites in patients younger than 40 years occurred in 90% of patients, only 53% of patients over age 40 years had adequate RAI uptake. The capacity for tumors to take up iodine falls with increasing age (55, 56). Treatment with RAI may not be sufficient especially in older patients, thus making CLND in this patient population even more important.

CLND may lead to more accurate disease staging, improve prognosis for patients at high risk for extensive disease especially among patients over 45 years of age who have an increased risk of nodal metastasis. A retrospective study conducted by Shindo et al compared the incidence of central lymph node involvement in patients younger than age 45 years to patients older than 45 years undergoing thyroidectomy for PTC; they demonstrated that 28% of tumors in the older patients would have been under-staged had CLND not been performed (53).

Surgery in elderly patients does appear to come with increased associated morbidity and may explain the age-related variation in treatment (57, 58). Sosa et al, in a study of more than 22,000 patients who underwent thyroidectomy for thyroid cancer, showed that complication rates for patients aged ≥80 years increased by 34% compared to patients aged 65-79 years. Length of hospitalization was longer by 60% for patients 80 years of age and above compared with patients between 65 and 79 years. Higher cost of treatment was also associated with older patients with almost a $2000 difference (50). In another study of patients with adrenalectomy, Kazaure and colleagues showed that patients older than 70 years of age had more complications than patients less than 60 years; 22.6% vs. 14.1% respectively. Patients who were 70 years or older also had increased length of hospital stay and mortality compared with younger patients (57). Thomas et al, who studied outcomes in patients undergoing parathyroidectomy (59), noted a similar result.

Older patients are also known to have co-morbidities such as other ailments and functional limitations that may lead to a higher risk of complications including non-thyroid cancer related deaths (60, 61). In Sosa's study, older patients had more co-morbidities, and major loss of function was found in about 10% of patients older than 84 years and barely 4% of patients between the ages 65-79 years. The number of co-morbidities also varied with older patients having 3 or more while younger patients had fewer. Another finding was provider characteristics that differed for the different age groups. Older patients were less likely to have their thyroidectomies in urban and academic medical centers compared with younger patients. In addition, more of the older patients received their care from low volume surgeons. With significant morbidity, a risk-analysis on cancer treatment options comes into play for the elderly and the risk of peri-operative cardiac or pulmonary complications may be more than the potential benefit of the surgical treatment of thyroid cancer (2). A surgeon's concern about the potential for higher complication rates and shorter overall life expectancy among older patients may in part explain our observed finding of lower rates of CLND.

In our analysis, patients who were black were also less likely to have CLND with thyroidectomy. Some studies have shown that although black patients tend to have larger tumors than white patients, they also may have lower rates of lymph node metastases (3,7). This may partly explain why CLND is less common among them, as our study demonstrates. Racial disparities in treatment have remained a concern over the years and numerous studies have been done to show disparate treatment across ethnic groups. A retrospective study by Bilimoria and colleagues in a study of factors that predict the use of total thyroidectomy found that black patients were 11% less likely to undergo a total thyroidectomy compared with white patients. Asian patients had a higher likelihood of undergoing a total thyroidectomy compared with white patients (18). In our study, Asian patients were more likely than blacks but less likely than whites to have CLND.

A robust finding across studies is that blacks and other racial and ethnic minority populations have less access to experienced surgeons or high quality care (29,62,63), and this may lead to these groups undergoing less aggressive cancer treatment. A retrospective study conducted by Brown et al to assess the effect of race on the presentation and management of thyroid cancer in an equal access healthcare system showed that black and white patients presented with large tumors at a similar rate. The rate of total thyroidectomy and radiation was also similar, 65.3% vs. 63.3% and 56.5% vs. 51.8% for blacks and whites respectively (7). The equal access healthcare setting of the study may limit its applicability to the general population. In addition, Sosa and colleagues investigated clinical and economic outcomes of thyroidectomy across different races and the result showed that black patients more commonly had a benign diagnosis compared with other groups. Black patients were more likely to have a subtotal or substernal thyroidectomy instead of total thyroidectomy when indicated and this may be due to limited access to high quality care (29).

Differences in the qualifications and competency of physician who treat black and white patients have been described (64, 65). Bach and colleagues studied the differences between primary care providers of white and black patients. Physicians who had more of a black patient population in their practice were more likely to practice in low-income areas and less likely to be board certified in their specialty than those with predominantly white patients. With regards to an assessment of their own ability to provide certain aspects of care, there were differences associated with the race of the patient population. 27.8 % of physicians with black patients stated their inability to provide high-quality care for all their patients compared with 19.3% of physicians treating white patients. They were less likely to provide access to subspecialists of high quality, high quality diagnostic imaging, non-emergency hospital admissions and ancillary services (65). This study was based on the subjective responses of physicians, and patient outcomes, which may verify the effect of the result, was not analyzed. The inability of some physicians to provide high quality care may be related to the inability of patients to bear the cost and not a deliberate act on the part of the physicians involved.

Although limited access of black patients to high quality care may be a contribution to the lower rates of thyroidectomy with CLND observed in the current study, it may not be as significant of a contributor as expected because some other studies have shown otherwise. Armstrong and colleagues, in a retrospective cohort study to compare surgical treatment in black and white women with endometrial cancer, found that black women sought treatment from physicians with higher training and in urban, large volume hospitals (66). Other factors such as cultural and religious differences or personal biases may also play a key role in the way people of different ethnicities approach health care. An example of such was observed in a study by Margolis and colleagues, who assessed the prevalence of the belief of tumor spread of lung cancer by air during surgery and the influence of this belief on the willingness to undergo surgery for lung cancer among black and white patients. 61% of blacks and 29% of whites had this belief. 19% of blacks gave the belief as the reason behind their refusal to undergo surgery and 14% of them did not believe their physician's statement of the falseness of the belief (67).

Racial disparities in treatment for other types of cancers have been reported, including treatment for early stage pancreatic cancer where black patients appear to have compromised access to pancreatic resection. These observed disparities were not believed to be due to patient refusal of standard of care; rather, it was postulated that black patients were less likely to be offered pancreatic surgery, in spite of the survival benefit it is known to convey (68). Similarly, Epstein and colleagues performed a literature review to detect if racial disparities in renal transplantation are clinically appropriate or a reflection of other factors. The result showed that, in patients with end-stage renal disease, fewer blacks were deemed appropriate for renal transplant compared with whites; 9% vs. 20.9%, and more blacks had incomplete evaluation, suggesting that even with equal access, fewer blacks will be referred for transplant or placed on the waiting list. This was also observed among those deemed appropriate for transplant (69). The possibility of fewer matching donors for black patients may also be a contributing factor to the observed disparity. Another study of patients with advanced breast cancer showed that black and Hispanic patients were associated with a decreased likelihood of receiving radiation therapy compared with their white counterparts (70).

Some have suggested that racial disparities in treatment are driven by geographical variations, with blacks and some other minority groups residing in regions of the country with relatively low-volume and or low-quality providers (71). This may explain the geographical variation in the utilization of CLND that was observed in our study. Living in the west is associated with having a higher likelihood of receiving CLND compared with patients in other regions. Patients in the South are least likely to undergo CLND. Improvement in racial disparities may not necessarily improve treatment on a national level and may be dependent on addressing the regional variations.

Our study found that men were less likely than women to undergo CLND. Although women have a higher rate of disease and present at a younger age than men, they have less aggressive disease. In a study examining the demographics of PTC, Mitchell et al demonstrated that tumors greater than 4cm and with evidence of lymph node involvement were more common in men than in women. Mortality rates also were higher in men (3). Machens and colleagues had similar findings, with larger tumor diameter in men than women, 26mm vs. 19.3mm. Lymph node metastasis was found in 60% of men and 44% of women in the study population. Distant metastasis was found in 29% of men and only 15% of women (72). Based on these findings, more aggressive surgery would seem to potentially benefit men; nevertheless, at the population level, men seem to undergo less CLND than women. Examinations of the influence of gender on surgical treatment for other types of tumors have been carried out in the past. O'Connell and colleagues examined the use of cancer directed therapies in patients with cancer of the breast, esophagus, stomach, pancreas, rectum, non-small cell lung carcinoma and sarcoma. They observed that the rate of cancer directed therapy was not affected by gender for most of the cancers studied except for lung cancer and sarcoma, in which women were favored (73).

The current study also revealed that having an advanced-staged tumor was a strong predictor of undergoing CLND. This observation may be attributed to large tumor size as a risk factor for lymph node involvement and the role that this knowledge plays in the decision to perform a CLND or not. Majority of the patients in this group may have received therapeutic and not prophylactic CLND. The current study could not distinguish between the two types of CLND.

The time-trend analysis showed an increase in utilization of CLND over time; this was particularly poignant for micro tumors. This observed trend might be explained in part by the fact that there is more widespread acceptance that even microPTCs can be associated with metastatic lymph nodes (74). We found that 11% of tumors 1cm or less in size had coincident malignant lymph node metastases. Other recent studies have shown that simultaneous lymph node metastasis may occur with microPTCs. Zuniga and colleagues, in a cohort study of patients with CLND, found that over 30% of patients with tumors less than or equal to 1cm had lymph node metastasis (34). Similarly, Bonnet et al found that 42% of patients with tumors less than 2cm in their study had lymph node metastasis (56). Lymph node information can also lead to a more accurate staging of tumors and inform the need for possible additional RAI therapy in small, node-negative thyroid cancers. In the same study by Bonnet and colleagues, lymph node involvement led to a modification for RAI requirement about 30% of patients with T1 tumors. With the increased utilization of high sensitivity serum thyroglobulin assays for detection of PTC recurrence, mild elevations in serum thyroglobulin levels may create distress among patients and physicians alike. Removal of central lymph nodes and its association with a reduced risk of positive thyroglobulinemia can make follow-up less stressful for patients, their endocrinologists and surgeons. This also may play a role in the observed increase in the performance of CLND in recent years.

Our study showed a thyroid cancer specific death of 0.2%. The study period was not sufficient to fully compare mortality rates between patients who underwent CLND and those who did not. In general, patients with thyroid cancer have been known to have a longer overall survival period than patients with other types of malignancies. A study by Scott and colleagues showed that patients with papillary thyroid cancer in the United States have a 10-year survival rate of 93% (Scott). The low mortality rate makes recurrent disease the outcome of choice when analyzing benefits of treatment modalities of thyroid cancer.

Limitations to this study include those associated with large administrative and clinical databases, such as sampling and coding errors; the SEER database has been validated since 1973 and is known to have a high level of accuracy. The lack of a consensus with regards to the definition of CLND makes coding in SEER likely to be inconsistent. Except for other types of cancer, SEER lacks information regarding co-morbidities; the “number of primary tumors” was used as a proxy for other co-morbidities. Patient co-morbidities may have influenced surgeons’ decision to perform a CLND. This could not be evaluated in our study. The information in SEER does not allow for a distinction between prophylactic and therapeutic CLND or ipsilateral and bilateral dissection. SEER also lacks data regarding laboratory values (i.e. thyroglobulin levels), disease recurrence, reoperations, and socioeconomic status of patients; therefore, these variables could not be analyzed.

In conclusion, this study is the first of its kind to examine at a population level the rates of utilization of thyroidectomy with CLND for patients with PTC. We were also able to look at the number of lymph nodes resected, determine patient demographic factors associated with CLND, and analyze trend of CLND over time. The fact that only 6% of our study population had enough lymph nodes resected to qualify for a true CLND according to existing guidelines speaks volumes to the observed variation in thyroid cancer care across the U.S. Prophylactic CLND remains controversial, as the benefits and risks balance remain debatable. While some surgeons may be concerned about complications associated with CLND, experienced surgeons have been shown to have low rates of complications overall. Patient access to experienced surgeons is often compromised by a relative paucity of these surgeons and their poor distribution in some geographic regions of the country, including the South. Additional studies should be undertaken to examine disease recurrence rates and need for reoperations in these patients.

Table 1: Demographic, clinical and pathological characteristics of patients with papillary thyroid cancer undergoing thyroidectomy with central lymph node dissection, SEER 2004-08. (N = 14257)

Patient characteristic	**N**	%
Demographics		
Age (years)	5169	36.3
- 18 – 44	6658	46.7
- 45 – 64	2120	14.9
- 65 – 79	310	2.2
≥ 80		
Gender		
- Female	11450	80.3
Race (N = 14139)		
- White	11913	84.3
- Black	968	6.8
- Asian/Pacific Islander	1139	8.0
- Other	119	0.9
Geography		
- Northeast	3558	25.0
- Midwest	1226	8.6
- South	2497	17.5
- West	6976	48.9
Clinical and pathologic characteristics		
Surgery at primary site		
- Lobectomy	2907	20.4
- Total thyroidectomy	11350	79.6
Tumor stage (based on size and extension)		
- T1a	6692	46.9
- T1b	3461	24.3
- T2	2772	19.4
- T3	993	7.0
- T4	339	2.4
Number of primary tumors		
- 1	12504	87.7
- 2	1506	10.6
≥ 3	247	1.73
Number of lymph nodes examined (N=14080)		
- 0	8973	63.7
- 1	1988	14.1
- 2-5	2184	15.5
- > 5	935	6.64
Metastases (N=14254)		
- None	14066	98.7
- Distant metastases	89	0.6
- Unknown	99	0.7

Table 2: Unadjusted analysis of demographic and clinical characteristics of patients with papillary thyroid cancer undergoing thyroidectomy with central lymph neck dissection, SEER 2004-2008

Patient characteristics (N = 14257)	**% CLND**	**P value**
Demographics		
Age (years)		<0.001
- 18 – 44	43.4	
- 45 – 64	35.2	
- 65 – 79	29.4	
≥ 80	25.1	
Gender		<0.001
- Male	34.8	
- Female	37.6	
Race (N = 14139)		<0.001
- White	38.3	
- Black	21.5	
- Asian/Pacific Islander	34.8	
- Other	39.5	
Geography		<0.001
- Northeast	41.8	
- Midwest	34.3	
- South	29.7	
- West	37.7	
Year of diagnosis		<0.001
- 2004	33.8	
- 2005	35.5	
- 2006	36.6	
- 2007	38.7	
- 2008	40.0	
Clinical characteristics		
Surgery at primary site		<0.001
- Lobectomy	23.1	
- Total thyroidectomy	40.6	
Tumor stage (based on size and extension)		<0.001
- T1a	32.1	
- T1b	42.5	
- T2	40.1	
- T3	36.5	
- T4	57.2	
Number of primary tumors		<0.001
- 1	37.6	
- 2	34.1	
≥ 3	29.6	
Metastases		<0.001
- None	36.8	
- Distant metastases	50.6	
- Unknown	56.6	

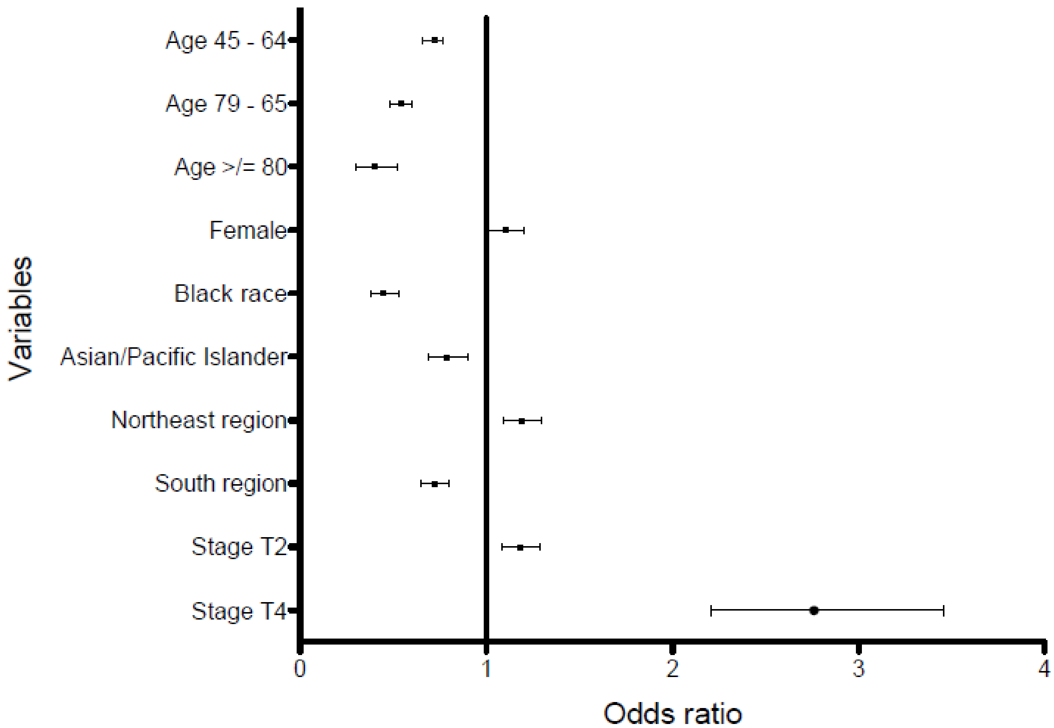
Table 3: Patients with papillary thyroid cancer who underwent thyroidectomy and central lymph node dissection by year of diagnosis, SEER 2004-08

Stage	**Patients who underwent thyroidectomy with CLND (%)**					
	2004 (N = 2573)	2005 (N = 2791)	2006 (N = 2775)	2007 (N = 2906)	2008 (N = 3212)	P value
T1a	28.1	32.0	32.0	33.0	34.2	< 0.001
TIb	36.7	42.4	41.6	42.7	48.0	< 0.001
T2	38.7	34.2	39.5	47.5	40.8	< 0.001
T3	30.8	33.4	35.2	37.5	44.4	< 0.001
T4	63.0	51.3	57.9	51.9	61.4	< 0.001

Table 4: Number of lymph nodes removed in patients undergoing thyroidectomy for papillary thyroid cancer, by T stage of primary tumor, SEER 2004-08

T stage	**% of patients by number of lymph nodes removed** (N = 14080) (all p<.001)			
	0	1	2 – 5	>5
T1a	68.6	13.8	13.4	4.2
TIb	58.3	15.4	18.0	8.2
T2	60.9	13.9	16.4	8.8
T3	64.1	13.3	15.3	7.2
T4	43.5	11.1	24.3	21.0

Figure 1.



LEGEND:

Figure 1 – Multivariate analysis of factors independently associated with patients undergoing thyroidectomy with CLND for papillary thyroid cancer, SEER 2004-08. (Referents are ages 18-44 years, male gender, white race, West geographic region, and T1 tumor stage)

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