Prophylactic Central Neck Dissection in Stage N0 Papillary Thyroid Carcinoma

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Objective: To assess the disease-free survival results of prophylactic central neck dissection for papillary thyroid carcinoma preoperatively staged as N0.

Design: Inception cohort.

Setting: Head and neck surgery unit at a national oncologic center.

Patients: Patients with a histologically confirmed diagnosis of stage N0 papillary thyroid cancer but no previous oncologic treatment, no recurrent tumor, and no distant metastasis.

Intervention: Central neck dissection intended as curative treatment.

Main Outcome Measure: Disease-free survival. Demographic, clinical, therapeutic, pathologic, and neck recurrence information was also collected.

Results: A total of 266 patients were included. Mean (SD) follow-up time was 6.9 (4.3) years. Ninety percent of patients had a follow-up longer than 2 years. Prophylactic central neck dissection was performed in 136 patients (51.3%). Of those patients who underwent central neck dissection, 112 had metastatic lymph nodes (82.3%). Neck recurrence occurred in 45 patients (16.9%). Overall, 5-year neck disease–free survival was 86.8%; it was 88.2% in the central neck dissection group vs 85.6% in the group that did not undergo central neck dissection ($P=.72$). In the multivariate analysis, factors related to central neck dissection were macroscopic extrathyroidal extension (odds ratio [OR], 2.12; 95% confidence interval [CI], 1.19-3.79) and multifocality (OR, 3.96; 95% CI, 2.08-7.53). In Cox multivariate analysis for disease-free survival, central neck dissection did not show any significant effect.

Conclusion: Prophylactic central neck dissection did not show any advantage in the rate of neck recurrence in patients with N0 clinical stage disease.

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T HYROID CARCINOMA IS THE most frequent neoplasm in the head and neck. The incidence of thyroid carcinoma has been increasing progressively in the last few years, primarily owing to early diagnosis facilitated by the wide use of ultrasonography.[1] In addition, the incidence has increased as the result of high exposure to radiation, such as occurred after the Chernobyl accident.[2] Moreover, a change in histologic type has been demonstrated, with a decrease in the number of undifferentiated tumors and an increase in the number of papillary tumors, as well as a change in the size of tumors detected. Previously, most clinically detected tumors were nodules of more than 4 cm. More recently, imaging examinations have found an increasing number of nodules smaller than 2 cm in diameter, but their earlier detection has not had any effect on long-term survival.[1]

Thyroid carcinoma treatment is essentially surgical. Total thyroidectomy has been recommended as the best treatment for differentiated thyroid carcinoma because of (1) its low morbidity when performed by experienced surgeons; (2) the possibility of performing postoperative radioiodine therapy; and (3) the feasibility of follow-up treatment with thyroglobulin. Furthermore, the American Thyroid Association Guidelines Taskforce[3] advises, in recommendation 27, that surgeons perform central neck dissection for papillary thyroid carcinoma. This recommendation is based on the results of studies suggesting an improvement in disease-free survival following central neck dissection for papillary thyroid carcinoma.[4-6] However, these studies examined small, heterogeneous populations, which included therapeutic and prophylactic neck dissections and did not control for other related prognostic variables. On the other hand, few studies have analyzed the effects derived from improved staging of patients who underwent central neck dissection. Further investigation is also required to discover the effects of neck dissection on disease-free survival.[7,8]

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The aim of the present study was to assess the disease-free survival results of prophylactic central neck dissection in patients with papillary thyroid carcinoma preoperatively staged as N0. We explored factors associated with the decision to perform central neck dissection that could act as confounding factors in evaluating the real effectiveness of this treatment.

METHODS

This is a historical cohort study. We reviewed the medical charts of all patients with a diagnosis of thyroid carcinoma who were treated at the National Cancer Institute in Bogota, Colombia, between January 1, 1983, and December 31, 1999. The decision to perform central neck dissection was made exclusively by the surgeon and was based on the surgeon's personal preference at the time of the operation, without consideration of any other preoperative variables. The same head and neck surgeons and endocrinologists treated all patients in the study.

The technique of central neck dissection was previously standardized for clinical purposes, including resection of all lymph nodes from the hyoid bone to the brachiocephalic trunk and between the internal borders of the sternocleidomastoid muscle after dissection of the laryngeal recurrent nerve. Postoperative radioiodine treatment with standard doses of 100 to 150 mCi was proposed for patients classified as high risk for recurrence (age >45 years, tumor size >2 cm, capsule invasion, extrathyroidal extension, and/or positive lymph node findings). After surgery, all patients underwent thyrotropin suppression treatment with oral thyroxin until thyrotropin levels remained below 0.1 mIU/L, with normal T4 levels, for at least 5 years.

INCLUSION CRITERIA

To be included in the study, patients had to demonstrate a histologically confirmed preoperative clinical diagnosis of stage N0 papillary thyroid cancer. In addition, they had to have the intention to undergo a curative treatment and no previous oncologic treatment, no recurrent tumor, and no distant metastasis. Ultrasonography was the only preoperative examination considered in the evaluation of the patient. Other imaging examinations were not considered for preoperative staging.

Patients with unresectable tumors or those treated with partial thyroidectomy lateral neck dissection were excluded owing to the risk of selection bias. We also excluded those patients for whom intraoperative detection of a suspect metastatic lymph node required a therapeutic neck dissection.

Data were collected from the medical records using a survey designed especially for this purpose by one of us (S.Z.). The form included demographic, clinical, therapeutic, and pathologic information (vascular and capsular invasion, extrathyroidal extension, histologic subtype, multifocality, and lymph node compromise) as well as prognostic information (neck recurrence). All patients were restaged by TNM staging.

STATISTICAL ANALYSIS

A sample size calculation was made using information from published articles.[4,9,10] We selected a basal recurrence risk of 15% and a 2-fold decrease in the risk of recurrence with central neck dissection. We used a power of 80%, an α of .05, and a time to event of 5 years for 1-tailed analysis by the Lachin formula.[11] The minimum number of patients to be included was 233.

The information from the forms was entered into a database (EPI-INFO, World Health Organization, Geneva, Switzerland). For statistical analysis, commercially available software was used

Table 1. Demographic Characteristics

Characteristic	Value[a]
Age, mean (SD) (range), y	41 (13.7) (14-86)
Women	243 (91.3)
Tumor size, cm	
≤1.0	15 (5.6)
1.1-3.0	94 (35.3)
3.1-5.0	84 (31.6)
>5.0	73 (27.5)
Tumor TNM stage	
1	181 (68.0)
2	38 (14.3)
3	42 (15.8)
4	5 (1.9)
AMES risk	
Low	111 (41.7)
High	155 (58.3)

Abbreviation: AMES, age, metastases, extent, and size.[12]
[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

(Stata 8.0, Stata Corporation, College Station, Texas). Descriptive statistics were used to show the distribution of variables. To establish clinical factors related to the decision to perform central neck dissection, we conducted a univariate analysis with 2×2 tables, and the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs) and P values. Statistical differences were assessed with the χ^2 and t tests. Furthermore, a logistic regression analysis of all clinically significant variables was used to assess statistical independence.

For prognosis, we used neck recurrence. Because this is a time-to-event outcome, we calculated the time from the date of the surgery until the last objective information registered in the clinical charts. Disease-free survival was defined as the time from surgery to detection of recurrence and confirmation by histopathologic or biochemical methods or to the last available date on the clinical chart.

Univariate analysis with the Kaplan-Meier method was used to explore the relationship between baseline variables and outcome events, and the results were reported using a Mantel-Cox hazard ratio (HR) with 95% CI. The log-rank test was used to define statistical significance. Cox proportional hazard regression analysis was used to assess the independent effect of neck dissection on recurrence. In cases of ordinal variables, an indicator variable was created for each level for use in the logistic and Cox proportional hazard regression analysis. For all statistical tests, $P < .05$ was considered statistically significant.

RESULTS

Clinical charts of 721 patients were examined at the hospital medical archives. A total of 266 patients were included. Demographic characteristics are summarized in **Table 1**. Mean (SD) follow-up time was 6.9 (4.3) years (median follow-up, 6.1 years; range, 19 days to 22.6 years). Ninety percent of patients had a follow-up longer than 2 years.

Prophylactic central neck dissection was performed in 136 patients (51.3%). Of those patients who underwent central neck dissection, 112 had metastatic lymph nodes (82.3%). The rate of positivity by size was 33% for tumors 1.0 cm or smaller (n = 2); 88% for tumors 1.1 to 3.0 cm (n = 45); 88% for tumors 3.1 to 5.0 cm (n = 37); and 76% for tumors larger than 5.0 cm (n = 28).
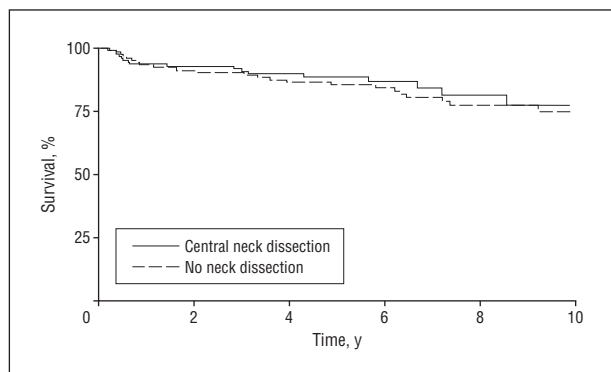
Figure. Five-year neck disease–free survival according to central neck dissection.

Neck recurrence occurred in 45 patients (17%). Twenty-six cases were in patients without central neck dissection (19%), and 19 cases were in patients who underwent central neck dissection (14%) (*P* = .19). All of these patients had positive node results. The mean (SD) time to recurrence was 3.9 (3.8) years (range, 74 days to 14.8 years). We observed that 71% of recurrences (n = 32) occurred during the first 5 years.

Overall, 5-year neck disease–free survival was 86.8% (95% CI, 81.6%-90.7%). In the central neck dissection group, 5-year disease-free survival was 88.2% (95% CI, 80.3%-93.1%) vs 85.6% (95% CI, 77.8%-90.8%) in the group that did not undergo central neck dissection (*P* = .72) (**Figure**). For patients who underwent central neck dissection, those with stage pN0 results had a 5-year disease-free survival rate of 100% compared with 85.9% for patients with pN+ results (*P* = .053).

It is possible that the group of patients who underwent central neck dissection had a selection bias owing to clinical, intraoperative, or histologic characteristics of the primary tumor, and this bias might have affected the therapeutic result of the dissection. Therefore, we explored these covariables (**Table 2**). In the multivariate analysis of factors related to central neck dissection, we found that only macroscopic extrathyroidal extension (OR, 2.12; 95% CI, 1.19-3.79) and multifocality (OR, 3.96; 95% CI, 2.08-7.53) were independent, statistically significant variables. Therefore, these variables should be used to adjust the calculation of disease-free survival for this procedure.

The other circumstance that might have influenced the calculation of disease-free survival was that patients who underwent central neck dissection should have received postoperative iodine 131 (^{131}I) therapy more frequently than their counterparts who did not undergo central neck dissection, owing to improved staging. Therefore, we also analyzed this variable (Table 2). However, in the multivariate analysis, ^{131}I therapy was not significantly associated with disease-free survival (OR, 1.68; 95% CI, 0.98-2.89), although a trend clearly existed.

To confirm the effect of central neck dissection on a decrease in neck recurrence, we performed a Cox multivariate analysis that included all the variables examined. The results are summarized in **Table 3**. The only statistically significant variable associated with neck recurrence was ^{131}I therapy. Central neck dissection did not show any significant effect on disease-free survival.

Table 2. Characteristic Distribution by Central Neck Dissection[a]

Variable	No Central Neck Dissection	Central Neck Dissection	P Value
Age, mean (SD), y	41.5 (13.3)	42.9 (14.1)	.36
Women	117 (90.0)	126 (92.7)	.44
Tumor size, cm			.76
≤1.0	9 (6.9)	6 (4.4)	
1.1-3.0	43 (33.1)	51 (37.5)	
3.1-5.0	42 (32.3)	42 (30.9)	
>5.0	36 (27.7)	37 (27.2)	
Macroscopic extrathyroidal extension	36 (27.3)	61 (44.8)	.004
Classic papillary carcinoma pattern	94 (72.3)	84 (61.8)	.06
Multifocality	17 (13.1)	52 (38.2)	<.001
Capsule invasion	27 (20.8)	36 (26.5)	.27
Vascular invasion	5 (3.9)	11 (8.1)	.14
Perithyroidal microscopic invasion	26 (20.0)	31 (22.8)	.57
^{131}I postoperative therapy	55 (42.3)	79 (58.15)	.01

Abbreviation: ^{131}I, iodine 131.
[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

Table 3. Multivariable Assessment of Variables Associated With Neck Recurrence

Variable	Hazard Ratio (95% Confidence Interval)
Central neck dissection	1.01 (0.53-1.91)
Macroscopic extrathyroidal extension	0.81 (0.42-1.57)
Multifocality	1.20 (0.55-2.58)
^{131}I postoperative therapy	0.51 (0.27-0.97)

Abbreviation: ^{131}I, iodine 131.

COMMENT

The indication for a surgical procedure requires the support of several lines of evidence from the results of case series, observational analyses, and results derived from randomized, controlled trials. Prophylactic central neck dissection has been widely recommended as a part of the initial treatment of patients with thyroid carcinoma as a measure to decrease the volume of tumor tissue remaining after total thyroidectomy and to limit the risk of neck recurrence.[3,13] However, until now it has been difficult to determine the real therapeutic effect of this procedure.

Some studies have suggested a decrease in neck recurrence after central neck dissection, while others do not demonstrate any effect.[9,14,15] In the case of thyroid cancer, certain characteristics related to the biological behavior of the tumor may have obscured the results of these studies.

Several studies have selected long-term survival as the outcome to assess the effectiveness of interventions in thyroid cancer.[1] However, in contrast to patients with other tumors, patients with thyroid carcinoma sometimes live more than 20 years, which makes the evaluation of this outcome almost impossible because common therapies do not show a clinically significant effect. Furthermore, long-term survival does not necessarily represent a better prog-

nosis because the natural history of thyroid cancer shows that multiple neck procedures in the same patient are often necessary, and these multiple procedures decrease the patient's quality of life. Therefore, recurrence should be accepted as the most important outcome for assessment owing to its potential impact on the quality of life.

Nonetheless, evaluating recurrence in relation to central neck dissection is also problematic. The first issue is that the commonly accepted theory of an ordered pattern of lymph node dissemination, beginning at the central compartment, spreading to the lateral cervical compartment, and finally producing systemic metastasis, is not as realistic as originally suggested.[16,17] The rate of skip metastases—nearly 10%—could explain neck recurrences even after a comprehensive central neck dissection, detracting from the reliability of central neck dissection as a therapeutic maneuver.

The second issue is related to the factors that could introduce a bias in the indication for central neck dissection. Some studies on routine central neck dissection mixed patients who underwent therapeutic and prophylactic neck dissections, and other studies did not specify whether metastatic central neck lymph nodes were detected during surgery forcing surgeons to make a therapeutic dissection.[4-6] It is clear that macroscopic suspect lymph nodes are prognostic markers for recurrence, but microscopic nodes are not. Wada et al[18] found a high incidence of central lymph node metastasis in a comparative study of (1) patients with micropapillary carcinoma who underwent prophylactic central neck dissection; (2) patients with clinically positive neck lymph nodes who underwent therapeutic central neck dissection; and (3) patients with incidental micropapillary tumors found during a thyroidectomy for benign conditions (without neck dissection). The incidence of central lymph node metastasis was higher for the therapeutic dissection group (95% vs 60%), as was the incidence of neck recurrence (16% vs 0.5%), but no difference was found between the prophylactic group and the group that did not undergo dissection (0.4% vs 0.6%). In a study of 43 patients, Pereira et al[19] found a 33% recurrence in the group that underwent dissection only after macroscopic suspect lymph nodes were found during surgery, as opposed to 0% recurrence in the group that underwent prophylactic dissection. If the objective of a study is to assess the effectiveness of prophylactic neck dissection as a procedure to decrease neck recurrence, the introduction of therapeutic dissections prompted by intraoperative findings could bias the results in favor of central neck dissection.

On the other hand, observational studies that compare prophylactic central neck dissection and no dissection could also be biased because patients undergoing neck dissection may have more risk factors for recurrence than patients who do not undergo dissection. In the present study, it is clear that extrathyroidal extension and multifocality, factors predictive of a worse prognosis and easily identifiable during surgery, were more frequent in patients who underwent neck dissection. We could not find a study assessing recurrence after central neck dissection that took extrathyroidal extension and multifocality into account; however, there are many studies confirming the prognostic effect of these 2 parameters.[20-22]

In addition, the biological behavior of lymph node metastasis in thyroid carcinoma is not predictable. While the frequency of central lymph node metastasis in thyroid carcinoma is high (60%-80%), recurrence rates remain at the low level of 0% to 15%, even in patients who underwent total or partial thyroidectomy.[23-25] It has not been possible to explain this difference, but it could be related to the extreme aggressiveness of some tumors, in which cases recurrence would not depend on local procedures such as central neck dissections.

We designed this study to consider all of these factors and to limit the effect of confounding factors that could introduce a bias in the results. Our results showed a high frequency of micrometastasis in the dissection group, similar to other series, but we could not detect any prognostic effect of central neck dissection on neck recurrence. Aside from univariate comparisons, we tried to assess other factors that could introduce bias and thereby attenuate the therapeutic effect of central neck dissection. We determined that the decision to perform central neck dissection under the guise of a prophylactic approach might have resulted from surgeon bias: macroscopic extrathyroidal extension and multifocality, findings that could be identified during thyroidectomy, were more frequent in this group of patients. If neck dissection is performed more frequently in high-risk patients, and it has a protective effect, its therapeutic effect might not be determined because recurrence rates will be inaccurately similar to those of control patients owing to a decrease in the rate of recurrence among the high-risk patients. However, when we adjusted our results to accommodate these factors, disease-free survival did not show any significant change.

Another factor of importance is the upstaging that results from neck dissection. As explained many years ago in the context of gastric cancer surgery, the Will Rogers phenomenon[26] could explain the lower recurrence observed in some studies, possibly derived from improved patient staging. In our study, the only clinical stage used was that described preoperatively, and we did not make any adjustment to the stage after neck dissection. Adjustment of disease-free survival using this variable did not reveal any significant difference between groups. However, other studies assess recurrence using the pathologic confirmation of lymph node metastases, in which case the Will Rogers phenomenon could affect results.

It is also possible that patients who underwent neck dissection might have received more intense postoperative treatment than controls. For thyroid cancer, the most important adjuvant treatment is radioiodine therapy. The more frequent use of radioiodine therapy in patients who underwent neck dissection, prompted by the pathologic findings of micrometastasis at central compartment lymph nodes, could decrease the rate of recurrence, again masking the therapeutic effect of the surgical procedure. In our study, it was evident that patients who underwent central neck dissection received more radioiodine therapy than those who did not. However, when we introduced this factor in a multivariate analysis of recurrence, central neck dissection did not show a statistically significant effect, while radioiodine therapy was clearly protective. This subject is currently a matter of ongoing discussion.[27]

Finally, central neck dissection is a procedure with potential postoperative complications. Roh et al[10] reported a

30% rate of transient hypocalcemia after central neck dissection compared with 9.6% in the control group. Palestini et al[28] reported a 31% rate of transient hypocalcemia in the dissection group compared with 13% in the control group. If the procedure does not result in less frequent recurrence or better long-term survival and has the risk of complications like laryngeal recurrent nerve injury or definitive hypocalcemia, the common recommendation to perform central neck dissection as a prophylactic measure is not valid. The procedure does not offer a good risk-benefit ratio.

In conclusion, prophylactic central neck dissection did not show any advantage related to the rate of neck recurrence in stage N0 clinical disease, even when certain predictor variables were included in a multivariate model. It is therefore possible to suggest that this intervention does not offer any advantage to patients, except for better pathologic staging. However, the question requires further investigation. This is an observational study that could have biases. Diagnostic technologies evolved during the 16-year course of the study. However, at no time during the study was ultrasonography capable of detecting metastatic central lymph nodes, so we consider that all patients were assessed similarly at the beginning of treatment.

The only way to obtain a definitive result would be to design a randomized controlled trial with standardized intraoperative and postoperative procedures that compares prophylactic central neck dissection with selective central neck dissection for patients with intraoperative findings of macroscopic metastasis. Until this type of study is done, it is not possible to define the best recommendation. Actual guidelines from the National Comprehensive Cancer Center[29] or American Thyroid Association[3] are based on observational studies as this one, so the results of this study provide more information for physicians and patients to make a more informed decision.

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