Central Neck Dissection for Papillary Thyroid Cancer

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Objective: To examine the role of central neck dissection (CND) in patients with papillary thyroid cancer (PTC).


Setting: Academic institution.

Patients: All patients diagnosed with PTC who underwent surgical therapy at our institution.

Main Outcome Measures: Recurrence, hypocalcemia, hypoparathyroidism, and recurrent laryngeal nerve (RLN) injury.

Results: A total of 136 patients were treated for PTC, 26 of whom were excluded because their initial resection was performed at another institution. Of the 110 patients who underwent initial surgical therapy, CND was performed in 22 patients (20%), 18 with and 4 without enlarged nodes at the time of surgery. A mean (SD) of 11 (4) lymph nodes were removed, and lymph node metastases were identified in 17 patients (77%). One patient developed a recurrence in the lateral neck at 15 months’ follow-up. Eighty-eight patients had no abnormal lymph nodes and did not undergo CND, 2 of whom developed a recurrence (2%) (P = .49) in the central neck at 14 months’ and 11 years’ follow-up. Permanent RLN injury occurred in no patient who underwent CND and in 1 patient without a CND (1%). Transient hypocalcemia occurred in 19 patients who underwent CND (86%) compared with 54 patients without a CND (61%) (P = .01). Permanent hypoparathyroidism occurred in 1 patient who underwent a CND (5%).

Conclusion: After total thyroidectomy and CND, recurrence in the central neck is uncommon, but hypocalcemia is more common, raising questions about the use of routine CND in patients with PTC.


THERE IS CONSIDERABLE DISAGREEMENT ABOUT WHAT CONSTITUTES APPROPRIATE MANAGEMENT OF PAPILLARY THYROID CANCER (PTC), INCLUDING WHEN TO PERFORM CENTRAL NECK LYMPH NODE DISSECTION. DISAGREEMENT CONTINUES, IN PART, BECAUSE OF THE LACK OF PROSPECTIVE RANDOMIZED TRIALS THAT MIGHT HELP GUIDE THERAPEUTIC DECISION MAKING. LARGE COHORTS OF PATIENTS WHO HAVE UNDERGONE THERAPY IN A NONRANDOMIZED FASHION PROVIDE MOST OF THE DATA ON CENTRAL LYMPH NODE DISSECTION.

For patients with macroscopic nodal disease, lymphadenectomy may reduce the risk of recurrence and mortality. A therapeutic central neck dissection (CND) should be performed in patients with biopsy-proven macroscopic lymph node metastases in the central neck identified on cervical ultrasonography or at the time of surgery. A compartment-oriented lymphadenectomy minimizes the risk of subsequent recurrence, which is more common with simple excision of enlarged lymph nodes.

The American Thyroid Association (ATA) recommends that a routine central compartment (level VI) neck dissection should be considered for all patients with papillary cancer. The ATA classifies this recommendation at level B, indicating that the recommendation is based on fair evidence that the service or intervention may improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.

The European Thyroid Association (ETA) also recommends that a routine central neck compartment dissection be considered for all patients with PTC. The rationale for prophylactic CND is based on 2 assumptions: (1) that patients with papillary cancer have high rates of metastases.
 ses and regional recurrence in the central compartment of the neck; and (2) that it is difficult to reoperate on patients with regional recurrence in the central neck. However, the benefit of a prophylactic CND in the absence of preoperative or intraoperative evidence of macroscopic lymph node metastases is unproven. The purpose of the present study was to determine the rate of metastases in the central neck and examine the morbidity and rate of recurrence in patients with PTC treated with or without a CND.

METHODS

A retrospective review was performed of all patients who underwent surgical treatment for PTC by a single surgeon from July 1993 through September 2008. All patients treated with total thyroidectomy or lobectomy followed by completion thyroidectomy were included in the study. Patients who received their initial surgical treatment at another institution were excluded from the study. The study was approved by the institutional review board at MetroHealth Medical Center, Cleveland, Ohio.

Patients were divided into 2 groups: those who underwent a thyroidectomy with CND, and those who underwent a thyroidectomy without CND. Central neck dissections were performed in all patients with abnormal lymph nodes identified by preoperative ultrasound or intraoperative examination. A CND consisted of the removal of all nodal and fibrofatty tissue from the hyoid bone superiorly to the brachiophalic artery inferiorly and between the common carotid arteries laterally. Level VI nodes included the prelaryngeal (delphian), pretracheal, and paratracheal lymph nodes. Level VII nodes were lymph nodes from the anterior mediastinum. Patients who had some lymph nodes removed with the thyroid specimen or had selective sampling of nodes were not considered to have a CND and were included with patients who received a total thyroidectomy alone. Patients who underwent a concomitant modified radical neck dissection were included in the appropriate group. A modified radical neck dissection consisted of removal of the anterior cervical (levels II, III, and IV) and posterior cervical and supraclavicular (level V) lymph nodes.

Postoperatively, surveillance was performed with physical examination. In addition, serum thyrotropin (TSH) and basal thyroglobulin levels and antithyroglobulin antibody titers were measured every 6 months at first and then annually if no evidence of recurrence was identified. If the thyroglobulin level was elevated, cervical ultrasonography was performed to evaluate for recurrence in the neck. The TSH-stimulated thyroglobulin level was measured at 12 months in conjunction with cervical ultrasonography. Even if the basal thyroglobulin or TSH-stimulated thyroglobulin levels were normal, cervical ultrasonography of the thyroid bed, central neck, and lateral neck compartments was performed at 6 months, 12 months, and then annually.

Within each study group, we determined the number of patients who developed a recurrence of PTC, hypocalcemia, permanent hypoparathyroidism, and recurrent laryngeal nerve (RLN) injury. Recurrence was defined as macroscopic disease identified on clinical examination or cervical ultrasonography that was not present at initial presentation. Macroscopic lymph node recurrence was diagnosed based on the presence of lymph nodes that were palpable on examination or larger than 1 cm on cervical ultrasonography along with 1 or more of the following additional abnormal ultrasonographic features: microcalcifications, irregular margins, hypoechoic signal, irregular halo, invasion of surrounding tissue, or intranodular hyperemia.

RESULTS

During the study period, 136 patients were treated for PTC. Twenty-six patients were excluded from the study because their initial surgical treatment was performed at another institution. Of the 110 patients who underwent initial surgical treatment at our institution, a CND was performed in 22 patients (20%): 12 for palpable lymphadenopathy at the time of operation (55%); 6 for lymphadenopathy identified on preoperative ultrasonography and confirmed intraoperatively (27%); and 4 without lymph node enlargement (18%). In the 4 patients without lymphadenopathy, a CND was performed to address extensive extrathyroidal tumor spread in 1 case and to remove tumors larger than 2 cm in the other 3 cases.

The overall patient population included 97 women and 13 men, with a mean age of 46.5 years. Postoperatively, 100% of the patients underwent follow-up care. The average duration of follow-up was 3.8 years for patients who did not undergo a CND compared with 2.8 years for patients who underwent a CND. Table 1 details the demographic characteristics for each study group, including sex, age, family history of thyroid disease, and the number of patients who had a preoperative neck ultrasonographic examination. In addition, Table 1 details some operative factors including the number of patients who had a substernal goiter resection, autotransplantation of parathyroid glands, and concomitant modified radical neck dissection.
The final pathologic results are detailed in Table 2. The 2 groups did not differ significantly with respect to thyroid gland weight, tumor size, the presence of concomitant Hashimoto thyroiditis, and the number of patients with bilateral disease. Tumors in the CND group were much more likely to be multicentric.

Of the 88 patients who did not undergo a CND, 53 had incidental nodes removed (60%). Eleven of the 53 patients had lymph nodes found to be positive for PTC metastases on final pathologic analysis (21%). Of the 22 patients who underwent a CND, 17 had lymph node metastases on final pathologic analysis (77%) (Table 2). A mean (SD) of 11 (4) central neck nodes were removed, with PTC metastases present in 4 (4) nodes. When analyzing the results based on the indications for CND, we found that 3 of the 4 patients who underwent a prophylactic CND had positive lymph node metastases on final pathologic analysis. Of the 6 patients with lymphadenopathy identified on preoperative ultrasonography, all of them had positive lymph node findings on final pathologic analysis. In the 18 patients with palpable lymphadenopathy at the time of surgery, 14 (78%) had positive lymph node findings on final pathologic analysis. Of the 4 patients whose lymph node findings were negative on final pathologic analysis, the lymphadenopathy was associated with diffuse Hashimoto thyroiditis in 3 patients. No pathologic process was identified in the fourth patient with lymphadenopathy identified at the time of surgery.

Recurrent PTC occurred in 2 of the patients who did not undergo a CND (2%). In both patients, the recurrence was in the central neck. One central neck recurrence was in a 48-year-old woman who initially presented with palpable lymphadenopathy in the lateral neck on physical examination. At her initial operation, she was found to have a 5-cm multicentric tumor and extrathyroidal tumor spread. She had a concomitant modified radical neck dissection with 7 of 25 lymph nodes found to be positive for PTC. Postoperatively, she received radioactive iodine ablation. Her recurrence manifested as a 1.8-cm, nonpalpable paratracheal lymph node identified on follow-up ultrasonography 11 years after the initial resection. The other patient who developed a central neck recurrence was a 38-year-old man with familial PTC. Preoperatively, his physical examination and cervical ultrasonography findings were negative for lymphadenopathy. At the time of surgery, he was found to have a 0.5-cm multicentric tumor with no extrathyroidal tumor spread or palpable lymphadenopathy. Postoperatively, he underwent radioactive iodine ablation. His recurrence manifested as a 0.7-cm, nonpalpable node identified on ultrasonographic evaluation 14 months after surgery. No significant differences were observed between the patients with or without a recurrence following total thyroidectomy alone with respect to age, performance of preoperative ultrasonography, extrathyroidal tumor extension, concomitant modified radical neck dissection, thyroid size and weight, tumor size, thyroid multicentricity or bilaterality, or in the number of patients who underwent 131I ablation postoperatively (P > .05).

No patient who underwent a CND developed a recurrence of PTC in the central neck. Recurrence occurred in the lateral neck in 1 patient who had a CND at the initial operation (5%). The patient was a 19-year-old woman who presented with lymphadenopathy identified on cervical ultrasonography. At the time of surgery, she was found to have a 2.3-cm, multicentric and bilateral tumor without extrathyroidal tumor spread. Eight of the 17 nodes removed from the central neck and 4 of 40 nodes from the lateral neck during a concomitant modified radical neck dissection were found to be positive for PTC. Postoperatively, she underwent radioactive iodine ablation. Her recurrence manifested as a 1.3-cm node and a 1.5-cm node in levels I and II in the lateral neck. Both lymph nodes were nonpalpable and were identified on follow-up ultrasonographic examination. In all 3 patients who developed recurrences, the recurrent disease was a nonpalpable lymph node that was identified and resected using intraoperative ultrasonographic guidance. None of the patients developed complications after treatment of their recurrent disease, and none of the patients developed distant metastases.

Complications, including postoperative hypocalcemia, permanent hypoparathyroidism, RLN injury, and distant metastases for each group of patients, are detailed in Table 3. No significant difference in RLN injury or distant metastases was identified between patients who

<table>
<thead>
<tr>
<th>Table 2. Pathologic Findings in Patients Treated for Papillary Thyroid Cancera</th>
<th>No CND (n=88)</th>
<th>CND (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Characteristic</td>
<td></td>
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<td></td>
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<tr>
<td>Thyroid weight, g</td>
<td>39.7 (40.0)</td>
<td>28.4 (10.8)</td>
<td>.16</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>1.93 (1.7)</td>
<td>2.49 (1.4)</td>
<td>.07</td>
</tr>
<tr>
<td>Thyroid multicentricity, No. (%)</td>
<td>43 (49)</td>
<td>18 (82)</td>
<td>.008</td>
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<tr>
<td>Bilateral disease, No. (%)</td>
<td>24 (27)</td>
<td>8 (36)</td>
<td>.44</td>
</tr>
<tr>
<td>Concomitant Hashimoto thyroiditis, No. (%)</td>
<td>13 (14.8)</td>
<td>4 (18.2)</td>
<td>.74</td>
</tr>
<tr>
<td>Positive central lymph nodes, No. (%)</td>
<td>11 (13)</td>
<td>17 (77)</td>
<td>ND</td>
</tr>
<tr>
<td>Nodes dissected</td>
<td>3 (3)</td>
<td>11 (4)</td>
<td>ND</td>
</tr>
<tr>
<td>PTC-positive nodes</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: CND, central neck dissection; ND, not determined; PTC, papillary thyroid cancer.

a Unless otherwise indicated, data are reported as mean (SD) value.

<table>
<thead>
<tr>
<th>Table 3. Recurrence and Complications in Patients Treated for Papillary Thyroid Cancera</th>
<th>No CND (n=88)</th>
<th>CND (n=22)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Complication</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Recurrence</td>
<td>2 (2)</td>
<td>1 (5)</td>
<td>.49</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>51 (58)</td>
<td>19 (86)</td>
<td>.01</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>0</td>
<td>1 (5)</td>
<td>.20</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>2 (2)</td>
<td>2 (9)</td>
<td>.18</td>
</tr>
<tr>
<td>Permanent</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Need for tracheostomy</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>2 (2)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviation: CND, central neck dissection.
a Unless otherwise indicated, data are reported as number (percentage) of patients.

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underwent CND compared with those who did not have a CND. Transient hypocalcemia occurred in 86% of patients who underwent a CND (n = 19) compared with 58% of patients who did not have a CND (n = 51) (P = .01), and the only patient who developed permanent hypoparathyroidism had a CND.

A bilateral CND involves the removal of all nodal and fibrofatty tissue from the hyoid bone superiorly to the brachiocephalic artery inferiorly and between the common carotid arteries laterally. This includes removal of the prelaryngeal (delphian), pretracheal, paratracheal, and anterosuperior mediastinal lymph nodes. A unilateral CND refers to the removal of the prelaryngeal, pretracheal, anterior mediastinal, and the ipsilateral paratracheal lymph nodes. The contralateral paratracheal lymph nodes are not removed to reduce the risk of injury to the contralateral RLN. In a prophylactic CND, all lymph nodes in the central compartment are removed even though they are considered normal, based on preoperative and intraoperative assessment. A therapeutic CND involves the removal of all lymph nodes in the central compartment after the presence of metastatic lymph node disease is confirmed in the central neck.

The role of lymph node dissection in the treatment of PTC is currently under debate. Patients with macroscopic lymph node metastases should undergo a therapeutic compartment-oriented lymph node dissection as opposed to removal of only pathologic nodes. Davidson and colleagues2 found that simple excision of pathologic nodes resulted in a 6.6% risk of recurrence. There is evidence that therapeutic lymphadenectomy for macroscopic lymph node metastases reduces recurrence and improves survival.1,13 However, controversy exists on how patients with clinically normal lymph nodes should be managed. The ATA4 recommends that prophylactic CND be considered for all patients with PTC, but the benefits are controversial, and there is no conclusive evidence that routine CND reduces recurrence or mortality.

The rationale for prophylactic CND is based on the assumptions that patients with PTC have high rates of metastases and regional recurrence in the central neck and that reoperation for central neck recurrence is difficult and carries increased risk of permanent hypoparathyroidism and unintentional RLN injury. In addition, the ETA,4 despite stating that there is no evidence that a CND improves recurrence or mortality rates, advocates its routine performance to obtain pathologic data for accurate staging of the disease, which may guide subsequent treatment and follow-up.

Many endocrinologists believe that the goal of initial therapy should be an undetectable thyroglobulin level6 to simplify follow-up and surveillance for recurrence. Qubain and colleagues7 demonstrated a relationship between lymph node metastases and elevated serum thyroglobulin levels in patients who underwent total thyroidectomy followed by radioactive iodine ablation. Qubain and colleagues7 also found an inverse relationship between the number of lymph nodes resected and thyroglobulin levels, suggesting that a more complete lymph node dissection may result in lower thyroglobulin levels. Grodski et al8 and Sywak et al9 confirmed lower levels of stimulated thyroglobulin and higher rates of athyroglobulinemia 6 months after a total thyroidectomy with ipsilateral CND. Whether this has any influence on outcome remains unclear.

Palestini and colleagues2 believe that CND should be performed routinely because neither ultrasonography nor intraoperative evaluation can rule out the presence of lymph node metastases. In their series, central lymph nodes from 21% of patients believed to have no central node involvement were found to contain metastatic disease on final pathologic analysis. A study by Roh and colleagues10 also showed that cervical ultrasonography has a low sensitivity for detecting nodal metastases in the central neck despite a high specificity and positive predictive value. When evaluating these results, consider that many, if not most, of the patients who have lymph node metastases not identified on ultrasonography or by palpation intraoperatively have occult microscopic disease of questionable significance rather than gross disease, and these patients are the ones who respond well to radioactive iodine ablation. Conversely, lymphadenopathy found by ultrasonography or palpable lymphadenopathy found at the time of surgery does not guarantee the presence of metastatic disease. In our study, 3 of the 18 patients with palpable nodes had lymphadenopathy due to diffuse Hashimoto thyroiditis (17%) as opposed to metastatic PTC. Similar results were seen by Sywak et al.8

The reasons for not performing prophylactic CND are the lack of proven benefit and the potential for increased morbidity, namely hypoparathyroidism and RLN injury. As White et al13 observe, no prospective randomized trials exist to establish the effect of CND on recurrence or disease-specific mortality in PTC. Even though up to 80% of patients will have at least microscopic metastatic disease involving cervical lymph nodes, this does not seem to affect prognosis, at least in patients younger than 45 years.12 In our study, 18 of 22 patients who underwent a CND had metastatic disease on final pathologic analysis (77%), but the rate of recurrence was only 2.3% in patients who did not receive a CND. Sadowski and colleagues13 performed routine CND in 180 patients with PTC, and 84 had lymph node metastases (46.7%). Despite the documented high incidence of central lymph node metastases, only 3.7% of patients who did not have a CND developed recurrence in the central neck after a mean 39-month follow-up.13 Yasemin and colleagues14 studied 343 patients who underwent thyroidectomy without CND for PTC, and only 6 patients developed a central neck recurrence after a median follow-up of 49 months (1.7%). The lack of correlation between the high rate of central node metastasis and the low rate of recurrence in the central neck may be explained by the differing behavior of macrometastases and micrometastases.15,16 The locoregional recurrence rate in patients with PTC and lymph node micrometastases has been shown to be equivalent to that in patients with PTC with no metastases.16

The comparative analysis of morbidity in our series raises concern for the potential for increased morbidity.
when a CND is added to a total thyroidectomy in patients with PTC. In our study, transient RLN injury occurred in 2 patients who underwent total thyroidectomy without CND (2%) and 2 patients who were treated with a total thyroidectomy and CND (9%). The only permanent RLN injury occurred in a patient who did not have a CND. We observed a higher incidence of transient hypocalcemia in patients who had a CND, 86% compared with 58% for patients who did not have a CND. The only patient who developed permanent hypoparathyroidism had a total thyroidectomy and a CND.

In a prospective cohort study, Henry and colleagues compared the outcomes of operations performed by 2 experienced endocrine surgeons in 50 patients with PTC who underwent total thyroidectomy and a prophylactic CND and 50 patients who underwent total thyroidectomy alone for benign multinodular goiter. No permanent RLN injuries occurred in either group of patients. Two patients treated with a CND developed permanent hypoparathyroidism (4%) compared with no patients treated with total thyroidectomy alone.

In another cohort study by Gemsenjäger and colleagues, prospective data were collected from 159 patients with PTC who underwent therapeutic, prophylactic, and no CND in 42, 29, and 88 cases, respectively. Of the patients who underwent a CND, 1 developed permanent hypoparathyroidism (1%) and 4 developed permanent RLN injury (6%). No patients in the group treated without CND developed permanent hypoparathyroidism or RLN injury.

In a third cohort study, Palestini et al collected prospective data on 305 patients with PTC who underwent therapeutic, prophylactic, and no CND in 64, 93, and 148 cases, respectively. No patients who underwent CND developed permanent RLN injury or hypoparathyroidism. Transient RLN injury occurred in 10 patients who underwent CND (6%) vs 2 who did not receive a CND (1%). Transient hypoparathyroidism occurred in 45 patients who underwent CND (29%) vs 20 who did not undergo CND (13%).

Several other recent studies of CND from specialized units have reported permanent hypoparathyroidism in 0% to 11% of patients and transient hypoparathyroidism in 14% to 60% of patients. These studies have also reported permanent RLN injury in 0% to 4.2% of patients and transient RLN injury rates of 0% to 7.3%.

Multiple studies have evaluated the complication rates of reoperative thyroid surgery for benign and malignant thyroid disease. Snook and colleagues evaluated a series of 10 patients treated for recurrent disease after being treated with a total thyroidectomy for benign multinodular goiter. None of the 10 patients developed permanent RLN injury or permanent hypoparathyroidism. Roh and colleagues examined a series of 22 patients who underwent comprehensive central and ipsilateral neck dissections for recurrent differentiated thyroid cancer in the lateral neck. In this series, 1 patient developed permanent RLN injury (5%) and 2 patients developed permanent hypoparathyroidism (9%). Of the 20 patients who underwent recurrent central neck surgery for recurrent or persistent thyroid cancer described by Kim and colleagues, no patients developed permanent RLN injury, and only 1 developed permanent hypoparathyroidism (5%). The rates of RLN injury and hypoparathyroidism following procedures performed by expert surgeons for recurrent central neck disease are not significantly different from the rates for initial surgical therapy. As a result, patients with recurrence in the central neck may be best managed by referral to a specialized center with expertise in endocrine surgery.

A major limitation of this study is the nonrandomized, retrospective design. The other limitation is the duration of follow-up. Considering the indolent nature of PTC, the short follow-up of only 3.8 years in the patients who did not have a CND and the 2.8-year follow-up in patients who had a CND probably makes the observed recurrence rate an underestimate of the true recurrence rate.

In conclusion, we recommend CND for PTC in patients with enlarged or sonographically abnormal cervical lymph nodes. Currently, no conclusive evidence exists to indicate that a prophylactic CND for patients with PTC without abnormal lymph nodes has a beneficial effect on recurrence or mortality rates. Our study indicates a low recurrence rate in patients who do not undergo a CND. Several studies, including the present study, provide evidence that prophylactic CND is associated with increased morbidity, even when performed by experienced surgeons. The low recurrence rate in the central neck combined with the potential for increased morbidity may outweigh the potential benefit for routine CND. Rather than advocating routine CND for all patients with PTC, physicians should involve patients in the discussion and decision making regarding whether to perform CND. Prophylactic CND might reduce recurrence in the central neck and prevent the need for reoperation, but there might be a higher risk for permanent hypoparathyroidism and RLN injury. Patients should be fully informed of risks and benefits and given the opportunity to decide whether they wish to proceed with prophylactic CND.

Submitted for Publication: April 24, 2009; final revision received June 28, 2009; accepted July 14, 2009.

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Author Contributions: Dr McHenry had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rosenbaum and McHenry. Acquisition of data: Rosenbaum. Analysis and interpretation of data: Rosenbaum and McHenry. Drafting of the manuscript: Rosenbaum. Critical revision of the manuscript for important intellectual content: Rosenbaum and McHenry. Statistical analysis: Rosenbaum. Study supervision: McHenry.

Financial Disclosure: None reported.

Previous Presentation: This research was presented at the American Head and Neck Society 2009 Annual Meeting; May 31, 2009; Phoenix, Arizona.
REFERENCES


