The Importance of Central Compartment Elective Lymph Node Excision in the Staging and Treatment of Papillary Thyroid Cancer

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Objective: To determine the incidence of nodal involvement and assess the role of elective lymph node (LN) exploration and/or dissection in staging of tumors and treatment of patients with papillary thyroid cancer.

Design: Retrospective medical chart review.

Setting: Academic tertiary care medical center.

Patients: One hundred patients diagnosed with papillary thyroid cancer by fine-needle aspiration or intraoperative frozen section who underwent total thyroidectomy with central compartment cervical LN exploration.

Main Outcome Measure: Incidence of positive LNs in patients 45 years or older (group A) vs those younger than 45 years (group B).

Results: Sixteen (39%) of 41 patients in group A had positive LN status following LN exploration and/or dissection. Seventeen (29%) of 59 patients in group B were found to have positive LNs. According to the American Joint Committee on Cancer staging system, the tumors of 11 patients (28%) in group A would be restaged from stage I/II to stage III after establishment of the positive pathologic nodal status.

Conclusions: Lymph node metastasis was present in the central compartment in 39% of patients in group A. Presence of LN metastasis in older patients has been reported to increase the risk of recurrence of papillary thyroid carcinoma. Furthermore, recurrence and reoperation in the central compartment is associated with a higher risk of vocal cord paralysis. In patients in group A diagnosed with papillary thyroid carcinoma, routine central compartment LN exploration and/or dissection at the time of thyroidectomy is advocated, which allows more accurate staging of tumors and appropriate treatment. Elective excision of central compartment LNs in this older age group may improve locoregional control and possibly reduce morbidity in the long run.


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The incidence of lymph node (LN) metastasis in cases of well-differentiated thyroid carcinoma (WDTC) has been reported to be 20% to 90%.1-9 The reasons for this wide range are unclear, and controversy still remains regarding whether LN dissection needs to be performed at the time of thyroidectomy. Nodal metastasis to the central compartment is difficult to establish by clinical examination, yet the presence of nodal metastasis can influence the staging of WDTC in patients 45 years or older. Currently, staging of thyroid cancer is generally based on extent of the primary tumor, clinical examination, and radiographic findings, particularly the postthyroidectomy radioactive iodine survey scan. Therefore, according to the 2002 American Joint Committee on Cancer staging guidelines, T1 and T2 lesions in patients who are 45 years or older would be staged as stages I and II, respectively, if no abnormal adenopathy is detected by clinical examination, radiographic means, or intraoperatively. In this age group, a previously assigned stage I or stage II WDTC would be reassigned to stage III if nodal involvement is established in the level VI central compartment (paratracheal, pretracheal, or prelaryngeal). Knowledge of the central compartment nodal status is important for accurate staging and formulating an appropriate paradigm for subsequent cancer surveillance. It may also help determine whether the patient would benefit from adjuvant treatment with radioactive iodine and/or thyroxin suppression. Furthermore, in older patients, removal of positive LNs may have therapeutic benefits. Vini et al10 conducted a study that followed 111 patients who were...
70 years or older with WDTC and found that 21% of them developed locoregional recurrent disease. In this older group of patients, recurrent disease occurred relatively soon after initial treatment. Studies suggest that there are biologic differences in the thyroid tumor cells of older patients that result in a reduced capacity to take up radioactive iodine. A study conducted by Schlumberger et al noted that only 53% of patients older than 40 years displayed radioactive iodine uptake at metastatic sites compared with 90% of patients younger than 40 years. Therefore, treatment with radioactive iodine may not be effective in treatment of residual nodal metastasis in the older patient population. In those patients’ tumors that are not iodophilic, excision of central compartment LNs may be therapeutic and may reduce recurrence in this compartment. Thus, elective excision of central compartment LNs at the time of thyroidectomy for papillary cancer would provide staging information that is more accurate and may have therapeutic and prognostic implications, particularly for patients who are 45 years or older. Previous studies have reported the incidence of cervical LN metastasis from papillary carcinoma but not specifically the incidence in the older age group. It is for this older group that there may be therapeutic and prognostic implications if their tumors are restaged from N0 to N1a. This study aims to determine the true incidence of LN metastasis to central compartment in the older vs younger age groups by routinely exploring and/or dissecting that compartment in patients diagnosed with papillary carcinoma.

Methods

This retrospective review was conducted under the approved guidelines of our institutional review board. From January 2000 to May 2004, the medical charts of 620 patients who underwent thyroidectomy performed by the senior author (M.S.) at our tertiary care medical center were reviewed. One hundred sixty patients were treated for WDTC. Of these, 60 patients who were diagnosed with cancers other than papillary carcinoma or who were unexpectedly diagnosed with papillary carcinoma in the final pathologic findings, and therefore did not undergo central compartment dissection, were excluded. Thus, the population in this study comprised 100 patients (group A, \( \geq 45 \) years old [41 patients], and group B, \(< 45 \) years old [59 patients]) who were diagnosed with papillary thyroid cancer preoperatively by fine-needle aspiration or intraoperatively on frozen section and treated with total thyroidectomy and central compartment LN exploration or dissection. Six of the 100 patients underwent single LN excision (2 in group A and 4 in group B). The rest underwent central compartment LN dissection, which consisted of removing the contents of the pretracheal and ipsilateral parastrachal compartments. Generally, when performing paratracheal compartment dissection, the contents between the trachea and the carotid artery were removed (Figure). Our surgical technique for paratracheal and pretracheal compartment dissection is as follows: the recurrent laryngeal nerve is usually identified distally near the lower border of the cricothyroid muscle. After the thyroid is removed, the nerve is dissected retrograde until it courses under the clavicles, the innominate artery, or the right carotid artery. The fat and fascia are dissected off the nerve and usually reflected medially, and then dissected off the trachea. If possible, the specimen is removed en bloc. However, additional nodal contents that are lateral or deep to the nerve may be removed separately. Every attempt is made to preserve the parathyroid gland(s). In some instances, a prominent vascular pedicle supplying the inferior parathyroid gland can be identified. In this setting, the gland, together with the pedicle, is microsurgically dissected and reflected laterally or inferiorly, preserving the gland and its blood supply. Any ischemic or removed parathyroid gland, which usually is the inferior gland, would be reimplanted. The superior parathyroid glands are meticulously dissected and preserved during removal of the thyroid gland. They are usually not affected by the paratracheal LN dissection.

The specimens were sent for routine histopathologic examination. Tumors were staged according to the AJCC Staging Manual. The distributions of the T stage for tumors in the 2 patient groups are as follows. For group A, the percentages (numbers of patients) were 56% (23) for T1, 27% (11) for T2, and 17% (7) for T3; for group B, 74% (44) for T1, 14% (8) for T2, and 12% (7) for T3. The incidence of positive LNs is determined from the reports of pathologic results. We used the t-test for statistical analysis. Vocal cord function was assessed preoperatively and postoperatively by laryngoscopy in all patients. In the data analysis, recurrent laryngeal nerve paralysis that resulted from removing a tumor that was significantly adherent to or encasing the recurrent laryngeal nerve was not considered a complication of central compartment dissection.

Table 1 and Table 2 show the incidence of LN metastasis in the central compartment. In each patient, the number of pathologically positive LNs identified ranged from 1 to 16 (mean, 6). A total of 33 patients (33%) were found to have LN metastasis. Sixteen (39%) of the 41 patients in group A were found to have positive LNs, and 17 (29%) of the 59 patients in group B were found to have positive LNs (\( P = .29 \)). Eleven of the 16 patients in group A with metastatic LNs had T1 and T2 primary tumors. The tumors of these patients were initially clinically staged as N0 or stage I/II and were subsequently restaged to stage III because of the positive LNs.

There were no cases of permanent vocal cord paralysis or permanent hypocalcemia in the 100 patients who underwent central compartment LN dissection. The incidence of transient vocal cord paresis was 1%, which had resolved at 6-month follow-up. None of the patients had...
unexpected recurrent laryngeal nerve paralysis. These complication rates were similar to those for patients who underwent thyroidectomy without central compartment LN dissection at our institution.

### Comment

Papillary carcinoma is often multifocal and has a high incidence of occult nodal disease. Clinical examination is not a reliable indicator of nodal involvement. Nodal metastasis from papillary cancer traditionally had not been considered a significant prognostic indicator. However, recent studies have demonstrated nodal involvement in high-risk groups to be a significant indicator of prognosis. A multivariate analysis conducted on survival data obtained from 2966 patients with papillary cancer by Noguchi et al in 1990 showed that LN metastasis was an independent risk factor. The guidelines of the American Association of Clinical Endocrinologists also indicate that LN involvement increases the risk of local and regional recurrence. Scheumann et al reported that nodal status significantly influenced the tumor recurrence, thereby advocating compartment-oriented LN dissection to enhance survival and lower tumor recurrence. Tisell et al showed improvement in survival of patients with papillary thyroid cancer after surgical microdissection of the central compartment. Thus, there have been opposing perspectives over the years regarding the role of elective lymphadenectomy at the time of initial treatment of differentiated thyroid carcinomas. It has been argued that microscopic nodal disease from papillary cancer can be treated with radioactive iodine. However, some papillary cancers may not concentrate iodine, and studies have shown that there are biologic differences in the tumor cells of older patients, resulting in a reduced capacity for radioactive iodine uptake. Because the incidence of central compartment nodal metastasis is greater than 30%, as confirmed herein, there may be a significant risk of recurrence in the central compartment. According to Tisell, central metastases are most unfavorable for survival, and the risk of complications is increased by repeated operations in the central area. Indeed, recurrent disease in the central compartment following failure of treatment with radioactive iodine requires surgical treatment, and reoperation in this compartment is associated with higher complication rates. In a prospective study by Hisham et al of 116 patients who underwent repeated operation for malignant and benign thyroid disease, the overall complication rate was 15%. Recurrent laryngeal nerve injury was noted in 2 patients (1.7%). However, the rate of not being able to identify the recurrent laryngeal nerve during surgery was much higher: 15% (17 of 116). The incidence of permanent hypocalcemia was 5.2%. Other complications included tracheal perforation in 3 patients (2.6%) and esophageal perforation in 1 patient (0.9%). Postoperative hematoma and wound infection were seen in 3 patients (2.6%). In another prospective study consisting of 1604 repeated thyroidectomies, the incidence of recurrent laryngeal nerve injury was as high as 6%. In contrast, central compartment selective lymphadenectomy at the time of primary thyroidectomy has been shown to be safe and without a higher morbidity rate compared with thyroidectomy alone. The low complication rates at our institution are comparable with those published in the literature. The results of our study indicate that in patients with the diagnosis of papillary cancer made preoperatively or intraoperatively, it would be important to perform central compartment LN excision at the time of the thyroidectomy. Our view is also supported by the consensus guidelines issued by the American Association of Clinical Endocrinologists and the American College of Endocrinology, which state that central neck dissection is an understaged procedure and should be the standard of care at initial operation for papillary thyroid cancer. Such a practice may reduce local recurrence rates when it is directed at the LNs most likely to be involved. This is especially important in patients who are older than 45 years because the incidence of metastasis to this compartment is high (39% in our series), and tumors in these older patients are not as likely to concentrate iodine as well as tumors in the younger age group.

At our institution, central compartment LN excision is therefore generally performed on patients diagnosed with papillary cancer by fine-needle aspiration or frozen section. Papillary thyroid cancer most commonly drains to the paratracheal compartment. These LNs can be readily explored and dissected at the time of the primary operation through the same incision and without additional risk of complications. Our study found that the incidence of metastasis to the central compartment was somewhat higher in group A compared with group B. More important, approximately 27% of tumors (11 of 41) of the patients in group A would have been understaged as stage I or II had they not undergone LN dissection. Knowledge of nodal status and accuracy of staging are important in the long-term follow-up of these patients, particularly those who are older than 45 years with small tumors. These T1 and T2 tumors are frequently regarded as being an early stage and having good prognosis. A multivariate analysis conducted on survival data obtained from 2966 patients with papillary cancer by Noguchi et al in 1990 showed that LN metastasis was an independent risk factor. The guidelines of the American Association of Clinical Endocrinologists also indicate that LN involvement increases the risk of local and regional recurrence. Scheumann et al reported that nodal status significantly influenced the tumor recurrence, thereby advocating compartment-oriented LN dissection to enhance survival and lower tumor recurrence. Tisell et al showed improvement in survival of patients with papillary thyroid cancer after surgical microdissection of the central compartment. Thus, there have been opposing perspectives over the years regarding the role of elective lymphadenectomy at the time of initial treatment of differentiated thyroid carcinomas. It has been argued that microscopic nodal disease from papillary cancer can be treated with radioactive iodine. However, some papillary cancers may not concentrate iodine, and studies have shown that there are biologic differences in the tumor cells of older patients, resulting in a reduced capacity for radioactive iodine uptake. Because the incidence of central compartment nodal metastasis is greater than 30%, as confirmed herein, there may be a significant risk of recurrence in the central compartment. According to Tisell, central metastases are most unfavorable for survival, and the risk of complications is increased by repeated operations in the central area. Indeed, recurrent disease in the central compartment following failure of treatment with radioactive iodine requires surgical treatment, and reoperation in this compartment is associated with higher complication rates. In a prospective study by Hisham et al of 116 patients who underwent repeated operation for malignant and benign thyroid disease, the overall complication rate was 15%. Recurrent laryngeal nerve injury was noted in 2 patients (1.7%). However, the rate of not being able to identify the recurrent laryngeal nerve during surgery was much higher: 15% (17 of 116). The incidence of permanent hypocalcemia was 5.2%. Other complications included tracheal perforation in 3 patients (2.6%) and esophageal perforation in 1 patient (0.9%). Postoperative hematoma and wound infection were seen in 3 patients (2.6%). In another prospective study consisting of 1604 repeated thyroidectomies, the incidence of recurrent laryngeal nerve injury was as high as 6%. In contrast, central compartment selective lymphadenectomy at the time of primary thyroidectomy has been shown to be safe and without a higher morbidity rate compared with thyroidectomy alone. The low complication rates at our institution are comparable with those published in the literature. The results of our study indicate that in patients with the diagnosis of papillary cancer made preoperatively or intraoperatively, it would be important to perform central compartment LN excision at the time of the thyroidectomy. Our view is also supported by the consensus guidelines issued by the American Association of Clinical Endocrinologists and the American College of Endocrinology, which state that central neck dissection is an understaged procedure and should be the standard of care at initial operation for papillary thyroid cancer. Such a practice may reduce local recurrence rates when it is directed at the LNs most likely to be involved. This is especially important in patients who are older than 45 years because the incidence of metastasis to this compartment is high (39% in our series), and tumors in these older patients are not as likely to concentrate iodine as well as tumors in the younger age group.

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progesterone. Recent studies have shown that nodal metastasis can be found in a significant percentage of T1 tumors, especially microcarcinomas. Furthermore, the presence of LN metastasis in this group is a good predictor of recurrence. Thus, accurate staging of LNs is very important, particularly in patients older than 45 years with small tumors, so that these patients with LNs classified as N+ can be treated more aggressively and followed up closely for recurrence. It provides the clinician with information on the risk of recurrence. It also can guide the physician as to how aggressive the cancer surveillance should be (ie, the frequency of follow-up surveillance studies, such as a thyroglobulin level or a whole-body radioactive iodine scan).

Currently, no consensus guideline exists regarding who should be treated with postoperative radioactive iodine treatment and what the most appropriate dose is (it ranges from 130-175 mCi [5550-6475 MBq] to a much lower remnant ablative dose of <100 mCi [<3700 MBq]). With accurate information on pathologic nodal status, one may be able to be more selective as to who should be treated with a high dose vs a remnant ablative dose, and who should also be treated with aggressive thyroid hormone suppression. In some institutions, patients with papillary thyroid cancer may routinely receive treatment with a higher dose of radioactive iodine (>100 mCi (>3700 MBq)). Because these treatments have potential adverse effects, it would be better to be more selective in deciding who really needs treatment. Higher doses of radioactive iodine can cause chronic sialostasis and sialoadenitis. Cumulative high doses of radioactive iodine may increase the risk of developing leukemia and also may reduce the sperm count in men. Long-term levothyroxine suppressive therapy may have adverse effects on bone and the heart, including accelerated bone turnover, osteoporosis, and atrial fibrillation. Therefore, for patients with T1 (and possibly even T2) lesions and true pathologically diagnosed N0 LNs, one could potentially take a more selective approach with administration of radioactive iodine and potentially spare the patient a high dose of radioactive iodine. Many radiation oncologists and endocrinologists do take a more selective approach and treat early-stage or low-risk patients with a lower dose to ablate the thyroid remnant. The typical dose of radioactive iodine used for remnant ablation ranges from 50 to 100 mCi (1850-3700 MBq), depending on the percentage of uptake in the thyroid remnant. High-risk patients are generally treated with higher doses (150-175 mCi [5550-6475 MBq]). When taking this more selective approach, the decision about who should receive the high dose is often based on the patient’s age and the extent of the primary tumor. Unless the surgeon has performed central compartment dissection, nodal metastasis is presumed not to be present if the patient’s LN is clinically diagnosed as being N0 and a postablative radioactive iodine scan does not show any clear-cut evidence of nodal metastasis. Postablative scans generally show a small area of uptake in the thyroid bed, which is usually interpreted as a thyroid remnant but certainly could represent residual central compartment metastasis. Furthermore, radioactive iodine may not detect small metastatic LNs, particularly if they do not concentrate iodine. Thus, if one does take a selective approach to adjuvant therapy, inaccuracy in nodal staging will certainly underestimate the LN of a patient who is older than 45 years, which could potentially result in undertreatment and place the patient at risk for recurrence. For example, the tumor of an older patient with a T1 lesion (ie, a 1-cm tumor) who did not undergo paratracheal LN dissection will be staged as stage I and that patient may not receive treatment with postoperative radioactive iodine or at most will be treated with a remnant ablative small dose of radioactive iodine. However, if positive LNs are found following central compartment dissection, the patient’s tumor will be restaged, and at our institution the patient will be treated with a higher therapeutic dose of radioactive iodine (150-175 mCi [5550-6475 MBq]). One can argue that those with larger (T3 or T4) primary tumors are generally treated with 150 to 175 mCi (5550-6475 MBq) of radioactive iodine and, therefore, that small nodal disease would be treated anyway and elective LN dissection is not necessary. This may be true; however, in older patients treatment with radioactive iodine may not be as effective. Furthermore, because T3 and T4 primary tumors and older patients are more likely to present with metastasis to regional LNs, those patients have a greater chance of recurrence in the central compartment LNs. Reoperation in this compartment predisposes the patient to increased risk of complications. For these reasons, central compartment dissection at the time of primary thyroidectomy not only is important for staging but also may be therapeutic in patients who are 45 years or older. We focused only on level VI in this study, primarily because it is our opinion that this compartment should be addressed at the time of thyroidectomy to minimize the risk of having to go back into it. One could argue that metastasis to the lateral neck can occur without nodal metastasis to level VI; however, it is our opinion that elective dissection of the lateral neck is not justified at the time of thyroidectomy in the clinically N0 neck (in contrast to opinions in the Japanese literature because the lateral neck that has not been operated on can be subsequently treated without any increased surgical risks.

In summary, performing routine elective LN dissection in the central compartment at the time of thyroidectomy in patients diagnosed preoperatively or intraoperatively with papillary carcinoma is important. It provides more accurate staging information, helps guide postoperative treatment, and may ultimately reduce the rate of recurrent disease in the paratracheal compartment. Whether a paratracheal LN dissection and selective approach to postoperative treatment with radioactive and suppression therapy will have significant impact on quality of life and disease outcome is unclear and can be determined only by long-term outcome studies. We hope to be able to answer those questions in the future through a multi-institutional study.

CONCLUSIONS

This study showed that the incidence of LN metastasis to the central compartment is 39% in patients 45 years or older and 29% in patients younger than 45 years. The
presence of LN metastasis in older patients has been reported to increase the risk of recurrence from papillary thyroid carcinoma. Furthermore, recurrence and reoperation in the central compartment can be associated with a high risk of vocal cord paralysis and hypocalcemia. In patients 45 years or older diagnosed with papillary carcinoma, routine central compartment LN exploration and/or dissection at the time of thyroidectomy allows more accurate staging and appropriate treatment, which may improve locoregional control. Furthermore, it may reduce the risk of having to reoperate in the thyroid bed, which is certainly associated with increased morbidity.

When total thyroidectomies and LN dissection are performed by experienced endocrine surgeons, morbidity and mortality rates are low. Although the role of LN involvement as a prognostic indicator in well-differentiated thyroid cancer is not yet conclusive, given the association of LN metastases with increased risk of tumor recurrence, central compartment LN exploration and/or dissection at the time of total thyroidectomy is advocated as the standard surgical procedure for treatment of papillary thyroid carcinoma. This retrospective study addresses only the central compartment and not the lateral compartment. At our institution, elective lateral neck dissection is not performed for the clinically N0 neck (nonpalpable disease). The use of ultrasound to assess lymphadenopathy in the lateral neck will likely play an important role in the future in the elective treatment of the lateral neck.

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REFERENCES


