Does central lymph node dissection in patients with papillary thyroid carcinoma increase morbidity rates? – A comperative study

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ABSTRACT

Objectives: To evaluate the incidence of hypocalcemia and recurrent laryngeal nerve disfunction secondary to level VI lymph node dissection in patients with papillary thyroid carcinoma.

Methods: This randomized prospective study investigated a group of 60 consecutive papillary thyroid carcinoma patients who initially underwent thyroidectomy plus level VI neck dissection (29 patients) - with or without lateral neck dissection - and thyroidectomy alone (31 patients). In order to evaluate the morbidity of central lymph node dissection, postoperative recurrent nerve dysfunction and hypocalcemia were compared between two groups.

Results: Early postoperative hypocalcemia was higher in the thyroidectomy plus neck dissection group (group 1) than the thyroidectomy without neck dissection group (group 2) (18/29-62.1% vs. 6/31-19.4%; p=0.001). Permanent hypocalcemia developed in 4 patients of group 1 (4/29-13.8%) and 2 patients of group 2 (2/31-6.5%) six months after surgery (P=0.672). No permanent vocal cord paralysis was observed in both groups. Transient vocal cord paralysis occurred in a patient of group 1.

Conclusions: According to the study results, central lymph node dissection can be safely applied in papillary thyroid carcinoma patients without increasing the risk of permanent morbidity in the hands of experienced surgeons.

Introduction

Papillary thyroid carcinoma (PTC) is the most frequent malignant disease of the thyroid gland. One of the most prominent features of PTCs, even for microcarcinomas, is high regional lymph node metastasis (LNM) in particular in the central compartment. Lymph node metastases of PTCs have never been accepted as poor prognostic factor in most of the proposed prognostic indexes. However recent studies have shown that regional LNM were associated with more frequent disease recurrence and the presence of LNM have been described as an independent risk factor of recurrence (1-3). A deleterious impact of cervical LNM on survival has also been reported (1, 4).

While there is an unanimity on performing a central neck dissection (CND) in case of clinically proven neck metastases, there is no consensus on the role of prophylactic CND for potential microscopic or undetectable LNM. Despite the benefits of prophylactic neck dissection in patients with potential microscopic or undetectable LNM, the potential risks of recurrent laryngeal nerve (RLN) and parathyroid injuries must be kept in mind. It is indicated that 3-6 % of the patients who went through thyroidectomy plus CND might have transient vocal cord paralysis and permanent hypoparathyroidism (5, 6).

The present study aimed to investigate serum calcium levels and RLN functions after total thyroidectomy (TT) with or without CND in patients who had surgery for PTC.

Methods

After the approval of local ethical committee, total of 60 newly diagnosed PTC patients who went through a TT with or without neck dissection were taken into this prospective controlled study. Patients with a history of any type of neck or thyroid surgery were excluded. A written consent was received from each patient before surgery. Prior to surgery, in the same day, serum calcium and parathyroid hormone (PTH) levels of all patients were measured. Two study groups were generated according to CND. Group 1 consisted of 29 patients who had TT plus neck dissection (ND), and Group 2 included 31 patients who underwent only TT. Clinical evaluation of the neck based on physical examination and high-resolution ultrasonography. In Group 1, all patients with clinically positive cervical lymph

nodes underwent therapeutic neck dissection which involved both lateral and bilateral central lymph nodes.

Patients with T3 or T4 tumors underwent prophylactic unilateral or bilateral CND according to the primary tumor localization even there were no evidence of clinically positive nodes. Patients with no evidence of clinically positive nodes underwent prophylactic unilateral or bilateral CND according to the primary tumor characteristics such as tumor extension, localization, multicentricity etc. CND was performed in a conventional way; lymph nodes between cranially to arteria thyroidea superior and the hyoid bone, caudally to innominate vessels, laterally to the carotid sheaths, and dorsally to the fascia prevertebralis were removed (7). Operations were performed by skilled head and neck surgeons who are experienced in thyroid surgery. All surgical specimens were attentively examined for the presence of accidentally removed parathyroid tissues. Autotransplantation of devascularized or surgically removed parathyroid glands were routinely done after confirmation by frozen-section analysis. In patients with extrathyroidal tumors and/or extracapsular lymph node spread, reimplantations were performed with caution not to inadvertently reimplant the tumor with parathyroid tissue. Patients' symptoms and postoperative serum calcium levels were monitored at the 6th, 24th, 48th, and 72nd postoperative hours. PTH levels were measured at the 1st postoperative hour. Patients who developed symptoms of hypocalcaemia, and/or with a >65% decline in postoperative PTH levels, received oral calcium and vitamin D replacements. At the presence of significant symptoms of hypocalcaemia, intravenous calcium gluconate was administered. All patients who had had medication for hypocalcaemia were hospitalized for a minimum of 3 postoperatively. Remainders were discharged 24 hours after the operation. Follow-ups of all patients were performed at the 1st week, 1st and 6th months to evaluate the RLN functions, and serum calcium levels.

Statistical analysis

The analysis of data was performed with SPSS version 15.0 (SPSS Inc., Chicago, IL). The groups were compared with the Pearson's chi-square and Fisher's exact test.

Results

There were 20 men and 40 women, with a mean age at the initial treatment of 46.8 years (12-77 years). In Group 1, 15 patients had clinically determined lateral LNM, and two patients had ultrasonographically determined suspicious level VI LNM. While 15 patients underwent both lateral and CND, 2 patients with suspicious level VI LNM and 12 patients with clinically negative neck had only unilateral or bilateral CND.

Histopathological investigation showed LNM in the central neck of 16 (16/29- 55.2%) and the lateral neck of 13(13/29-44.8%) patients in Group 1. Among the 12 patients with clinically negative neck, 5 were found with occult central lymph node metastases (5/12- 41.7%).

Parathyroid gland autotransplantations were performed in 10 and 1 patients in Groups 1 and 2 respectively. Postoperative hypocalcaemia requiring calcium supplements of Group 1 (18/29- 62.1%) was higher than Group 2 (6/31-19.4%, P=0.001). Permanent hypocalcaemia requiring calcium supplements occurred in 4 patients of Group 1 (4/29-13.8%) and 2 patients of group 2 (2/31-6.5%) six months after surgery (P=0.672). All patients with permanent hypocalcaemia in Group 1 had bilateral CND.

In Group 1, postoperative hypocalcemia incidence was found higher in patients who underwent both lateral neck dissection (LND) and CND (11/15-73.3%) than the patients who had only CND (7/14-50%) (P=0.264). TT plus combined LND and CND significantly increased hypocalcemia risk when compared with TT alone (11/15 73.3%- 6/31 19.4%) (P=0.001) (Table).

No permanent vocal cord paralysis developed in both groups. Transient vocal cord paralysis occurred in a patient of Group 1 who underwent LND plus CND.

Discussion

PTC is the most common malignant disease of the thyroid worldwide. One of the most prominent features of the PTCs is, even for microcarcinomas, its susceptibility to make metastasis to cervical lymph nodes in the central and lateral compartments (8). Within the central compartment, lymph nodes of the pretracheal and ipsilateral paratracheal are frequently involved (7). Involvement of lateral lymph nodes without central lymph nodes (skip lesion) is rare. This nodal involvement patern is similar for both microcarcinomas and larger papillary carcinomas.

Patients with clinically positive neck disease must be treated in terms of neck involvement without doubt, and the preferred method is performing a regular neck dissection rather than berry picking procedure. In case of a T3 or T4 tumor and N1a neck, a CND; but in case of a N1b neck a lateral ND involving levels II, III, IV, V plus the levels VI and VII must be dissected with a compartmental dissection technique. But the indication for CND in patients with T1 and T2 tumors and N0 neck is still controversial.

Although definitions may vary, the term CND is used for dissecting the lymphatic and fibro-fatty tissue within the central compartment of the neck, with preserving the main veins and arteries, nerves and viscera. It includes the level VI and may extend to level VII. It may be uni-bilateral. It may or not include thymectomy. It can be prophylactic or therapeutic (9).

The rate of oOccult LNM are alsois high in PTC patients. Seventy percent to 90% of patients with PTC and clinically (-) neck disease might have micrometastases in adjacent lymph nodes (10). Existence of metastatic central lymph node prevalence in the surgical specimens ranges from 30% to 65% in patient with clinically node-negative neck (7). These high rates of nodal metastases may contribute to persistent and recurrent disease of PTC. Indeed, recent studies indicate that the presence of LNM in patients with PTC increases locoregional recurrence rate and disease-related mortality (11). It has been reported that 5% to 20% of PTC patients treated with TT without lymph node dissection have developed palpable local recurrence within 10 years (12). Such recurrences localized to the cervical lymph nodes in 60% to 75% of cases with the central compartment being the most frequently involved site (13). In the study of Leboulleux et al. (2), persistent disease was seen only in patients with central LNM, and 73% of lymph node foci of uptake on post ablation total body scanning were located in the central compartment. The authors suggested that either a complete central compartment dissection is difficult to achieve or that central LNM reflect a more aggressive disease.

In PTC management, optimizing patient outcomes should be balanced with the risk of disease and risk from treatment. The only way not to perform an under or overtreatment is perceiving which patients with N0 disease have LNM at the time of

surgery. Unfortunately, no test is currently available to verify the presence of metastases preoperatively in patients with an N0 neck. Metastasis in this area are not reliably identified by preoperative high resolution ultrasound (12, 14). Similarly, in the present study, ultrasonography pointed out level VI metastasis with suspicion in 2 patients among 16 patients with level VI metastases (12.5%). It is also difficult to define these nodes intraoperatively. Despite the fact that lymph node staging is part of the surgical treatment of most cancers and determines the necessity of adjuvant therapies, prophylactic central lymph node dissection for lymph node staging as the initial treatment of PTC remains controversial in the absence of LNM detected at preoperative assessment or intraoperatively by palpation (15, 16).

According to opponents, histopathologically diagnosed central compartment LNM does not affect survival (14). Moreover, prophylactic CND might increase the risk of complications like hypoparathyroidism and RLN injury. The reported incidence of permanent hypoparathyroidism and temporary vocal cord paralysis is 3% to 6% in patients with thyroidectomy plus CND (17). If LNM of PTC are not detrimental for patients and do not affect the quality of life, it is debatable whether routine neck dissection should be performed for all such carcinomas right after the diagnosis.

There is no prospective, randomized study to specify whether the inclusion of CND to TT for PTC makes a way for an elevated risk of permanent hypoparathyroidism and nerve injury.

Kyoung So et al. (18), found that the frequency of transient hypocalcemia was higher in patients with TT with CND than the ones with only TT for papillary thyroid microcarcinoma. However, no statistically significant difference was present (41.2% vs 33.6%, respectively; P= 0.235). Permanent hypocalcemia frequency was also 3 times greater in the TT with CND patients (5.6% vs 1.8%). Among the 232 patients, the authors reported 8 (3.4%) temporary and 3 (1.3%) permanent vocal cord palsy; of those 11 patients 6 had TT alone and 5 TTs with CND. Although these differences were also not statistically significant (P=0.105), they suggested that prophylactic CND should not be proposed in the majority of cN0 papillary thyroid microcarcinoma patients, even though a greater incidence of subclinical LNM is expected.

Roh et al (19), have shown that TT combined with CND (pretracheal, bilateral paratracheal, and superior mediastinal) in patients with PTC significantly elevates the rate of transient hypocalcemia. Permanent hypoparathyroidism has been reported as 2.5%, a finding akin to rates of 1.5% to 4.0% in the literature.

In a retrospective study performed with 1087 clinically N0 PTC patients, Giardano et al (20) reported that ipsilateral and bilateral CND were associated with higher transient hypoparathyroidism rate and if CND is bilateral the risk of permanent hypoparathyroidism is highest. No significant differences were found in terms of transient and permanent RLN injury rate. They concluded that the increased rates of transient and permanent hypoparathyroidism proposed an analytical inspection of indications for the routine prophylactic CND in patients with PTC. Prophylactic ipsilateral CND with TT might represent a useful strategy for lessening the permanent hypoparathyroidism rate. According to the authors, complementary completion contralateral paratracheal LND should be performed in existence of LNM on peroperative frozen-section evaluation (21).

Although the lateral neck dissection is performed away from the parathyroid glands, it is said that it might increase the risk of injury with dissection near the carotid artery which may affect the inferior thyroid artery by interrupting its blood supply to the parathyroid glands. In the study by Roh et al., hypocalcemia was highest in patients underwent combined central and lateral neck dissection with total thyroidectomy (46.2%). Addition of lateral to CND resulted in an elevated risk of postoperative hypocalcemia when compared with TT plus CND (19). On the contrary, in a study by Cheah et. al. (22), the hypocalcemia rate was %75 in CND, %67 in CND + lateral neck dissection %46 in lateral neck dissection alone. In the current study, the hypocalcemia was higher when lateral dissection was added to CND.

Proponents of routine central node dissection claim that CND may lower the recurrence and improve survival. The procedure grants more accurate staging of the tumor, treatment of micrometastases, and more appropriate adjuvant treatment. Routine CND can achieve lower thyroglobulin levels, facilitate radioactive iodine ablation, eliminate the need for reoperation, and eliminate or decrease the dose of adjuvant radioiodine. Moreover, reoperation for regional recurrence in the central compartment is difficult because of scar tissue, fibrosis, and lack of surgical dissection planes secondary to initial surgery. It becomes a complicated process. There is increased risk for both RLN and parathyroid gland injury. Although the prognosis of patients with PTC is generally fine, patients who experience lymphatic recurrence, especially in the central compartment, will suffer from higher rates of morbidity and mortality usually from trachea or great vessel invasion, or from involvement of the RLN.

Routine central LND in patients with PTC and suspected Hurthle cell carcinoma has been proposed by the American Thyroid Association (ATA) Guidelines Taskforce (23). But, these recommendations caused serious controversy among the clinicians because of the insufficiency of secure supporting data. Therefore, the revised management guidelines in 2009 suggested that prophylactic central lymph node dissection may be performed when advanced primary PTC (T3 or T4; Grade C recommendation) is present (24). It`s also expressed that “the recommendations should be depicted in the light of available surgical expertise”. Otherwise, this approach can be associated with increased morbidity in the hands of inexperience surgeons.

Gemsenjager et al. (25) reported that, patients who underwent

Table1. Early postoperative and permanent hypocalcemia rates of groups

	Group 1 (Thyroidectomy and Neck Dissection) n=29	Group 2 (Thyroidectomy Alone) n=31	P
Postoperative Hypocalcemia	18 (62.1%)	6 (19.4%)	0.001
Permanent Hypocalcemia	4 (13.8%)	2 (6.5%)	0.672

prophylactic CND and those not, display neither permanent hypoparathyroidism nor nerve injury. In therapeutic CND group one patient (2.4%) displayed permanent hypoparathyroidism and 3 patients (7.1%) permanent RLN injuries. All of the patients with nerve injury had extended nerve dissection for the excision of nodal metastases. Sacrification of the nerve was required in a patent because of the central compartment disease.

In a retrospective study, Henry et al (6). enrolled 100 patients: 50 with benign multinodular goiter and 50 with PTC. All patients had TT, and the patients with malignant disease underwent an additional prophylactic bilateral CND. They reported that none of the patients presented permanent hypoparathyroidism, but two patients in the group with bilateral prophylactic CND displayed permanent hypoparathyroidism. No patient had permanent nerve injury.

Shan et al (21), made a meta-analysis and a systematic review concentrating on surgical morbidities and locoregional recurrence after TT with CND versus TT alone. They`ve analyzed 16 trials. No increased risk of temporary or permanent RLN injury, and permanent hypocalcemia was present when CND was performed with TT. However, postoperative transient hypocalcemia was more frequent after TT with CND than after TT alone.

The current study involving 60 patients with PTC, compared hypocalcemia and RLN injury between 29 patients who underwent a TT plus CND and 31 patients who underwent a TT without CND. The study revealed that patients undergoing CND experienced greater hypocalcemia (4/29- 13.8 %) compared to patients who underwent a TT alone (2/31-6.5%). The findings of the study also indicate significant hypocalcemia occurs if an LND is also performed. In the current study, hypocalcemia was mostly present in patients who underwent combined CND plus LND with TT (11/15-73.3%). This can be explained by increased vascular compromise secondary to extension of nodal dissection (18).

The current study also showed that increased hypoparathyroidism appeared to be associated with bilateral surgical dissection of level VI, and high rate of incidentally removed parathyroid glands. Routine investigation of surgical specimen for incidentally removed parathyroid glands and autotransplantation of such glands after frozen section confirmation are suggested to minimize this problem.

Serum PTH levels were an earlier predictor of postoperative hypocalcemia and led more active management of the patients as stated by Noordzij et al (26). Considering the high incidence of transient hypocalcemia after TT plus CND, especially if it is done bilaterally or with concomitant LND, to prevent prolonged hospitalization, routine oral administration of calcium and vitamin D during the early postoperative period can be an alternative (27).

Only one patient developed transient nerve palsy in group 1, because of accidental nerve injury secondary to extended nerve dissections to excise extensive paratracheal lymph node metastases.

The main goal of treatment is simply avoiding morbidity and mortality. The secondary goals are achieving athyroglobulinemia, to avoid reoperative surgery and its complications, and simplifying follow-up. Despite the potentially surgically treatable nature of loco-regional PTC recurrence, the acute psychosocial impact of secondary interventions shouldn`t be ignored. This experience may be emotionally overwhelming for some patients (26).

In conclusion, noninvasive identification of microscopic deposits of metastatic disease in the cervical nodes of patients with N0 disease of PTC patients might become possible in the future. Until this is realized, elective neck dissection seems to be reasonable when weighed against the risk of neck relapse in patients with N0 neck. Although the number of patients presented is not large enough to achieve a certain result, according to this study it can be interpreted that CND can be safely performed during initial thyroid surgery as a routine by experienced surgeons specifically performing thyroid surgery. During surgery, the parathyroid glands should precisely be preserved, and the devascularized or accidentally removed glands should be transplanted after histopathological confirmation in terms of normal histological appearance.

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Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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