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Recurrence in regional lymph nodes after total thyroidectomy and neck dissection in patients with papillary thyroid cancer

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SUMMARY

Background: We investigated the risk factors of the regional lymph node (LN) recurrence in papillary thyroid cancer (PTC) patients underwent thyroidectomy and neck dissection according to the clinicopathologic features, preoperative clinical nodal status and the recurrence in previously dissected or undissected compartment of the neck.

Methods: A retrospective analysis was performed on 297 patients who underwent total thyroidectomy and LN dissection between 2004 and 2010. Patients with and without regional recurrence were compared by the various clinicopathological factors. Recurrence-free survival rates were estimated by the Kaplan–Meier and Cox regression method.

Results: With a median follow-up of 53 months, 22 (7.4%) patients developed regional LN recurrence. Initial LN metastasis and tumor size ≥ 1 cm were independent predictive factors for regional recurrence. In patients without preoperative clinical LN, Tumor size ≥ 1 cm and extrathyroidal extension were significant risk factors for regional recurrence. In cases with preoperative clinical LN, there was no specific significant factor for recurrence. Tumor size ≥ 1 cm, capsular invasion, extrathyroidal extension, and lymphovascular invasion were significant risk factors of regional recurrence in previously dissected compartments. Tumor size ≥ 1 cm and extrathyroidal extension were significant predictive factors of regional recurrence in previously undissected compartments.

Conclusions: Tumor size and LN metastasis were independent predictors of regional LN recurrence in PTC patients after total thyroidectomy and central neck dissection. Patients with tumor size >1 cm or extrathyroidal extension were more likely to have tumor recur both within the previously dissected field as well as the un-dissected compartments.

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Introduction

The thyroid cancer is the most common endocrine malignancy and papillary thyroid cancer (PTC) is the most common type of thyroid cancer accounting for approximately 85% of all thyroid cancer [1,2]. Most of the PTC shows good prognosis but some of them show aggressive behavior such as local invasion, lymph node (LN) or distant metastasis [3]. There are various factors which have been known to be associated with prognosis of PTC; age, gender,

tumor size, extrathyroidal extension, and distant metastasis [3–7]. Besides, there are a lot of reports that cervical LN metastasis at the time of diagnosis affects patient's loco-regional recurrence rate although it does not affect the survival rate unlike other head and neck cancers, but this is still controversial [5–7].

The recurrence of regional LN in PTC is not infrequent, and is closely related to patient's quality of life and sometimes survival rate [6,7]. Therefore, a lot of clinicians have made efforts to prevent the regional LN recurrence. There are many studies about risk factors associated with the recurrence of regional LN. Based on previous research, more extensive treatment such as wide range of surgery and postsurgical radioactive iodine treatment as well as prophylactic central neck dissection as an initial treatment are necessary for the patient with high risk of regional LN recurrence. In this study we investigated the pattern and the clinicopathologic

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risk factors of the regional LN recurrence in PTC patients underwent total thyroidectomy and neck dissection including prophylactic central LN dissection, therapeutic central LN dissection and/or therapeutic lateral LN dissection. In addition, we analyzed risk factors of regional LN recurrence in patients groups with or without initial preoperative clinical positive LN and patients groups with recurrence in previously dissected or undissected compartment of the neck, respectively.

Patients and methods

We retrospectively reviewed the medical records of 297 patients who received total thyroidectomy and cervical LN dissection for the PTC at Department of Otolaryngology – Head and Neck Surgery in Chungnam National University Hospital from January 2004 to December 2010. All the subject patients received LN dissection. Central LN dissection was extended superiorly to the hyoid bone, inferiorly to the innominate vein, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. The thymus was commonly preserved by separation from the central nodes. Prophylactic central LN dissection was performed in 213 patients without clinical evidence of positive LN on imaging or palpation, 35 patients with clinically evident positive central LN received therapeutic central LN dissection, and the remaining 49 patients received central and lateral LN dissection due to evidence of metastatic LN in the lateral neck before surgery. Lateral LN dissection was performed using a modified radical operation that involved complete removal of level II through V lateral cervical LNs. Level I dissection was not performed if there was no clinical evidence of metastases in level I. The patients who received lobectomy only, who did not receive central LN dissection, whose disease recurred at thyroid bed, or whose medical record is unclear were excluded in our study population. Among our 297 patients, 136 had no postsurgical metastatic LN as a result of permanent biopsy and the remaining 161 were diagnosed with pathological metastatic LN. All the 49 patients who received lateral cervical LN dissection additionally were diagnosed with lateral cervical metastasis together with central LN metastasis. All the patients received postsurgical thyroid stimulating hormone suppression therapy, and the 198 patients who were diagnosed with LN metastasis, capsular invasion, or extrathyroidal extension according to postsurgical biopsy received additional postsurgical radioactive iodine treatment. I-131 ablative therapy was administered after levothyroxine withdrawal for at least 4 weeks. A whole body scan (WBS) was performed 7 days after I-131 therapy in order to evaluate whether ablation was successful. The postoperative follow-up period was 28–110 months (average 53 months), and patients received a routine periodic clinical examination (every 3 months in the initial year and then at yearly intervals) including neck ultrasound, WBS, measurement of serum free T4, thyroid-stimulating hormone (TSH), Thyroglobulin (Tg) and anti-Tg antibodies. For patients suspected for disease recurrence, we conducted fine needle aspiration cytology and CT scan. The following criteria were used to define nodal recurrence: either pathologic evidence of disease on excision or cytology, or recurrent disease confirmed by elevated Tg and WBS. Nodal recurrence was diagnosed after finding new evidence of nodal disease in patients who initially met the criteria for remission. Persistent disease was defined as not meeting the criteria for remission throughout the whole documented observation period. The criteria for remission were: no clinical or imaging evidence of tumors, serum Tg level <2 ng/ml during TSH suppression, and stimulation in the absence of interfering antibodies. Patients with persistent disease were excluded in our study.

We investigated the pattern and the risk factors of the regional LN recurrence in terms of 3 groups of patients: (1) total PTC patients according to the clinicopathologic features, (2) prophylactic central

ND group (patients without initial preoperative clinical positive LN) vs. therapeutic central ND ± lateral LN group (patients with initial preoperative clinical positive LN) and (3) recurrence group in the previously dissected compartments vs. undissected compartment. Regional LN recurrence was defined as a recurrent disease in both lateral and central cervical lymph nodes while distant metastasis refers to lesions outside the neck region.

SPSS version 18.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Several clinicopathologic factors potentially associated with regional recurrence were addressed by univariate analysis using Fisher's exact or chi-squared tests. Significant variables in the univariate analysis were included in multivariate analysis using a binary logistic regression test. In addition, we used Kaplan–Meier method and Cox regression model for regional recurrence-free survival analysis. Statistical significance was defined as a *P* value less than 0.05.

Results

Correlation between regional lymph node recurrence and clinicopathologic factors

Among the total 297 patients, 22 (7.4%) had recurrence at their cervical LN. It took 25 months on average from initial treatment to recurrence. Among 22 patients with cervical LN recurrence, 20 had cervical LN metastasis at the time of initial treatment, and 2 had no cervical LN metastasis (Table 1). Three recurred at the central cervical LN, 16 at the lateral cervical LN, and 3 at both. Among the 3 patients with recurrence at the central cervical LN, 1 received total thyroidectomy and central lymphadenectomy and the other 2 received total thyroidectomy and central and lateral cervical lymphadenectomy as the initial treatment. Among the 16 patients with recurrence at the lateral cervical LN, 11 received total thyroidectomy and central cervical lymphadenectomy while 5 received lateral cervical lymphadenectomy additionally as the initial treatment. The 3 patients with recurrence at both central and lateral cervical LNs, 2 received total thyroidectomy and central LN dissection, and the remaining 1 received lateral LN dissection additionally as the initial treatment. Among those 16 patients with recurrence only at lateral cervical LN, 4 recurred at Level IV only, 3 simultaneously at Level II, III, and IV, 3 at Level III and IV, 3 at Level III only, 2 patients recurred at Level II only and 1 at Level III, IV, and V simultaneously. In the 3 patients with recurrence at both lateral cervical and central LNs, recurrence also developed at Level II, III, IV, VI and level II, III, VI, and level IV, both VI.

Table S1 show the relationships between regional LN recurrence and several clinicopathologic factors in the 297 PTC patients. In a univariate analysis, the regional LN recurrence rate was significantly higher in patients with a primary tumor size of ≥ 1 cm, extrathyroidal extension, lymphovascular invasion, high-risk of MACIS score criteria above 6 or LN metastasis at the time of initial treatment ($p < 0.05$). Twelve patients (10.7%) out of 112 with metastasis only at central LN at the time of initial treatment recurred but 8 (16.3%) out of 49 patients with metastasis both at central and lateral cervical LN showed recurrence, indicating higher recurrence rate at the patients with metastasis both at central and lateral cervical LN but no statistically significant difference ($p = 0.228$).

Table 1

The recurrence rate based on pathological N0, N1a, or N1b disease.

| Recurrence patients no./total patients no. | N0 | N1a | N1b |
|--------------------------------------------|-------------|---------------|-------------|
| 22/297(7.4%) | 2/136(1.5%) | 12/112(10.3%) | 8/49(16.3%) |

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