Refining the eighth edition AJCC TNM classification and prognostic groups for papillary thyroid cancer with lateral nodal metastasis

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ABSTRACT

Background: In the eighth edition, TNM staging system omits location of nodal metastasis as a criterion for staging patients with papillary thyroid cancer (PTC). Accordingly, all of non-metastatic N1b PTC patients are classified as stage I or II solely according to an age-cutoff of 55 years. We hypothesized that incorporating other lymph node (LN) factors into TNM staging system would better predict cancer-specific mortality (CSM) in N1b patients.
Methods: We enrolled 745 N1b PTC patients without distant metastasis. Alternative prognostic LN factors and cut-off points were assessed using Cox regression and time-dependent ROC analysis. Alternative prognostic groupings were derived based on minimal hazard differences for CSM among groups stratified by LN risk and age. We assessed accuracy of CSM prediction.
Results: Lateral LN ratio (LNR) > 0.3 and largest LN size > 3 cm were prognostic factors for CSM. Stage II patients (eighth edition) with LN risk (lateral LNR > 0.3 or largest LN size > 3 cm) had a much higher CSM rate (20.9%) than those in the same stage without LN risk (3.2%). Alternative prognostic grouping (Group 1, < 55 years without LN risk; Group 2, < 55 years with LN risk or ≥55 years without LN risk; and Group 3, ≥55 with LN risk) achieved higher proportions of variance explained (PVEs) for predicting CSM (10.7%) than those of the eighth edition TNM staging system (4.8%).
Conclusions: The proposed grouping for N1b patients using LN risk can distinguish patients with poor prognosis from those with good prognosis better than the eighth edition TNM staging system.

Introduction

Papillary thyroid cancer (PTC) is one of the most common cancers, with an incidence rate that continues to rise annually. The cancer is usually indolent with excellent prognosis, but cases with lateral nodal metastasis (N1b) require extended neck surgery and are considered to have relatively poor prognosis [1–3]. In the seventh American Joint Committee on Cancer (AJCC) TNM staging system, all N1b patients 45 years or older were classified as stage IV regardless of other factors [4,5], and the mortality risk of N1b was therefore exaggerated [6]. In

contrast, in the proposed eighth edition TNM staging system, all patients assigned to stage IV N1b according to the seventh edition are down-staged to either stage I or II solely according to an age cutoff of 55 years because the new system omits the location of nodal metastasis when forming stage groupings. This change was proposed based on the hypothesis that associations between lymph node (LN) location and survival outcomes could be confounded by the effects of size and number of LN metastases [7]. However, there is significant evidence that the survival prognosis of patients with N1b disease is significantly worse than that of patients with N1a [8–10], and there is growing

concern that the mortality risk for N1b patients is underestimated in the eighth edition TNM staging system [11].

Other than the location of metastatic LN, a number of LN factors are associated with oncological outcomes of PTC. Number of positive LNs and extra-nodal extension are among LN factors thought to be related to oncological outcomes of N1b PTC patients [12]. Large LN size > 3 cm [12] and LN burden > 17% in the lateral neck [13] have been demonstrated as predictive of recurrence. In a previous study, we found that patients with the largest LN size and lateral LNR had the highest cancer-specific mortality (CSM) and recurrence [6].

Considering that N1b patients comprise a heterogeneous group according to these LN factors, we hypothesized that incorporating LN factors into the eighth edition of the TNM staging system could improve the prediction of CSM. No previous study has attempted to reclassify N1b patients to improve prognostication using the upcoming eighth edition of the TNM staging system. The aim of the current study was to assess alternative prognostic LN factors with optimal cut-off points for CSM in PTC N1b patients. We also evaluated the predictive ability of alternative prognostic groupings that reflect LN factors compared to the eighth edition of the AJCC TNM staging system.

Materials and methods

Study subjects

After receiving approval from the Institutional Review Board of Samsung Medical Center (IRB No. 2016-09-078), we retrospectively collected information on 1196 patients who underwent initial thyroid surgery and were diagnosed with N1b PTC disease at Samsung Medical Center, Seoul, Korea, from 1994 to 2011. Of these, patients under 18 years old at surgery (n = 20), with distant metastasis at initial presentation (n = 21), with less than 5 years of follow up (n = 314), who experienced recurrence within six months after surgery (n = 24), had other coexisted metastatic cancers (n = 9), or lacked available data for LNs (n = 24) were excluded. To obtain accurate lymph node ratio (LNR) measurements, patients who underwent LN dissection with an inappropriate number (n = 39) were also excluded, based on recently proposed criteria that 6, 9, and 18 LNs are sufficient numbers to indicate the need for LN dissection in patients with T1b, T2, and > T3 disease, respectively [14]. Ultimately, we identified 745 patients for inclusion in the present study.

Initial treatment and follow up

Before surgery, we performed thyroid ultrasonography (USG), thyroid computed tomography, and chest X-rays. All enrolled patients underwent total thyroidectomy with traditional (remove the LNs of levels I–V and LNs that surround the tip of the parotid glands, the spinal accessory nerves, the internal jugular veins, and the sternocleidomastoid muscles) or modified radical LN dissection. No cases were treated by 'berry picking' resection, in which only grossly abnormal LNs are excised [15]. Radioactive iodine (RAI) was considered for all enrolled patients, and dose of RAI was determined by patient age, extrathyroidal extension (ETE) status, size of metastatic LN, co-morbidities, and preference of patient or clinicians. Every 6–12 months, the patients were regularly followed up with physical examinations and measurements of thyroid function, serum thyroglobulin (Tg), serum anti-Tg antibody, and thyroid USG.

Definitions

Largest LN size was defined as the longest diameter of the largest LN among metastatic cervical LNs in preoperative thyroid USG. Central, lateral, and total LNR were calculated by dividing the number of metastatic LNs by the number of dissected LNs from central, lateral, and both compartments, respectively. To redefine gross ETE according to

the newly proposed eighth edition TNM staging system, we reviewed operating records and pathologic reports. Because gross ETE only invading the strap muscles (T3b category) was not related to worse CSM [16], only the T4 category in the eighth edition TNM staging system (gross ETE invading subcutaneous soft tissues, larynx, trachea, esophagus, muscle, recurrent laryngeal nerve, prevertebral fascia, or encasing the carotid artery/mediastinal vessels) was counted as 'gross ETE (T4)' for adjustment variable in this study. According to the 2015 American Thyroid Association (ATA) guidelines for DTC management, therapeutic RAI is defined as a dosage of RAI 100 mCi or higher [5]. The primary endpoint for survival analysis was CSM, which is defined as mortality cases recorded as code C73 (malignant neoplasm of the thyroid gland) according to the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD 10) for cause of death. CSM-free survival was defined as the time interval (in months) between initial surgery and death for patients with CSM and the time between the date of initial surgery and the most recent follow-up for patients without CSM [17].

Study design and statistical analysis

The analyses were performed in three stages. First, the impacts of possible prognostic LN factors on CSM were suggested by comparison of demographics and tumor characteristics between mortality and survival cases, and further evaluated using Cox proportional hazards analysis. Conventional prognostic factors for CSM of age, sex, gross ETE (T4 stage only), and therapeutic RAI were adjusted. In the second stage, after determining that lateral LNR and largest LN size were associated with CSM as continuous variables, we calculated the most optimal cut-off point combination of lateral LNR and largest LN size for predicting CSM. For this purpose, cut-off points ranging from 0.2 to 0.5 for lateral LNR and from 1 to 4 cm for largest LN size were serially matched. Then, each combination was analyzed by Cox proportional hazards analysis and time-dependent ROC curves for 5 and 10 years. We selected cut-off point combinations with significant *P*-values in the Cox proportional hazards analysis and greatest area under the curve (AUC) values in the time-dependent ROC curves [18]. In the last stage, to derive alternative prognostic groupings, we identified groups with LN risk (largest size or lateral LNR over the cut-off point) and without LN risk (both largest size and lateral LNR under the cut-off point). Four re-stratified groups were derived using a combination of LN risk status and age criteria in the eighth edition TNM staging system. Cox regression was used to calculate adjusted hazard ratios for risk of CSM in each group, and alternative prognostic groupings were derived after considering minimal hazard differences. The predicted performances of the alternative prognostic groupings were evaluated by comparing proportions of variance explained (PVEs) (range from 0 to 100, larger numbers suggest better predictability) [19] and C-statistics [20] in Cox proportional regression models.

All variables, including baseline characteristics, are presented as number and percentage for categorical variables, mean ± standard deviation (SD) for continuous variables following a normal distribution, and median with interquartile range (IQR) for continuous variables not following a normal distribution. All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY, USA). Significance was defined as $P < .05$ for two-sided tests.

Results

Baseline characteristics

A total of 745 N1b PTC patients without initial distant metastasis were enrolled (median age at diagnosis, 44 years [IQR 35–53 years], 84% female). Median (IQR) largest metastatic LN size was 1.06 cm (0.80–1.57 cm), and 47 (6.3%) patients had lateral cervical LN metastasis larger than 3 cm. The median number of total metastatic LNs was 9