Oral Oncology 66 (2017) 22–27

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Lymph node characteristics for predicting locoregional recurrence of papillary thyroid cancer in adolescents and young adults

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ARTICLE INFO

Article history:
Received 10 September 2016
Received in revised form 4 November 2016
Accepted 27 December 2016
Available online 6 January 2017

Keywords:
Papillary thyroid cancer
Adolescents
Young adults
Lymph node
Locoregional recurrence
Prognosis

ABSTRACT

Purpose: To determine lymph node (LN) characteristics predictive of locoregional recurrence (LRR) in adolescent and young adult (AYA) ages 15–39 years presenting with papillary thyroid cancer (PTC) and cervical pathologically proven LN metastases (pN1).

Methods and materials: Retrospective chart review was performed for all patients with PTC and nodal metastases who had undergone total thyroidectomy, LN dissection, and postoperative radioactive iodine therapy in a university hospital between 2006 and 2014. Clinical and histopathologic markers that were independently associated with tumor recurrence were evaluated.

Results: In all, 329 consecutive AYA patients were included. At a median follow-up of 57 months, twenty patients (6.08%) experienced LRR. No patients had distant metastases, and no patients died during follow-up. Based on Cox regression analysis, the presence of extranodal extension and more than six metastatic LNs at presentation were independent predictive factors for LRR. However, age, male sex, total number of LNs resected, pN1b, LN ratio, size of the largest metastatic LN, extrathyroidal extension, tumor size, bilateral tumor, multifocality, vascular invasion, and Hashimoto thyroiditis were not correlated with an increased risk for LRR. A cutoff of more than six positive nodes optimally predicted future LRR with sensitivity and specificity values of 85.0% and 60.2%, respectively.

Conclusion: The presence of extranodal extension and more than six metastatic LNs were independent predictors of LRR in AYA patients with pN1 disease. Evaluation of these prognostic factors appears to help identify patients who require close monitoring.

Introduction

The biology of malignant diseases in adolescents and young adults (AYAs) between the ages of 15 and 39 years is different than in younger and older persons [1]. Thyroid cancer is the fifth most common cancer in AYAs, and its incidence is rapidly increasing worldwide [1,2]. Papillary thyroid cancer (PTC) accounts for >90% of all cases [3]. The prognosis is generally excellent with appropriate therapy [4]. Compared with older adult patients, the AYA age group often presents with more advanced disease and a higher prevalence of nodal metastases [5]. Furthermore, the presence of cervical lymph node (LN) metastases is an independent risk factor for disease recurrence [6,7], and local or regional recurrence of PTC heralds a poor prognosis following the initial surgery and is associated with a significant degree of morbidity because of additional treatment [8–10].

According to the current American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system [11], AYA patients with cervical LN metastases are considered to have stage I disease and categorized as N1a for positive LNs located in the central neck compartment and N1b for those located in the lateral neck compartment. Recently, several studies in younger patients have identified various clinical and pathologic features predictive of prognosis that were not reflected in the staging system [12–14]. However, the results of these studies have varied, and further investigation is warranted. The hypothesis for the present study was that the pathologic spectrum of LN involvement could influence locoregional recurrence-free survival in the AYA population with PTC and pathological N1 disease. The objective of the present investigation was therefore to identify predictive factors for

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http://dx.doi.org/10.1016/j.oraloncology.2016.12.028
1368-8375/

disease recurrence with special consideration of the impact of LN features.

Patients and methods

Study population

After receipt of approval by the institutional review board, we reviewed the electronic medical records of 1758 consecutive subjects with differentiated thyroid cancer that were initially referred for radioiodine treatment at the Nuclear Medicine Department in Zhujiang Hospital of Southern Medical University from March 2006 to February 2014. Subjects were included if they fulfilled the following criteria: (i) were adolescents or young adults (age range, 15–39 year); (ii) had previous total thyroidecomy and neck dissection; (iii) have pathologically confirmed papillary thyroid cancer and pN1 disease; (iv) have undergone postoperative radioactive iodine (RAI) treatment. We excluded patients with detectable anti-Tg antibody (TgAb). We excluded patients whose data were not complete or missing because of loss to follow-up. Patients with multiple cancer diagnoses and/or distant metastases at presentation were also excluded. Thus, a total of 329 patients were selected for the study.

Patient demographic information, surgical details, and histopathologic details, including size of primary cancer, extrathyroidal invasion, multifocality, vascular invasion, Hashimoto thyroiditis, number of positive cervical LNs, total number of LNs removed, size of largest LN (diameter of the largest LN was defined as containing a focus of metastatic thyroid cancer), extranodal extension (ENE, defined as tumor cells extending beyond the capsule of the node), and LN ratio (LN ratio was defined as the percentage of positive LNs out of total number LNs resected), were recorded. Details of postoperative use of RAI were recorded.

Treatment and follow-up protocol

At our institution, total thyroidectomies were performed in patients with extrathyroidal extension, multifocality, or cervical LN metastases at preoperative or intraoperative examination, or clinically apparent metastases to distant sites. Prophylactic central-compartment neck dissection was routinely performed in patients with total thyroidectomy. For patients with lateral neck metastases diagnosed at preoperative ultrasound-guided fine-needle aspiration or on an intraoperative frozen section, therapeutic lateral neck dissection, including LNs at level II-V, was performed. Postoperative RAI therapy was given to all patients. ^{131}I was typically administered 3 weeks after withdrawal of levothyroxine. All patients were asked to adhere to a low iodine diet for two weeks prior to the planned RAI treatment. The choice of RAI-administered activity was at the discretion of the treating physician.

After the initial radioiodine treatment, patients were followed up every 6 months for the first 2 years and at 12-month intervals thereafter. The routine follow-up protocol consisted of regular clinical examination; the measurement of serum thyroglobulin (Tg), TgAb, and thyroid-stimulating hormone (TSH); and neck ultrasonography. Before 2008, our institutional policy was to routinely schedule a diagnostic whole-body ^{131}I scan (DxWBS) under levothyroxine withdrawal every 6–8 months during the first two years and then at 1- to 2-year intervals thereafter. Since 2008, our attending physicians have altered the surveillance DxWBS, which was performed once a year for the first 2 years and selectively thereafter as determined by the patient's risk for recurrent disease and Tg status. Computed tomography (CT) or fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) was performed if persistent or newly identified evidence was suspected. Postoperative TSH suppression was practiced for all patients according to recurrence risk.

Definition of clinical outcome

Disease outcomes of interest were locoregional recurrence (LRR) and recurrence-free survival (RFS), based on reassessment at each follow-up visit after surgery and RAI therapy. Patients were considered to have no clinical evidence of disease (NED) at final follow-up if they had no biochemical (suppressed Tg < 1 ng/mL, stimulated Tg < 2 ng/mL, no detectable TgAb), structural (no cytology-proven disease and morphologic evidence of disease at cross-sectional imaging), and or functional evidence of disease (negative WBS or PET/CT). A recurrence was defined as new biochemical, structural or functional evidence of disease that was detected following any period of NED [15]. The LRR included a recurrence of PTC in the operated thyroid bed and/or in the regional lymph nodes. The RFS was defined as a period without disease recurrence after an initial treatment.

Statistical analysis

Continuous data are presented as the means and standard deviations or medians and ranges, as appropriate for each variable. Either a Chi-square or Fisher's exact test was used to evaluate differences in categorical variables between 2 independent groups. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test. The data that were not normally distributed were compared by the Mann-Whitney test. Categorical cutoff values for the number of metastatic LNs was based on ROC curves. The value at which sensitivity and specificity were maximized for RFS was selected for analysis. The RFS curves were constructed using the Kaplan-Meier method, and groups were compared using the log-rank test. The Cox proportional hazard model was used to assess predictors of LRR. The hazard ratio (HR), 95% confidence interval (CI), and *P-value* were reported. Statistical analysis was carried out by SPSS software, version 19 (IBM, Armonk, NY). A *P-value* of <0.05 was considered significant.

Results

Patient characteristics

A total of 329 patients were included in this study. Their baseline characteristics are listed in Table 1. We only included patients with papillary thyroid cancer with pathologic N1 disease without clinical evidence of distant metastases at the time of thyroid cancer diagnosis. The mean age of the study population was 29.6 years, and 227 (69.0%) patients were female. The mean primary tumor size was 1.84 cm. Most did not have vascular invasion (90.6%). Extrathyroidal extension and multiplicity were found in 14.0% and 26.1% patients, respectively. Bilateral cancer of the thyroid was seen in 41.9% of total thyroidectomy patients. One hundred and thirty (39.5%) patients had lymph node metastases involving the central compartment (N1a), and 199 (60.5%) patients had involvement of lateral compartments (N1b). The mean number of dissected and positive LNs was 16.18 and 6.34, respectively. The mean size of the largest metastatic LN was 1.01 cm. Extranodal extension of cancer was found in 147 patients (44.7%). The mean LN ratio was 48.5%.

Lymph node features predictive of locoregional recurrence

Analysis of the 329 AYA patients with PTC with lymph node involvement followed for ⩾12 months revealed that 20 (6.08%)