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Original research

The significance and the predictive factors of microscopic lymph node metastasis in patients with clinically node negative papillary thyroid cancer: A retrospective cohort study

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HIGHLIGHTS

- We investigated clinically node negative patients without RI treatment.
- We analysed the predictive factor of node metastasis with cN0 PTC patients.
- Prognostic meaning of pN1b was often found in the elders with larger PTC indicating the necessity for adjuvant treatment.

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ABSTRACT

Background: The management of pathological lateral node involvement (pN1b) from papillary thyroid cancer (PTC) are controvertial.
Methods: A consecutive series of 246 patients, diagnosed with clinically node negative (cN0) PTC who had undergone surgery with prophyractic lateral node dissection, and without postoperative radioactive iodine administration from 2001 to 11, were reviewed to clarify the significance of pN1b.
Results: Eighty-five (35%) patients had pN1b disease. One-half and 30% had pN1b in younger (age less than 45) and older patients (age 45 or over), respectively. Tumor size (≥21 mm) could predict pN1b disease in older patients. Patients with pN1b disease recurred more frequently (9 cases, 10.6%) than those without (4 cases, 2.4%), and 2 cases with pN1b died of the disease.
Conclusions: pN1b disease was commonly found in patients with PTC even when they were diagnosed clinically as node negative. pN1b disease with prognostic meaning was often found in the older patients with larger PTC indicating the necessity for adjuvant treatments.

1. Introduction

Papillary thyroid cancer (PTC) often demonstrated metastatic spread to the regional lymph nodes. Therapeutic lymph node dissection for patients with the clinically overt lymph node metastasis (LNM) had been reported to contribute to the prolonged overall survival and recurrence free survival, and has been performed world-wide [1]. On the contrary, the application of prophylactic lymph node dissection (PND) for clinically node-negative (cN0) patients is controversial [2–5]. Computed tomography (CT) or ultrasound would be useful to diagnose lymph node metastasis pre-operatively, although its diagnostic accuracy is not sufficient enough to detect every small metastatic lesion within the nodes. Therefore, microscopic lymph node metastasis could often be identified during the pathological evaluation of the surgical specimens [6]. Many surgeons agree that PND is necessary for staging of the disease that may guide subsequent adjuvant treatment and follow-up [7]. PND could modify the indication for radioactive iodine treatment in up to 30% of PTC patients [8]. On the other hand, the risks for surgical complications, such as recurrent nerve palsies, hypoparathyroidism, chyle-leakage, etc., during PND could not be avoided completely. Local or regional recurrence has been reported to be equivalent in patients with or without microscopic node metastasis [9]. Therefore, indication of PND in patients with

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cN0 disease might strictly be considered.

We routinely performed LN dissection, including central and lateral compartments, for patient with PTC. It is because we have found that the initial LNM occurs equivalently in central or in lateral compartment [10], and considered that accurate staging according to microscopic lymph node metastasis should be important for planning strategies for postoperative treatment and follow-up, especially in our country where the capacity for the post-operative "adjuvant" radioisotope (RI) treatment was not enough. In Japan, RI treatment after operation has been performed only for the patient with residual disease, and was not indicated for the purpose of remnant ablation because of the strict regulations for RI use, the public revulsion for radiation, and the abundant uptake of iodine in the daily diet that complicated the iodine restriction before RI therapy, as well as the shortage in the facilities. Therefore, many surgeons and patients preferred preserving thyroid function by choosing lobectomy with PND for the standard surgical treatment of PTC. The results from this thyroid function preserving therapy has to be verified along with the recent trend toward the expansion of RI use and the logical selection of the patient who should be indicated with RI treatment after operation.

PTC is a unique entity that showed the age at treatment was identified as one of the significant clinical factors to influence the disease progression and prognosis. Lymph node metastasis was known to be found more frequently in younger patients with PTC. These observations were considered to be due to the differences in the molecular background of the disease according to the age, although not completely elucidated. In this study using a consecutive patient series of cN0 PTC having performed a standardized surgical treatment including PND and without radioactive iodine ablation, we investigated the significance of microscopic node metastasis in the outcome of the patients with cN0 PTC, and analyzed the predictive factors for microscopic node metastasis in an aim to seek for the possibility to select the patient group required additional therapeutic effort by evaluating pathological nodal status by PND according to the characteristics of the tumor and the patients, including age at onset.

2. Patients and methods

2.1. Subjects

We enrolled 246 consecutive patients who underwent curative resection with standardized PND, as described below, for cN0 PTC without postoperative radioactive iodine therapy between 2001 and 2011 in our institute. All patients were diagnosed to have papillary thyroid cancer by preoperative aspiration cytology and post-operative pathological examination.

For preoperative staging in all cases, the ultrasonography (US) of the neck and the CT scan of the neck and the chest were performed. US examination and evaluations of nodal status were performed under observation of experienced surgeons according to the criteria suggested by Antonelli et al. [11,12], and if necessary fine needle aspiration cytology for lymph node was applied to confirm nodal metastasis. Preoperative staging of PTC was stratified according to the UICC classification system [13].

The neck US, the chest X-ray, and the serum thyroglobulin evaluation (for patients after total thyroidectomy) were performed once to twice per a year. The CT scan of the neck and the chest was added if needed.

2.2. Statistical analysis

Variables were analyzed in correlation by Mann–Whitney U test, and in predictive factor of pN1a and pN1b by a univariate logistic regression model. All variables that demonstrated a statistically significant difference in univariate tests were then analyzed in a multivariable regression model. Recurrence free survival was analyzed by Kaplan–Meier curves and log-rank test.

Statistical analysis was performed with SPSS 16 software (SPSS, Inc., Chicago, IL). A probability level of random difference of $P < 0.05$ was considered significant.

3. Results

The patients' age was 54.6 years in average (ranged from 16 to 84), consisted of 36 males and 210 females. Sixty-six patients with age less than 45 years-old (younger patients), and 180 patients with 45 years-old or over (older patients) were included. The average tumor size was measured as 17 mm in maximal diameter by the preoperative US. Total thyroidectomy was undergone in 46 cases, and 200 cases had subtotal thyroidectomy or lobectomy. Central and lateral prophylactic lymph node dissection was added in all cases. Central node dissection is defined as the removal of level VI, and lateral node dissection is defined as the removal of level III, IV, and VB of the affected side. Dissection of the level II and VA was not performed. All cases did not undertake postoperative radioactive iodine administration. The median postoperative follow-up time was 65 months. Thirteen cases (5.3%) showed local or lymph node recurrence, and 2 cases (0.8%) died of PTC.

Table 1 showed the clinicopathological features of all cases. One hundred forty five patients (59%) had microscopic lymph node metastasis. Sixty patients (24%) had pN1a disease, 85 patients (35%) had pN1b disease, and 7cases (8.2%) of those had lymph node

Table 1
Characteristics of clinically node negative PTC patients.

Variables	Total	(%)	Younger	(%)	Older	(%)
Age (years)	54.6 ± 15.3		33.8 ± 6.6			
					62.2 ± 9.3	
Male: Female	36: 210		10: 56		26: 154	
Tumor location						
Upper third	65	(26.4)	15	(22.7)	50	(27.8)
Lower 2/3	181	(73.6)	51	(77.3)	130	(72.2)
Multifocal lesions						
Positive	23	(9.3)	3	(4.5)	20	(11.1)
Negative	223	(90.7)	63	(95.5)	160	(88.9)
Tumor size (mm)	17.0 ± 11.8		19.0 ± 12.4			
					16.2 ± 11.5	
cT						
1a	51	(20.7)	9	(13.6)	42	(23.3)
1b	68	(27.6)	22	(33.3)	46	(25.6)
2	21	(8.5)	10	(15.2)	11	(6.1)
3	99	(40.2)	24	(36.4)	75	(41.7)
4	7	(2.8)	1	(1.5)	6	(3.3)
Extrathyroidal extension						
No	147	(59.8)	45	(68.2)	102	(56.7)
Yes	99	(40.2)	21	(31.8)	78	(43.3)
pN						
0	101	(41.1)	14	(21.2)	87	(48.3)
1a	60	(24.4)	20	(30.3)	40	(22.2)
1b	85	(34.6)	32	(48.5)	53	(29.4)
p stage						
I	107	(43.5)	66	(100)	41	(22.8)
II	8	(3.3)	0	(0)	8	(4.4)
III	77	(31.3)	–		77	(42.8)
IVA	54	(22.0)	–		54	(30)
Extent of thyroidectomy						
Lobectomy	200	(81.3)	58	(87.9)	142	(78.9)
Total	46	(18.7)	8	(12.1)	38	(21.1)
Lymph node dissection						
Unilateral	223	(90.7)	62	(93.9)	161	(89.4)
Bilateral	23	(9.3)	4	(6.1)	19	(10.6)
Total	246		66	(26.8)	180	(71.2)