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Original Article

Cytologic, clinicopathologic, and molecular features of papillary thyroid carcinoma with prominent hobnail features: 10 case reports and systematic literature review

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Abstract: The hobnail variant of papillary thyroid carcinoma (PTC) is a rare, aggressive variant in which > 30% of the tumor cells have hobnail features. The clinical behavior and pathologic characteristics of these tumors are still unclear due to the rarity of the entity. The present study aimed to investigate cytologic, clinical, pathological, and molecular features of the hobnail variant from our data and from the literature. We retrospectively retrieved 10 cases of hobnail variant from 2,904 consecutive PTC patients. Cytologic and histopathologic slides from those 10 patients were reviewed. We performed molecular analysis for *BRAF*, *ALK*, and *TERT* promoter mutations on paraffin blocks from surgical specimens, and further analyzed the clinicopathologic characteristics of all case reports published in the literature until now. Cytologically, all tumors were characterized by single cells with eccentric nuclei and tapering cytoplasm (comet-like cells), and syncytial or micropapillary clusters with apically placed nuclei resulting in a hobnail appearance in both conventional smears and liquid-based cytology. The *BRAF* V600E mutation was found in 8 cases (80%) whereas no cases had *ALK* fusion or *TERT* promoter mutations. In the literature review of 55 patients including our cases, most patients presented with advanced stage cancer, and disease-specific survival rates were 83%, 71%, and 54% at 5, 10, and 20 years after the initial surgery, respectively. Characteristic cytologic features can allow a preoperative diagnosis of the hobnail variant of PTC based on cytology specimens. Further studies should be performed to identify the molecular genetics of the variant.

Keywords: Thyroid cancer, hobnail variant, fine needle aspiration, BRAF, ALK, TERT

Introduction

Papillary thyroid carcinoma (PTC) usually displays an indolent clinical course. However, a few patients with PTC die of distant metastasis and radioactive iodine-refractory, progressive disease. The types of PTC associated with aggressive clinical behavior include tall cell, columnar cell, solid, diffuse sclerosing and hobnail variants [1].

The hobnail variant of PTC demonstrates discohesive growth and single cells with a loss of polarity and is characterized by exhibition in > 30% of the tumor cells of apically placed nuclei and a surface bulge [2, 3]. This rare variant is associated with aggressive clinicopathologic features and a higher mortality rate compared with classic PTC [4-6].

The most commonly occurring mutation in patients with PTC is a *BRAF* V600E mutation that is associated with extrathyroidal extension, lymph node metastasis, distant metastasis, recurrence, and mortality [7-9]. The *BRAF* V600E mutation has been frequently found in the hobnail variant of PTC [4, 10, 11]. *TERT* promoter mutations have recently been found in the aggressive thyroid cancers [12, 13]. However, these mutations have not been investigated in the hobnail variant of PTC.

Fine needle aspiration cytology (FNAC) has been widely used as the most effective preoperative evaluation tool for the screening of thyroid nodules [14]. The definitive diagnosis of the hobnail variant in FNAC specimens plays an important role in the planning of surgical management. However, the cytologic diagnosis of the hobnail variant is difficult not only because of its rarity, but because the cytologic features of the hobnail variant on conventional smears have been reported as small series of cases or single case reports.

The present study aimed to investigate the clinicopathologic characteristics and cytologic features of conventional smears and liquid-based cytology of the hobnail variant of PTC. We further performed a systematic review and analysis of studies that investigated the clinicopathologic features and prognosis of the hobnail variant of PTC.

Materials and methods

Patient selection

We retrospectively reviewed the pathology slides of all 2,904 consecutive patients who underwent thyroid surgery for PTC at Seoul St. Mary's Hospital, The Catholic University of Korea over a three year period. A total of 10 patients were selected as having the hobnail variant of PTC according to the diagnostic criteria as previously reported [2].

Fine needle aspiration cytology

All patients underwent ultrasound-guided FNAC. Of the 10 FNAC specimens, seven were directly smeared on the slides and three were processed with ThinPrep™ (Hologic Inc., Marlborough, MA, USA) liquid-based preparations (LBPs). The specimens were stained with Papanicolaou staining and/or hematoxylin and eosin. Cell block preparations (CBPs) were made from the LBPs. All cytologic slides were reviewed by two independent pathologists (CKJ. and YSL). The cytologic diagnosis on the FNAC specimens was performed according to the Bethesda system for reporting thyroid cytopathology [15].

Immunohistochemistry

Immunohistochemistry was performed on paraffin-embedded tissue sections of surgical specimens. The following antibodies were used: ALK antibody (clone p80, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK), p53 (clone DO-7, Ventana Medical Systems, Inc., Tucson, AZ, USA), cyclin D1 (clone SP4, Thermo Scientific, Fremont, CA, USA), HBME1 (clone HBME-1, Dako Corporation, Carpinteria, CA, USA), and CD56 (clone 1B6, Novocastra). The p53 expression was measured as the percentage of positive nuclear immunostaining among tumor cells. For other markers, immunostaining was categorized as negative, focally positive (< 50% of the tumor cells), or diffusely positive (≥ 50% of the tumor cells).

Mutational analysis

Genomic DNA was isolated from the microdissected paraffin-embedded tissue sections from surgical resection specimens using the QIAamp DNA Mini Kit (Qiagen GmbH, Hilden, Germany). The presence of *BRAF* V600E and *TERT* promoter mutations was investigated by Sanger sequencing, as described earlier [13, 16]. Fluorescence in situ hybridization (FISH) for the ALK fusion gene was performed using a ZytoLight SPEC ALK Dual Color Break Apart Probe and Kit (ZytoVision GmbH, Bremerhaven, Germany) according to the manufacturer's protocol. ALK FISH-positive cases were defined as > 15% of split signal separation and/or isolated red signal in at least 100 tumor cells as previously described [17].

Literature review

We searched the literature for hobnail variant of PTC using a comprehensive PubMED search (http://www.ncbi.nlm.nih.gov/pubmed/) with a combination of the search words "thyroid" and "hobnail" or "micropapillary". After further manual analysis, 45 cases from eight articles were determined to meet the diagnostic criteria for the hobnail variant of PTC and were selected for statistical analysis [3-6, 11, 18-20]. Disease-specific survival rates were obtained using the life-table method.

Results

Clinical features

The clinicopathologic characteristics of the 10 patients are summarized in **Table 1**. The age of the patients (6 women and 4 men) ranged from

Table 1. Demographic and clinicopathologic characteristics of patients with the hobnail variant of papillary thyroid carcinoma in the present study and the literature review

Characteristic	Number of cases (%)		
	Present study (n = 10)	Review of the literature (n = 45)	Total cases (n = 55)
Female:male ratio	6:4 (1.5:1)	32:13 (2.5:1)	38:17 (2.2:1)
Mean age (years) (range)	50.4 (32-68)	56.9 (21-86)	55.7 (21-86)
Mean tumor size (cm) (range)	1.63 (0.6-4)	3.81 (0.5-11)	3.41 (0.5-11)
Multifocality	3/10 (30%)	12/28 (43%)	15/38 (40%)
Tumor site			
Right lobe	6/10 (60%)	0/14 (0%)	6/24 (25%)
Left lobe	4/10 (40%)	0/14 (0%)	4/24 (17%)
Right and left lobe	0/10 (0%)	14/14 (100%)	14/24 (58%)
Results of fine needle aspiration cytology			
Atypia of undetermined significance	0/10 (0%)	1/18 (5.6%)	1/28 (3.6%)
PTC	10/10 (100%)	16/18 (89%)	26/28 (93%)
PTC, tall cell variant	0/10 (0%)	1/18 (5.6%)	1/28 (3.6%)
Original histologic diagnosis			
PTC	0/10 (0%)	24/45 (53%)	24/55 (44%)
PTC, classic	2/10 (20%)	2/45 (4.4%)	4/55 (7.3%)
PTC with hobnail features	1/10 (10%)	1/45 (2.2%)	2/55 (3.6%)
PTC, hobnail variant	7/10 (70%)	18/45 (40%)	25/55 (46%)
Chief complaint			
Incidental finding	9/10 (90%)	3/15 (20%)	12/25 (48%)
Neck mass	1/10 (10%)	8/15 (53%)	9/25 (36%)
Cervical lymphadenopathy	0/10 (0%)	2/15 (13%)	2/25 (8.0%)
Dyspnea	0/10 (0%)	2/15 (13%)	2/25 (8.0%)
Extrathyroidal extension	7/10 (70%)	26/44 (59%)	33/54 (61%)
Tracheal invasion	1/10 (10%)	5/43 (12%)	6/53 (11%)
Mean mitotic count (/10HPFs) (range)	0.2 (0-1)	2.7 (0-9)	2.1 (0-9)
Necrosis	2/10 (20%)	3/45 (6.7%)	5/55 (9.1%)
Lymyphovascular invasion	8/10 (80%)	27/43 (63%)	35/53 (66%)
Lymph node metastasis	8/10 (80%)	26/41 (63%)	34/51 (67%)
Lateral lymph node metastasis	4/10 (40%)	14/40 (35%)	18/50 (36%)
Bone metastasis	0/10 (0%)	3/42 (7.1%)	3/52 (5.8%)
Lung metastasis	0/10 (0%)	9/42 (21%)	9/52 (17%)
AJCC staging			
I	4/10 (40%)	13/41 (32%)	17/51 (33%)
II	0/10 (0%)	2/41 (4.9%)	2/51 (3.9%)
III	4/10 (40%)	9/41 (22%)	13/51 (25%)
IVA	2/10 (20%)	8/41 (20%)	10/51 (20%)
IVC	0/10 (0%)	9/41 (22%)	9/51 (18%)
Mutational analysis			
BRAF V600E mutation	8/10 (80%)	17/24 (71%)	25/34 (74%)
RET/PTC1 rearrangement	NA	2/10 (20%)	2/10 (20%)
TERT promoter mutation	0/10 (0%)	NA	0/10 (0%)
ALK fusion	0/10 (0%)	NA	0/10 (0%)
Regional/local recurrence	1/10 (10%)	11/42 (26%)	12/52 (23%)
Outcome			
No evidence of disease	9/10 (90%)	24/42 (5.7%)	33/52 (64%)
Alive with disease	1/10 (10%)	8/42 (19%)	9/52 (17%)
Died of disease	0/10 (0%)	10/42 (24%)	10/52 (19%)

PTC, papillary thyroid carcinoma; HPFs, high power fields; NA, not available; AJCC, American Joint Committee on Cancer.

Table 2. Fine needle aspiration cytologic features of hobnail variant of papillary thyroid carcinoma

Case No.	Specimen type	Cellularity	Papillary	Micro-papillary	Syncytial fragments	Hobnail features	Single cells	Comet-like cells	Soap-bubble-like nuclear inclusions	Nuclear features of PTC	Psammoma bodies	Giant cells
1	Smear	Marked	+	+	++	+	++	++	+	++	-	-
2	Smear	Marked	+	+	++	+	++	++	++	++	+	+
3	Smear	Marked	+	+	++	+	++	++	+	++	-	-
4	Smear	Marked	++	+	++	++	++	++	+	++	-	+
5	Smear	Marked	++	++	++	++	++	++	+	++	+	-
6	Smear	Marked	+	+	++	+	+	++	+	++	+	-
7	Smear	Marked	++	+	++	++	++	++	+	++	+	-
8	LBP	Marked	+	+	++	+	++	++	+	++	-	-
9	LBP	Marked	+	+	++	+	++	++	++	++	-	-
10	LBP	Marked	+	+	++	+	++	++	++	++	+	-

LBP, liquid-based preparation; -, absent; +, present; ++, frequently present; PTC, papillary thyroid carcinoma.

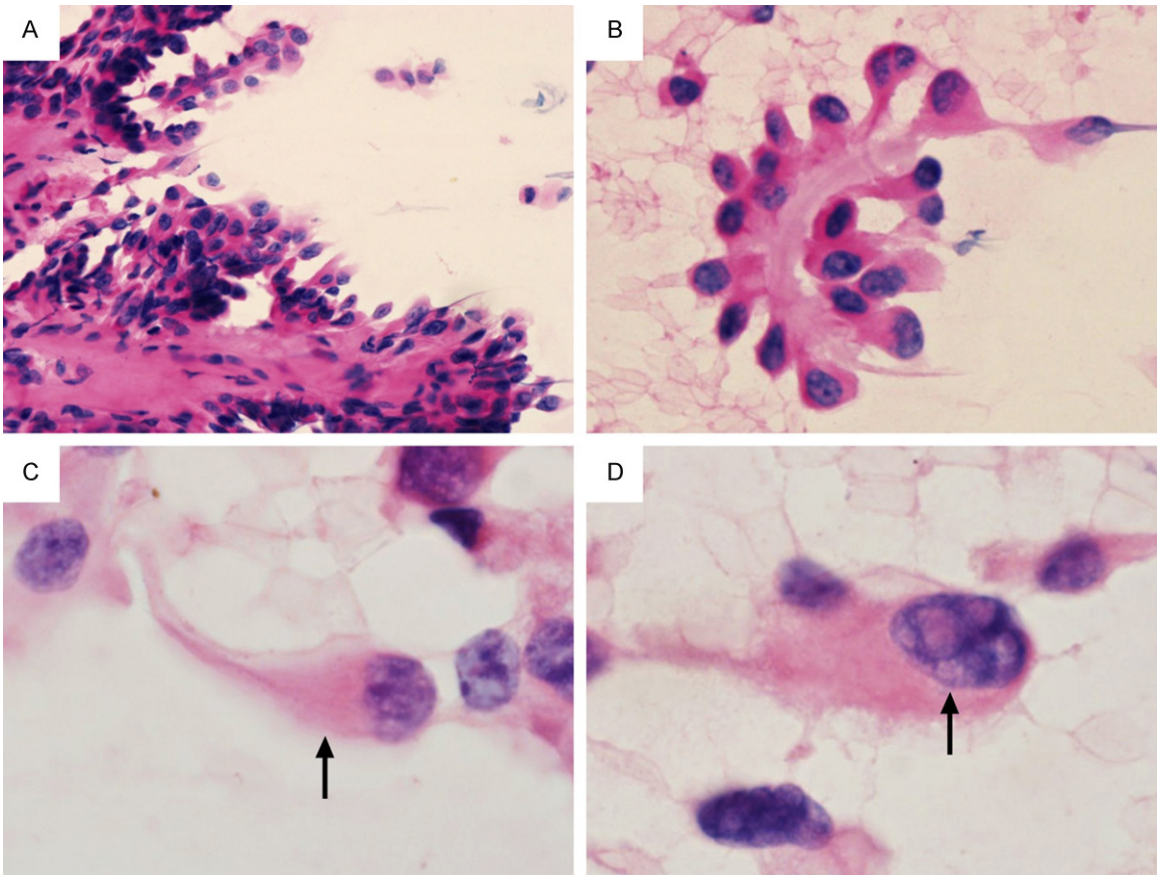

Figure 1. Cytologic features of hobnail variant of papillary thyroid carcinoma in a conventional smear. A. A papillary fragment lined by hobnail cells (H&E × 200). B. A micropapillary fragment showing hobnail appearance (H&E ×400). C. A comet-like cell (arrow), showing nucleus protruding toward one side and cytoplasm tapering toward the opposite side (H&E × 1000). D. Isolated single cells with multiple soap-bubble-like intranuclear inclusions (arrow) (H&E × 1000). H&E, hematoxylin and eosin.

32 to 68 years (median 50.5 years). All patients underwent ultrasound-guided FNAC and were diagnosed with PTC. Tumor size ranged from 0.6 to 4.0 cm (median 1.3 cm). All patients underwent total thyroidectomy and cervical lymph node dissection. The follow-up period after thyroidectomy ranged from 9 to 28 months (median 12 months). One patient (case 1) developed a regional lymph node recurrence 21 months after the initial surgery. No patients died from the disease during the follow-up period.

Cytologic features

The cytologic features of the tumors are summarized in **Table 2**. All seven conventional smears were highly cellular with little colloid. The hobnail features were frequently found in the papillary, micropapillary or discohesive cell clusters (**Figure 1A** and **1B**). Isolated single cells showed eccentric nuclei with a tear-drop cytoplasm, so-called comet-like cells (**Figure 1C**). Multiple soap-bubble-like intranuclear inclusions were seen in all cases (**Figure 1D**). Mitosis was found in two cases. In three LBP samples, papillary and micropapillary structures were less frequently found than in conventional smears whereas syncytial cell clusters with apically-placed nuclei were frequently seen (**Figure 2A**). Comet-like cells and multiple soap-bubble-like intranuclear inclusions, as well as typical nuclear features of PTC were easily detected (**Figure 2B** and **2C**). All cell blocks showed papillary fragments lined by hobnail cells (**Figure 2D**).

Histopathology and immunohistochemistry

The histologic features and immunohistochemistry of the hobnail variant are summarized in **Table 1**. In three patients (cases 1, 6 and 7)

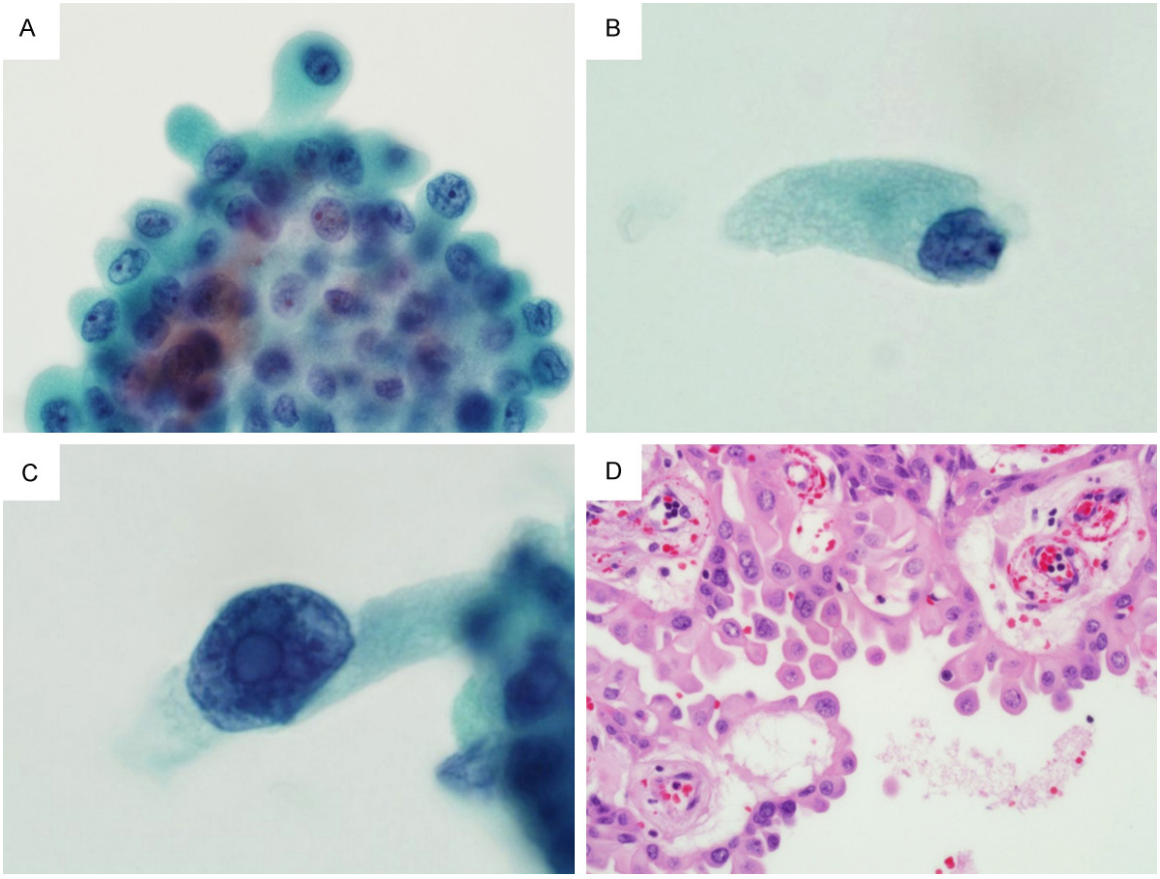

Figure 2. Cytologic features of hobnail variant of papillary thyroid carcinoma in a liquid-based cytology (ThinPrep™). A. A syncytial cell cluster showing apically placed nuclei and a surface bulging (Papanicolaou stain × 400). B. A comet-like cell, characterized by eccentric nucleus and tapering cytoplasm (Papanicolaou stain × 1000). C. Multiple soap-bubble-like intranuclear inclusions (Papanicolaou stain × 1000). D. A cell block showing papillary structures with prominent hobnail features (H&E × 200).

with two tumor foci, the largest tumor was hobnail variant (**Figure 3A**) and the smaller was classic type, tall cell variant, and non-invasive encapsulated follicular variant, respectively. Mitosis was found only in two cases (cases 4 and 7) which also showed tumor necrosis. Extrathyroidal extension was seen in seven cases and lymph node metastases were found in eight cases. Vascular invasion was observed in only one case (case 1). The percentage of tumor cells positive for p53 immunostaining ranged from 1% to 48% (**Figure 3B**). All cases were diffusely positive for cyclinD1 and HBME1, and focally positive for CD56. No cases demonstrated expression of ALK.

Mutational analysis

Eight cases (80%) harbored *BRAF* V600E mutation. No cases had *ALK* fusion or *TERT* promoter mutations (**Table 1**).

Analysis of cases in our study and the literature

We analyzed the clinicopathologic and molecular features of 55 patients (45 in the literature as well as our 10 cases) with the hobnail variant of PTC (**Table 1**). Women were affected more frequently than men (2.2:1). The age of patients ranged from 21 to 86 years (mean, 55.7 years). The patients often presented with incidental ultrasound findings or a neck mass. Mean tumor size was 3.4 cm (range, 0.5-11.0 cm). Almost all patients were diagnosed with PTC before undergoing surgery. Extrathyroidal extension and tracheal invasion were found in 61% and 11%, respectively. More than half of patients presented with stage III (25%) or IV (38%) cancer. The tumors developed bone and lung metastases in 5.8% and 17% of cases, respectively. Clinical follow-up data were available in 52 patients (follow-up period, 4-274

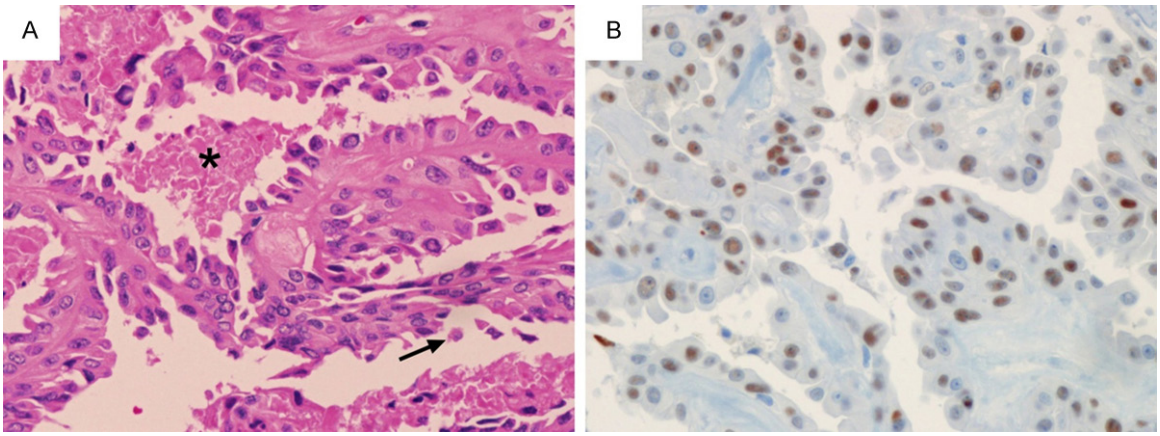

Figure 3. A. Histology of hobnail variant of papillary thyroid carcinoma. Thin arborizing papillae are lined by hobnail cells. Single detaching cells (arrow) and tumor necrosis (asterisk) are also noted (H&E × 200). B. Immunohistochemistry reveals positivity for p53 (× 200).

months). The local recurrence rate was 23% during the follow-up period. Disease-specific survival rates were 83%, 71%, and 54% at 5, 10, and 20 years after surgery, respectively (**Figure 4**). The *BRAF* V600E mutation was present in 25 (74%) of 34 cases. The rate of *RET/PTC1* rearrangement was 20% (2/10) in one series [11].

Discussion

We have shown that the hobnail variant of PTC is an aggressive variant characterized by a higher rate of initial presentation at an advanced tumor stage and poor outcome. Although the number of reported cases of hobnail PTC is small, it is important to note that the long-term survival rate of the variant is much lower than that of classic PTC.

Preoperative FNAC diagnosis of thyroid nodule is important in planning surgical strategy. When the result of FNAC is positive for PTC, National Comprehensive Cancer Network guidelines indicate a total thyroidectomy as primary treatment in patients with any one of the following: radiation history, distant metastasis, bilateral nodularity, extrathyroidal extension, tumor > 4 cm in diameter, cervical lymph node metastases, or poorly differentiated features (http://www.nccn.org/). Current guidelines for PTC do not specifically mention treating patients with hobnail PTC. We suggest that total thyroidectomy should be considered for the initial treatment of patients with hobnail PTC because the variant has a poor outcome in comparison to poorly differentiated thyroid cancer.

The preoperative diagnosis of the histologic subtypes of PTC may be challenging in FNAC samples. In our study using conventional smears and LBPs, the most characteristic cytologic features were hobnail appearance, comet-like cells and soap-bubble-like intranuclear inclusion. These findings were in concordance with previous studies reporting cytologic features of hobnail PTCs in the conventional smears, although there have been no studies investigating LBPs of the tumor [5, 19, 20]. These cytologic features should therefore be mentioned in FNAC results and can allow a preoperative diagnosis of the hobnail variant of PTC.

The differential diagnosis of hobnail PTC in FNAC includes tall cell variant of PTC characterized by eccentric nuclei, columnar and abundant cytoplasm, distinct cell borders, and soap-bubble-like intranuclear inclusions [21]. However, tall cell variant lacks the cytologic features of the hobnail appearance and comet-like cells. The cytologic features of other variants needing to be differentiated from hobnail PTC are well summarized in a previous study [5].

The overexpression of p53 is generally found in poorly differentiated and anaplastic thyroid cancers and associated with tumor progression from well-differentiated to undifferentiated cancer [22]. One previous study reported that p53 overexpression (> 25% of the tumor cells) was found in all of a series of 14 hobnail PTCs [3]. In our study, three of 10 cases showed

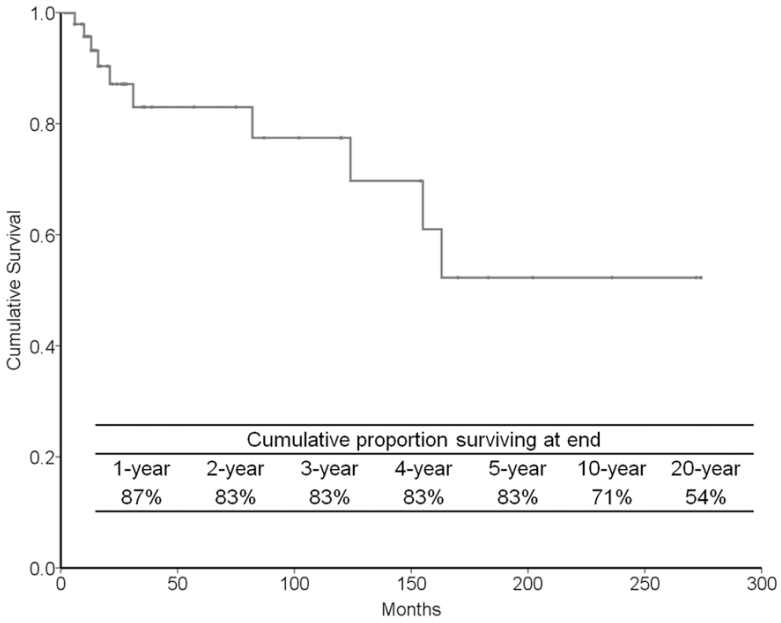

Figure 4. Cumulative survival probabilities of 52 patients with hobnail variant of papillary thyroid carcinoma calculated by the life-table method.

> 10% immunoexpression of p53 and the highest percentage of the immunostaining was 48%. Data regarding mitotic activity were available for analysis in 40 cases from four published reports as well as the present study [3-5, 20]. The mean number of mitotic figures per 10 high-power fields was 2.1 ranging from 0 to 9. These findings support the aggressive biologic behavior of the hobnail PTC.

We investigated whether molecular alterations known to be associated with aggressive thyroid cancer can also be identified in the hobnail variant of PTC. Three studies reported a 71% (17/24) mutation rate of *BRAF* V600E (**Table 1**) [4, 11, 19]. In our study, the 80% mutation rate falls in the range of overall prevalence found in Korean PTC patients [16, 23]. *ALK* fusion and *TERT* promoter mutation are more prevalent in aggressive thyroid cancers [12, 13, 24]. In our study, all 10 cases were negative for *ALK* fusion and *TERT* promoter mutation. From our literature review, these mutations have not been studied in the hobnail variant of PTC. Further studies in a large number of cases are needed to confirm whether those genetic alterations are related to the hobnail variant of PTC.

In conclusion, the rare hobnail variant of PTC may require more aggressive treatment than classic PTCs due to its aggressive clinicopathologic features and poor outcome. The cytologic features of the hobnail variant are characteristic and can allow a preoperative diagnosis on the basis of FNAC specimens. The *BRAF* V600E mutation is the most common event frequently found in the hobnail variant. Further studies are needed to identify more precise molecular genetics.

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Disclosure of conflict of interest

None.

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