

THE RELATION BETWEEN PURE PAPILLARY AND FOLLICULAR VARIANT IN PAPILLARY THYROID CARCINOMA

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Objective. Pure papillary thyroid carcinoma and the follicular variant papillary thyroid carcinoma are the most common subtypes of papillary thyroid carcinoma. The aim of this study was to investigate the effects of prognostic factors of these two subgroups in our series.

Patients and methods. Histopathological type of carcinoma was retrospectively revised in 199 patients who were then divided according to such type. Patients' age and gender as well as the size and multicentricity of tumor, association with Hashimoto's thyroiditis, serum thyroglobulin and anti-thyroglobulin antibodies levels, metastatic lymph node and distant metastases status for both groups were evaluated.

Results. Gender, size, multicentricity of tumor, serum thyroglobulin and anti-thyroglobulin levels were similar in both groups. It was found that, although the tumor size of pure papillary thyroid carcinoma was smaller than that of follicular variant papillary thyroid carcinoma, lymph node metastases occurred more frequently when both subgroups were examined.

Conclusion. The pathological and clinical signs of pure papillary thyroid carcinoma and follicular variant papillary thyroid carcinoma were found similar. According to these results, this study does not support the literature which claims that follicular variant papillary thyroid carcinoma is more aggressive than pure papillary thyroid carcinoma. Moreover, it could be assumed that the number of patients who are diagnosed as pure papillary thyroid carcinoma may be higher when associated with Hashimoto's thyroiditis.

Key words: Thyroid carcinoma - Papillary carcinoma - Follicular variant - Prognostic factors

Differentiated thyroid carcinoma represents nearly 90 % of malignant thyroid tumors. According to their histopathological features; 85-90 % of cases represent papillary thyroid carcinoma (PTC) and 10-15 % follicular thyroid carcinoma (FTC) (ALBORES-SAAVEDRA et al. 1991). The most common subgroups of PTC are pure papillary thyroid carcinoma (PPTC) and follicular variant papillary thyroid carcinoma (FVPTC). The occurrence rate of PPTC is 55-60 %, while this rate is 23-41 % for FVPTC were reported (JOSSART and CARCANGIU et al. 1985a; CLARK

1994; SEBASTIAN et al. 2000; BALOCH and LIVOLSI 2002). Microscopically, in PPTC, in addition to specific nucleus features of papillary thyroid carcinoma, there are also papillary row formations. In follicular variant, however, papillary formations do not occur (ZIDAN et al. 2003). Clinical progress of FVPTC is similar to PTC. However, among the literary data, in addition to reports on more aggressive FVPTC as compared to PPTC, there are also studies showing that lung metastases occur more frequently especially in FVPTC (BALOCH and LIVOLSI 2002).

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Even though FVPTC has been known for 50 years, there are still controversial points about the diagnosis and clinical progress of this type of thyroid carcinoma (HAY 1990; CHAN 2002; PASSLER et al. 2003).

Different morphological structures of such tumors lead to the problems in the diagnosis of FVPTC (HIROKAWA et al. 2002; RENSHAW and GOULD 2002; IVANOVA et al. 2002). Taking this into account, we aimed to explain the effects of prognostic factors on the progress of this illness and different clinical behavior between FVPTC and PPTC was found in our series.

Patients and Methods

A total number of 199 patients who were diagnosed histopathologically as PTC and who were operated between January 2001 and August 2005 was evaluated retrospectively and all patients were divided in those with PPTC (Group 1) and those with FVPTC (Group 2). The evaluation of nuclear features in the histopathological diagnosis of papillary carcinoma was carried out according to the WHO 2004 classification (HEDINGER et al. 1988). Nuclear nicks and intranuclear pseudo inclusions, which are the microscopically evidences of psammoma bodies, hypertrophy in nucleus becoming oval or extended, hyperchromatic nucleus and nuclear membrane disorders in addition to the nucleus transparency and frosted glass appearance, were the nuclear features which are used in the diagnosis of papillary carcinoma. Tumors with those features and of papillary structural character were diagnosed as PPTC, whereas only the tumors with follicular structure were diagnosed as follicular variant.

After the admission of each patient, physical examination, complete blood count, the levels of serum tri-

iodothyronine (T_3), thyroxine (T_4), thyroid stimulating hormone (TSH), thyroglobulin as well as thyroglobulin antibodies, chest x-ray, complete body scintigraphy and neck ultrasonography were examined. Gender, age (<40, >40), histopathological type and size of tumor, occult (<1 cm) and multicentric tumor, association with Hashimoto's thyroiditis, occurrence of metastatic lymph node, medical treatment options carried out and occurrence of distant metastasis for both groups were evaluated.

Statistical evaluation. For evaluation of the differences between the values chi-square test was used, while Mann-Whitney U test was used for the comparison of average values. Obtained $p < 0.05$ was considered as significant.

Results

Among a total of 199 patients, 158 were classified as PPTC (Group 1) and 41 as FVPTC (Group 2). Female/male ratio, average size of tumor, occurrence of multicentric tumor, average thyroglobulin and anti-thyroglobulin levels were similar in both groups (Table 1). Occult tumor rate was found higher in PPTC than FVPTC. It was also observed that the occurrence rate of metastatic lymph node and the association with Hashimoto's thyroiditis was higher in the group with PPTC as compared to that with FVPTC. In both groups, no distant metastases were observed.

Although total thyroidectomy was performed in all patients, in 2 patients from PPTC (Group 2) the functional neck dissection was applied to the same side (Table 2). Lymph node dissection was performed in the patients in whom metastases were detected by physical examination or imaging methods and confirmed by intraoperative frozen section.

Table 1
The characteristic of the patients with pure papillary thyroid carcinoma and follicular variant papillary thyroid carcinoma

	PPTC (n=158)	FVPTC (n=41)	P
Female/male	129/29	30/11	ns*
Size of tumor (cm)	1.34±1 (0.1-6.5)	1.65±1.08 (0.5-5)	ns _A
Multicentric tumor	14	4	ns*
Thyroglobuline level (range)	125.14 (0.1-1500)	212.39 (0.5-1289)	ns _A
Anti-thyroglobuline level (range)	171.45 (10-339)	227.5 (15.74-4000)	ns _A

PPTC: Pure Papillary Thyroid Carcinoma; FVPTC: Follicular Variant Papillary Thyroid Carcinoma; _A: Mann-Whitney U test; *: Chi-Square test

Table 2
The prognostic parameters of the patients with pure papillary thyroid carcinoma and follicular variant papillary thyroid carcinoma

	PPTC (n=158)	FVPTC (n=41)	P
Age (<40/>40)	121/37	10/31	0.046*
Occult tumor	59	8	0.041*
Metastatic lymph node	16	–	0.047*
Hashimoto thyroiditis	33	4	0.43*
Neck dissection	2	–	NS*
Distant metastasis	–	–	–

PPTC: Pure Papillary Thyroid Carcinoma; FVPTC: Follicular Variant Papillary Thyroid Carcinoma; *: Chi-Square test

Discussion

FVPTC is one of frequent papillary thyroid carcinoma subtypes. Their emergency type and response to treatment are generally similar to PPTC (HUNDAHL et al. 1998; BURNINGHAM et al. 2005). However, there are some differences between FVPTC and PPTC in gender, age, size of tumor, multicentric tumor occurrence and lymph node metastases. In this study, the differences between those two groups were presented.

Although FVPTC occurs more frequently in women than in man, in this study no substantial difference between man/women ratio was observed (RENSHAW and GOULD 2002). Studies carried out so far showed that, in patients under 40 years, there was no substantial difference between PPTC and FVPTC. However, in this study we observed that FVPTC occurred more frequently in patients over the age of 40 (CARCANGIU et al. 1985a).

In FVPTC, tumor size is higher than that in PPTC. For such reason, the FVPTC is usually diagnosed in more advanced stages than PPTC (BURNINGHAM et al. 2005). Although some studies showed that the tumor size in patients with FVPTC is meaningfully small than that in patients with PPTC, there are also some studies stating that the tumor size is similar in both groups (CARCANGIU et al. 1985a; TIELENS et al. 1994). In this study, however, it was observed that patients are more frequently diagnosed as PPTC when occult tumor occurs.

Multicentric tumor occurrence is explained in different ways in literature. Although there are some studies which concluded that there is no difference between PPTC and FVPTC in multicentric tumor occurrence (BURNINGHAM et al. 2005), there are also studies which put forward the opposite. For instance, while the rate of multicentric tumor in FVPTC cases was 32 %, it

was only 15 % in PPTC (PASSLER et al. 2003). In the literature, one of the most important reasons for this difference is the scope of medical treatment. The possibility of detecting the multicentric tumor increases in parallel with the rate of total thyroidectomy (BURNINGHAM et al. 2005). Although total thyroidectomy has been carried out in all our patients, it was found that the rate of multicentric tumor occurrence is similar in both groups.

According to the literature, there are different findings of local invasion and lymph node metastases between PPTC and FVPTC. Some studies showed that even though FVPTCs have wider tumor size, they cause less local invasion and lymph node metastases. For instance, cervical lymph node metastases were found in 32 % in FVPTC and 45 % in PPTC (PASSLER et al. 2003). However, in recent studies no differences were found in local invasion and lymph node metastases between these two tumor types (CARCANGIU et al. 1985a; TIELENS et al. 1994; Sebastian et al. 2000; BURNINGHAM et al. 2005). In this study, there were no FVPTC patients with local invasion and lymph node metastases, while in PPTC patients the rate of lymph node metastasis was 10 %. In comparative studies, the rate of distant organ metastases was similar. In FVPTCs distant organ metastases usually occur in lungs (CARCANGIU et al. 1985b). However, in this study no distant metastases were observed.

The relation between Hashimoto's thyroiditis and PTC was first defined in 1950 (DAILEY et al. 1955). In this study the association with Hashimoto's thyroiditis was observed more frequently with PPTCs, especially in patients who were younger than 40 and had occult tumor (?1 cm). Although in the literature the 10-year disease free survival rates were found higher in PPTCs with negative Hashimoto's thyroiditis (e.g.

96 % vs. 78 %), the overall survival rates were similar in both groups (SINGH et al. 1999). Because of that, the reason why the Hashimoto's thyroiditis is more associated with PPTC than FVPTC cannot be satisfactorily explained. Actually, the patients who are followed up as Hashimoto's thyroiditis have a more intensive follow up program than the other patients. Because of that the shape of malignant nodules detected in those patients are thought to be smaller. Moreover, applying total thyroidectomy to the patients with Hashimoto's thyroiditis increases the possibility of casual papillary carcinoma. Because of the technical difficulties mentioned above it is more difficult to diagnose as FVPTC those tumors which are usually smaller than 1 cm. Therefore, it could be assumed that the number of patients who are diagnosed as PPTC may be higher when associated with Hashimoto's thyroiditis.

There are not so many data on the levels of serum thyroglobulin and anti-thyroglobulin between PPTC

and FVPTC. In this study, both groups had similar characteristics of serum thyroglobulin and anti-thyroglobulin levels.

In conclusion: although the tumor size is higher, FVPTC cause less local invasion and more limited lymph node metastasis. However, although PPTC show similar tumor size at the time of diagnosis, they may be seen with more intense lymph node metastasis. There are studies which show that the prognosis is better in PTC associated with Hashimoto's thyroiditis. The reason is that the patients who are monitored more closely, are also detected with smaller tumor size. It is found that although the tumor size in PPTC patients is smaller than in those with FVPTC, lymph node metastasis occurs more frequently when both subgroups are examined. According to these results, this study does not support the literature findings which claim that FVPTC is more aggressive than PPTC. Also the limitation of this study is the insufficient follow-up period for papillary thyroid carcinoma.

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