Endocrine Journal 2006, **53** (5), 627–632

Frequent, Aggressive Behaviors of Thyroid Microcarcinomas in Korean Patients

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Abstract. The incidence of thyroid microcarcinoma is rising due to the frequent use and improvement of fine-needle aspiration biopsy and ultrasonography. Since the recent update of the TNM (Tumor, Node, Metastasis) staging system for thyroid cancer, the importance of lymph node metastasis became more prominent. In the present study, we evaluated the prognostic factors and extension of thyroid microcarcinomas in Korean patients. The clinical and pathological findings in patients with thyroid microcarcinomas in a Korean hospital from January through December 2004 were evaluated. A total of 302 (50.2%) out of 601 cases of thyroid cancers were microcarcinomas. Evaluation of the histology revealed that nearly all of the cases (300 of 302) were of the papillary type. Analyzing patients of papillary thyroid microcarcinomas, 273 (91.0%) out of 300 patients of papillary microcarcinomas were women. Seventy-eight (26.0%) cases contained multiple tumor masses (≥2), including 49 (16.3%) cases that were bilateral. There were 84 (28.0%) cases of extrathyroidal extensions and 89 cases (29.7%) of lymph node metastasis, but no cases of distant metastases. Application of the new staging system revealed 7 (2.3%) cases that changed from stage III to stage IVA. Thyroid microcarcinomas were also associated with poor prognostic factors and appear to exist at relatively higher cancer stages. Therefore, it is important to treat them as early and as vigorously as possible with extensive surgery, radioactive iodine therapy, and thyroxine suppression.

Key words: Thyroid cancer, Papillary carcinoma, Prognosis

(*Endocrine Journal* **53**: 627–632, 2006)

THE World Health Organization (WHO) defines thyroid microcarcinoma as a carcinoma measuring 1.0 cm or less in its greatest dimension [1]. Thyroid microcarcinoma is being identified in an increasing proportion of treated, differentiated thyroid carcinomas. This is mainly due to the more frequent use and improvement of ultrasonography, fine-needle aspiration biopsy, and other diagnostic procedures [2].

The size of the tumor is an important prognostic factor in patients with thyroid carcinoma. There is evidence that tumors less than 1.5 cm in size do not increase the mortality associated with thyroid carcinoma [3]. However, loco-regional recurrences were reported in up to 20% of papillary thyroid microcarcinoma (PTMC) patients, and several cases of distant metastases with fatal outcomes were described in some studies [4]. Thus, defining the prognostic factors to differentiate between silent and potentially aggressive microcarcinomas is important, but they have not been well defined until now.

Thyroid carcinomas have several prognostic factors. Significant factors include: sex of the patient, age at diagnosis, multiplicity or bilaterality of tumors, extrathyroidal extension, lymph node involvement, and distant metastases [5–11]. The recently updated TNM (Tumor, Node, Metastasis) staging system, however, places greater emphasis on metastasis to the lymph nodes [12]. Several studies were performed to evaluate

Received: January 19, 2006
Accepted: April 26, 2006
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the clinical characteristics of prognostic factors for thyroid microcarcinomas. Trials to define reasonable therapeutic guidelines are currently underway. However, there are no studies to date on thyroid microcarcinomas in the Korean population. Papillary thyroid carcinomas in Koreans rarely show RET/PTC rearrangements. Instead, they commonly exhibit increased RET gene expression [13]. This finding is different from those found in Western populations, but there are no studies indicating whether this different pathogenesis contributes to the disparate clinical behaviors of thyroid carcinomas.

In the present study, the clinical characteristics of papillary thyroid microcarcinomas, with special reference to the prognostic factors in Koreans, were investigated. The stages of the tumors were also reevaluated using the recently updated TNM staging system.

Materials and Methods

Study population

This study included 601 patients who underwent surgery for thyroid carcinoma at Severance Hospital in Korea from January 1 through December 31, 2004. In this group of 601 patients, 302 (50.2%) were found to have a thyroid microcarcinoma. The clinical records, including the operation records, of 302 patients were reviewed.

Evaluation of the histology revealed that nearly all of the cases (300 of 302) could be characterized as the papillary type. There was only one case each of follicular and medullary cancer. These two cases were excluded from the analysis, because they would not be expected to behave the same way as the papillary thyroid carcinomas. This is especially true for the one patient with a medullary thyroid carcinoma.

The findings from the postoperative pathology were collected. This information was then used to investigate the clinical characteristics of the prognostic factors of thyroid microcarcinomas in Korean patients. Tumors were staged according to both the fifth and sixth editions of TNM staging: T and N were determined on the basis of pathological data, and M was based on the findings of the first postoperative ^{131}I-whole body scan.

Statistical analysis

Data analysis was performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL). The Pearson chi-square test was used to analyze differences between tiny and minute carcinomas, and between the prevalence of extrathyroidal extensions and lymph node metastases.

Results

Features of patients studied

302 (50.2%) of the patients had thyroid microcarcinoma. Three hundred (99.4%) patients accounted for cases diagnosed as the papillary type. There was only one case each of the follicular and medullary type. Only data from the papillary thyroid microcarcinomas were included in the analysis (Table 1).

Among these 300 cases of papillary thyroid microcarcinomas, 273 (91.0%) of the cases were women. The mean patient age was 46.1 ± 10.4 years (range: 17–72 years) and 176 patients (58.6%) were older than 45 years (Fig. 1).

There were 299 patients that had a larger thyroid carcinoma compared to the microcarcinoma, the mean age of patients in this group was 45.7 ± 14.1 years (range: 14–83 years), and most of these patients were women, 252 patients (84.3%).

Clinical characteristics of microcarcinomas

A thyroid lobectomy was performed on 246 (82.0%) of the 300 patients. Fifty-two patients (17.3%) under-

Table 1. Characteristics of 300 patients with papillary thyroid microcarcinomas

Characteristics	
Gender ratio (Male/Female)	27/273 (9.0/91.0%)
Age (years)	46.1 ± 10.4 (17–72)
Age ≥45	176 (58.6%)
Tumor size (mm)	6.4 ± 2.4 (1–10)
Tiny/Minute (5–10/<5 mm)	238/62 (79.3/20.7%)
Bilaterality	49 (16.3%)
Multifocality	78 (26.0%)
Extrathyroidal extension	84 (28.0%)
Lymph node metastasis	89 (29.7%)
Distant metastasis	0

Data on Age and Tumor size are presented by mean ± SD (range).

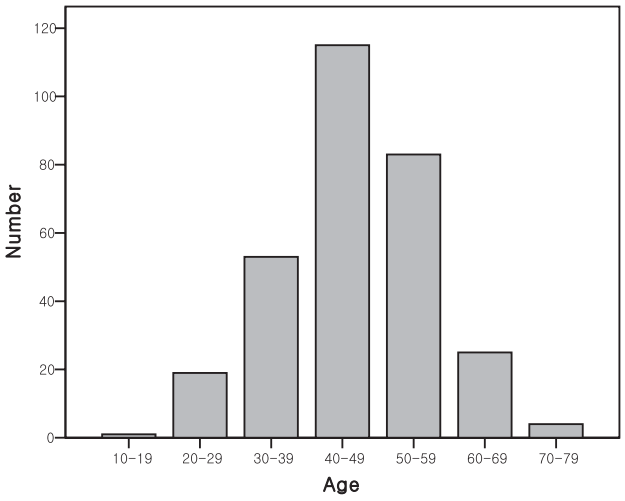

Fig. 1. Age distribution of 300 patients with papillary thyroid microcarcinomas

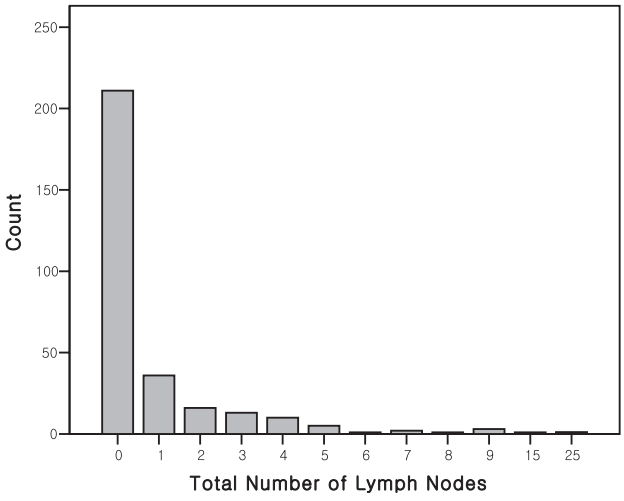

Fig. 3. Total number of lymph nodes involved in each patient (lymph node metastasis)

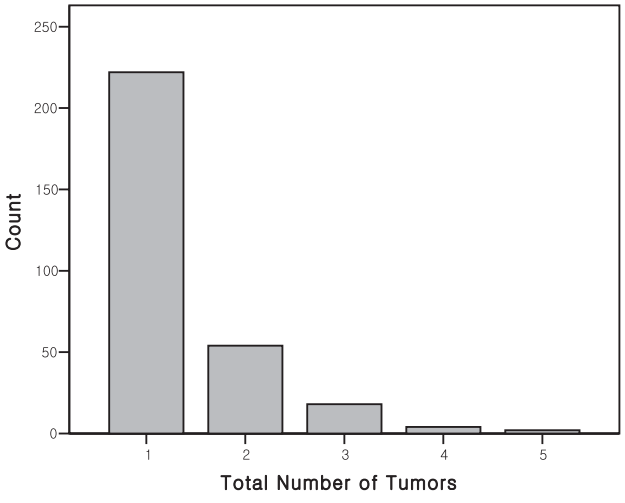

Fig. 2. Total number of tumors in each patient (multiplicity of tumors)

went a total thyroidectomy, 1 patient (0.3%) had a subtotal thyroidectomy, and 1 patient (0.3%) had a partial thyroidectomy. A central compartmental neck dissection (CCND) was performed on 268 of the 300 patients (89.3%).

The mean size of the tumors was 6.4 ± 2.4 mm (range: 1–10 mm). Seventy-eight (26.0%) patients had two or more tumors (Fig. 2). The mean number of tumors in each patient was 1.4 ± 0.7 (range: 1–5). There were 54 (18.0%) patients with two tumors, 18 (6.0%) patients with three tumors, 4 (1.3%) patients with four tumors, and 2 (0.7%) patients with five tumors. There were 49 cases (16.3%) of bilaterality. Eighty-four (28.0%) patients had extrathyroidal extensions, of which 20 cases (6.7%) involved capsular invasion.

There were 89 patients (29.7%) with lymph node metastasis. The mean number of lymph nodes involved was 0.9 ± 2.3 (range: 0–25). Thirty-six (40.4%) cases involved only one lymph node. However, there were 16 (18.0%) patients with two involved lymph nodes, 13 (14.6%) with three, 10 (11.2%) with four, 5 (5.6%) with five, 1 (1.1%) with six, 2 (2.2%) with seven, 1 (1.1%) with eight, and 3 (3.4%) cases with nine lymph nodes involved. There was also one case involving 15 lymph nodes, and one patient with 25 affected lymph nodes (Fig. 3). In total, there were 53 cases involving two or more lymph nodes. This accounted for 59.6% of cases with lymph node involvement, and 17.7% of thyroid microcarcinomas overall. There were 25 (9.4%) cases of lymph node involvement at level II, 38 (14.2%) at level III, 27 (10.1%) at level IV, 3 (1.1%) at level V, and 174 cases (65.2%) at level VI. However, there were no cases of distant metastasis.

Thyroid microcarcinomas can also be subclassified as tiny or minute. For the purposes of this study "Tiny" was defined as a PTMC between 5–10 mm, while "Minute" was defined as less than 5 mm in the maximum diameter. A total of 238 patients (79.3%) had tiny microcarcinomas, and 62 patients (20.7%) were classified as having minute carcinomas. We found that extrathyroidal extensions were more prevalent in the tiny carcinomas; they were found in 77 (32.4%) cases of tiny vs. in 7 (11.3%) cases of minute carcinomas (*p*-

value = 0.001). However, the prevalence of lymph node metastases was not significantly different, 73 (30.7%) cases in the tiny vs. 16 (25.8%) cases in the minute carcinomas (p-value = 0.455).

Features of staging by the new TNM staging system

According to the fifth edition of the TNM staging system, 71 patients older than 45 years had stage III disease with components of T4 and/or N1. Stage T4 disease was identified in 84 patients (28.0%), while N1 disease was identified in 89 patients (29.7%).

Recently, the TNM staging system for thyroid carcinomas was updated to a sixth edition [7]. Data were analyzed by a new updated staging system and compared with results using the previous edition. T stage was analyzed using postoperative biopsy results, and N stage was analyzed by postoperative biopsy of the lymph nodes, excised irrespective of excision range. M stage was assigned after confirming distant metastasis using a radioactive iodine whole-body scan, performed during postoperative radioactive iodine therapy. Whole-body scan was performed only in patients that had undergone a total thyroidectomy. Those cases were analyzed with the supposition of no distant metastasis because there was not any other evidence of distant metastasis.

After applying the updated staging system, the cases that had been identified as stage T4 were all changed to T3. The 89 cases of N1 were subsequently changed to 66 cases (22.0%) of N1a and 23 (7.7%) cases of N1b. Seven patients (2.3%) were upgraded from stage III to stage IVA, but 64 (21.3%) patients remained at stage III with no change.

Discussion

The optimal treatment for thyroid microcarcinoma remains controversial. In the case of well-differentiated thyroid cancer, tumors less than 1.5 cm in size have previously not been associated with an increase in mortality [3]. However, as all advanced carcinomas were microcarcinomas at some point, there must be cases of tumors diagnosed as microcarcinoma which have the potential to develop and become life-threatening for the patient in the future [14]. Surgical treatment has been recommended as a choice of therapy because a high incidence of lymph node metastasis has been reported [10, 15–19]. Loco-regional recurrences were reported in up to 20% of PTMC, and several cases of distant metastases with fatal outcomes were described in some studies [4]. Here, we reconfirmed that thyroid microcarcinomas show previously identified poor prognostic factors and exist at relatively advanced cancer stages.

Comparing known prognostic factors with the results of this study, we found 89 (29.7%) cases with lymph node metastases, 78 (26.0%) cases with multiple tumors, 49 (16.3%) cases with bilaterality, and 84 (28.0%) cases with perithyroidal tissue invasion. Therefore, despite the smaller size of the thyroid microcarcinomas, poor prognostic factors were frequently observed in this study.

Recently, the TNM staging system for the staging of thyroid carcinoma was updated to its 6th edition [12]. One of the striking changes from the previous edition is that the size of the tumor defined as T1 was changed from 1 cm to 2 cm [20]. In addition, the N1 classification was subdivided into N1a and N1b. Previously, a T1 carcinoma could not be ranked as a stage IV cancer in the absence of distant metastasis. However, with the updated staging system, a T1 carcinoma can be ranked as stage IVA in patients older than 45 years, even without distant metastasis. This infers that lymph node metastasis is considered more important than the size of the tumor for tumor staging. Upon analysis of the results of this study according to the updated TNM staging system, N1b-stage carcinomas were found in 23 patients. This represents only 7.7% of the total thyroid microcarcinoma cases, but 25.8% of cases with lymph node metastasis. Thus, in thyroid microcarcinoma, lymph node metastasis (even to lymph nodes distant to the primary tumor) is not uncommon. As a result, 7 cases previously classified as stage III were classified as stage IVA.

It was proposed that the pathogenesis of thyroid carcinoma in Koreans varies slightly from that of Western populations [13]. RET/PTC rearrangements were reported to occur in approximately 11–40% of papillary thyroid carcinomas, of which the frequency varies depending on the country. Papillary thyroid carcinomas among Koreans rarely showed RET/PTC rearrangements, but commonly showed increased RET gene expression [13]. We could not find any significant differences between the Korean and Western populations with regard to clinical characteristics of thyroid microcarcinomas. Therefore, the factors identified above

might play a minor role in determining the behavior or clinical outcome of thyroid microcarcinomas.

Kasai and Sakamoto suggested a further subdivision of PTMC based on tumor size: tiny versus minute. Tiny was defined as a PTMC between 5–10 mm, while minute was defined as less than 5 mm in maximum diameter [21]. Kasai and Sakamoto found the prevalence of lymph node metastasis in tiny and minute to be 59% and 13%, respectively. They also found extrathyroidal extension to be 10% in tiny versus only 3% in minute [21]. In the present study, definite differences were seen between tiny and minute microcarcinomas. The prevalence of lymph node metastasis was observed to be 82.0% in tiny, and only 18.0% in minute carcinomas. Extrathyroidal extension was also significantly more prevalent in tiny than in minute carcinomas (91.7% and 8.3%, respectively).

In this study, the complications of hypoparathyroidism or recurrent laryngeal nerve injury did not occur after total thyroidectomy as a treatment for thyroid microcarcinoma. Bhattacharya *et al.* reported that postoperative hypocalcemia occurs in about 6% of patients, and recurrent laryngeal nerve injury occurs in only 1% of postoperative patients in the United States [22]. As thyroid microcarcinomas often occur in bilateral or multifocal fashion, residual tumor was assumed to be frequently left behind in the contralateral lobe after simple lobectomy [5]. Several studies have already reported recurrence rates for PTMC patients treated with lobectomy to be higher than those with total thyroidectomy [2, 23]. The risk of reoperation was also decreased when total thyroidectomy was performed after the initial diagnosis [5]. In this study, it was not possible to compare recurrence rates according to operation methods because we could not analyze recurrence cases due to the short duration of follow-up. However, there were no major postoperative complications, such as persistent hypocalcemia or recurrent laryngeal nerve injury, in any of the cases, including the total thyroidectomies.

Thyroid carcinoma is frequently multifocal. Shattuck *et al.* established that individual tumor foci in patients with multifocal papillary thyroid carcinoma often arise as independent tumors [24]. They analyzed the patterns of X-chromosome inactivation of multiple distinct foci of well-differentiated multifocal papillary thyroid carcinomas using a polymerase chain reaction assay involving the human androgen receptor gene (HUMARA). According to the authors, their findings imply that any thyroid tissue remaining after surgery for multifocal thyroid carcinoma may contain or be likely to develop additional foci of cancer that could become recurrences. This is one piece of evidence that supports the appropriateness of total thyroidectomy and radioactive iodine therapy of the remaining tissue. The estimated frequency of multiplicity of thyroid tumors ranges between 18 and 87%, depending on the techniques used [24–26]. Multiplicity of thyroid microcarcinoma is also not uncommon compared to thyroid carcinoma, as shown in this study. Therefore, it is reasonable to assume that thyroid microcarcinomas require aggressive therapy, similar to that required for thyroid carcinomas.

There are some investigators that have suggested that observation is the preferred course of management for patients with papillary microcarcinomas, arguing that these tumors often remain latent with no life-threatening consequences [2, 27]. The final word on the best management approach for these patients will require further investigation with a prospective randomized study design.

We encountered several limitations when trying to investigate the effects of known factors associated with recurrence. First, these patients were diagnosed and operated on early in their course. Second, there was not enough time to follow up these patients due to the retrospective nature of this cross-sectional study. Finally, objective evidence that there was not any distant metastasis could not be confirmed because whole-body scans were not performed in cases other than total thyroidectomies. In the future, there is a need for prospective studies in this area that involve much larger cohorts of the Korean population with different pathogenesis of thyroid carcinoma.

In conclusion, a significant proportion of thyroid microcarcinomas showed poor prognostic factors and existed at relatively higher cancer stages. Therefore, it is important to treat thyroid microcarcinomas as early and as vigorously as possible with extensive surgery, radioactive iodine therapy, and thyroxine suppression.

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