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Clinical Features of Bone Metastases Resulting from Thyroid Cancer: A Review of 28 Patients over a 20-year Period

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Abstract. Bone is the second most frequent site of metastasis resulting from thyroid cancer. Many studies have investigated clinical features and prognostic factors of distant metastases stemming from thyroid cancer in Western countries. The purpose of this study was to review clinical characteristics of Korean patients with bone metastasis originating from thyroid cancer. Between January 1985 and August 2004, 28 patients with thyroid cancer were diagnosed with bone metastases at the Yonsei Severance Hospital in Seoul, Korea. Their clinical characteristics were analyzed retrospectively. Incidence of bone metastasis from follicular thyroid cancer was 6.8% (9 of 132 patients), and 0.4% (13 of 3,154 patients) from papillary thyroid cancer, with an odds ratio of 17.67 (95% confidence interval; 7.41–42). Twelve patients had no symptoms of bone metastasis. Overall mean number of metastasis sites was 2.6 ± 1.9, and 12 patients had a solitary bone metastasis. Survival rates between the synchronous and metachronous metastasis groups were not significantly different, and the number of metastasis sites did not affect survival. However, the survival of patients that underwent curative treatment was longer than those with palliation ($P = 0.0317$). In Korea, the overall incidence of bone metastasis resulting from thyroid cancer was less than our expectation. Many patients were asymptomatic, and had a tendency of undergoing less aggressive or palliative treatment, even though the long-term survival of distant metastasis resulting from thyroid cancer with active treatment is relatively good. Further studies of the prognostic factors and effectiveness of various treatments of these patients are needed to enhance survival.

Key words: Thyroid cancer, Bone metastasis, Synchronous, Metachronous

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DISTANT metastasis in thyroid cancer is well known and develops in 7% to 23% of patients with differentiated thyroid cancer [1]. In anaplastic thyroid cancer, 25% to 50% of patients may have synchronous pulmonary metastases at the time of diagnosis [2], while 20% of patients with sporadic medullary thyroid carcinoma had distant metastases at the time of diagnosis [3]. Bone is the second most common site of metastasis resulting from thyroid cancer after lung. The incidence of bone metastasis varies along with the degree of differentiation and histologic subtypes of thyroid cancer. Follicular thyroid cancer is the most common histologic origin of bone metastasis among well-differentiated thyroid cancer, with incidences ranging from 7% to 28% [4, 5], but papillary thyroid cancer has been identified as the least likely subtype to cause bone metastases with incidences ranging from 1.4% to 7% in many reports [6–8]. According to the time interval from thyroid cancer diagnosis to detection of distant metastasis, metastatic thyroid cancer is classified into two types: synchronous metasatsis (SM) and metachronous metastasis (MM). The differences between these two

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groups seem to be affected by tumor biology and histology [9]. The incidence of synchronous metastasis is 11% in follicular thyroid cancer, and 2% in papillary thyroid cancer [7]. The incidence of MM for follicular and papillary thyroid cancer is 20% and 10% respectively [10, 11].

There is little data about Korean patients with bone metastasis resulting from thyroid cancer. In this study, we investigated the clinical characteristics, incidences and survival of thyroid cancer patients with bone metastases diagnosed at a single Korean institution.

Materials and Methods

Study population

Among the patients with distantly metastatic thyroid cancer who were treated at the Severance Hospital from January 1985 to August 2004, 28 patients were identified as having bone metastases. A retrospective study was performed with the review of all available medical records including personal charts, surgical reports, pathology reports and radiographies. Patient survival was verified by telephone and medical records. Only concrete data regarding survival was considered. Mean time of follow-up was 5.3 ± 7.8 years from the diagnosis of thyroid cancer, and 2.4 ± 2.6 years from the date of bone metastasis presentation. Sixteen patients (57%) were diagnosed as having thyroid cancer with bone metastasis at the time of initial presentation, and were categorized as the SM group. Twelve patients (43%) had their thyroid cancer recur distantly in bones after the completion of previous treatment of primary lesions, and were categorized as the MM group.

Statistical analysis

Mean values are reported with accompanying standard deviations. Associations between categorical variables were evaluated using a chi-square test or Fisher's exact test. Ages at the diagnosis of thyroid cancer and metastasis were compared using the Mann-Whitney test. Survival curves were plotted with the Kaplan-Meier method and log-rank test. Statistical analysis was performed using SPSS 11.0 for Windows (Chicago, IL, USA) software. A P value<0.05 was considered significant.

Results

Clinical and pathologic characteristics

Clinical and pathologic features are presented in Table 1. There were 5 male and 23 female patients. All patients were over 45 years of age except four of them. Mean age at the diagnosis of thyroid cancer was 56 ± 14.7 years, and was not significantly different between the two groups. Incidences of bone metastasis according to histologic subtypes were 6.8% (9 of 132 patients) for follicular thyroid cancer and 0.4% (13 of 3,154 patients) for papillary thyroid cancer. The odds ratio of bone metastasis between the two subtypes was 17.67 (95% CI; 7.41–42.14). In the SM group, 6 patients (37.5%) had symptomatic bone metastases including bone pain and motor weakness, but the others were totally asymptomatic. In three cases, biopsies of the lumbar spine and ribs indicated the origins of these cancers were the thyroid. Bone metastases of two patients (16.6%) from the MM group were asymptomatically diagnosed by regular follow-up tests, at 1 and 3 years, respectively, after surgical removal of the thyroid cancer. Asymptomatic metastases in the SM group were 8.3 times more frequent than those in the MM group (95% CI; 1.34–51.67). Motor weakness, paraplegia and quadriplegia in all 4 patients resulted from spinal cord compression due to vertebral metastases at the cervical or lumbar spine. In the MM group, bone metastases were diagnosed at 2 months to a maximum of 29 years following the diagnosis of thyroid cancer, and a total of 8 patients (66.6%) were diagnosed within 5 years. Thirteen of 28 patients had performed radioactive iodine scan and all had positive uptake of radioactive iodine at metastatic sites (Table 1).

Regarding the size of primary thyroid cancers, there were no significant differences between SM and MM group. Mean size of tumor was 3.33 ± 1.3 cm (Table 2). But there were more metastasized lymph nodes in the MM group than in the SM one ($p = 0.018$). In the aspect of capsular and vascular invasion, there were no significant differences between the two groups (Table 2).

Site and treatment of bone metastasis

Twelve patients (42.8%) had a solitary bone metastasis, and four patients (14.2%) had more than 5 metastasis sites, while the mean number of sites was 2.6 ± 1.9. Simultaneous presence of metastasis sites other than

Table 1. Characteristics of patients with bone metastasis resulting from thyroid cancer

Characteristics	Total patients (n = 28)	Synchronous metastasis (n = 16)	Metachronous metastasis (n = 12)	*P* value
Male : Female	5 (18%) : 23 (82%)	1 : 15	4 : 8	0.133[a]
Age at diagnosis of thyroid cancer (y)	56 ± 14.7 (26–83)	57.3 ± 13.2 (41–83)	53.8 ± 16.9 (26–81)	0.693[b]
Age at diagnosis of metastasis (y)	58.6 ± 13.2 (28–83)	57.3 ± 13.2 (41–83)	59.9 ± 13.6 (28–82)	0.329[b]
Pathological diagnosis				—
Well-differentiated	22 (78.6%)	12	10	
Papillary carcinoma	13	7	6	
Follicular carcinoma	9	5	4	
Poorly differentiated carcinoma	2 (7.1%)	1	1	
Anaplastic carcinoma	1 (3.5%)	1	0	
Medullary carcinoma	2 (7.1%)	2	0	
Unknown histology*	1 (3.5%)	0	1	
Primary tumor treatment				—
Total thyroidectomy	14 (50%)	9	5	
Lobectomy	4 (14.3%)	0	4	
Non surgical therapy	10 (35.7%)	7	3	
Symptoms of bone metastasis				0.023[c]
Bone pain	12 (42.8%)	5	7	
Back pain	5	3	2	
Flank pain	1	1	0	
Headache	2	1	1	
Pelvis & L/E† pain	4	0	4	
Motor weakness	4 (14.2%)	1	3	
No symptom	12 (42.8%)	10	2	
^{131}I uptake at metastatic site				—
Positive	13 of 13	7 of 7	6 of 6	
Negative	0 of 13	0 of 7	0 of 6	

* Unknown histology: follicular or papillary adenocarcinoma, † L/E: low extremities
[a] Fisher's exact test
[b] Mann-Whitney test
[c] Fisher's exact test with two independent variables classified as symptom and no symptom

Table 2. Surgical pathology of primary tumor in the thyroid

Surgical pathology	Total patients (n = 18 of 28)	Synchronous metastasis (n = 9)	Metachronous metastasis (n = 9)	*P* value
Hospital for surgery				
Severance Hospital	12	7	5	
Other hospitals	6[c]	2	4	
Primary tumor size (cm)	3.33 ± 1.3	3.02 ± 0.58	3.76 ± 1.10	0.53[a]
Metastasized lymph node	0 (0–17)[b]	0 (0–1)	6 (0–17)	—
Capsular invasion	10	5	5	—
Papillary cancer	8	3	5	
Follicular cancer	2	2	0	
Vascular invasion	3	2	1	—
Papillary cancer	2	1	1	
Follicular cancer	1	1	0	

[a] Mann-Whitney test
[b] Median number and range of metastasized lymph node
[c] Five of 6 patients were treated at four other Korean hospitals (Seoul National University Hospital, Hallym Medical Center, Korea Cancer Center Hospital, and Samsung Medical Center), and one patient at Bolivia. The data of surgical pathology from these 6 patients were excluded in the above description because of incompletion.

bone was noticed in 11 patients (39.2%): at the lung in 9 patients, liver in 1 patient and adrenal gland in 1 patient. The specific sites of bone metastasis are listed in Table 3. The most frequent site was the spine followed by the rib. Ten of 22 patients with well-differentiated thyroid cancer refused or abandoned the curative treatment for bone metastasis (Table 4).

Survival analyses

The survival curves and rates are described in Fig. 1. Median patient survival rate of well-differentiated thyroid cancer with bone metastasis was 3 years, ranging from 0 to 11 years, after diagnosis of bone metastasis. Two patients with undifferentiated thyroid cancer showed one and three months of survival time, respectively. Survival rates at more than 3 years after diagnosis of bone metastasis remained stable in both SM and MM groups, and most of the mortality with thyroid cancer occurred within 3 years. Among the patients with well-differentiated thyroid cancer, the median survival time of the MM group was 3 years (range, 2 months to 11 years), and that of the SM group was 2 years (range, 0 to 10 years). Fig. 1B demonstrates that survival from the diagnosis of metastasis is not significantly different between the SM and MM groups. Regardless of the treatment and timing of metastasis, patients with solitary bone metastasis showed a similar survival rate, compared with those with multiple bone metastases, as shown in Fig. 1C. Patients treated aggressively showed prolonged survival, compared with those treated with palliative therapy (Fig. 1D).

Discussion

Most published studies on bone metastasis resulting from thyroid cancer were focused on well-differentiated

Table 3. Frequencies of metastatic sites and histologic subtypes

	Spine			Rib	Pelvis and femur head	Skull	Condyle	Lung	Liver	Adrenal gland
	C	T	L							
Histologic diagnosis										
Papillary (n = 13)	3	2	6	9	0	3	2	4	0	1
Follicular (n = 9)	0	2	6	2	5	0	0	3	0	0
Insular carcinoma (n = 1)	0	0	0	0	1	0	0	1	0	0
Anaplastic (n = 1)	0	0	0	0	0	0	0	1	0	0
Poorly differentiated (n = 1)	0	0	1	0	0	0	0	0	0	0
Medullary (n = 2)	0	1	0	3	0	0	0	0	1	0
Timing of metastasis										
Synchronous (n = 16)	2	9	7	9	2	2	2	5	1	1
Metachronous (n = 12)	2	2	6	4	5	1	0	3	0	0

C: cervical spine, T: thoracic spine, L: lumbar spine

Table 4. Treatment of metastatic bone cancer from well differentiated and undifferentiated thyroid cancer

Treatment modalities at metastatic focus	Well-differentiated		Poorly or undifferentiated	
	Synchronous n = 12	Metachronous n = 10	Synchronous n = 2	Metachronous n = 1
Resection or excision only	1	0		
Radioactive iodine only	2	3		
External radiation only	0	2		
Resection + Radioactive iodine	1	1		
External radiation + Radioactive iodine	1	0	1	
Resection + radiation + systemic chemotherapy	1	0		
Palliative treatment	6 (50%)	4 (40%)	1	1
External radiation	2	3		1
Conservative care without treatment	4	1	1	

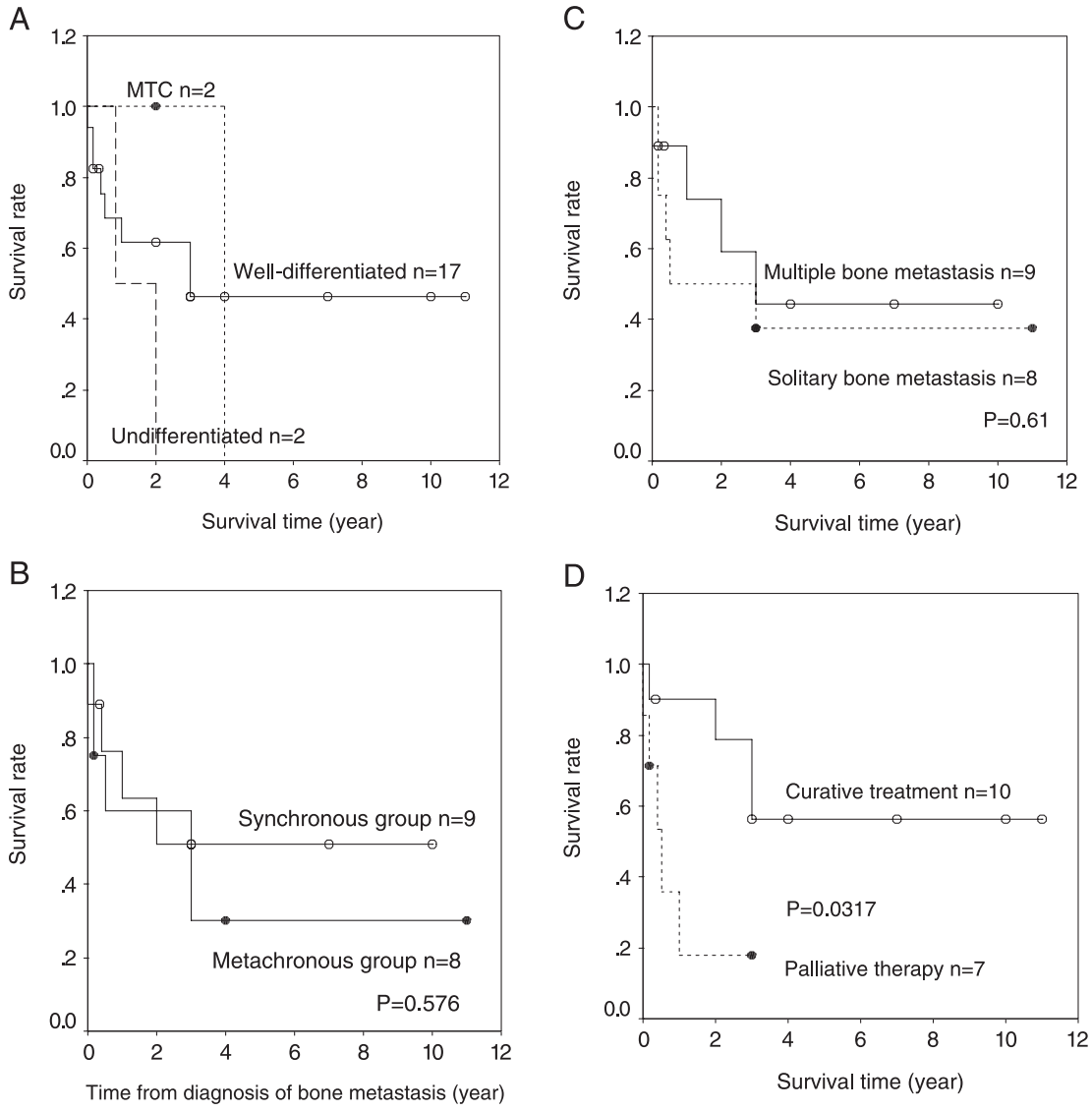

Fig. 1. Survival curves using the Kaplan-Meier method and log-rank test after diagnosis of bone metastasis.
A. Survival curves of differentiated and undifferentiated thyroid cancer.
B. Comparison of survival between synchronous and metachronous groups (P = 0.576).
C. Comparison of survival based on the number of metastatic sites (P = 0.61).
D. Comparison of survival between palliative and actively treated groups, after correction of time to metastasis (P = 0.0317).

thyroid cancer, such as papillary and follicular types. In general, these cancers are some of the most indolent solid neoplasms, with favorable long-term survival [12]. Papillary thyroid cancer shows a 10-year overall survival rate, ranging between 74% and 93%, as compared to follicular thyroid cancer, with a 10-year survival rate of 43% to 94% [13]. For metastatic diseases from well-differentiated thyroid cancer, a 10-year survival was reported as 13% to as high as 61% [7, 14–16]. Anaplastic thyroid cancer is one of the most aggressive and lethal undifferentiated cancers, and has a median survival of 4 to 5 months from the time of diagnosis [17]. The relative long-term survival rate of well-differentiated thyroid cancer has aroused many authors' interest in the metastatic subgroup. Lung metastasis is easily and frequently found in routine radiography of the chest during the follow-up process. On the contrary, imaging of bone is not a common examination site for workup, and therefore the effect of bone metastasis on prognosis and survival has not

been the focus of several investigations.

The relative incidence of papillary thyroid cancer among bone metastases is higher than that of follicular thyroid cancer, as reported by recent studies [18, 19] and in our study as well. Papillary thyroid cancer is responsible for 46.4% of bone metastases, compared with follicular thyroid cancer accounting for 32.1%. This seems to be due to the fact that papillary thyroid cancer constitutes the largest portion of thyroid cancer, approximately 80% to 85% of malignant epithelial thyroid tumors [20]. However, papillary thyroid cancer is less likely to metastasize to bone than follicular thyroid cancer.

Bone metastasis detected at the time of diagnosis of thyroid cancer, SM, was reported to occur in 40% to 75% of patients who initially diagnosed as thyroid cancer [1, 14, 21, 22], and in 57% in our cases. This SM is a strong predictor of a relatively poor outcome, but the long-term survival is still quite satisfactory [23]. MM is also a poor prognostic factor, as are solid tumors of other organs. Our study analyzed the survival times of the SM and MM groups, without any significant differences between these groups. Although this survival analysis could not be statistically confirmed because of the small number of subjects, Shoup *et al.* produced a similar result from an investigation with 242 patients [1]. This fact could indicate that there is no predominance of biological aggressiveness between the cancer cell types of these two groups.

Symptoms from metastatic diseases are an important clue in detecting metastasis, but these do not significantly affect survival, compared with asymptomatic bone metastasis [14]. Asymptomatic bone metastasis in the metachronous group can be detected through serial thyroglobulin measurement and regular radioiodine scans, but at the time of initial presentation, asymptomatic disease is difficult to discover. Multisite metastasis is generally considered to be associated with decreased survival, and limited extent of metastatic disease is a favorable factor for survival [7, 15], although Pittas *et al.* reported that the survival in patients who had a single bone lesion was not better than in those with multiple bone lesions [14]. Age is considered as a prognostic factor of improved survival [24, 25], but in our study, age at diagnosis of bone metastasis was not statistically significant, maybe due to the small number of patients less than 45 years old (not described in above results). Early detection could initiate prompt therapy and improve survival. Also noteworthy is that many Korean patients in our study chose a conservative therapy without any further treatment. In our study, the survival of patients treated with only conservative therapy was reported to be significantly shorter than actively treated patients. Because long-term survival is generally possible even in patients with bone metastasis from well-differentiated thyroid cancer, active and optimal treatment must be carried out.

In conclusion, the overall incidence of bone metastasis from thyroid cancer was less than our expectation in Korea. Time at the detection of metastasis from diagnosis of thyroid cancer and the number of metastasis sites was not a prognostic factor for survival. Active treatment for metastastic disease improved survival, and the long-term survival of distant metastasis resulting from thyroid cancer is relatively good. Further investigation is required to establish the true effect of bone metastasis on the survival and prognosis of this specific group of thyroid cancer patients.

References

1. Shoup M, Stojadinovic A, Nissan A, Ghossein RA, Freedman S, Brennan MF, Shah JP, Shaha AR (2003) Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. *J Am Coll Surg* 197: 191–197.
2. Nel CJ, van Heerden JA, Goellner JR, Gharib H, McConahey WM, Taylor WF, Grant CS (1985) Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. *Mayo Clin Proc* 60: 51–58.
3. Brunt LM, Wells SA Jr (1987) Advances in the diagnosis and treatment of medullary carcinoma. *Surg Clin North Am* 67(2): 263–279.
4. McCormack KR (1966) Bone metastases from thyroid carcinoma. *Cancer* 19: 181–184.
5. Harness JK, Thompson NW, McLeod MK, Eckhauser FE, Lloyd RV (1984) Follicular carcinoma of the thyroid gland: trends and treatment. *Surgery* 96: 972–980.
6. Tickoo SK, Pittas AG, Adler M, Fazzari M, Larson SM, Robbins RJ, Rosai J (2000) Bone metastases from thyroid carcinoma. A histopathologic study with clinical correlates. *Arch Pathol Lab Med* 124: 1440–1447.
7. Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP, Fragu P, Lumbroso J, Caillou B, Parmentier C (1986) Long term results of treatment of

283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 63: 960–967.
8. Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J (1985) Papillary carcinoma of the thyroid: a clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer* 55: 805–828.
9. Stojadinovic A, Shoup M, Ghossein RA, Nissan A, Brennan MF, Shah JP, ShahaAR (2002) The role of operations for distantly metastatic well-differentiated thyroid carcinoma. *Surgery* 131: 636–643.
10. Beierwaltes WH, Nishiyama RH, Thompson NW, Copp JE, Kubo A (1982) Survival time and "cure" in papillary and follicular thyroid carcinoma with distant metastases: statistics following University of Michigan therapy. *J Nucl Med* 23: 561–568.
11. Niederle B, Roka R, Schemper M, Fritsch A, Weissel M, Ramach W (1986) Surgical treatment of distant metastases in differentiated thyroid cancer: indication and results. *Surgery* 100: 1088–1097.
12. Joensuu H, Klemi PJ, Paul R, Tuominen J (1986) Survival and prognostic factors in thyroid carcinoma. *Acta Radiol Oncol* 25: 243–248.
13. Rossi RL, Cady B, Silverman ML, Wool MS, ReMine SG, Hodge MB, Salzman FA (1988) Surgically incurable well-differentiated thyroid carcinoma. *Arch Surg* 123: 569–574.
14. Pittas AG, Adler M, Fazzari M, Tickoo S, Rosai J, Larson SM, Robbins RJ (2000) Bone metastases from thyroid carcinoma: Clinical characteristics and prognostic variables in one hundred forty-six patients. *Thyroid* 10: 261–268.
15. Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M, Parmentier C (1996) Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med* 37: 598–605.
16. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA (1988) Distant metastases in differentiated thyroid carcinoma: A multivariate analysis of prognostic variables. *J Clin Endocrinol Metab* 67: 501–508.
17. Tan RK, Finley RK 3rd, Driscoll D, Bakamjian V, Hicks WL Jr, Shedd DP (1995) Anaplastic carcinoma of the thyroid: a 24-year experience. *Head Neck* 17: 41–47.
18. Mizukami Y, Michigishi T, Nonomura A, Hashimoto T, Terahata S, Noguchi M, Hisada K, Matsubara F (1990) Distant metastases in differentiated thyroid carcinomas: a clinical and pathologic study. *Hum Pathol* 21: 283–290.
19. Wood WJ Jr, Singletary SE, Hickey RC (1989) Current results of treatment for distant metastatic well-differentiated thyroid carcinoma. *Arch Surg* 124: 1374–1377.
20. Jossart GH, Clark OH (1994) Well-differentiated thyroid cancer. *Curr Probl Surg* 31: 933–1012.
21. Fanchiang JK, Lin JD, Huang MJ, Shih NH (1998) Papillary and follicular thyroid carcinoma with bone metastases: A series of 39 cases during a period of 18 years. *Chang Keng I Hsueh Tsa Chih* 21: 377–382.
22. Marcocci C, Pacini F, Elsei R, Schipani E, Ceccarelli C, Miccoli P, Arganini M, Pinchera A (1989) Clinical and biologic behavior of bone metastases from differentiated thyroid carcinoma. *Surgery* 106: 960–966.
23. Shaha AR, Shah JP, Loree TR (1997) Differentiated thyroid cancer presenting initially with distant metastasis. *Am J Surg* 174: 474–476.
24. Casara D, Rubello D, Saladini G, Gallo V, Masarotto G, Busnardo B (1991) Distant metastases in differentiated thyroid cancer: long-term results of radioiodine treatment and statistical analysis of prognostic factors in 214 patients. *Tumori* 77: 432–436.
25. Dinneen SF, Valimaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, Hay ID (1995) Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. *J Clin Endocrinol Metab* 80: 2041–2045.