

## Bone Metastases from Thyroid Carcinoma: Clinical Characteristics and Prognostic Variables in One Hundred Forty-Six Patients

Anastassios G. Pittas,<sup>1</sup> Michael Adler,<sup>1</sup> Melissa Fazzari,<sup>2</sup> Satish Tickoo,<sup>3</sup> Juan Rosai,<sup>3</sup> Steven M. Larson,<sup>4</sup>  
and Richard J. Robbins<sup>1</sup>

To describe the clinical characteristics and define the indicators that best predict survival in patients with bone metastases from thyroid carcinomas. We collected data from medical records of 146 patients with documented bone metastases from thyroid carcinoma seen at our medical center over a 38-year period. Univariate and multivariate analyses of prognostic indicators for survival were performed. Bone metastases were present at the initial diagnosis in 47% of patients. Vertebrae (29%), pelvis (22%), ribs (17%), and femur (11%) were the most common sites of metastases. Multiple lesions were present in 53% of the cases. The overall 10-year survival rate from the time of diagnosis of thyroid cancer was 35%, and from diagnosis of initial bone metastasis was 13%. By univariate analysis from the time of the initial bone metastasis, radioiodine uptake by skeletal metastases, the absence of nonosseous metastases and treatment with radioiodine were significant prognostic factors. By multivariate analysis, radioiodine uptake by skeletal metastases and the absence of nonosseous metastases were independent favorable prognostic variables for survival. In a subgroup of patients in which histologic specimens were available and were reviewed, Hürthle cell carcinoma was the most favorable histologic subtype for survival with the undifferentiated subtype being the worst. The spread of thyroid carcinoma to bone is more common in patients over 45 years of age, is usually symptomatic, and is often multicentric. Overall survival is best in those whose lesions concentrate radioactive iodine and those who have no nonosseous metastases.

### Introduction

CARCINOMA OF THE THYROID GLAND is one of the most curable cancers (1), yet more than 1,000 individuals die of it in the United States alone each year. Patients with distant metastases, especially to bone, have a markedly reduced survival (2–9). At the time of initial diagnosis, 1%–3% of patients with thyroid cancer have distant metastases whereas another 7%–23% will develop distant metastases during the course of their disease (2,5–8,10–12). Bone metastases are diagnosed clinically in 4%–13% of patients with differentiated thyroid cancer (9,13,14). Several smaller reviews of patients with thyroid cancer metastatic to bone have suggested that skeletal involvement is difficult to treat and is associated with a poor prognosis (5,8,14,15). The clinical impact of the bone metastases by themselves has been difficult to assess because they are often analyzed in conjunction with distant metastases to other organs. In this report, we describe the clinical features of patients with bone metastases from thyroid carcinoma who were seen at one cancer center over a

38-year period. In this retrospective analysis, we examined several prognostic variables and tested the impact of each on overall survival, using univariate and multivariate analyses.

### Patients and Methods

#### Patients

Patients with thyroid carcinoma who were referred to Memorial Sloan Kettering Cancer Center (MSKCC) between 1960 and 1998 were registered in a clinical research database (MSKCC-CRDB). Information from this database was used for this study. This was supplemented with data from patient chart review. From the database, 1,812 patients were formally registered at MSKCC during that time interval. Full clinical and pathological information was available in 1,636 patients. Of these, 91 patients had bone metastases listed as a specific diagnosis, while 206 additional patients were listed as having metastatic disease of unspecified sites. Among the 91 patients with known bone metastases, information from

<sup>1</sup>Endocrinology, <sup>2</sup>Biostatistics, <sup>3</sup>Departments of Medicine, Epidemiology and Biostatistics, Radiology, and Pathology, <sup>4</sup>Nuclear Medicine Services, Memorial Sloan Kettering Cancer Center, New York, New York.

the database and/or charts was insufficient in 16 patients. Of the remaining 206 patients, 76 with bone metastases were identified after chart review, 96 patients had only nonskeletal metastatic disease and were not included, and 34 had insufficient evidence to confirm the clinical diagnosis of bone metastases. Five thyroid cancer patients who also had a second malignancy were excluded from the study due to lack of histologic proof of thyroid carcinoma in bone. A total of 146 patients (8.9% of all patients with available data) with well-documented bone metastases from thyroid carcinoma diagnosed during life, either at the time of the initial diagnosis (within 2 months of the initial pathological diagnosis) or at subsequent follow-up are presented here. One hundred twenty-seven patients received radioactive iodine at some time during the course of their disease, either as ablation or to treat metastatic lesions. The median follow-up was 81 months after the diagnosis of the thyroid cancer (range, 1–404) and 41 months after the diagnosis of the initial bone metastasis (range, 1–274). By the end of the study (June 1998), 112 of the 146 patients had died, 12 patients were alive, and 22 had been lost to follow-up.

#### *Surgical pathology*

Pathological reports were available for all 146 cases. Primary thyroid carcinomas were histologically classified as either papillary (including follicular variant of papillary), follicular, Hürthle, poorly differentiated (eg, insular, tall cell variants, etc.), or anaplastic. Of the 1,636 patients in the 1960–1998 cohort, 1,255 (77%) had papillary carcinoma, 206 (12%) had follicular carcinoma, 47 (3%) had Hürthle cell carcinoma, 20 (1%) had poorly differentiated carcinoma, 13 (1%) had anaplastic carcinoma, and 95 (6%) had other cell types (medullary and lymphoma). In 83 of the 146 bone metastasis cases, the original slides were reread by a single (blinded) expert thyroid pathologist (J.R.). Because more than half of the cases were reclassified based on newer histologic subcategorizations, we chose not to rely on the initial histologic analysis in the 63 cases in which the original slides were not available. The influence of histologic subtype, *per se*, on survival was therefore calculated only on this subset of 83 cases.

#### *Treatment of the primary thyroid tumor*

Primary thyroid surgery was performed in 70% of patients. Of these, 82% had a total or near-total thyroidectomy and the rest had a hemithyroidectomy with isthmectomy. The remaining 30% of the patients had no primary thyroid surgery due to: patients' refusal, poorly differentiated thyroid carcinoma, widely metastatic disease at presentation, or poor operative risk. Thirteen patients who did not have any thyroid surgery, and were appropriate candidates, received <sup>131</sup>I ablation of the thyroid.

#### *Diagnosis of bone metastases*

Patients were followed for recurrence of thyroid carcinoma with clinical examination, chest roentgenogram, and radioiodine (RAI, <sup>131</sup>I) whole-body scanning. Monitoring for recurrence of thyroid carcinoma with measurement of serum thyroglobulin did not become clinically reliable until the mid-1980s. Thyroglobulin levels are, therefore, not included in this report. Bone metastases were detected by chest or

skeletal roentgenograms, computed tomography (CT), magnetic resonance imaging (MRI), or RAI uptake either on routine follow-up or as directed by patients' symptoms. Most patients with bone metastases presented with symptoms of skeletal pain or soft tissue swelling. A small percentage presented with cord compression from metastatic involvement of the vertebral column. The rest were asymptomatic and were found to have bone metastases on routine evaluation done at the time of the initial diagnosis or at subsequent follow-up. Thyroid origin of metastatic disease was confirmed by histology of surgical specimen or presence of RAI uptake by metastases in 56% of patients. It was presumed in all other patients with thyroid carcinoma, documented lytic bone lesions, and no other known malignancy.

#### *Treatment of bone metastases*

Patients with metastatic RAI uptake ( $n = 63$ , 43%) were treated with <sup>131</sup>I up to the maximum permissible dose based on quantitative dosimetry studies (16,17). Eleven patients (7.5%) without metastatic RAI uptake on whole-body scans were also treated with <sup>131</sup>I per the attending physician's judgment. External beam radiotherapy (XRT) was given to 75% of patients alone or in association with other treatment modalities, for palliation or for cure in solitary lesions. Non-thyroid surgery was performed in 26% of patients for diagnosis, orthopedic or neurological complications or those at high risk for complications. Chemotherapy (Adriamycin, cis-Platin, actinomycin Pharmacia & Upjohn Co., Bridgewater, NJ) was given to 12% of the patients alone or in association with other treatment modalities.

#### *Statistical methods*

The univariate association of the variables: age, gender, treatment, RAI uptake, and presenting symptom of bone metastases (Table 1), with respect to survival time from diagnosis of bone metastases, was performed using the log-rank test (18). All  $p$  values given correspond to two-sided tests. Survival curves were estimated using the method of Kaplan and Meier (19). Multivariate analysis was performed to assess the relationship between survival time and several variables simultaneously. For analyses of this type, the Cox's proportional hazards model was used. Potential subsets of variables were evaluated using the Score criterion and the final model was determined to be the most efficient model that maximizes this criteria. Variables adding little or no information were not included in the final models.

## **Results**

#### *Total survival*

The overall 5-year and 10-year survival rate from the time of diagnosis of thyroid cancer (total survival) was 53% and 35%, respectively (Fig. 1). Fifty-eight percent of the patients in this cohort were women. The mean age at diagnosis of thyroid cancer for the 146 patients with bone metastases was 55.4 years (81% of the patients were over age 45). The mean age at diagnosis of thyroid cancer for all MSKCC thyroid cancer patients from 1960 to 1998 ( $n = 1,636$ ) was 46.7 years. Bone metastases were diagnosed at the initial presentation of thyroid cancer in 47% of patients. Ninety percent of patients had their bone metastases diagnosed within 10 years of the primary thyroid tumor diagnosis (Fig. 2). Of the 75

TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS AT DIAGNOSIS OF FIRST BONE METASTASIS<sup>a</sup>

	Number of Patients (%)	5-year Survival rate (CI)	p value
Sex			
Male	62 (42%)	0.23	0.43
Female	84 (58%)	0.32	
Age (years)			
<45	19 (13%)	0.30	0.90
≥45	127 (87%)	0.25	
Presenting Symptoms			
Asymptomatic	46 (32%)	0.25	0.45
Symptomatic <sup>b</sup>	100 (68%)	0.30	
Extent of Metastases			
Bone only	93 (64%)	0.40 (0.31, 0.53)	0.001
Bone and other sites <sup>c</sup>	53 (36%)	0.08 (0.03, 0.22)	
Number of Metastases			
Single	69 (47%)	0.38	0.27
Multiple	77 (53%)	0.21	
RAI Uptake			
Yes	63 (43%)	0.42 (0.30, 0.58)	0.003
No/Unknown	83 (57%)	0.19 (0.12, 0.31)	
Treatment			
RAI—Yes	74 (51%)	0.39 (0.28, 0.53)	0.001
RAI—No	72 (49%)	0.19 (0.11, 0.32)	
XRT—Yes	101 (69%)	0.25	0.70
XRT—No	45 (31%)	0.38	
Surgery—Yes	38 (26%)	0.30	0.19
Surgery—No	108 (74%)	0.29	

<sup>a</sup>Histology data not included.

<sup>b</sup>Symptoms of bone metastases included: pain ( $n = 73$ ), swelling (16), pathologic fracture (6), cord compression (5).

<sup>c</sup>Other organs included: lung, brain, mediastinum, liver, skin, and distant lymph nodes. Patients with metastatic disease to the regional cervical lymph nodes are not included.

RAI, radioiodine; XRT, external beam radiotherapy.

patients whose bone metastases were discovered more than 2 months after the initial diagnosis, 26 had known lung metastases, 3 had brain metastases, and 3 had liver metastases. Approximately half of the thyroid cancer patients in this series presented with a neck mass. Symptoms related to skeletal involvement were the initial manifestation of the primary thyroid cancer in 28% of patients.

#### Metastatic survival

It is clinically helpful to have information about the prognosis of patients once bone metastases are discovered. The clinical characteristics of the 146 patients with bone metastases and prognostic variables for survival from the time of the first clinically recognized bone metastasis are shown in Table 1. The overall 5-year and 10-year survival rate from the time of diagnosis of bone metastases (metastatic survival) was 25% and 13%, respectively (Fig. 3).

The mean age at diagnosis of bone metastases was 58.7 years (87% of patients were over age 45). Age at diagnosis of bone metastases was not a significant factor for survival from the diagnosis of bone metastases. At the time of the discovery of the bone metastases, the majority of patients (68%) had symptoms related to their bone lesions, most commonly pain. The rest of the patients were found to have bone metastases by RAI whole-body scanning and/or other imaging modalities during routine follow-up. Twenty-seven percent

of patients suffered a pathologic fracture and 14% developed cord compression at some point in their illness.

The presence of additional nonskeletal organ involvement at presentation of bone metastases was a significant negative prognostic variable ( $p = 0.001$ ). A clear and significant survival advantage was present in the 43% of patients whose bone lesions concentrated radioiodine ( $p = 0.003$ ). A further analysis was performed by separating the No uptake group from the Unknown group. When the survival of the No uptake group was set as the baseline, the risk ratio of the Unknown group is 1.05 (NS,  $p = 0.86$ ). The positive uptake group ( $n = 63$ ) had a risk ratio of 0.544 ( $p = 0.007$ ), which was significantly better than the No uptake group. None of the patients with anaplastic or medullary thyroid cancer had extrathyroidal RAI uptake.

With univariate analysis, treatment with <sup>131</sup>I was a significant prognostic variable for survival from the diagnosis of metastatic bone disease ( $p = 0.001$ ). However, treatment with surgery or XRT was not a significant prognostic indicator. There was a trend for patients who had a surgical procedure to survive longer than patients who did not have surgery. This was evident only initially and did not persist to provide a survival benefit. The majority of surgical procedures were palliative in nature to prevent a fracture or a cord compression. An intention to completely resect a solitary bone metastatic lesion only occurred in four cases. Too few patients were treated with chemotherapy to allow mean-

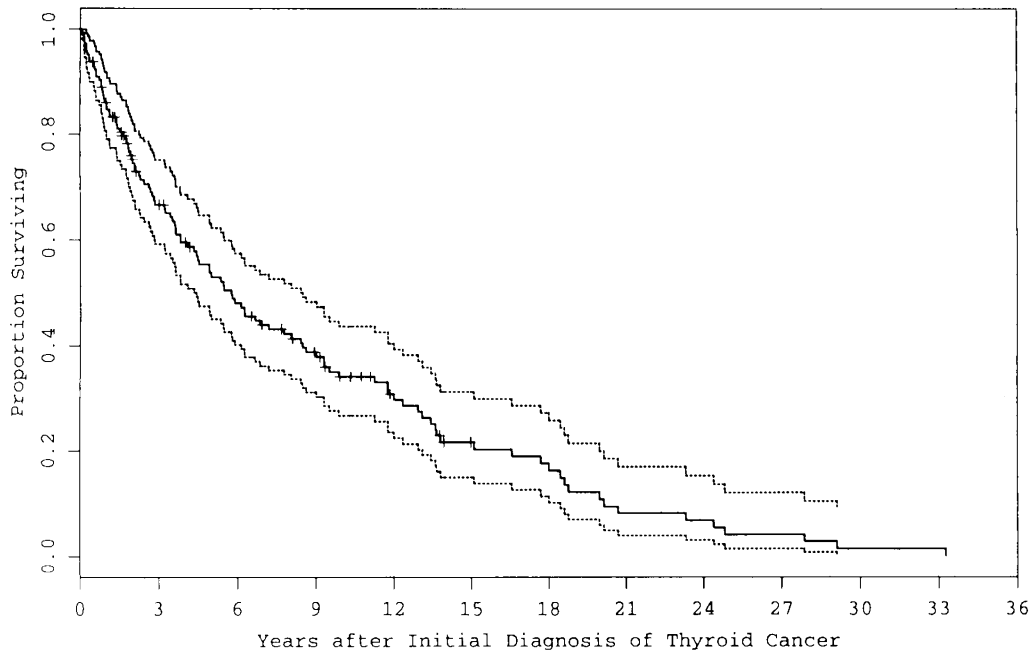


FIG. 1. Overall survival from initial diagnosis of thyroid cancer with 95% confidence intervals.

ingful data analysis. Separate univariate analyses were performed on the 43 patients who did not have primary thyroid surgery and on the 103 who did. No differences in the factors that were significant predictors of survival were present between the groups.

The variables shown in Table 1 were analyzed using the Cox multivariate model. RAI uptake by skeletal metastases and lack of extraosseous metastases were independent favorable prognostic factors when all variables were taken into account (Table 2). Treatment with RAI did not have an influence on survival after adjusting for all variables.

The distribution of the metastatic skeletal sites is shown in Table 3. The vertebral bodies were the most common sites for lesions that could be clinically detected. Multiple skeletal lesions were present in 78 patients (53%). The percentage of patients with each presenting symptom is shown in Table 4. Bone pain was the presenting symptom in over one-half of the patients.

#### Histopathology

The cell type of the primary thyroid tumor in the 83 cases that were re-reviewed by our thyroid pathologist were as follows: papillary well differentiated in 19; follicular in 17; Hürthle cell in 9; undifferentiated in 10; medullary in 6; and lymphoma in 3. For purposes of analysis, we grouped the tall cell variants of papillary and the insular histology into a category called poorly differentiated ( $n = 19$ ). Given the small number of medullary and lymphoma cases to acquire meaningful data, these variants were excluded from this analysis. To assess if the histology classification of the patient had any prognostic impact with respect to survival, the final models obtained using the full data set of 146 patients

was also applied to the above subset of patients ( $n = 74$ ) on whom we were able to obtain histology data. The histology classification was utilized in the Cox model as follows. The Hürthle group was considered to be the baseline group and the effect of any other histology group with respect to survival time was judged relative to this baseline group. Univariate analyses using the log-rank test and multivariate analysis utilizing the Cox proportional hazard model from diagnosis of the initial bone metastasis were performed. In univariate analysis, the Hürthle subtype was associated with the best prognosis among all histologic types while the undifferentiated subtype had the shortest survival (Fig. 4).

In the multivariate model for survival from diagnosis of the initial bone metastasis with histology taken into account, undifferentiated, papillary, poorly differentiated, and follicular subtypes, as compared to Hürthle cell, were all additional negative prognostic variables for survival in that order (Table 5).

#### Discussion

Bone metastases are an uncommon but serious complication of aggressive thyroid carcinoma. To gain insight into the biology of bone metastases, we summarized the clinical features and performed univariate and multivariate analyses on these features to determine which significantly influenced survival. Of 1,636 thyroid cancer patients referred to MSKCC from 1960 to 1998, we found that approximately 9% (146) had bone metastases. This is higher than previous reports (9,14) and it most likely reflects the nature of referrals to a major cancer center.

In our patient population, the overall 10-year survival rate from the time of diagnosis of thyroid cancer was 35% and

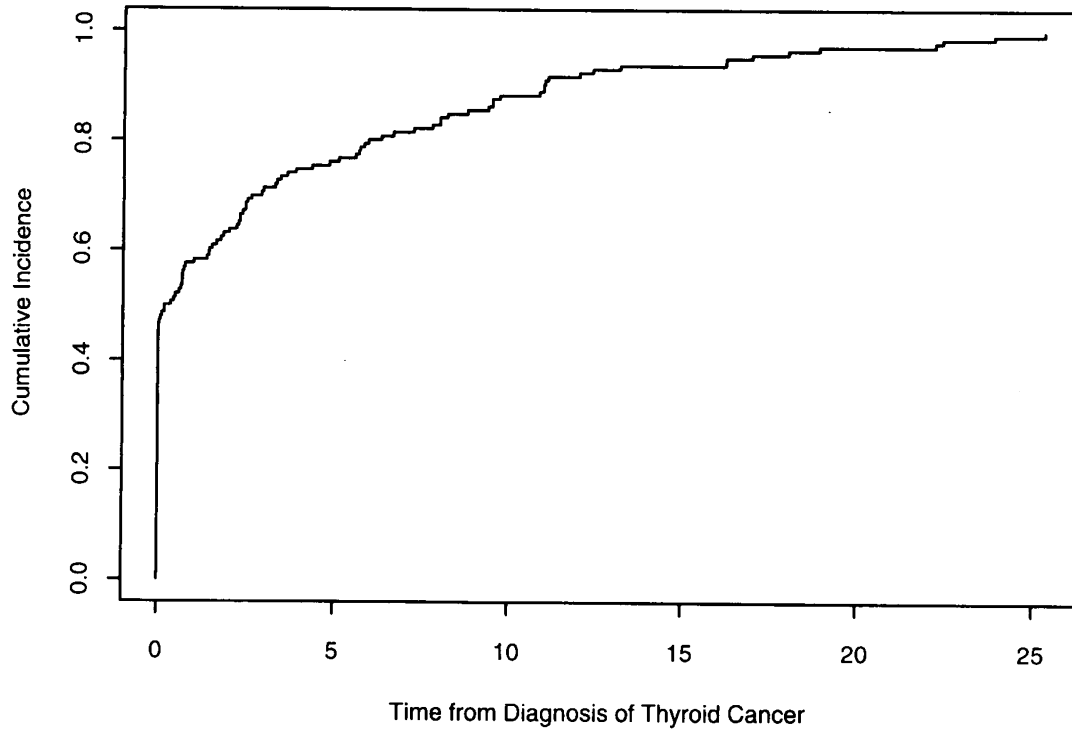


FIG. 2. Cumulative incidence of bone metastases from the time of initial diagnosis of thyroid cancer.

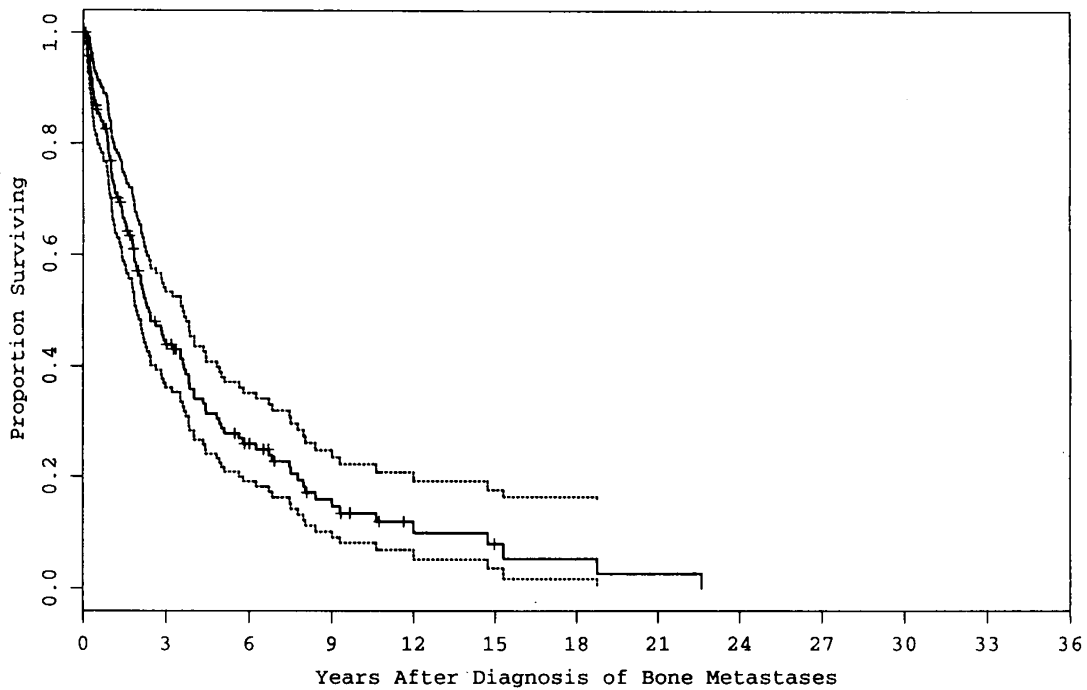


FIG. 3. Overall survival from first diagnosis of a bone metastasis with 95% confidence interval.

TABLE 2. MULTIVARIATE ANALYSIS OF PROGNOSTIC VARIABLES FOR SURVIVAL FROM DIAGNOSIS OF FIRST BONE METASTASIS<sup>a</sup>

Variable	Relative death risk	p value
Positive RAT <sup>b</sup> uptake in bone metastases	0.547	0.0025
Extent of metastases— Bone only	0.342	0.0001

<sup>a</sup>Histology data not included.

<sup>b</sup>RAT, radioiodine.

from diagnosis of initial bone metastasis was 13%. This is comparable to those reported by Marcocci et al. (9) and Proye et al. (14). Schlumberger et al. (6,8) found a 10-year survival of 13%–14% for patients with lung and bone metastases, 21%–27% for bone metastases only, and 57%–61% for lung metastases only. Ruegemer et al. (5) found a 10-year survival of 25% from all causes in patients with distant metastatic disease from thyroid cancer. A recent report by Fanchiang et al. (15) found a 5-year survival rate of 65% in patients with bone metastases from differentiated thyroid cancer. This compares to the 85%–90% 10-year survival of all patients with differentiated thyroid carcinoma (1).

At time of diagnosis of the initial bone metastasis, age was not found to be a significant prognostic factor. This may be due to the small number of patients under 45 years of age in our study. The mean age of our patient cohort at diagnosis of initial bone metastasis was 58.7 years, which is higher than the average age of all patients with thyroid cancer at diagnosis (45 to 50 years) (1). This age difference is consistent with previous reports (9,13–15). Older patients may have a more aggressive form of thyroid cancer that is associated with metastatic disease and reduced survival.

Almost half of our patients had their bone metastases detected at the time of the initial diagnosis of the thyroid cancer. This is somewhat lower than that reported by Proye et al. (14) (54%), Marcocci et al. (9) (60%), and Fanchiang et al. (15) (75%). Twenty-eight percent of our patients had a symptom related to bone metastases as their manifestation of thyroid cancer. The large number of patients with thyroid cancer who present with bone metastases makes it important that the clinician who is faced with skeletal metastatic disease of unknown primary considers thyroid cancer.

TABLE 3. SITE OF FIRST BONE METASTASIS IN 146 PATIENTS WITH THYROID CANCER AND BONE METASTASES<sup>a</sup>

Sites	Number of patients
Vertebrae	78 (54%)
Pelvis	59 (50%)
Ribs	45 (31%)
Femur	30 (21%)
Skull	19 (13%)
Humerus	16 (11%)
Clavicle	7 (5%)
Scapula	5 (3%)
Manubrium	6 (4%)
Other <sup>b</sup>	7 (5%)
Multiple sites	78 (54%)

<sup>a</sup>Patients may have more than one metastatic bone site.

<sup>b</sup>Other include: radius, shoulder, tibia, fibula.

In our cohort, the clinical features at the time of discovery of bone metastases that best predicted survival were radioiodine uptake by bone metastases and the absence of extraosseous metastases. Limited extent of metastatic disease was a favorable factor for survival from time of diagnosis of initial bone metastasis. This is in accordance with other studies (6,8). One important negative finding was that survival was no better in those who had a single bone lesion compared to those with multiple bone lesions. One possible explanation of this is that once a single bone lesion is discovered other smaller subclinical bone lesions are likely present. It is the rare patient with a single bone lesion who is successfully treated with no further bone metastases being discovered. Metastatic bone disease is virtually always a multicentric process.

Although treatment with radioactive iodine did not predict survival better than our two-variable model, it was a significant univariate prognostic variable suggesting that treatment with <sup>131</sup>I may be beneficial in patients who demonstrate uptake. The uptake of radioiodine by the metastatic cells provides a biological marker of differentiation and is an intrinsic property of the cell. The response of the lesions to treatment with radioiodine is influenced by many factors (eg, the serum iodide level, the dose of radioiodine, the degree of hypothyroidism when treated, the radiation dose to the tumor, etc.), which are not reflections of the biology of the cells. The radioiodine uptake therefore reflects on the nature of the tumor whereas the response to radioiodine is influenced by many other confounding variables. Surgical intervention in our study conferred an early benefit but did not have a statistically significant benefit in overall survival. Other reports of surgical removal of resectable metastases have shown favorable effect on prognosis (20). Surgery to prevent or treat complications of metastatic bone disease can be a useful adjunct to improve morbidity in patients with skeletal disease. The use of an intraoperative probe after preoperative administration of <sup>131</sup>I may allow accurate localization and removal of metastatic disease in difficult cases (21). The use of bisphosphonates, which reduce symptoms and complications of bone metastases in patients with metastatic breast cancer (22) and multiple myeloma (23), seems reasonable for bone metastases in thyroid cancer patients until formal clinical trials are performed.

In our subanalysis of the 74 patients with well-characterized histopathologic diagnosis of their primary thyroid tumor, Hürthle cell carcinoma proved to be the most favorable histologic type in univariate analysis. This is surprising because Hürthle cell carcinoma is associated with reduced survival in general when compared with more differentiated thyroid cancers. Multivariate analysis at discovery of bone

TABLE 4. PRESENTING SYMPTOM OF BONE METASTASIS

Symptom	n	% Total
None	33	22.9
Pain	73	50.7
Swelling	16	11.1
Fracture	7	4.9
Cord compression	5	3.5
Unclear	12	8.3

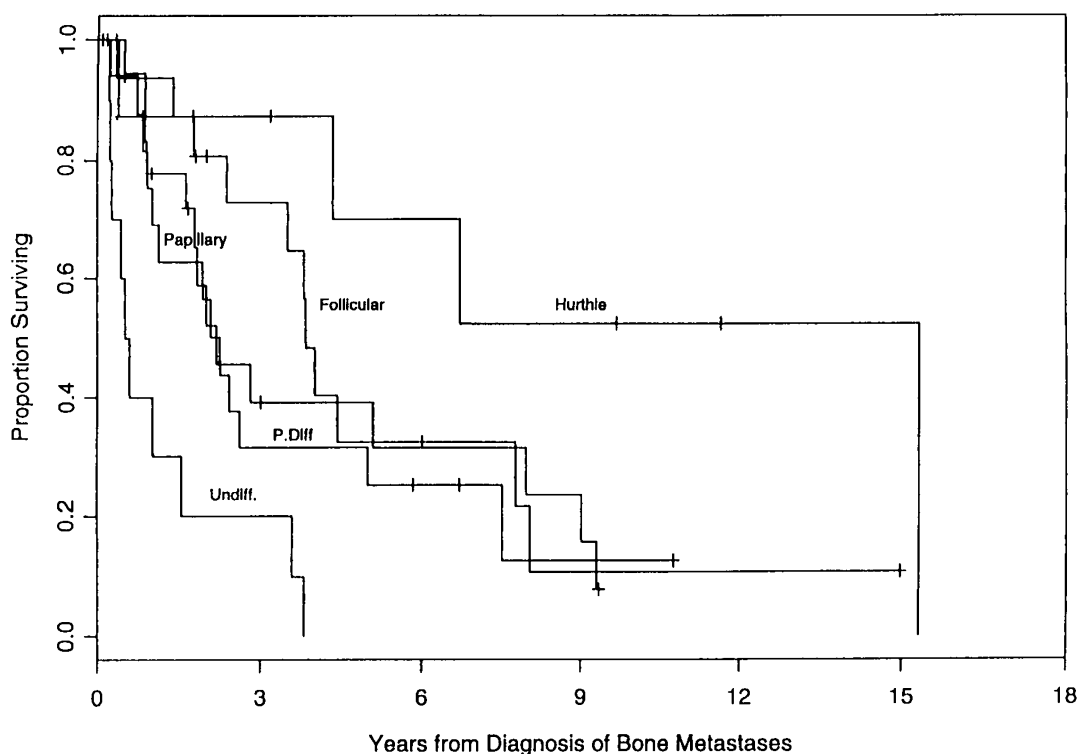


FIG. 4. Kaplan-Meier plot of proportion surviving after diagnosis of bone metastasis stratified by histologic subtype.

metastases found that any histology other than Hürthle constituted an additional negative indicator for survival. The hazard ratios for poorly differentiated tumors, papillary, and follicular tumors were surprisingly similar. We hypothesize that skeletal metastatic disease in patients with well differentiated primary thyroid cancers occurs secondary to dedifferentiation of the original tumor to a more aggressive type, characterized by the ability to spread to distant sites such as bone, lungs, and other organs. We are currently investigating this hypothesis by examining the histology of the surgical specimens from skeletal metastases and correlating these with the histology from the primary thyroid tumor of each patient. It was recently discovered that bone sialoprotein, an

integrin that is normally found in developing bone, is often expressed in neoplastic thyroid cells (24). Dedifferentiation of the primary tumor and expression of this protein may play a role in the osseous metastatic potential of thyroid cancer.

In conclusion, thyroid cancer patients who developed bone metastases at our medical center between 1960 and 1998 had a markedly reduced overall survival, compared to all thyroid cancer patients. The presence of additional nonosseous metastases and the lack of radioiodine avidity significantly reduced survival even further. In a subgroup of patients, where histologic data were available, Hürthle cell was the most favorable histologic subtype for survival at diagnosis of bone metastases, with the undifferentiated subtype

TABLE 5. MULTIVARIATE ANALYSIS OF PROGNOSTIC VARIABLES FOR SURVIVAL FROM DIAGNOSIS OF FIRST BONE METASTASIS IN 74 PATIENTS WITH COMPLETE HISTOLOGIC DATA

Variable	Hazard ratio	95% confidence interval	p value
Positive RAI uptake	0.38	(0.21, 0.72)	0.003
Extent of Metastases—bone only	0.25	(0.13, 0.49)	0.001
Histology <sup>a</sup>			0.018 <sup>b</sup>
Undifferentiated	27.1	(6.6, 112.5)	
Poorly differentiated	7.20	(1.8, 27.8)	
Papillary	6.33	(1.7, 24.0)	
Follicular	3.93	(1.1, 14.7)	

<sup>a</sup>Baseline category is Hürthle.

<sup>b</sup>p value based on overall significance of histology. This tests the null hypothesis that all of the additional variables corresponding to the histology categories are equal to zero.

RAI, radioiodine.

being the worst. The identification of histologic markers in the original thyroid tumor that would predict future aggressiveness irrespective of histology would be invaluable in caring for thyroid cancer patients. In the absence of very effective treatment for skeletal metastatic disease from thyroid carcinoma, the use of bisphosphonates as an additional treatment modality should be further investigated.

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Address reprint requests to:

Richard J. Robbins, M.D.

Endocrinology Service

Memorial Sloan Kettering Cancer Center

1275 York Avenue

New York, NY 10021

E-mail: robbinsr@mskcc.org



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