

Bone Metastases From Thyroid Carcinoma

A Histopathologic Study With Clinical Correlates

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● **Context.**—Only limited information exists on the pathologic aspects of thyroid carcinomas with bone metastases, most large studies having concentrated mainly on their clinical features.

Objective.—To study in detail the morphologic features of thyroid carcinomas with skeletal metastases.

Design.—Seventy-nine cases of thyroid carcinoma with bone metastases treated at Memorial Sloan-Kettering Cancer Center, New York, NY, between 1964 and 1998 were investigated, with emphasis on the pathology of the primary and/or metastatic tumors and comparison of the morphologic features of the tumors at both the sites, wherever possible. The tumors were also compared for various clinical parameters.

Results.—The cohort consisted of 22 papillary, 17 follicular, 16 insular, 10 anaplastic, 9 Hürthle cell, and 5 medullary carcinomas. Of these cases, 68% had poorly differentiated or undifferentiated features in the primary and/or metastatic tumors. The metastatic tumors were better differentiated than the primary in one third of the cases (6 of

18). Only one case showed a less differentiated metastasis. The overall 5- and 10-year survival probabilities after the bone metastases were 29% and 13%, respectively (Kaplan-Meier method). Although both the tumor type and differentiation seemed to affect survivals after bone metastasis ($P = .007$ and $.012$, respectively) (log-rank test), this was primarily due to the much worse prognosis in the cases of anaplastic and medullary carcinoma. Cases of Hürthle cell carcinoma showed the longest median survival. There was no significant difference in survival among patients up to or older than 45 years at the time of metastases ($P = .31$).

Conclusions.—Most thyroid carcinomas with bone metastases are of papillary type, and most have poorly differentiated or undifferentiated features. The influence of the microscopic tumor type and tumor differentiation on survival after bone metastasis primarily appears to be due to the much worse prognosis among anaplastic and medullary carcinomas. Age at diagnosis of bone metastases does not influence survivals.

(*Arch Pathol Lab Med.* 2000;124:1440–1447)

After lung, bone is the most common site of systemic metastasis from thyroid carcinoma,^{1,2} the overall reported incidence ranging from 1%³ to more than 40%.⁴ This incidence varies according to the primary tumor type, with follicular carcinoma showing a much higher frequency than the papillary or anaplastic subtypes in most reported series.^{1,2,5–8} This may, however, not reflect the exact situation, since the term *follicular carcinoma* has been used as a generic term in the older literature and may have included several other subtypes of thyroid carcinomas.

Most large published studies on bone metastases in thyroid cancer have primarily dealt with the clinical aspects, with only a brief mention of the pathology. Many of these studies have been on differentiated thyroid carcinoma, dividing these simply into papillary and follicular types.^{1,2,7,9} Only a few studies have included other histologic categories.^{6,8} Thus, only limited information exists on histopathologic description of thyroid carcinomas with bone

metastasis. The purpose of this study was to investigate in detail the pathologic aspects of thyroid cancers with bone metastasis and to compare these with various clinical parameters.

MATERIALS AND METHODS

One hundred forty-six documented cases of patients with thyroid carcinoma with bone metastasis, who received treatment at Memorial Sloan-Kettering Cancer Center from 1964 to 1998, were identified. As per the policy of the institution, the histologic features of the primary and/or metastatic lesions had been reviewed on all these cases in the Department of Pathology before any therapy was instituted. Radioactive iodine (RAI) uptake was considered to constitute sufficient evidence of bone metastasis in cases where no bone biopsies had been performed. Relevant histologic material was currently available in the files of the Department of Pathology for review by the authors on only 79 cases; the other cases had been sent back to the original referring institutions. These 79 cases form the basis of this clinicopathologic study. One to 34 (mean: from the primary site, 7; from bone metastases, 4; overall, 5) hematoxylin-eosin-stained slides from each case were available for review. In some cases, immunostains for thyroglobulin, calcitonin, carcinoembryonic antigen, and lymphoid markers, as well as Congo red stain for amyloid, had also been performed, and these were available for review. The material available for review consisted of the following: primary tumor and bone metastases, 18 cases; primary tumor only, 21 cases; and bone metastases only, 40 cases.

Accepted for publication April 19, 2000.

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Table 1. Distribution of Cases by Histologic Type and Differentiation According to the Site

Diagnosis	Number of Cases			
	Total	Overall*	Primary Site†	Metastatic Site†
Follicular carcinoma	17			
Well differentiated (pure)		11	3	10
With poorly differentiated component		6	2	4
Papillary carcinoma	22			
Classical		11		
Well differentiated (pure)		4	3	3
With poorly differentiated component		7	5	2
Follicular variant		8		
Well differentiated (pure)		2	1	2
With poorly differentiated component		6	2	4
Tall cell variant		3	3	3
Hürthle cell carcinoma	9			
Well differentiated (pure)		3	1	3
With poorly differentiated component		6	2	5
Insular carcinoma	16			
Poorly differentiated (pure)		11	4	9
With well differentiated component		4	3	4
With anaplastic component		1	1	0
Anaplastic carcinoma	10‡			
Undifferentiated (pure)		5	3	3
With well differentiated component		5	4	2
Medullary carcinoma	5	5	3	4
Total	79	79	39	58

* By worse differentiation at either the primary or metastatic site.

† The sum exceeds the total number of cases, since 18 cases had material available from both the sites.

‡ One case was a collision tumor with malignant lymphoma.

The tumors were classified according to current criteria¹⁰ into the following categories: follicular carcinoma, papillary carcinoma, Hürthle cell carcinoma, insular carcinoma, anaplastic carcinoma, and medullary carcinoma (Table 1). The papillary carcinomas were subdivided into classic, follicular variant, and tall cell variant. Within each category, tumors were graded into well differentiated and poorly differentiated, depending on the cytologic and/or architectural features. Tumors with any solid areas were considered to be architecturally poorly differentiated. Tumors with high-grade cytologic features (ie, nuclear hyperchromasia, mitotic activity, and/or tumor necrosis) qualified as cytologically poorly differentiated. The architectural and cytologic grades were analyzed, both individually and together, to investigate for any influence on the clinical outcome. Since neither the architectural nor the cytologic grades influenced survivals among cases of follicular, papillary, or Hürthle cell carcinoma groups (vide infra), for the purpose of this study, all insular carcinomas and other tumors with insular carcinoma-like foci (regardless of the cytologic features) were regarded as poorly differentiated tumors, as were the cases of the tall cell variant of papillary carcinoma.¹¹ The anaplastic carcinomas were classified as an undifferentiated tumor. Since medullary carcinomas, in general, have a solid growth pattern and because of their small number in this series, no attempt was made to further subcategorize them. Whenever a combination of patterns was present, the tumor was classified according to its predominant component. Thus, a carcinoma with predominantly follicular histologic features and a focal insular component was placed among the follicular carcinomas, whereas an insular carcinoma with a focal well-differentiated component was placed in the insular carcinoma category.

Comparison of morphologic aspects between the primary and metastatic tumors, particularly regarding the differentiation, was performed in cases where material from both sites was available.

Examination of the association between survival after the diagnosis of bone metastases and the microscopic tumor type or tumor differentiation, as well as some clinical parameters (in-

cluding age at bone metastasis and RAI uptake by the bone metastasis), was performed. For the purpose of the association between tumor differentiation and survival, tumor differentiation at both the primary and metastatic sites was evaluated individually and by the overall worse grade irrespective of the site. In addition, the association between the microscopic tumor type or tumor differentiation and other variables, such as age, presence or absence of bone metastases at initial presentation, and RAI uptake, was also examined.

The Kaplan-Meier method was used to estimate the survival curves, and the log-rank test was used to assess the differences among the different groups with respect to survival functions. All other comparisons of variables were assessed by the non-parametric Kruskal-Wallis method.

RESULTS

The distribution of the different tumor types, by morphologic structure and differentiation, and their clinical correlates are shown in Tables 2 and 3.

Tumor Type

Follicular Carcinoma.—Seventeen cases (22%) were classified as follicular carcinoma. Eleven of these showed a complete lack of solid or trabecular areas and were classified as well-differentiated follicular carcinomas. Six others, although predominantly well differentiated, also contained poorly differentiated (solid) areas and were, therefore, categorized as poorly differentiated follicular carcinomas.

Papillary Carcinoma.—Papillary carcinomas constituted the largest group (22 cases or 28%) in this series. Although 11 of these showed the classic morphologic structure with well-formed papillae, 8 others were the follicular variants of

Table 2. Case Distribution by Histologic Type with Clinical Correlates

Tumor Type (Number)	Male-Female Ratio	Presenting Site (Bone/Thyroid and Bone/Other)*	Age at Bone Metastasis, y, Mean (Range)	RAI Uptake† Y/N/NK	Follow-up‡ DOD/Alive/NK	Median Survival, y§ (95% CI)
Follicular (17)	10:7	6/6/5	64.4 (48.2–77.9)	12/1/4	11/1/5	3.8 (3.5, 7.8)
Papillary (22)	10:12	5/2/15	58.4 (26.7–77.4)	13/8/1	16/4/2	2.2 (1.8, 5.0)
Classical (11)	6:5	0/1/10	53.8 (26.7–72.0)	5/6/0	8/2/1	1.79 (0.88, 2.19)
Follicular variant (8)	3:5	5/1/2	61.1 (45.3–77.4)	6/2/0	6/2/0	5.09 (2.0, 9.3)
Tall cell (3)	1:2	0/0/3	65.3 (54.9–83.8)	2/0/1	2/0/1	2.17 (2.08, 2.25)
Insular (16)	10:6	5/4/7	58.8 (39.3–75.6)	10/4/2	11/3/2	2.42 (1.0, 7.51)
Anaplastic (10)	4:6	3/5/2	58.1 (40.4–71.9)	2/3/5	10/0/0	0.55 (0.27, 1.54)
Hürthle cell (9)	6:3	3/0/6	54.6 (28.4–66.9)	2/4/3	4/4/1	15.3 (4.33, 15.6)
Medullary (5)	1:4	2/1/2	50.6 (36.0–68.3)	0/2/3	5/0/0	2.1 (0.14, 3.21)
Total (79)	41:38	24/16/39	62.2 (26.7–83.8)	39/22/18	57/12/10	2.42 (2.2, 3.81)

* Other includes thyroid, 22; lung, 5; lung and brain, 2; lung and cervical lymph nodes, 1; cervical lymph nodes, 1; brain, 2; soft tissue, 5; and oral cavity, 1.

† RAI indicates radioactive iodine; Y, yes; N, no; and NK, not known.

‡ DOD indicates died of disease.

§ *P* = .012. CI indicates confidence interval.

Table 3. Case Distribution by Tumor Differentiations with Clinical Correlates

Tumor Differentiation (Number)	Male-Female Ratio	Presenting Site (Bone/Thyroid and Bone/Other)*	Age at Bone Metastasis, y (Mean)	RAI Uptake† Y/N/NK	Follow-up‡ DOD/Alive/NK	Median Survival, y§ (95% CI)
Well differentiated (20)	10:10	6/2/12	66.2 (38.2–80.1)	13/3/4	14/3/3	3.84 (2.2, 6.71)
Poorly differentiated (44)	26:18	13/8/23	61.6 (27.5–83.8)	24/10/10	28/9/7	2.8 (2.0, 7.5)
Undifferentiated (10)	4:6	3/5/2	58.1 (40.4–71.9)	2/3/5	10/0/0	0.55 (0.27, 1.54)
Medullary (5)	1:4	2/1/2	50.6 (36.0–68.3)	0/2/3	5/0/0	2.1 (0.14, 3.21)
Total (79)	41:38	24/16/39	62.2 (26.7–83.8)	39/22/18	57/12/10	2.42 (2.2, 3.81)

* See Table 2 for list of “other” presenting sites.

† RAI indicates radioactive iodine; Y, yes; N, no; and NK, not known.

‡ DOD indicates died of disease.

§ *P* < .007. CI indicates confidence interval.

papillary carcinoma. Among both these subtypes, approximately two thirds (13 of 19) contained some poorly differentiated areas. Only 6 appeared well differentiated throughout. The other 3 cases in the papillary group were tall cell variants. Thus, 16 (73%) of 22 cases from this group had a poorly differentiated morphologic structure.

Insular Carcinoma.—Twenty percent (16 cases) of the cases were classified as insular carcinoma. In only 4 of these were focal, better differentiated areas of follicular or papillary carcinoma identified. One additional case showed a microscopic focus of anaplastic (spindle cell) change.

Anaplastic Carcinoma.—This group of cases showed the greatest degree of morphologic variability. Of the 10 cases of anaplastic carcinoma in this series, 3 had predominantly squamoid or squamous features, 4 were predominantly spindle cell type, and in 3 cases squamoid, spindle cell, and pleomorphic areas were almost equally represented. Two cases showed foci of osteoclast-like giant cells, whereas 2 showed areas of osteoid deposition. In 5 cases, well-differentiated foci of follicular (3 cases), papillary (1 case), and Hürthle cell (1 case) carcinoma were also observed, and in 4 of these transitions from well to poorly differentiated to undifferentiated areas were present. In one case, the anaplastic carcinoma was closely apposed to malignant lymphoma, large cell type, of B-cell phenotype; this case was considered to represent a collision tumor.

Hürthle Cell Carcinoma.—There were 9 cases of Hürthle cell carcinoma in this series. Only 3 of these were considered well differentiated; all of the others (6 cases) contained focal solid areas, upgrading these to the poorly differentiated category.

Medullary Carcinoma.—Five cases of medullary carcinoma were encountered. One of these contained multiple foci of squamous differentiation.

Tumor Differentiation

As already stated, in addition to the 16 cases of insular carcinoma, there were 25 cases of largely well-differentiated carcinomas (6 follicular, 13 papillary, including the follicular variants, and 6 Hürthle cell carcinoma) that contained poorly differentiated areas at the primary, metastatic, or both sites (Figure 1). All these, in addition to the 3 cases of tall cell variant of papillary carcinoma, were classified as poorly differentiated, for a total of 44 cases. There were 20 cases of well-differentiated carcinoma, including 11 of follicular, 6 of papillary, and 3 of Hürthle cell type. Thus, overall three fourths (59 of 79 or 75%) of the cases belonged to the poorly differentiated, undifferentiated, or medullary category. According to the site, 31 (79%) of 39 tumors with available material from the primary site and 40 (69%) of 58 tumors with material from the metastases were classified as poorly differentiated, undifferentiated, or medullary carcinoma (Table 1).

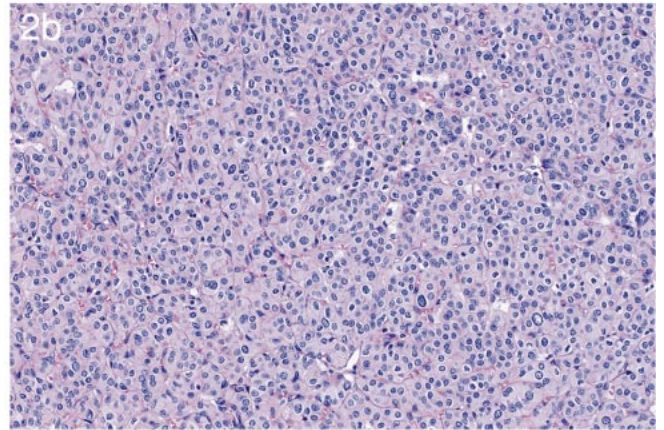
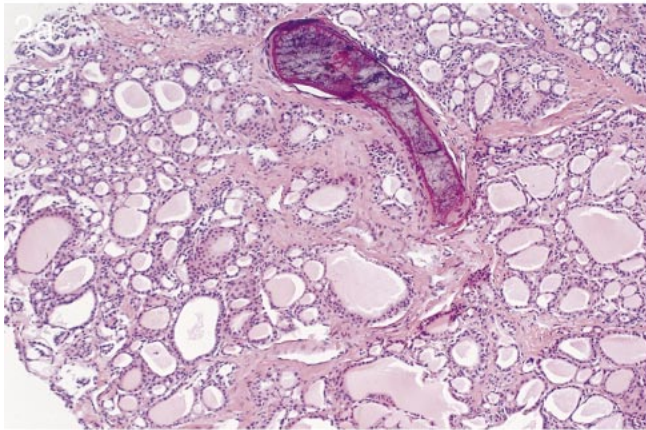
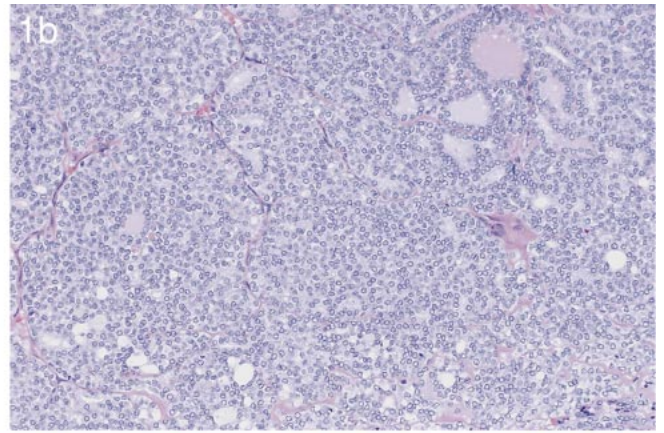
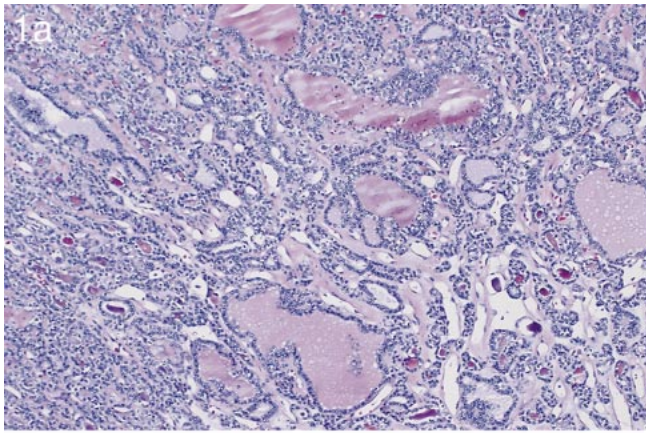


Figure 1. Follicular variant of papillary carcinoma in the thyroid, combining well-differentiated (a) and poorly differentiated (b) areas. This tumor was placed in the poorly differentiated category.

Figure 2. The bone metastasis of this thyroid carcinoma (a) has a better differentiated appearance than the primary tumor (b).

Comparison Between Primary and Metastatic Tumors

Morphologic comparison of the primary tumor with the metastatic lesions showed the metastasis to be better differentiated than the primary tumor in one third (6 of 18) of the cases (Figure 2). In only one case did the primary tumor appear better differentiated than the metastasis. In the rest (11 of 18), the primary tumor and bone metastasis did not show any significant differences in tumor differentiation. Cases in which the primary tumor was less differentiated included 2 cases each of insular carcinoma and follicular carcinoma and 1 case each of Hürthle cell and anaplastic carcinoma. The metastasis in each of these was either well differentiated or contained only focal solid areas. The single case with a better differentiated primary was a follicular variant of papillary carcinoma, in which the primary tumor was well differentiated, whereas the metastatic lesion contained many insular carcinoma-like foci, although still maintaining the papillary nuclear features in most parts.

Clinical Features

Men and women were almost equally represented in this group (male-female ratio, 41:38).

Material from bone metastases was reviewed at some stage in the Department of Pathology in 70 (89%) of the 79 cases. However, this material from only 58 cases was currently available for review by the authors (in 12 cases the material had been returned to the referring institu-

tions). In the remaining 9 cases (11%), RAI uptake alone was considered sufficient evidence of bone metastasis.

Forty patients (51%) were diagnosed as having bone metastasis at the time of initial diagnosis. Of these, 24 presented with the signs and symptoms of bone metastasis (ie, bone pain, pathologic fracture, or cord compression). The diagnosis of bone metastasis was histologically confirmed in each of these 24 cases. In 16 others, synchronous bone metastases were found on routine workup at the time of initial diagnosis of thyroid carcinoma, and this was histologically confirmed in 13 cases. In the rest (39 cases), bone metastases were diagnosed 1 month to 25 years following the initial diagnosis, with overall 66% being diagnosed within the first year of initial presentation. Age at the time of first diagnosis of bone metastasis ranged from 26.7 to 83.8 years (mean, 62.2 years), and it did not vary significantly among the different groups by microscopic tumor type ($P = .80$) or by the overall tumor differentiation ($P = .56$).

At the time of the last follow-up, 57 patients had died of disease, 12 were alive with disease, and the other 10 were lost to follow-up. Among the patients dead of disease, survival after bone metastasis ranged from 0.1 to 15.3 years (median, 2.42 years; 95% confidence interval [CI], 2.0–3.81). The follow-up periods among the 12 surviving patients ranged from 1.80 to 14.96 years (median, 6.35; 95% CI, 4.38–9.70). The overall 5- and 10-year survival probabilities after detection of bone metastases were

29% (95% CI, 0.20%–0.93%) and 13% (95% CI, 0.06%–0.26%), respectively (Kaplan-Meier method). Overall survivors showed significant association with the microscopic tumor type and tumor differentiation ($P = .012$ and $.007$, respectively) (Figure 3). However, these statistically significant associations appeared to be influenced by the relatively poorer prognosis in the groups of anaplastic and medullary carcinoma. All patients with anaplastic and medullary carcinoma were dead within 3.8 years of the diagnosis of bone metastases, 6 of the 10 patients with anaplastic carcinoma dying within the first year. Exclusion of these 2 categories from the analysis showed no significant association between tumor differentiation and survival by either the architectural ($P = .93$) or cytologic ($P = .35$) grades separately or by a combination of both the cytologic and architectural grades ($P = .10$). Comparison of survival between insular carcinomas (median, 2.42; 95% CI, 1.0–7.51) and other poorly differentiated tumors (median, 4.0; 95% CI, 2.48–5.52) also did not reveal any significant difference ($P = .237$) (log-rank test). On excluding the anaplastic and medullary carcinomas, the survival was also not significantly associated with tumor differentiation, when analyzed by the individual site (primary tumors, $P = .52$; metastases, $P = .61$).

The RAI whole-body scan was performed in 61 patients, with the uptake by skeletal metastasis being demonstrated in 39 patients (65%). This was the case in 86% of the follicular carcinomas, 59% of the papillary carcinomas, 77% of insular carcinomas, and 40% of the anaplastic carcinomas. No uptake was observed in the 2 patients with medullary carcinoma in whom scans were performed. The RAI uptake failed to show any significant correlation with tumor differentiation. However, the patients with RAI uptake in the metastatic lesions had a significantly better survival than those without any uptake ($P = .007$) (log-rank test).

Although no significant differences in survival were observed between patients 45 years or younger and those older than 45 years at the time of diagnosis of bone metastases ($P = .31$), patients with nonskeletal metastases at the time of initial presentation had significantly shorter survivals than those without such metastases ($P = .024$).

COMMENT

Metastases to the skeletal system from thyroid carcinoma are a well-known event, constituting the second most common systemic site of involvement after lungs.^{1,2,12} Depending on the study design, such as duration of follow-up, the type of pathology practice (community practice versus large centers with a significant number of referred cases), or the diagnostic parameters used (RAI uptake, histologic testing on the resection or biopsy material, or postmortem examination), the overall reported incidence of bone metastasis from thyroid carcinoma has ranged from less than 1% to more than 40%.^{2–4,8,12–14} Among the different histologic subtypes, follicular carcinoma is most likely to show bone metastases, with reported incidences ranging from 7% to approximately 28%.^{8,12,15} The outstanding exception is the autopsy series of 71 cases of follicular carcinoma reported by Heitz et al,⁶ in which the incidence of bone metastases was approximately 70%. Some studies report Hürthle cell carcinoma to be the most common subtype with bone metastases.¹⁶ In most studies, papillary carcinoma has been found the least likely subtype to show bone metastases (1.4%–7%).^{1,2,5,8,12,15}

Most of the large published studies that deal with bone

metastases in thyroid carcinoma have been on differentiated thyroid carcinoma,^{1,2,7,9,13,16–19} an all-inclusive term that has been loosely applied to papillary carcinoma with all its variants, follicular carcinoma, and Hürthle cell carcinoma.²⁰ Few other studies have included a wider spectrum of thyroid carcinomas with metastases to bones; most of these have been reported in the non-English-language literature.^{6,8,12,14,15,21–31} In addition, most of the reported larger series on bone metastases in thyroid carcinoma have primarily dealt with the clinical aspects and management, the details of the pathologic findings being very sketchy or altogether absent.^{16,19,32}

Most studies of thyroid carcinomas that result in bone metastases show a preponderance of follicular over papillary carcinoma (46%–93% versus 7%–40%) or other types of thyroid cancers.^{8,14,32,33} However, the relatively recent studies by Wood et al,¹⁹ Ruegger et al,¹⁶ and Mizukami et al¹³ report a much higher relative incidence of papillary carcinoma among their cases with bone metastases (41%–77%). In our study as well, papillary carcinoma constitutes the single largest group of cases (28%). Despite the much lower chances of developing bone metastases in papillary carcinoma compared with the follicular type, this high relative incidence of papillary carcinoma among the metastases is not surprising, since papillary carcinomas constitute an overwhelming majority of the primary thyroid cancers.³⁴ The marked preponderance of follicular carcinomas in other studies may also be partially attributable to the generic use of the term *follicular carcinoma* in the older literature. In more recent years, a number of subtypes of thyroid carcinoma with distinctive histologic and/or clinical features have been separated from this all-encompassing term. These include the follicular variant of papillary carcinoma,³⁵ insular carcinoma,³⁶ and Hürthle cell carcinoma.³⁷

Well-differentiated carcinomas constitute the overwhelming majority of primary thyroid carcinomas.¹² Also, in most series on bone metastases in thyroid carcinoma that mention tumor differentiation in one form or the other, well-differentiated tumors have been considered to be more common than moderately differentiated, poorly differentiated, not so well-differentiated, or solid tumors.^{1,8,14,22,23} Nagamine et al³³ also report all their 12 cases with skull metastases to be well differentiated. Other authors have reported a different experience. Thus, Schlumberger et al² considered 121 of their 160 follicular carcinomas with bone metastases to be moderately differentiated. Similarly, 27 of the 30 cases of follicular carcinomas with bone and/or lung metastases reported by Massin et al⁷ contained trabecular areas. Finally, Hwang et al,³⁸ on the review of the histologic findings of 5 of their patients with thyroid carcinoma who had shown aggressive behavior, including metastases to the skeletal system, found all these to be poorly differentiated (insular and columnar cell variants). In our series, more than two thirds of the cases had either a poorly differentiated or undifferentiated morphologic structure at the primary, metastatic, or both sites. It is likely that the differences among these series simply reflect the nonuniformity of the grading systems of thyroid tumors.¹⁰

Bone metastases from thyroid carcinoma, particularly of the follicular type, reportedly often exhibit a better differentiated appearance than the primary tumor; this peculiar phenomenon has given rise to terms such as *benign metastasizing thyroid tumor*, *metastasizing adenoma*, and *malignant*

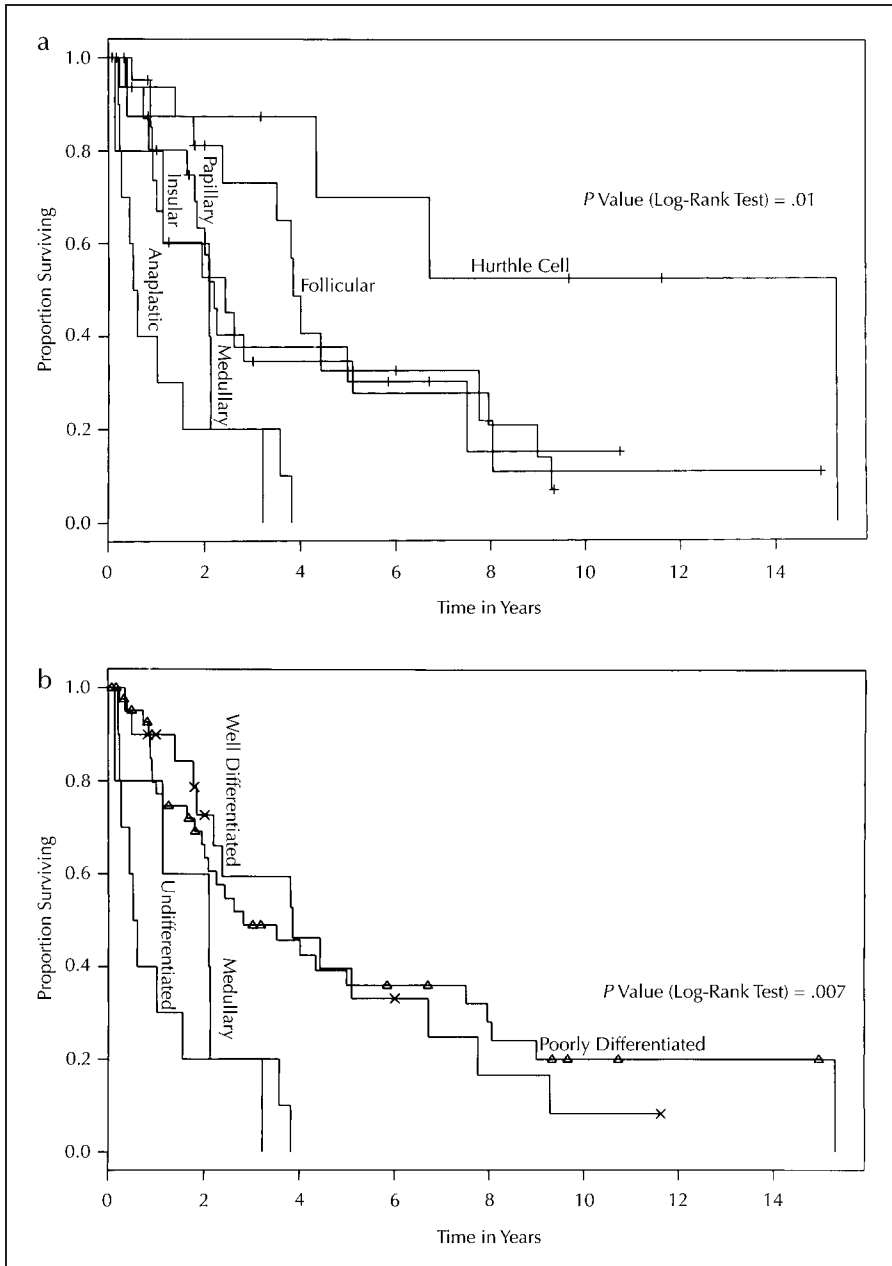


Figure 3. Kaplan-Meier curves illustrating the influence of tumor microscopic type (a) and tumor differentiation (b) on survival, following the diagnosis of bone metastasis in cases of thyroid carcinoma.

adenoma.^{39,40} We found that in one third of the cases (6 of 18) in which the morphologic structure between the primary and the metastatic tumors could be compared, the metastases had a better differentiated appearance than the primary site. However, only in 3 of these cases was the morphologic appearance in the metastasis so well differentiated as to be considered benign if taken out of context.

The presence of distant metastases is considered one of the most important indicators of unfavorable prognosis in differentiated thyroid carcinomas.⁴¹⁻⁴³ Our results reaffirm the fact that, whatever the histologic tumor type or differentiation, once bone metastases develop in thyroid carcinomas, the prognosis is uniformly poor (overall 5- and 10-year survival probabilities, 29% and 13%, respectively). However, the histologic tumor type does seem to influence survival. Thus, in this series the anaplastic or undifferentiated and medullary carcinomas did the worst, as expected. All such patients were dead within 3.8 years, with

60% of the patients with anaplastic carcinoma dying within the first year of the diagnosis of bone metastasis. Interestingly, Hürthle cell carcinomas, irrespective of the degree of differentiation, tended to have the longest survivals. This is unlike the series of Wood et al¹⁹ and Ruegger et al,¹⁶ in which no significant differences were observed in the survivals between patients with Hürthle cell carcinoma and those with follicular or papillary carcinoma with metastases. As such, Hürthle cell carcinomas are believed by many authors to be more malignant than follicular carcinomas of nonocytic type,^{20,37,40,44} although others have expressed their opinions to the contrary.^{45,46}

The influence of tumor differentiation on survival among the patients with distant metastases still remains unclear. For example, among their patients with differentiated thyroid carcinomas with distant metastases, Schlumberger et al² report better survivals among those with follicular well-differentiated and papillary carcino-

mas compared with those with follicular moderately differentiated carcinomas. Similarly, Mizukami et al¹³ indicate a better prognosis for patients with metastatic well-differentiated papillary and follicular carcinomas over those with the trabecular or solid types. On the other hand, Ruegger et al¹⁶ found no significant differences in survival between their grade 1 versus combined grades 2, 3, and 4 cases with distant metastases. In our series, although the tumor differentiation appeared to influence the overall survivals, these seemed mainly to be the effect of the markedly worse outcome among undifferentiated (anaplastic) and medullary carcinomas. Survival among other groups did not show any significant statistical association with tumor differentiation. Even among the poorly differentiated tumors, insular carcinomas did not show any significant differences in survival compared with noninsular carcinoma cases. The survivals were also not significantly different by differentiation, whether the poorly differentiated morphologic structure was present at the primary, metastatic, or both sites.

The RAI uptake by the metastatic lesions did not differ significantly among our different histologic and differentiation categories. Although apparently surprising, this possibly reflects the presence of better differentiated areas in many of our poorly differentiated and undifferentiated tumors. The RAI uptake by the metastases did influence survivals, as has been shown in many other previous studies.^{2,13,16}

Another feature of note in this study was the lack of influence of age at the time of detection of bone metastases (45 years or younger or older than 45 years) on survival, being that age at presentation is one of the most important prognostic factors in primary thyroid carcinoma.^{34,40} Even in the reported series on differentiated thyroid carcinoma with distant metastases, age at metastasis has been influential in survivals.^{2,16} Lack of such an association in this study, therefore, is unexpected. Since we also failed to find a significant correlation between age and the tumor histologic type or differentiation, this lack of influence of age at bone metastasis on survivals in our cases remains difficult to explain.

To conclude, this large series on bone metastases of thyroid carcinoma with emphasis on the pathologic findings shows that most thyroid carcinomas associated with bone metastases are of the papillary type; that most cases have poorly differentiated or undifferentiated features in the primary tumor, in the bone metastasis, or both; that the overall survival after the bone metastasis has been detected is generally poor; that tumor type tends to influence survival, whereas tumor differentiation, when undifferentiated and medullary carcinomas are excluded, does not; and that, once bone metastases have developed, patient's age at the time of diagnosis of bone metastasis does not significantly affect survival.

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