Different Features of Pulmonary Metastases in Differentiated Thyroid Cancer: Natural History and Multivariate Statistical Analysis of Prognostic Variables

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We studied 134 patients with differentiated thyroid cancer and pulmonary metastases. All were treated with total or near total thyroidectomy, radioiodine and L-thyroxine. The prognostic value of the following variables in three groups of patients were evaluated by univariate and multivariate analysis: age at diagnosis, sex, histologic type, tumor extension, cervical lymph node metastases, mediastinic metastases, presence of metastases in distant sites other than lungs (multiple distant metastases) and morphological (chest x-rays) and functional (^{131}I uptake) features of lung metastases. Univariate analysis identified patient age ($p < 0.0001$), morphological and functional features of lung metastases ($p < 0.0001$), presence of multiple distant metastases ($p < 0.0001$) and histologic type ($p = 0.04$) as significant prognostic factors. Multivariate analysis showed only morphological ($p = 0.0014$) and functional ($p < 0.0001$) features of lung metastases and the presence of multiple distant metastases ($p = 0.01$) as significant and independent variables. The data show that early (pre-radiological) scintigraphic diagnosis and ^{131}I therapy of lung metastases appear to be the most important elements in obtaining both a significant improvement in survival rate and a prolonged disease-free time interval in these patients.

J Nucl Med 1993; 34:1626–1631

At the time of diagnosis, differentiated thyroid cancer (DTC) is more often intrathyroid or spread only to cervical lymph nodes because of its typical slow-growing pattern. Consequently, prognosis is generally favorable (*1–8*). Distant metastases represent a rather uncommon event in DTC, even if a wide range in prevalence (5% to 23%) has been reported (*1–14*). Among distant metastases, the lungs represent the most common site. Patients with pulmonary localizations show extremely variable clinical behavior, ranging from rapid fatal outcome to complete disease remission (*5,13–16*). Factors involved in determining prognosis in these patients still remain unclear. Previous observations suggest that micronodular lung metastases (detected by ^{131}I scintigraphy but not by chest x-ray) can be associated with a favorable response (*16–18*). On the other hand, no significant results using radioiodine therapy in DTC patients with lung metastases have been reported (*12*). In the present study, the primary factors of recognized prognostic value in DTC patients were correlated to the different patterns of pulmonary metastases in a large series of patients. One of the purposes of the study was to determine whether early diagnosis and therapy of DTC lung metastases could significantly improve survival and disease-free time intervals in these patients.

Received Dec. 3, 1992; revision accepted June 17, 1993.

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MATERIALS AND METHODS

Patients

The Department of Radiotherapy and Nuclear Medicine, Padua Hospital, treated 1,726 (1,281 female; 445 male; female-to-male ratio: 2.87) patients with DTC in the 22-yr period from January 1967 to December 1989. Among these patients, 264 (15.3%) had distant metastases at diagnosis of DTC and over 50% of these patients (134) had lung involvement. This study focuses on these 134 (86 female; 48 male; female-to-male ratio 1.79) patients with lung involvement.

Papillary tumor was diagnosed in 78 of 134 patients, follicular tumor in 56 patients (papillary-to-follicular ratio 1.39). Both the pure papillary and the mixed papillary-follicular histotypes (provided that some papillary features such as ground glass nuclei and psammoma bodies were present) were classified as papillary tumors. Tumors were considered follicular in the absence of papillary elements. Cancers with evident anaplastic components were excluded from the series.

Lungs alone were involved in 100 patients (74.6%) while 34 patients (25.4%) also had metastases to bones (27 patients), to the brain (4 patients) and to the liver (3 patients). Age at diagnosis ranged from 9 to 77 yr (mean ± s.d. = 50.9 ± 18.2 yr). On the basis of morphological and functional features of lung metastases, patients were divided into three groups. Group 1 included patients

with negative chest x-rays but positive whole-body scan (WBS); Group 2 included patients with both positive chest x-rays and WBS; Group 3 included patients with positive chest x-rays but negative WBS. The following prognostic variables were compared in the three groups of patients: age at diagnosis, sex, histologic type, local tumor extension, cervical lymph node involvement, mediastinic involvement and presence of metastases in distant sites other than lungs (multiple distant metastases).

Therapeutic Approach and Follow-Up Schedule

All patients had undergone total or near-total thyroidectomy, with attention paid to saving the parathyroid glands. After surgery, L-triiodothyronine (L-T3) was administered at thyroid stimulating hormone (TSH) suppressive doses (1 μg/kg b.w.). A WBS was performed 8–10 wk after a 2-wk period of L-T3 withdrawal in order to obtain a TSH increase up to 50 μU/liter or more. Anterior and posterior whole-body scans and spot images (each lasting 10 min) were obtained 48, 72 and 120 hr after a 185-MBq ^{131}I tracer dose administration with a large field-of-view gamma camera (Orbiter 7500, Siemens Medical Systems, Hoffman Estates, IL) equipped with a high-energy collimator and using a 15% window centered on the 364 KeV photopeak. Images were recorded in a computer system (Digital Microvax Computer, Maynard, MA) for subsequent analysis.

To calculate ^{131}I uptake (RIU) by metastatic foci, a 1850-KBq source was used as the standard for the gamma camera. Activity in any interested site(s) was measured with the gamma camera at 48, 72 and 120 hr after ^{131}I administration. Conjugate views of the gamma camera standard in a water phantom with a thickness similar to that of the patient at the site of interest were also obtained. Metastatic tissue was considered to be nonfunctioning when RIU was very low (single neoplastic foci RIU less than 0.05% of administered dose). At the time of WBS, a blood sample for TSH, thyroglobulin (Tg) and anti-Tg antibodies (TgAbs) was taken (*19*). In patients with functioning metastases, a therapeutic dose of ^{131}I was given, each dose ranging from 5.55 GBq to 7.4 GBq. The total amount of radioiodine administered ranged from 5.55 GBq to 29.6 GBq, mean 20.35 GBq. After radioiodine therapy, TSH-suppressive hormonal therapy was resumed by means of L-thyroxine (L-T4) (2–3 μg/kg b.w.). The L-T4 doses were periodically modulated on the basis of serum thyroid hormones and TSH measurements.

A new WBS control was performed within 3–6 mo, and in cases with residual disease a new ^{131}I therapy was applied. Subsequently, patients with persistent disease had WBS controls and additional ^{131}I therapy at least annually. In some patients with nonfunctioning metastases and disease progression, chemotherapy (generally a combination of cisplatin, bleomycin and doxorubicin) was administered in efforts to palliate the condition (*20*).

Complete disease remission was defined as negative WBS, normal chest x-ray and serum Tg levels less than 3 ng/ml after L-T3 withdrawal and in the absence of circulating TgAbs. During follow-up, other than ^{131}I scintigraphies, chest x-rays, bone x-rays, bone radionuclide scans, neck-chest CT scans and neck and liver echographies were utilized. Moreover, serum Tg and TgAbs were periodically performed both during L-T4 and after hormonal therapy discontinuation at the moment of the WBS control. Follow-up ranged from 2 to 25 yr, mean 6.6 yr. Tumor staging was established according to the International Union Against Cancer (UICC) classification (*21*).

Assays

Serum Tg was measured by immunoradiometric method (Sorin, Italy). After total thyroid ablation, serum Tg values above 3 ng/ml were considered abnormal. Circulating TgAbs were measured by radioimmunoassay (Biodata, Italy), negative values were less than 50 U/ml. The TgAb assay was used to confirm Tg determination. Presence of circulating TgAbs invariably determines an underestimation of measured Tg levels using the method employed in our laboratory for Tg assay. Thus, Tg values were considered reliable only when Tg levels were above 3 ng/ml in patients with detectable TgAbs (*22*). Total thyroxine was measured by fluorescent polarization immunoassay (TDx-Abbott, Abbott Park, IL), normal values 4.5–12 μg/dl; free thyroxine by radioimmunoassay (Biorad, Annaheim, CA), normal values 0.8–2.3 ng/dl; total triiodothyronine by radioimmunoassay (Mallinckrodt, Dietzenbach, Germany), normal values 80–200 ng/dl; TSH by immunoradiometric method (CIS, Gifsur Yvette, France), normal values 0.2–4 μU/ml.

Statistical Methods

Patient data were analyzed at the Statistical Department of Padua University. Univariate analysis was performed by means of log-rank test and multivariate analysis using the Cox proportional hazard model (*23*). Survival curves were estimated according to the Kaplan-Meier method (*24*). Chi-square, Analysis of variance (ANOVA) and the Bartlett test were used to estimate differences between groups ($p < 0.05$ were considered significant). Calculations were made using the statistical packages SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC) and GLIM (Generalized Linear Interative Modelling, Royal Statistical Society, London, UK).

RESULTS

Descriptive analysis of prognostic variable distribution in the three groups of patients with pulmonary metastases is shown in Table 1. Considering patient age, it is interesting to observe that age at diagnosis tended to increase from Group 1 to Group 3. The female-to-male ratio shifted toward females in all groups, maintaining the typical characteristic of DTC patients. However, it was lower than that observed in the general series of DTC patients, which means that lung metastases are relatively more frequent in male patients. Prevalence in papillary and follicular tumors was equal in Group 2 and Group 3 while a higher prevalence of papillary tumors was observed in Group 1. Regarding local tumor extension, stages T2 and T4 had the highest prevalence in all three groups. However, the T2-to-T4 ratio shifted in favor of T2 in Groups 1 and 2, and in favor of T4 in Group 3. It is interesting to note that nine patients had a primary tumor less than 1 cm in diameter (occult cancer). No cervical lymph node metastases were found in five of the patients. Thus, 3.7% of DTC patients with lung metastases were T1 N0 following UICC classification (*21*), suggesting that small-sized tumors are not always risk-free.

The prevalence of cervical lymph node metastases was high in all groups, even higher than that reported in the other series of DTC patients (*1–8,25*). Moreover, cervical lymph nodes were almost always involved in Group 1

TABLE 1
Descriptive Analysis of Prognostic Variables Distribution in Three Groups of Patients with Lung Metastases

Factor	Group 1 RIU+ x-rays−	Group 2 RIU+ x-rays+	Group 3 RIU− x-rays+	Total (by row)	p value equality test
Number of patients (%)	42 (31.3%)	54 (40.3%)	38 (28.4%)	134 (100%)	
Age					
0–30	17 (40.5%)	5 (9.3%)	— (0.0%)	22 (16.4%)	
31–50	20 (47.6%)	9 (16.7%)	6 (15.8%)	35 (26.1%)	<0.001
51–65	5 (11.9%)	26 (48.1%)	16 (42.1%)	47 (35.1%)	(**)
66 ≧	— (0.0%)	14 (25.9%)	16 (42.1%)	30 (22.4%)	
Mean age yr (±s.d.)	33.5 (13.8)	56.7 (15.6)	61.9 (11.1)	50.9 (18.2)	
Metastases					
only lungs	42 (100%)	30 (55.6%)	28 (73.7%)	100 (74.6%)	<0.001
multiple	— (0.0%)	24 (44.4%)	10 (26.3%)	34 (25.4%)	
Histology					
papillary	32 (76.2%)	27 (50.0%)	19 (50.0%)	78 (58.2%)	0.02
follicular	10 (23.8%)	27 (50.0%)	19 (50.0%)	56 (41.8%)	
Mediastinum					
positive	6 (14.3%)	14 (25.9%)	12 (31.6%)	32 (23.9%)	
negative	36 (85.7%)	40 (74.1%)	26 (68.4%)	102 (76.1%)	N.S.
Sex					
males	17 (40.5%)	20 (37.0%)	11 (28.9%)	48 (35.8%)	N.S.
females	25 (59.5%)	34 (63.0%)	27 (71.1%)	86 (64.2%)	
T					
T1	2 (4.8%)	3 (5.6%)	4 (10.5%)	9 (6.7%)	
T2	21 (50.0%)	24 (44.4%)	10 (26.3%)	55 (41.0%)	N.S.
T3	4 (9.5%)	7 (13.0%)	2 (5.3%)	13 (9.7%)	
T4	15 (35.7%)	20 (37.0%)	22 (57.9%)	57 (42.6%)	
N					
0	4 (9.5%)	14 (25.9%)	10 (26.3%)	28 (20.9%)	
1a	12 (28.6%)	11 (20.4%)	11 (29.0%)	34 (25.4%)	N.S.
1b	26 (61.9%)	29 (53.7%)	17 (44.7%)	72 (53.7%)	
Status vitae*					
complete disease remission	32 (78.0%)	2 (3.7%)	— (0.0%)	34 (25.6%)	<0.001
disease persistence	9 (22.0%)	52 (96.3%)	38 (100%)	99 (74.4%)	

*One patient deceased for other causes than disease; excluded from this analysis.
**ANOVA and Bartlett test.

patients (90.5% of cases). No incidence of multiple metastases was observed among patients in Group 1.

Survival rate related to group distribution is shown in Figure 1, to RIU in Figure 2, to radiologic findings in Figure 3, to distant metastases pattern in Figure 4, to patient age in Figure 5 and to histologic type in Figure 6. Table 2 summarizes results of univariate statistical analysis. Patients were subdivided into age groups (0–30, 31–50, 51–65, >65 yr), a grouping that represents a compromise between a standardized subdivision and a statistical requirement for a higher power of tests. Table 3 illustrates results obtained using multivariate analysis. Age was considered a continuous variable.

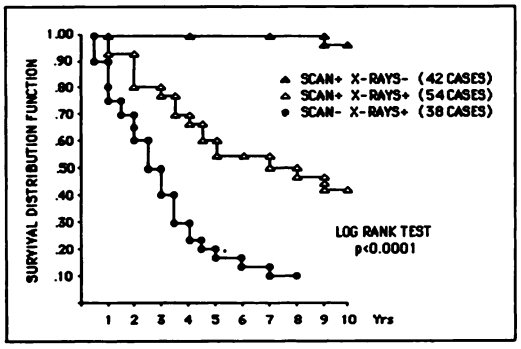

FIGURE 1. Survival rate related to group distribution.

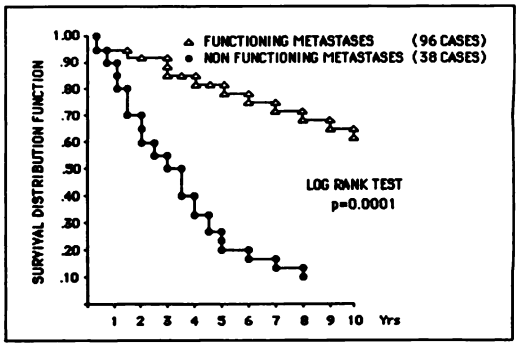

FIGURE 2. Survival rate related to ^{131}I uptake by metastatic tissue.

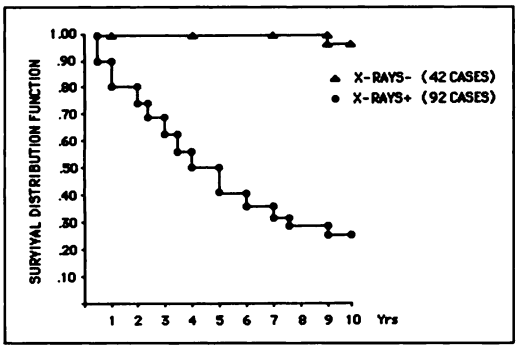

FIGURE 3. Survival rate related to radiologic findings.

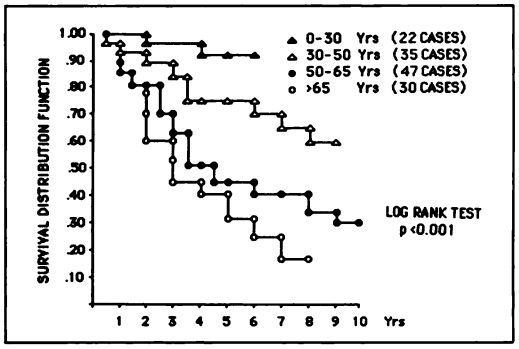

FIGURE 5. Survival rate related to patients' age at diagnosis.

DISCUSSION

The study concerns a large volume of DTC patients with pulmonary metastases. Therapeutic management and follow-up schedule were the same in all cases, providing homogeneous characteristics for the group of patients selected from the entire universe of patients. Three major prognostic factors were examined: (1) the size of lung metastases; (2) lung capability of uptaking radioiodine; and (3) the presence of metastatic foci in distant sites other than lungs, such as bones, brain or liver. On the basis of these data, prognoses were strictly correlated to morphological and biological features of the pulmonary metastases. This observation justified subdivision of patients into three groups: Group 1 = WBS positive and chest x-rays negative; Group 2 = both WBS and chest x-rays positive; Group 3 = WBS negative and chest x-rays positive.

The increase in size of lung metastatic foci and their loss of capability in uptaking radioiodine were responsible for an evident worsening in prognosis. It is important to point out that the micronodular pattern of lung metastases was invariably related to good ^{131}I uptake, while macronodular metastases rather frequently showed poor ^{131}I uptake. The clinical meaning of these findings appears evident. Patients from Group 1 showed the best prognosis, with a 10-yr survival rate of 96% and complete disease remission in 78% of patients. The 10-yr survival rate was significantly lower in Group 2 (36%) and complete disease remission rarely achieved (3.7% of patients). In Group 3 the 10-yr survival rate was only 11% and no instance of complete disease remission was observed.

When pulmonary metastases are <5 mm in diameter (negative chest x-rays), complete disease remission following ^{131}I therapy almost always occurs. When metastases are >5 mm in diameter (positive chest x-rays) the survival rate is still considered fairly good, but the probability of obtaining complete disease remission is very low despite good ^{131}I uptake. Moreover, when the macronodular metastases lose the capability of radioiodine uptake, a fatal outcome is almost always observed.

The favorable meaning of good ^{131}I uptake for prognosis of DTC lung metastases has recently been supported in a paper by Schlumberger et al. (*16*). On the other hand, Ruemeger et al. (*12*) found no favorable influence related to ^{131}I therapy on survival rate in DTC patients with pulmonary metastases. However both the present study and Schlumberger et al. performed total thyroidectomies while Ruemeger performed only partial thyroidectomies. It is likely that partial thyroidectomy, which leaves consistent thyroid remnants, does not allow any diagnostic ^{131}I procedure making lung metastases detection impossible at an early stage when metastases show a micronodular pattern and when the probability of complete cure by radioiodine is high.

Presence of metastases in distant sites other than lungs, such as bones, brain or liver, is an important unfavorable prognostic variable (*11,13,14*). Using multivariate analysis in the present study, the presence of multiple distant metastases was demonstrated to represent a significant and independent prognostic factor. It is interesting to note that no incidence of multiple distant metastases was observed among patients from Group 1, who showed the most fa-

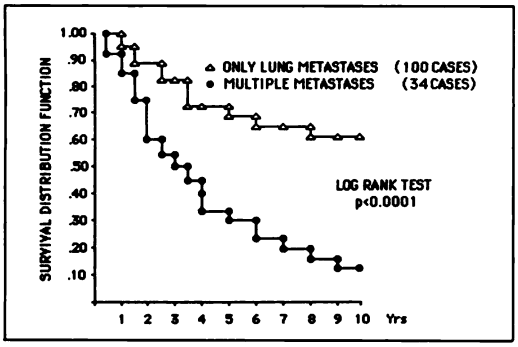

FIGURE 4. Survival rate related to the pattern of distant metastases (single or multiple distant metastases).

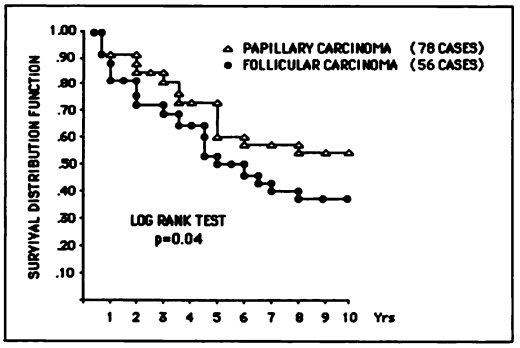

FIGURE 6. Survival rate related to histologic type.

TABLE 2
Results of Univariate Statistical Analysis of Prognostic Factors (log-rank test)

Factor	No. of patients	No. of deaths	2-yr survival rate	5-yr survival rate	10-yr survival rate	p value log-rank test
Group						
G-1	42	1	100	100	96	
G-2	54	29	83	59	36	<0.0001
G-3	38	31	55	16	11	
Age (yr)						
0–30	22	2	100	90	90	
31–50	35	12	89	76	58	<0.0001
51–65	47	29	68	45	29	
66 ≧	30	18	77	39	26	
Metastases						
only lungs	100	34	85	69	62	<0.0001
multiple	34	27	68	36	10	
^{131}I uptake						
yes	96	30	91	77	62	<0.0001
no	38	31	55	16	11	
Chest x-rays						
positive	92	60	72	41	25	<0.0001
negative	42	1	100	100	96	
Histology						
papillary	78	29	85	66	59	0.04
follicular	56	32	75	53	34	
Mediastinum						
positive	32	20	72	41	38	0.06
negative	102	41	83	67	51	
Sex						
males	48	18	77	64	56	N.S.
females	86	43	83	58	44	
T						
T1	9	4	89	67	33	
T2	55	25	91	70	53	N.S.
T3	13	4	85	75	63	
T4	57	28	68	45	45	
N						
0	28	14	82	61	36	
1a	34	14	82	64	57	N.S.
1b	72	33	79	57	47	
Total	134	61	81	60	48	

vorable prognosis, while multiple metastases were not uncommon in patients from Groups 2 and 3. Morphologic and biologic patterns of lung metastases were strictly correlated to patient age. Patients with micronodular and functioning metastases (Group 1) were significantly younger than the others (mean age 33.5 yr). Patients in Group 2 were of an intermediate age (mean age 56.7 yr) while patients with macronodular and nonfunctioning metastases (Group 3) were the oldest (mean age 61.9 yr). Most likely because this strict interrelationship exists between patient age and metastatic pattern, age was found by univariate analysis to be a significant prognostic factor, but was not identified as an independent variable by multivariate analysis.

TABLE 3
Results of Multivariate Statistical Analysis of Prognostic Factors* (Cox Model)

Factor	Regression coefficient	Relative death risk	p value
RIU	1.344	3.83	<0.0001
Chest x-rays	3.259	26.02	0.0014
Multiple metastases	0.671	1.96	0.01
T4	0.488	1.63	0.06

*Age was considered a continuous variable.

Similar observations may be made about histologic type. Histology was found to be a significant prognostic factor when univariate analysis was applied, but multivariate analysis did not assign an independent value to this variable which is in agreement with other studies (*8,12*). Patients with papillary tumors had a better prognosis than those with follicular tumors. Papillary tumors were more frequently observed in patients from Group 1 (76.2% of cases) than in patients from Groups 2 and 3 (50% of cases). The high prevalence of papillary tumors in Group 1 patients could explain the relatively higher percentage of lymphatic metastases in these patients than in those in Groups 2 and 3.

The T distribution was similar in patients from Group 1

and 2, although a higher prevalence of stage T4 was found in Group 3. This characteristic could be related to the more advanced patient age in Group 3 in comparison with the other two groups. It has been reported that thyroid cancer in elderly patients locally shows an aggressive pattern with frequent extracapsular growth (*25*). Stage T4 was found to represent a significantly weak ($p = 0.06$) prognostic variable by multivariate analysis.

Sex and cervical and mediastinic metastases did not play a prognostic role either in univariate or multivariate analysis. It is interesting that the female-to-male ratio was lower in patients with pulmonary metastases than in the general series of DTC patients. This allows the hypothesis that, even though the prognosis is similar for males and females, lung metastases are more frequently observed in male patients.

Lastly, the prevalence of cervical lymph node metastases was very high in our series, particularly in patients in Group 1. These findings require some consideration from a therapeutic point of view. In particular, although lymphatic metastases alone do not significantly influence DTC patient survival (*1,2,5,6,8*), our results suggest that their presence must compel the surgeon to consider a higher prevalence of metastatic foci in distant sites, making radical surgery in these patients recommendable.

Our data strongly suggest that early diagnosis of pulmonary metastases in DTC patients (i.e., micronodular and functioning metastases) assures higher efficacy in radioiodine therapy as well as higher probability of obtaining complete remission. Because the absence of thyroid remnants is a necessary condition to correctly perform WBS, total thyroidectomy appears to be the most adequate surgical approach for these patients.

ACKNOWLEDGMENTS

The authors thank Giovanni Casara for his expert technical assistance.

REFERENCES

1. Mazzaferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current therapy. *Semin Oncol* 1987;14:315–332.
2. DeGroot LJ, Kaplan EL, McCormick M, Straus F. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990;71:414–424.
3. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 1985;55:794–804.
4. McConahey WM, Hay ID, Woolner LB, van Heerden J, Taylor WF. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 1986;61:978–996.
5. Samaan NA, Maheshwari YK, Nader S, et al. Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. *J Clin Endocrinol Metab* 1983;56:1131–1138.
6. Tennvall J, Biorklund A, Moller T, Ranstam J, Akerman M. Is the EORTC prognostic index of thyroid cancer valid in differentiated thyroid carcinoma? Retrospective multivariate analysis of differentiated thyroid carcinoma with long follow-up. *Cancer* 1986;57:1405–1414.
7. Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1,578 patients. *Int J Radiat Oncol Biol Phys* 1988;14:1063–1075.
8. Thoresen SO, Akslen LA, Glattre E, Haldorsen T, Lund EV, Schoultz M. Survival and prognostic factors in differentiated thyroid cancer, a multivariate analysis of 1,055 cases. *Br J Cancer* 1989;59:231–235.
9. Pochin EE. Prospects from the treatment of thyroid carcinoma with radioiodine. *Clin Radiol* 1967;18:113–118.
10. Hoie J, Stenwig AE, Kullmann G, Lindegard M. Distant metastases in papillary thyroid cancer. A review of 91 patients. *Cancer* 1988;61:1–6.
11. Marcocci C, Pacini F, Elisei R, et al. Clinical and biologic behavior of bone metastases from differentiated thyroid carcinoma. *Surgery* 1989;106:960–966.
12. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab* 1988;67:501–508.
13. Schlumberger M, Tubiana M, De Vathaire F, et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986;63:960–967.
14. Casara D, Rubello D, Saladini G, Gallo V, Masarotto G, Busnardo B. Distant metastases in differentiated thyroid cancer: long-term results of radioiodine treatment and statistical analysis of prognostic factors. *Tumori* 1991;77:432–436.
15. Pacini F, Lippi F, Formica N, et al. Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med* 1987;28:1888–1891.
16. Schlumberger M, Arcangioli O, Piekarski JD, Tubiana M, Parmentier C. Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest x-rays. *J Nucl Med* 1988;29:1790–1794.
17. Casara D, Zorat PL, Busnardo B, Girelli ME. Pulmonary metastases from differentiated thyroid carcinoma detected only by radionuclide imaging. *Br J Radiol* 1981;54:640–644.
18. Fassina A, Rubello D, Casara D. Thyroid cancer in pediatric age: clinical behavior, therapeutic approach and long-term results. In: Schmidt HAE, Hofer R, eds. *Nuclear medicine. Nuclear medicine in research and practice*. Schattauer: Stuttgart-New York; 1992:611–614.
19. Rubello D, Casara D, Girelli ME, Piccolo M, Busnardo B. Clinical meaning of anti-thyroglobulin antibodies in differentiated thyroid cancer: a prospective study. *J Nucl Med* 1991;33:1478–1480.
20. De Besi P, Busnardo B, Toso S, Girelli ME, Casara D, Fiorentino MV. BAP (bleomycin, doxorubicin and cisplatin) regimen in advanced thyroid carcinoma. *J Endocrinol Invest* 1991;14:475–480.
21. TNM classification of malignant tumors. UICC international union against cancer. Hermanek P, Sobin LH, eds. Germany: Springer Verlag; 1987.
22. Rubello D, Girelli ME, Casara D, Piccolo M, Perin A, Busnardo B. Usefulness of combined antithyroglobulin and thyroglobulin assay in the follow-up of patients with differentiated thyroid cancer. *J Endocrinol Invest* 1990;13:737–742.
23. Cox DR. Regression model and life tables. *J R Stat Soc* (B) 1972;34:187–220.
24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Ass* 1958;53:457.
25. Casara D, Rubello D, Saladini G, De Besi P, Fassina A, Busnardo B. Differentiated thyroid carcinoma in the elderly. *Aging Clin Exp Res* 1992; 4:333–339.