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A Prognostic Index for Thyroid Carcinoma. A Study of the E.O.R.T.C. Thyroid Cancer Cooperative Group*

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Abstract—*Using survival from all causes of death as an endpoint, the prognostic significance of age, sex, cell type, clinical extent of tumor, lymph node status and number of metastatic sites (all recorded at the time of diagnosis) was studied in a set of data for* 500 *patients with histologically confirmed thyroid carcinoma. Each of these variables was found to have prognostic significance when examined singly, but some were strongly correlated with others.*

A simple prognostic index based on a multivariate analysis using a Weibull survival model is presented which allows one to assess the joint effects of the prognostic variables and indentifies patients with markedly different survival probabilities. The index may be used to predict survival for individual patients as an adjustment variable in treatment comparisons, or as a stratification variable in designing prospective randomized trials of treatment.

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INTRODUCTION

PREVIOUS work has demonstrated that a number of factors are of prognostic importance in thyroid carcinoma [1–6]. Among these are the age of the patient at diagnosis, sex, cell type of the lesion, the extent of the primary tumor, lymph node status and the presence or absence of metastases. It is often difficult in the presence of so many known prognostic factors, especially when they are correlated, to attempt to predict survival in a single case or to define groups of patients with similar survival probabilities. The purpose of this article is to re-examine the relative importance of these variables in a large set of data and to assess, by multivariate statistical techniques, their importance when they are all allowed to act together.

MATERIALS AND METHODS

Patients studied

In 1966 the E.O.R.T.C. Thyroid Cancer Co-operative Group began a registry of data on patients with thyroid carcinoma. Entry into this data set was continued until 1977 after some 1183 patients from 23 hospitals from various European countries had been registered.

Patients were treated by surgery, X-ray therapy, radioactive iodine, thyroid hormones and chemotherapy as seemed appropriate. It is certain that none of these therapies were given in the same fashion at all centers and the indications for their use also differed according to the beliefs and experience at the various centers. Although extensive attempts were made to compare the various therapies while adjusting for prognostic factors, we finally decided that such analyses could be misleading, so therapy will be ignored in this analysis.

All tumors were reviewed by a central pathology panel using a descriptive classification recognizing the following patterns: papillary, follicular well-differentiated, follicular less-differentiated, medullary, epidermoid and anaplastic [7]. A comparison between the evaluation of these data by the WHO diagnostic classification [8] and by the descriptive classification followed here will be separately presented. The clinical assessment was performed in accordance with the TNM system [9].

For this article all patients with known follow-up times, known cell type, and information on the relevant variables were used. Since in many instances the data were incomplete the numbers of patients in the various analyses of single variables differ according to the available information. In the later part of the paper where multivariate methods are employed, the sample was restricted to 507 patients with follow-up for whom information was available on all variables needed for the analysis. For this portion of the analysis the median follow-up was 40 months (54 months for patients last known alive [censored] and 10 months for dead patients), but 20% of the censored patients were followed longer than 76 months, justifying the construction of survival curves out to 6 yr.

Statistical methods

Actuarial survival curves [10] were constructed when the numbers of patients were sufficient to justify their use. All survival curves were based on all causes of death combined since information on the cause of death was unavailable. differences in actuarial survival curves were tested using the Mantel–Haenszel procedure [11]. Prognostic significance was also examined by comparing death rates defined as the number of deaths divided by the total patient-months for all patients in a specific category. The joint effects of the prognostic variables were examined by means of the Weibull survival model which incorporates covariate information and is suitable for censored survival data. Details of this model and its use in constructing risk groups are discussed in the appendices.

RESULTS

The median age at diagnosis of 591 patients with known follow-up and cell type was 50 yr (range = 6–90), but 10% were under age 23 and 10% over age 70. The effect of age on survival for patients with thyroid carcinoma is shown in Fig. 1. It is apparent that age is strongly related to survival, with older patients being more likely to die. Other analyses (not presented here) confirmed the propensity for older patients to die more rapidly, even when adjustments were made for other causes of death by constructing relative survival curves based on national life table figures. Comparison of actuarial survival reveals no significant differences between patients less

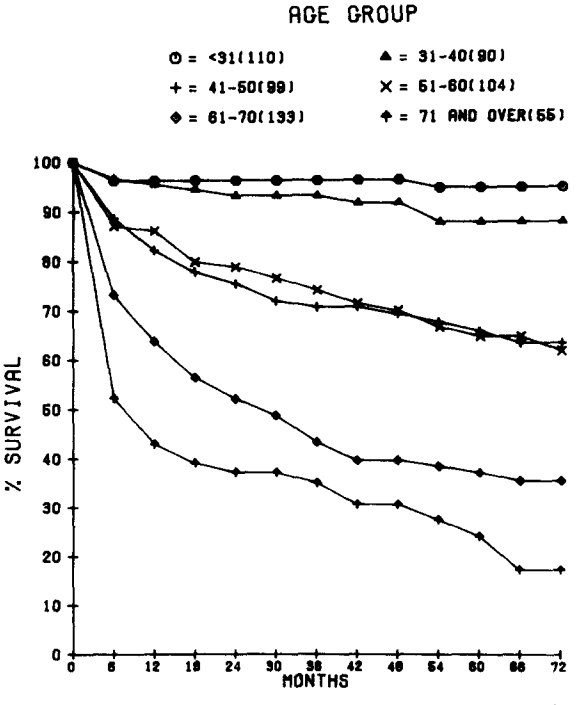

Fig. 1. Survival curves by age at diagnosis. Numbers of patients in parentheses.

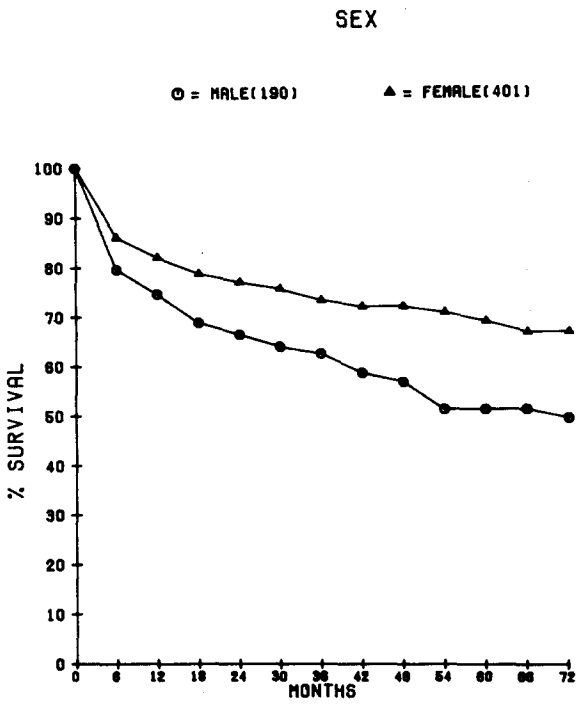

Fig. 2. Survival curves by sex of the patient. Numbers of patients in parentheses.

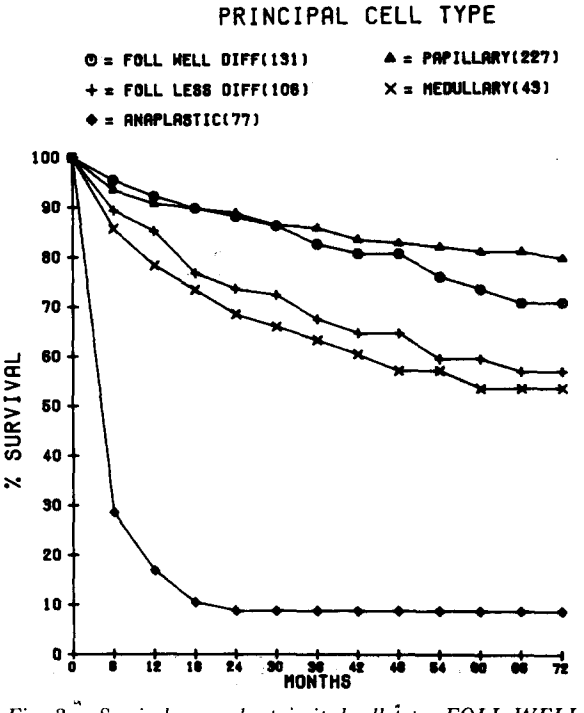

Fig. 3. Survival curves by principal cell type. FOLL WELL DIFF = follicular well-differentiated, FOLL LESS DIFF = follicular less-differentiated. Numbers of patients in parentheses.

than 31 vs those 31—40 as suggested by the curves. Likewise there is no significant difference between patients 41–50 vs those 51–60. However, patients aged 61–70 at diagnosis survived significantly longer than those 71 and over ($P<0.006$). All other curves in Fig. 1 differ very significantly with $P<0.0003$ in all instances.

Sex of the patient was also an important prognostic factor (Fig. 2). The female:male ratio for patients with follow-up information was 2.11, and female patients survived significantly longer ($P=0.001$).

Survival by principal cell type is shown in Fig. 3. For each case both principal and associated cell type were recorded. However, about 56% showed a single cell type. The curves in Fig. 3 indicate that principal cell type is a very important prognostic variable. However, no significant differences in survival were noted between follicular well-differentiated and papillary tumors, nor between follicular less-differentiated and medullary tumors. Survival of patients with a follicular well-differentiated pattern was significantly better than those whose biopsies showed follicular less-differentiated ($P<0.006$) or medullary tumors ($P<0.012$). All other differences between these curves are significant, at least at the $P<0.001$ level of significance. Similar curves (not shown here) were constructed for the associated cell types as well as for all combinations of principal and associated cell type. The high correlations between principal and associated cell types and their relationship to age require care in interpretation and will be explored in a separate publication. Other analyses (not presented here) showed that the presence of anaplastic areas of carcinoma (whether principal, associated, or pure) were associated with extremely poor survival. Therefore, in our multivariate analysis the presence of anaplastic carcinoma is treated as a separate variable.

The extent of the primary tumor was classified as follows; T0 = no palpable tumor, Ti = mobile tumor limited to the thyroid gland without deformity, T2 = single or multiple mobile tumors deforming the thyroid gland, T3 = tumors extending beyond the thyroid gland with fixation or infiltration of adjacent structures. Figure 4 indicates that survival curves for patients with T0, T1 and T2 lesions were similar and differed quite markedly from that for T3 lesions. The first three categories do not differ significantly from each other except for the comparison of T1 and T2 ($P<0.03$). Each of the three differ at $P<0.0001$ from T3 lesions, however. In the subsequent multivariate analyses the first three categories are combined.

The status of the regional lymph nodes was assessed clinically as follows: N0 = no palpable cervical adenopathy, N1 = homolateral mobile cervical adenopathy, N2 = contralateral or bilateral mobile cervical adenopathy, N3 = fixed

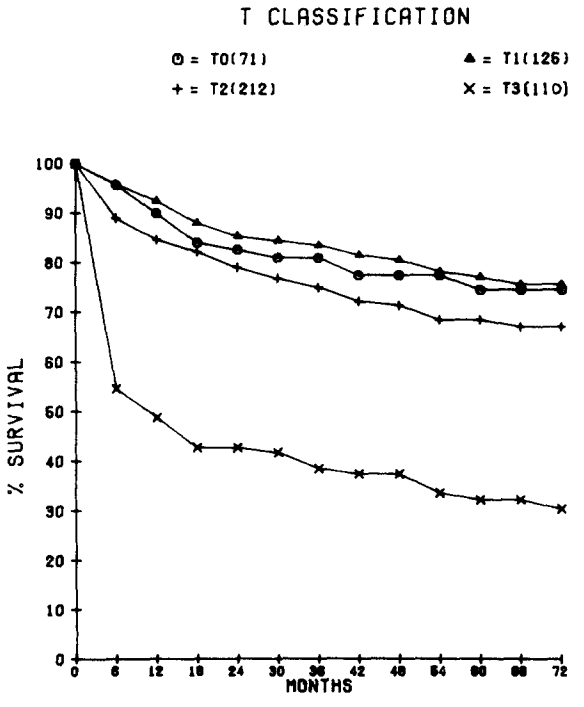

Fig. 4. Survival curves by extent of primary tumor. See text for definitions of T0, T1, T2 and T3. Numbers of patients in parentheses.

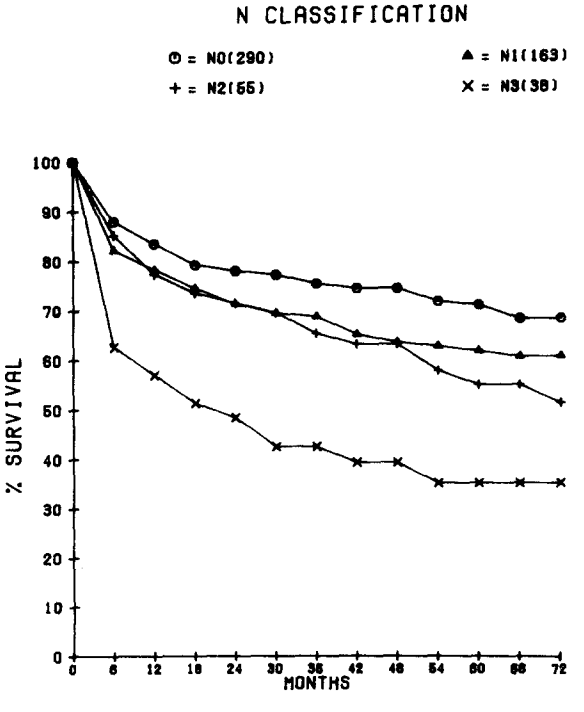

Fig. 5. Survival curves by clinical evaluation of regional lymph nodes. See text for definitions of N0, N1, N2 and N3. Numbers of patients in parentheses.

cervical nodes. The curves in Fig. 5 indicate that N1 and N2 lesions did not differ significantly in survival, although both curves differ from that for N0 lesions approaching the $P=0.05$ level of significance. The three top curves all differ significantly from that for N3 lesions (for N0 vs N3, $P<0.0001$, for N1 vs N3, $P=0.002$ and for N2 vs N3, $P=0.03$).

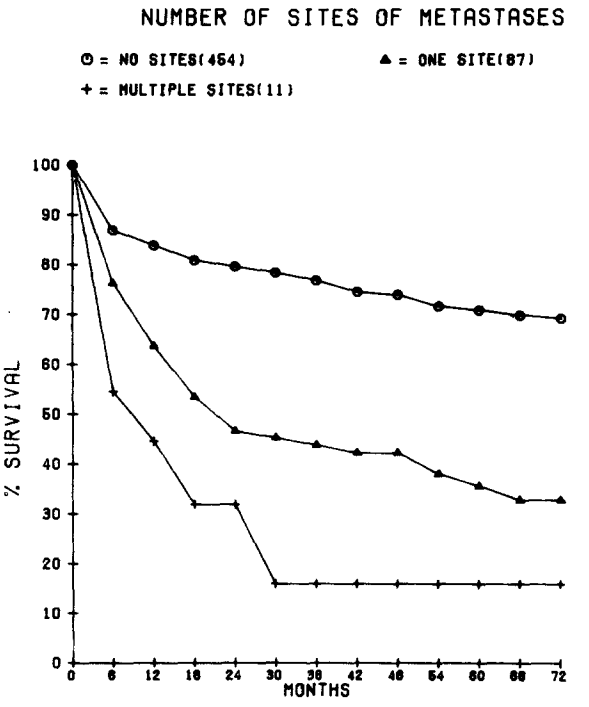

Fig. 6. Survival curves by number of metastatic sites. Numbers of patients in parentheses.

Sites of distant metastases were recorded whether detected by clinical examination, X-rays, or scans. Survival was significantly ($P<0.0001$) worse for patients presenting with single or multiple metastases (Fig. 6). The survival curves for single and multiple sites do not differ significantly ($P=0.17$), probably because of the small number of patients presenting with multiple sites; but since the trend is so strong, the multiple site category has been retained in subsequent analyses.

Multivariate analysis

Some of the variables just described are highly correlated with one another. For example, anaplastic tumors are more common than papillary ones in old age and are more likely to present with metastasis. Generally, the extent of the primary tumor, status of nodes, and presence of metastases are correlated and tend to differ depending on the cell type. For this reason it is difficult to make prognostic assessments for individual patients, or even for groups of patients, without multivariate analyses which allow the variables to act together. Plots of log survival vs time indicated that, for most groups of patients, survival did not tend to follow the exponential law which is governed by a constant death rate. Instead, survival prospects improved

with time suggesting the need for a survival model which allows a decreasing death rate with time. For this reason we selected the Weibull survival model (see Appendix I). This model permits many variables to be studied at once and statistical tests are available for judging which variables do not add appreciably to our ability to predict survival in the presence of other variables. Applying a step-down procedure to these data, we found that the following variables were sufficient to predict survival: age (in years) at diagnosis, sex, principal cell type, presence of anaplastic carcinoma, T-category, and number of metastatic sites. Details of coding for the variables and the fitted regression coefficients are given in Appendix I. Death rates for these variables (Table 1), based on just those 507 patients with complete information, indicated that all were strongly related to prognosis. In the initial fitting of the model, we learned that lymph node status could be omitted since, because of its correlation with the other variables, it did not add significantly to our ability to predict survival. Although age at diagnosis is presented in categories in Table 1, we found that better prediction was obtained when it was introduced into the model as a continuous variable.

Based on the regression coefficients from the model, a simple scoring system was devised for assigning patients to prognostic risk groups (see Appendix II). The scoring system is presented in Table 2 and the cut-points for forming five risk groups are shown in Table 3. The value of forming these risk groups is demonstrated by the marked differences in their observed 5-yr survival rates. To illustrate the use of this system, let us consider a male patient age 41 at diagnosis of a fixed thyroid carcinoma with multiple metastases which upon histologic examination was a pure medullary carcinoma. The total score for this patient would be 41 (age) +12 (male) +10

Table 2. Proposed E.O.R.T.C. prognostic index for thyroid carcinoma

Age at diagnosis (yr)
+ 12 if male
+ 10 if medullary or if principal cell type is follicular less-differentiated provided that the associated cell type is not anaplastic
+ 45 if principal or associated cell type is anaplastic
+ 10 if T-category is T3
+ 15 if there is at least one distant metastatic site
+ 15 in addition to above if there are multiple distant metastatic sites
=Total score

Table 1. Prognostic variables used to develop risk groups

Variable	Levels	Number of patients	Number of deaths	Total months follow-up*	Death rate†
Age	0–30	91	4	5077.5	0.79
	31–40	79	9	4176.5	2.15
	41–50	84	25	3746.0	6.67
	51–60	87	30	3666.5	8.18
	61–70	119	69	3637.5	18.97
	71+	47	38	933.5	40.71
Sex	female	342	103	15,428.0	6.68
	male	165	72	5809.5	12.39
Cell type	Anaplastic‡	77	68	760.5	89.41
	MED§ or FLD‖	121	45	4769.5	9.43
	All other	309	62	15,707.5	3.95
T-category	T0, T1, T2	401	106	18,242.5	5.81
	T3	106	69	2995.0	23.04
Metastatic sites	None	421	122	19,041.5	6.41
	Single	78	46	2142.0	21.48
	Multiple	8	7	54.0	129.63
All patients		507	175	21,237.5	8.24

*Because only completed months were recorded, 0.5 has been added to all follow-up times.
†Death rates expressed in deaths/1000 patient months.
‡Whether principal or associated.
§Medullary.
‖Principal cell type follicular less-differentiated, provided associated type is not anaplastic.

Table 3. Risk groups based on total scores with observed survival rates

Total score	Risk group	Observed 5-yr survival (%)
<50	1	95
50–65	2	80
66–83	3	51
84–108	4	33
≧109	5	5

*Calculated by the actuarial method (see reference 10).

(medullary) + 10 (T3) + 30 (multiple metastases) = 103 and we would therefore assign this patient to risk group 4.

Observed (actuarial) and predicted survival curves for the survival model are shown in Fig. 7. Although the agreement of the predicted curves with the actuarial curves for those same groups of patients are far from perfect, the figure nevertheless shows that we have been successful in defining groups of patients with widely differing survival probabilities. The characteristics of the patients in each risk group are shown in Table 4. The average age of the patients increases in risk groups 1–4, but the ages of patients in risk groups 4 and 5 are similar. Other characteristics of risk groups can be deduced from studying this table, but perhaps the most marked finding is that 94% of patients in risk group 5 had anaplastic tumors. What is perhaps more surprising is that even though risk group 4 contains 18% anaplastic tumors, the survival probabilities for these patients,

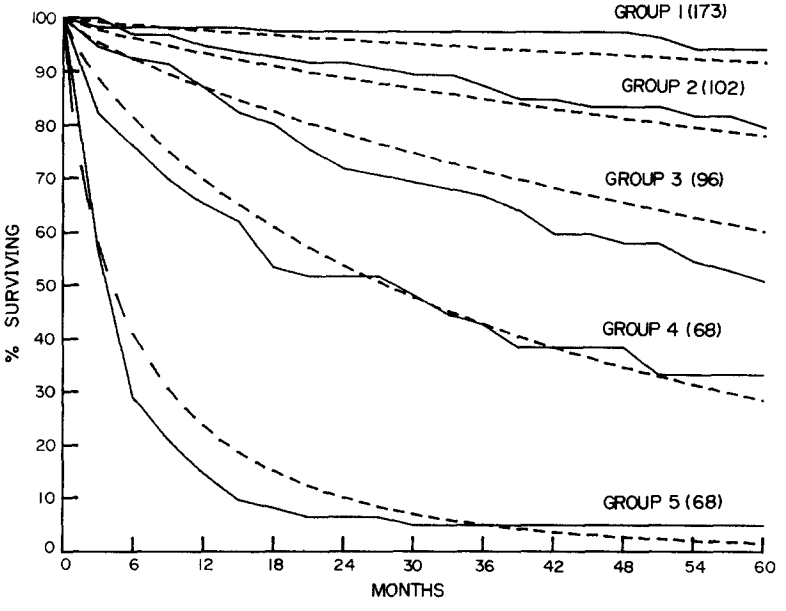

Fig. 7. Observed (—) and predicted (- - - -) survival curves for the five risk groups. Numbers of patients in parentheses.

Table 4. Characteristics of risk groups*

Risk group	Number of patients	Average age (range)	% Male	%MED or* FLD	%ANAP	% T3	% Single mets	% Multiple mets	Observed 5-yr survival (%)†
1	173	29.6 (6–47)	22.5	5.8	0.0	4.0	1.2	0.0	95
2	102	49.6 (20–65)	33.3	33.3	0.0	4.9	5.9	0.0	80
3	96	59.7 (29–79)	35.4	41.7	1.0	19.8	22.9	0.0	51
4	68	64.3 (40–90)	44.1	50.0	17.6	45.6	45.6	1.5	33
5	68	66.6 (37–87)	41.2	4.4	94.1	64.7	25.0	10.3	5
All	507	48.9 (6–90)	32.5	23.9	15.2	20.9	15.4	1.6	64

*Abbreviations used: MED = medullary cell type, FLD = follicular less-differentiated principal cell type, ANAP = anaplastic cell type, principal or associated, mets = metastatic sites.
†Calculated by the actuarial method (see reference 10).

because of their other characteristics, are markedly better than those for risk group 5. Tests of significance between the 5 observed actuarial curves reveal that they all differ at $P < 0.001$ except the comparison of groups 3 and 4 ($P = 0.01$). The observed 5-yr survival rates range from 95% for risk group 1 to 5% for risk group 5.

DISCUSSION

In agreement with previous studies, we have shown that age, sex, cell type, extent of primary tumor, lymph node status and number of metastatic sites are all important in predicting survival in patients with thyroid carcinoma. The most important contribution of our study has been the development of a summary prognostic index which can be used to predict survival of individual patients, somewhat in the manner of staging systems for other cancers. It can also be used as a single stratifying variable in designing prospective randomized clinical trials or as an adjustment variable in comparing uncontrolled series with other sets of data or historical controls.

A striking feature of thyroid carcinoma revealed by this analysis is the importance of age. Age is often a risk factor, with many cancers showing increased incidence as the population ages, but rarely is age such an important prognostic factor, especially when adjusted for other variables. In this analysis we have confirmed the findings of others [2, 4, 5] that age and cell type are closely related, particularly for the differentiated cell types, and this will be the subject of a separate publication.

Our analysis may help clarify some points already discussed in the literature. The fact that age, cell type, T-category, and number of metastatic sites were all retained in our multivariate survival model implies that however highly correlated these variables are, they nevertheless add appreciably to each other in predicting survival. Examining the contribution of a single variable in a multivariate model is equivalent to studying this variable while adjusting for the other variables in the model, a feature of our analysis which may help explain why our findings sometimes differ from those of others who studied only one variable at a time in populations whose composition with respect to these variables may have differed considerably from ours. Thus we cannot support the speculation of Gerard-Marchant and Bok that the effect of sex may be explained by a different distribution of cell types for the two sexes [3]. Franssila found only weak evidence of different prognosis according to sex [5], but our analysis suggests that this variable is quite important. He also speculated that age effects may be explained by differences in cell type by age, another idea not supported by our multivariate analysis. Franssila found that microscopic involvement of regional lymph nodes did not correlate with survival. We found that the clinical condition of the regional lymph nodes was correlated with survival, but that the regional node status did not add to our ability to predict survival in the presence of the other variables in our model.

We are aware that prognostic factors other than those we have studied have been discussed in the literature. For example, Woolner *et al.* [1] showed the importance of the size of the primary tumor in papillary carcinoma and the extent of vascular invasion in follicular carcinoma. In addition to these, it is possible that other factors such as TSH receptor status may prove to be important. However, the separation of the survival curves based on our risk groups is so great that we think it likely that any additional prognostic factors will be correlated with those we have studied. Further study of prognostic factors may nevertheless be useful if more precise or objective measurements can be found.

Since we have ignored therapy in these analyses, we must admit the possibility that the effects of therapy, if taken into account, might alter the importance of some prognostic factors. Technically, one is entitled to ignore therapy in studying prognostic factors only if it is known that therapy has no effect on the natural history of the disease. This is probably not the case in thyroid carcinoma. For some cell types it is quite likely that surgery, X-ray therapy, radioactive iodine and hormone treatment are effective therapies, even though their precise roles have not been demonstrated to our knowledge in properly designed prospective randomized trials. For lesions of good prognosis it would be difficult to carry out such trials because the disease is relatively rare and mortality is quite low, implying that large samples and prolonged follow-up would be necessary. Also, the fact that our analysis revealed a decreasing death rate with time is consistent with the idea that some patients are being cured. We cannot say whether these apparent cures are due entirely to the treatments used, or rather to co-operation between therapy and the natural defences of the body. In any case, it seems most likely that thera-

peutic progress is to be made by randomized comparisons of treatments in risk groups 3–5 where appreciable mortality may be expected.

Perhaps the most interesting finding is the enormous importance of prognostic variables in determining the survival of patients with thyroid carcinoma. The differences demonstrated with these variables are so great that they are likely to overshadow any improvements due to therapy unless such improvements are studied in well-designed randomized clinical trials. Incorrect conclusions could easily be drawn in comparing survival of patients with thyroid carcinoma treated by different methods unless particularly close attention is paid to prognostic factors. Our analysis also suggests that the TNM system [9] alone is inadequate for stratification or comparison of groups of patients with thyroid carcinoma since it does not take into account three of the most important variables, age, sex and cell type.

STATISTICAL APPENDICES

I. *The Weibull model for survival incorporating covariates*

Examination of the survival curves suggested that the Weibull model might serve as an adequate parametric summary of the data. This model allows the death rate (hazard) to change with time and these data suggested that the death rate decreased with time.

We assume that the probability of death at time t for the ith patient ($i=1, 2, \ldots, n$) is given by

$$f(t)=\lambda_i k t^{k-1} \exp(-\lambda_i t^k) \quad (1)$$

where $\lambda_i=\exp(\boldsymbol{\beta}'\mathbf{X}_i)$. If there are m covariates then $\mathbf{X}_i$ is an $m+1$ column vector of elements X_{ij}, $j=0, 1, \ldots, m$. The element X_{i0} is taken as 1 to represent an intercept and the X_{ij}, $j=1, 2, \ldots, m$, represent the values of the m covariates, whether continuous or categorical. The $m+1$ column vector $\boldsymbol{\beta}$ represents the regression coefficients associated with the covariates and k is a parameter governing the shape of the survival curve. The hazard (instantaneous death rate) for patient i at time t is given by $h(t)=\lambda_i k t^{k-1}$. The hazard increases with time if $k>1$ and decreases if $k<1$. For $k=1$ the Weibull model reduces to the simple exponential distribution with a constant hazard. The cumulative survival curve at time t is given by

$$S(t)=1-F(t)=\exp(-\lambda t^k). \quad (2)$$

The log likelihood for a right-censored sample is given by

$$\ln L=\sum_{i=1}^{n}[z_i(\boldsymbol{\beta}'\mathbf{X}_i)+z_i \ln k+z_i(k-1)\ln t_i - \exp(\boldsymbol{\beta}'\mathbf{X}_i)t_i^k] \quad (3)$$

where $z_i=\begin{cases}1 \text{ if patient } i \text{ died at time } t_i\\ 0 \text{ if patient } i \text{ was alive (censored) at time } t_i.\end{cases}$

The parameters k and $\boldsymbol{\beta}$ were estimated by the method of maximum likelihood using an interative procedure based on a vector analog of the Newton–Raphson procedure.

In this analysis the age (in years) at diagnosis was entered as a continuous variable. All other variables were categorical, coded as follows: sex (1 = male, 0 = female), principal cell type (1 = medullary or follicular less-differentiated provided the associated pattern was not anaplastic, 0 = all other), anaplastic (1 = anaplastic principal or associated cell type, 0 = all other), T-category (1 = T3, 0 = all other), and metastatic sites (2 = more than one site, 1 = one site, 0 = no metastases). The values of the regression coefficients were −7.4015 (intercept $=\beta_0$), 0.045847 (age $=\beta_1$), 0.55865 (sex $=\beta_2$), 0.47858 (principal cell type $=\beta_3$), 2.0489 (anaplastic $=\beta_4$, 0.47704 (T-category $=\beta_5$) and 0.67901 (metastatic sites $=\beta_6$). The value of k, the Weibull shape parameter, was 0.80593 indicating a decreasing death rate with time. This value differs significantly from 1.0 ($P<0.0002$), implying that the death rate was not constant.

II. *Forming risk groups*

Risk groups of patients with similar prognosis were formed by determining values of λ such that given the fitted value of k, say $\hat{k}$ and the vector of estimated regression coefficients $\hat{\boldsymbol{\beta}}$, the survival predicted by the model at time t was $\geqq P$, solved for various specified values of P. Since λ_i includes the intercept parameter β_0 for all $i=1, 2, \ldots, n$, this value can be subtracted in finding the cut-points which define the risk groups. Specifically, let c_l be the lth cut-point, $l=1, 2, \ldots, g$-1, where g is the number of risk groups to be formed. Then

$$c_l=\ln[(-\ln p_l)/t^k]-\hat{\beta}_0 \quad (4)$$

and for patient i the quantity $\Sigma\beta_j X_{ij}$ for $j=1$ to m is compared with each of the c_l to determine risk group membership. Equation (4) follows from equation (2) where $p_l=S(t)$. In this analysis t was taken as 36 months and 5 risk groups were formed by choosing $p_1=0.9$, $p_2=0.8$, $p_3=0.6$ and $p_4=0.2$.

To obtain the integer scores given in Table 2 for the various prognostic factors, we divided each of the regression coefficients by the smallest and rounded the result to the nearest integer. To obtain the integer cut-points given in Table 3, we

divided the "true" cut-points obtained by equation (4) by the smallest regression coefficient and then rounded to the next higher integers, corresponding to the rule that patients were classified as belonging to the risk groups defined by total scores < the integer cut-points.

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