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Multivariate Analysis of Survival in Differentiated Thyroid Cancer: the Prognostic Significance of the Age Factor

LODEWIJK J.D.M. SCHELFHOUT,* CARIEN L. CREUTZBERG,* JACOB F. HAMMING,† GERT JAN FLEUREN,‡ DONALD SMEENK,* JO HERMANS,§ CORNELIS J.H. VAN DE VELDE† and BERNARD M. GOSLINGS*

*Departments of *Endocrinology, †Surgery, ‡Pathology and §Medical Statistics, University Hospital, PO Box 9600, 2300 RC Leiden, The Netherlands*

Abstract—*A retrospective analysis of tumour and patient characteristics was performed in 202 patients with papillary (n = 132) or follicular (n = 70) thyroid carcinoma, in order to identify prognostic factors related to survival. The following facts were found to be unfavourably related to survival: follicular histology, extrathyroidal growth of the primary tumour (stage pT4), regional lymph node involvement (stages pN1–3), presence of distant metastases at diagnosis (stage pM1), male sex (in papillary cancer) and old age (only death due to thyroid tumour was evaluated). For 190 patients sufficient material was available to permit extensive histopathological investigation. In patients with papillary cancer the presence of small anaplastic foci and/or > 25% solid structures (n = 18) was correlated with a reduced survival rate. Our study underlines the importance of distinguishing, histologically, between papillary and follicular cancer and in addition demonstrates the prognostic value of histological grade in papillary (but not follicular) carcinoma. We applied Cox's proportional hazard model to the survival data of these 190 patients and, after stage grouping, found that tumour stage (locoregional vs. advanced disease) was the most important prognostic factor. The second most important factor was the histological (sub)type (well differentiated papillary carcinoma vs. moderately differentiated papillary carcinoma and follicular carcinoma). Age at diagnosis and sex appeared to be of lesser importance. Therefore our study does not recommend the use of age as a guide for therapeutical decisions in differentiated thyroid cancer.*

INTRODUCTION

A number of factors have been described which are related to the survival of patients with papillary and follicular thyroid cancer. These include histological features, extent of the primary tumour, lymph node involvement, presence of distant metastases and patient-related factors such as age at diagnosis and sex [1–9]. However, there is a considerable disagreement about the relative importance of these factors. In particular age is considered by some authors to be far more important than other factors [7]. Tumour stage, age and histological (sub)type are interrelated, which obscures their relative influence on survival when analysed only univariately [4, 7, 10, 11]. Multivariate analysis is appropriate to determine the order of importance of several prognostic factors. Many studies have been made on thyroid cancer, in which prognostic factors were analysed separately, whereas only a limited number of multivariate studies have yet been published [11–22]. However, these multivariate studies also raise conflicting views, again mostly concerning the age factor. We performed a retrospective analysis of a consecutive series of 202 uniformly treated patients in order to establish the relative importance of several well-known prognostic factors and to examine how these factors should influence the choice of therapy.

MATERIALS AND METHODS

Between 1970 and 1983, 202 patients (female/male ratio 2; mean age 49 years, range 11–85 years) with papillary and follicular thyroid cancer were treated in the University Hospital, Leiden. Sixty-two per cent of these patients had been operated

Address for correspondence and reprints: Dr L.J.D.M. Schelfhout, Department of Endocrinology, University Hospital, Building 1 C4-R, PO Box 9600, 2300 RC Leiden, The Netherlands.

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upon initially in other medical centres and were referred to our hospital for further surgical or medical treatment and follow-up. The mean follow-up from diagnosis was 7.3 years (range 4–15 years). Thirty per cent of the patients could be followed for more than 10 years, permitting calculation of the patient survival rate over a period of up to 10 years. All patients were treated according to a standard protocol including total thyroidectomy (either primarily or as a secondary intervention), picking out the clinically involved regional lymph nodes at operation, ^{131}I administration and substitution with thyroid hormones in TSH suppressive doses. ^{131}I was given after surgery to ablate remnants of normal thyroid tissue (standard dose 75 mCi) and subsequently to treat persistent thyroid cancer in the neck and/or distant metastases (one or more standard doses of 150 mCi; mean total dose 350 mCi).

All slides were histopathologically reviewed without information concerning the clinical outcome. A distinction was made between papillary and follicular cancer according to the WHO classification [23]. Cases of medullary and anaplastic cancer and also patients with thyroid lymphomas were deliberately left out of the present study because of the different nature of these malignancies. In 190 patients the available histological material permitted a detailed investigation as to whether the grading of tumours could be correlated to survival rate. In 12 cases (6%) insufficient histological material was available. Histological grading was performed as follows: fields with a mild degree of atypia not suggesting anaplastic carcinoma were defined as solid structures; small foci composed of spindle or giant cells were described as anaplastic.

Tumour staging was performed according to the post-operative UICC-pTNM classification [24]. Most statistical calculations were performed using the SPSS-X program [25]. They included group comparisons for qualitative parameters using chi-square tests, and for quantitative parameters using Kruskal–Wallis tests, and also correlation studies. Actuarial Survival analyses were performed using the log-rank test. The survival interval was calculated from diagnosis to death related to thyroid cancer. A multivariate analysis was performed according Cox's proportional hazard model [26], using the SAS program.

RESULTS

Univariate analyses

In four cases (2%) the original histopathological diagnosis was revised from follicular carcinoma to papillary cancer and in two cases (1%) from papillary cancer to follicular carcinoma. Since these different histological diagnoses would not have entailed a different therapeutic approach our histopathological revision does not affect the present evaluation. The 10-year survival of all patients according to histological (sub)type, stage of the tumour, age at diagnosis and sex is shown in Table 1. In the group of patients with papillary cancer seven (5%) died of causes related to thyroid cancer as compared to 20 patients (23%) in the follicular group: whereas, respectively, 10 and six patients died due to intercurrent disease. The 10-year survival rate was significantly more favourable for patients with papillary cancer as compared to those with follicular cancer (94% vs. 67%; $P < 0.0001$). In patients with papillary cancer the presence of an admixture of small anaplastic foci and/or the presence of 25% solid structures (moderately differentiated papillary cancer; $n = 18$) could be related to reduced 10-year survival rate when compared to patients without these features (well differentiated papillary carcinoma; 78% vs. 98%; $P < 0.001$). In the group with follicular carcinoma these patterns did not seem to be related to survival rate (see Table 1). Therefore we evaluated both these histological subgroups together. Although the 10-year survival of patients with moderately differentiated papillary cancer was higher than of patients with follicular cancer (78% vs. 67%), this difference was not statistically significant. Extrathyroidal growth of the primary tumour (stage pT4) was found in 24% ($n = 17$) of the patients with follicular cancer and in 28% of the cases with papillary tumours ($n = 33$). This difference was not significant. In all patients with either papillary or follicular cancer, the presence of stage pT4 compared to the stages pT1–3 (intrathyroidal disease) was related to a significantly reduced 10-year survival.

In both papillary and follicular carcinoma, the presence of lymph node metastases was related to a reduced 10-year survival. However, in papillary cancer this was not the case if only stages pN1–2 were considered: 10-year survival in stages pN1–2 vs. stage pN3 respectively 95% and 79% ($P<0.001$).

The presence of initial distant metastases was correlated with a strongly reduced survival rate in both histological groups. In the group of papillary cancer patients 90% of all cases with initial distant metastases ($n = 9$) were to be found in the group of patients with extrathyroidal growth of the primary tumour (stage pT4) and/or fixed regional lymph node involvement (stage pN3). Taking this correlation into account we compared the advanced stage group, in which we placed stages pT4, pN3 and pM1, with the remaining patients exhibiting locoregional disease. In the patient group with follicular tumours the presence of initial distant metastases only correlated significantly with extrathyroidal primary tumour growth (stage pT4; $P < 0.01$) but not with lymph node involvement. Nonetheless, the 10-year survival of patients with follicular cancer

Table 1. Ten-year survival (only cancer-related death regarded) of 202 patients with differentiated thyroid cancer by histological (sub)type, stage of tumour, age at diagnosis and sex

	Papillary carcinoma						Follicular carcinoma				
			10-year survival		overall				10-year survival		overall
	*n**	%	*n*†	%	*P*-value		*n**	%	*n*†	%	*P*-value
Total	132		42	94			70		13	67	$P < 0.0001$
Histological type‡											
PWD§	105	85	51	98		FWD¶	37	55	11	70	
PMD‖	18	15	3	78	$P < 0.001$	FMD**	30	45	6	64	ns
Stage											
pT1–3	95	72	32	99			53	76	9	69	
pT4	37	28	10	83	$P < 0.001$		17	24	4	50	$P < 0.05$
pN0	81	61	29	98			66	94	11	69	
pN1–2	37	28	10	94	$P < 0.001$		4	6	1	25	$P < 0.01$
pN3	14	11	3	79			—	—	—	—	
pM0	122	92	36	97			47	67	10	96	
pM1	10	8	1	59	$P < 0.001$		23	33	3	20	$P < 0.001$
LRD††	87	66	30	100			41	59	8	97	
AD‡‡	45	34	12	74	$P < 0.001$		29	41	5	30	$P < 0.001$
Age											
< 40 years	46	35	13	100			15	21	2	67	
40–60	52	39	20	94	ns		21	30	5	56	$P < 0.05$
> 60	34	26	9	86			34	49	6	46	
Sex											
Male	38	29	8	81			23	33	6	63	
Female	94	71	34	100	$P < 0.005$		47	67	7	66	ns

*Number of patients entering the study.
†Actual number of patients with follow-up of at least 10 years.
‡Histological subclassification evaluated in 190 patients.
§PWD: Well differentiated papillary cancer.
‖PMD: Moderately differentiated papillary cancer.
¶FWD: Well differentiated follicular cancer.
**FMD: Moderately differentiated follicular cancer.
‡‡AD: advanced disease (stages pT4 and/or M3 and/or M1)
††LRD: locoregional disease (all other stages).
ns: non significant

presenting with regional lymph node metastases was as low as that of patients harbouring distant metastases at the time of diagnosis. In both papillary and follicular cancers, the 10-year survival of patients with advanced disease compared unfavourably to the survival of patients with locoregionally confined disease. The mean age of patients with papillary tumours was significantly lower than of patients with follicular cancer (46 years, range 11–79 years vs. 54 years, range 16–85 years; $P < 0.05$). In the follicular group increasing age was significantly correlated with a decreasing survival. In the papillary group only the difference in survival between the age-groups < 40 years of age and > 60 years of age was found to be significant (100% vs. 86%; $P < 0.05$). Only in the papillary carcinoma group was male sex correlated with a reduced survival.

Multivariate analysis

We applied Cox's proportional hazard model to those prognostic factors that were found to have a significant influence on survival on 190 patients in the aforementioned univariate analyses [histological (sub)type and stage of the tumour, sex (in papillary cancer) and age of the patient]. The histological subtype was tested as a variable with three classes i.e. well differentiated papillary cancer, moderately differentiated papillary cancer and follicular carcinoma. There were no apparent differences in the relevant clinical or histological characteristics between the patients included in this multivariate analysis and those who were left out. The factor age at diagnosis was introduced into the model as a continuous variable. The tumour stage factor was limited to two categories, namely locoregional disease and advanced disease. The resulting model is shown in Table 2. It shows that tumour stage (advanced disease vs. locoregional disease) has a primary prognostic importance. Histological (sub)-type (follicular and moderately differentiated papillary vs. well differentiated papillary cancer) both add prognostic value. The factors age and sex

Table 2. Factors affecting survival, expressed as the relative risk of dying from thyroid cancer as established by Cox's model in 190 patients with differentiated thyroid cancer

Factor	*P*-Value	Beta	SE (beta)	Relative risk
Advanced disease*	$P < 0.0001$	3.72	1.02	41.3
Follicular cancer†	$P < 0.005$	2.38	0.62	10.8
Moderately differentiated papillary cancer†	$P < 0.005$	2.23	0.78	9.3
Age	ns			
Sex	ns			

*Compared to locoregional disease.
†Compared to well differentiated papillary cancer.
ns:non significant.

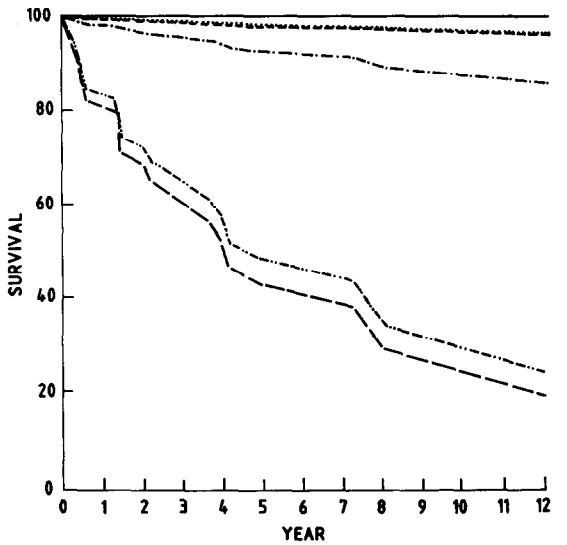

Fig. 1. Survival (%) of risk groups in differentiated thyroid cancer, as calculated by Cox's proportional hazard model. ——— Well differentiated papillary cancer/locoregional disease; ----- moderately differentiated papillary cancer/locoregional disease; ..... follicular cancer locoregional disease; —·—·— well differentiated papillary cancer/advanced disease; ·—·—·— moderately differentiated papillary cancer/advanced disease; — — follicular cancer— advanced disease.

did not contribute any more significantly to the prognosis. Based on these two relevant stage groups and the three histological groups, curves of six risk groups were constructed with Cox's model representing the estimated survival of hypothetical patients within these risk groups, assuming that at each moment the relative risk of dying from thyroid cancer between these groups remained constant. These model curves are shown in Fig. 1.

DISCUSSION

The question 'which therapeutic approach is optimal for patients with papillary and follicular thyroid cancer?' still remains unanswered. This is to a large extent related to the fact that differentiated thyroid cancer is a fairly rare malignant disease exhibiting a relatively indolent course. Therefore prospective randomized trials evaluating different treatment modalities are difficult to perform. However, useful information on prognostic factors as a basis for therapeutic decisions, can be obtained from retrospective studies, if appropriate statistical methods are applied. In most univariate studies the prognosis of patients with papillary cancer is found to be more favourable than of patients with follicular cancer [1, 2, 5, 7]. These findings are confirmed by our results, which again underline the clinical relevance of the histopathological distinction between these two entities. In contrast, Donohue *et al.* and also Beierwaltes *et al.* found that matching their patients on the basis of age and sex eliminated the differences in survival between papillary and follicular cancer [27, 28]. Also, Sakamoto *et al.* reported that the survival of patients with papillary and follicular cancer was similar after matching for histological grade, i.e. the presence of solid, trabecular and/or scirrhous patterns [29]. In these studies the influence of the histological (sub)type of the tumours on the patient survival was tested only univariately which precludes an insight in the interrelation between the factors age, stage and histological grade. But also in the multivariate study of Ladurner *et al.* there was a similarity in survival between patients with papillary and follicular tumours which was ascribed by these authors to the high proportion of distant metastases in patients with papillary carcinomas, i.e. 33% [16]. There are differences in opinion concerning the clinical usefulness of histological grading in papillary and follicular thyroid cancer [30, 31]. Some authors state that the presence of solid structures as a parameter of tumour grade, in papillary cancer, is not related to prognosis [1, 30, 31]. We found, however, that the presence of anaplastic foci and of more than 25% solid structures was correlated with a less favourable survival in patients with papillary carcinoma. Our results are in agreement with the findings of Sakamoto *et al.* as well as with Tscholl-Ducommun and Hedinger [4, 29]. On the other hand, in the WHO

Table 3. The effect of age at diagnosis on the relative risk of dying from differentiated thyroid cancer within 10 years after diagnosis

	Controls	Thyroid cancer	*rr* (cancer:controls)*
r (40 *years*)†	A‡	2A	2 (2.50§)
r (65 *years*)	9A	18A	2 (2.25§)
rr (65:40 years)¶	9 (9.6)**	9 (6.1)**	

**rr* (cancer:controls): relative risk of dying between patients with differentiated thyroid cancer compared to age-matched subjects from the normal population.
†*r* (40 years): risk of dying within 10 years after 40 years of age.
The risk of dying within 10 years after 40 years of age for subjects in the normal population is arbitrarily set to A.
§Actual data quoted from Ref. [20].
‖ *r*(65 years): risk of dying within 10 years after 65 years of age.
¶*rr* (65:40) = *r* (65 years)/*r* (40 years): relative risk of dying within 10 years after 65 years of age compared to the risk of dying within 10 years after 40 years of age.
**Actual data quoted from Ref. [19].

classification of 1974, follicular cancer is divided into well and moderately differentiated type according to the presence of trabecular and solid structures [23]. Only a few studies have correlated this subclassification with the patients' prognosis [1, 20, 32]. We found no relation between the presence of anaplastic and solid structures (generally considered as criteria for lesser differentiation) and the survival of patients with follicular cancer. A recent study of Lang *et al.* confirms this observation. Moreover, in the ongoing revision of the actual WHO classification, this subdivision will not be maintained (Chr Hedinger, personal communication). The study of Lang *et al.* reemphasizes the importance of the degree of invasiveness for the prognosis of patients with follicular cancer [32]. We have not investigated this factor. However, in our opinion the distinction between 'encapsulated' or 'minimally invasive' vs. 'invasive' seems more a characteristic of the stage of the primary follicular tumour than a subdivision of histological type. In the present study we concluded that the most important prognostic factor was the tumour stage. In agreement with our results, all other multivariate studies identified tumour stage, represented either by primary tumour extension, lymph node involvement or the presence of distant metastases, as one of the most important prognostic parameters [11–22]. However, the most striking result of our study was the unimportance of age at diagnosis. Some authors, who did not conduct a multivariate study, consider age at diagnosis as the single most important prognostic factor and therefore as the main guide for therapeutic decisions [7]. Differences between univariate and multivariate studies with regard to the age factor can be explained by the close relationship beween the factors age, histological grade and tumour stage [10, 11]. Also in some multivariate studies, age is found to be the primary significant prognostic factor for survival [12, 15, 18, 20, 22]. Most discrepancies between the results of various multivariate analyses can be explained by differences in patient selection, the variables included and the coding of the variables. This severely hampers the application of the results from one multivariate study to other populations. But even when different populations are (artificially) homologized and the same statistical method is applied (as has been done by Hannequin *et al.*) unresolved discrepancies between the results cannot be attributed to different biological behaviour of the tumour as long as the covariance matrices in these populations are not known and differences in treatment are not measured [14]. We agree with these authors that one should be cautious in trying to explain differences between multivariate studies. When examining the relative importance of the age factor in a low mortality disease such as differentiated thyroid cancer, the choice between the total death rate and the tumour related death rate is of utmost importance. In some studies the total death rate is taken as the end point [12, 16, 22]. This is justified for tumours with a high mortality rate but not for those cancers with a higher survival rate where death from causes unrelated to the cancer becomes increasingly probable. Therefore by taking the total death as the end point, one underestimates the importance of tumour related factors and overestimates the effect of age [12, 19]. Another aspect of the interpretation of the effect of age on survival is illustrated in Table 3 which we adapted from literature data [19, 20]. It presents a situation where the relative risk of dying for patients with

differentiated thyroid cancer is 2 for subjects of 40 years of age as well as for 65 years of age. The other way round, the relative risk of dying at 65 years of age compared to 40 years of age is 9 for controls as well as for thyroid cancer patients. So the factors thyroid cancer and age act here independently. Our chosen risk values correspond reasonably to actual data. We conclude from these data that the treatment of differentiated thyroid cancer in younger patients should not be less aggressive, as suggested by some authors [7]. Moreover, the findings of Beierwaltes and Leeper that distant metastases in young patients with differentiated thyroid cancer can be treated more effectively than in older patients supports the opposite, namely, to pursue a more radical treatment approach in younger age groups [28, 33].

In summary, we conclude from our retrospective multivariate study that the prognosis of patients with differentiated thyroid cancer can be estimated by the factors tumour stage and histological type alone. We found that age is not of major prognostic importance. In our opinion, this reduces the significance of this factor in the design of treatment protocols. We stress the need for more uniformity between future multivariate studies. Our findings also invite confirmation through prospective trials.

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