Clinically Significant Prognostic Factors for Differentiated Thyroid Carcinoma

A Population-Based, Nested Case–Control Study

Catharina Ihre Lundgren, M.D.[1,2]
Per Hall, M.D., Ph.D.[1]
Paul W. Dickman, Ph.D.[1]
Jan Zedenius, M.D., Ph.D.[2]

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

[2] Department of Surgery, Karolinska University Hospital, Stockholm, Sweden.

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Address for reprints: Catharina Ihre Lundgren, M.D., Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, E-17 S-171 77 Stockholm, Sweden; Fax: (011) 46-831 49 75; E-mail: cia.ihre-lundgren@ki.se

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BACKGROUND. Different scoring systems currently are being used to stratify patients with differentiated thyroid carcinoma (DTC) into risk groups. DTC is usually subdivided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). The objective of the current study was to identify those factors that predict long-term unfavorable prognosis and to evaluate the predictive accuracy of the TNM staging system.

METHODS. The authors conducted a nested case–control study within the cohort of all patients (n = 5123) diagnosed with DTC in Sweden between 1958–1987 who survived at least 1 year after diagnosis. One control, matched by age at diagnosis, gender, and calendar period, was randomly selected for each case (patients who died of DTC). All patients were classified at the time of diagnosis according to the TNM staging system. The effect of prognostic factors on DTC mortality was evaluated using conditional logistic regression.

RESULTS. Patients with widely invasive FTC experienced a significantly higher mortality compared with PTC patients. The grade of differentiation was found to influence mortality significantly. Patients with TNM Stage IV disease had a higher mortality rate compared with patients with Stage II disease (odds ratio [OR] = 9.1; 95% confidence interval [95% CI], 5.7–14.6). Patients with lymph node metastases experienced a higher mortality (OR = 2.5; 95% CI, 1.6–4.1) and patients with distant metastasis at the time of diagnosis were found to have a nearly 7-fold higher mortality rate (OR = 6.6; 95% CI, 4.1–10.5). Incomplete surgical excision was associated with higher mortality, particularly in patients with Stage I disease.

CONCLUSIONS. In the current study, the following were found to be clinically significant prognostic factors for patients with DTC: histopathologic subgroup, TNM staging including lymph node metastases and distant metastases, and completeness of the surgical excision. ***Cancer*** **2006;106:524–31.**

KEYWORDS: thyroid carcinoma, papillary, follicular, survival, prognosis, scoring system, nested case–control study.

The prognosis for patients with nonmedullary differentiated thyroid carcinoma (DTC) is known to be excellent, with a 10-year survival rate exceeding 90%.[1] DTC usually is subdivided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). FTC is generally considered to be the more aggressive subtype.

Different scoring systems have been created for prognosis stratification.[2–7] Some scoring systems only apply to PTC[3,4] and some to FTC,[8] whereas others include both entities.[2,5,7,9] The scoring systems enable the identification of an optimal therapy aimed at decreasing the risk of disease recurrence or death from DTC. Age at diagnosis,

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gender, extent and size of the primary tumor, and occurrence of distant metastasis are variables that are included in the majority of scoring systems (AGES [patient age, histologic grade of the tumor, tumor extent (extrathyroidal invasion or distant metastases), and size of the primary tumor],[3] MACIS [metastasis, patient age, completeness of surgical resection, local invasion, and tumor size (from the Mayo Clinic)],[4] AMES [patient age, presence of distant metastases, and extent and size of the primary tumor],[2] and the European Organization for Research and Treatment of Cancer [EORTC][7]). Local invasiveness, the presence of distant metastasis, and older age at the time of diagnosis convey a worse prognosis.

To our knowledge, few scoring systems include tumor differentiation,[5,10] and vascular invasion and Hurthle cell differentiation usually are not considered. To our knowledge, only MACIS takes completeness of the primary tumor resection into consideration.[4] The TNM system[5,6,11] is to our knowledge one of the few scoring systems that incorporates information regarding lymph node metastases. Patients with PTC are more often diagnosed with regional lymph node metastases, a clinical finding that is predictive of locoregional recurrence.[12]

Because of the low incidence of and favorable survival associated with DTC, large study populations are needed to adequately address the effect of treatment. Differences in methodology, the selection of patients, and the duration of follow-up, as well as low statistical precision due to few cases, makes comparisons between studies difficult and results difficult to interpret.

The objective of the current study was to identify clinically significant factors that are predictive of long-term unfavorable prognosis for patients diagnosed with DTC. The purpose was to examine how histopathologic features, TNM stage, and completeness of the surgical excision influence survival.

MATERIAL AND METHODS

Patient Material

The Swedish Cancer Registry (SCR) was established in 1958 and covers the entire population of Sweden (8.4 million inhabitants in 1987). All Swedish residents are assigned a unique national registration number that is used to index health registers. Reporting of incident tumors has been mandatory for clinicians and cytologists/pathologists since 1958. The proportion of all thyroid carcinomas reported to the SCR for the period up to 1978 was estimated to be 98%.[13] Coverage is now considered to be close to 100%.[14] Cases detected incidentally at autopsy were excluded from the current study. The SCR does not register tumors in cases in which the death certificate is the sole source of information. Between 1958–1987, 7906 thyroid carcinomas were reported to the registry. A total of 1405 patients (18%) with anaplastic and medullary thyroid carcinomas and 947 patients (12%) with follicular thyroid adenomas were excluded, leaving 5554 individuals who were diagnosed with DTC in the study. Among the 5123 patients who survived at least 1 year after diagnosis (of the 431 deaths occurring during the first years, 296 were due to DTC) matching with the Swedish Causes of Death register for the period 1959–1999 identified 693 patients with thyroid carcinoma as the underlying cause of death.

Information regarding histopathology, growth patterns, tumor differentiation, surgical procedures, and follow-up data was abstracted from the medical records for the 693 potential cases. A group of three specialists (a cardiologist, an oncologist, and an endocrine surgeon) independently evaluated the medical records to confirm DTC as the cause of death in cases in which this was not obvious to us. The cause of death was reclassified for 42 patients (6%) who died of cardiovascular disease ($n = 22$), other malignancies ($n = 11$), and thyroid carcinoma other than DTC ($n = 9$). We did not routinely confirm the cause of death for the patients classified as dying of causes other than thyroid carcinoma. Thirty-six potential cases were excluded because the medical records were not available to us, and 14 cases were excluded because they were diagnosed before the year of 1958, leaving a total of 601 cases. A nested case–control study with time since diagnosis as the timescale was generated by randomly sampling 1 control for each case, matched based on age at the time of diagnosis (5-year age groups), gender, and 10-year calendar periods of diagnosis. Each control had to survive the matching case. Among the initially selected controls, 26 of the medical records could not be located and 26 patients were found to never have had DTC. A second control therefore was randomly selected. A third control had to be randomly selected for an additional three cases because of missing medical records.

Six of the cases were age > 90 years at the time of diagnosis and were excluded because no matching control could be identified, leaving 595 sets of cases and controls in the current analysis.

Histopathology

Two specialists, both of whom were blinded with respect to the mortality outcome, independently classified tumor histopathology based on the histopathology reports. If the report lacked information regarding subgroup, the specimens were reexamined by one experienced pathologist. All tumors were classified as

well, intermediately, or poorly differentiated.[15] Mixed forms of differentiation were found in 5% of the cases and 4% of the controls and were assigned the lower grade. If the histopathology report contained information indicating lymphocyte infiltration, Hurthle cell differentiation, the presence of excessive connective tissue, and/or vascular invasion, these data were recorded in the protocol.

TNM Classification

The TNM classification for DTC, according to the World Health Organization (WHO) criteria,[11,15,16] is age dependent. Patients age < 45 years are considered to have a superior survival even if they are diagnosed with distant metastases.[11] Using information from medical records and the initial histopathology reports, we reclassified all patients according to the latest TNM staging system. Lymph node metastases were recorded and subclassified according to the surgical procedure performed (lymph node picking, unilateral or bilateral radical cervical lymph node dissection, or modified cervical lymph node dissection) and the histopathologic report. We classified metastases as either locoregional (in the head and neck region) or distant.

Completeness of Surgical Excision

The definition of complete surgical excision was based on information indicating complete removal of the entire primary tumor from the surgical and histopathologic reports, regardless of the presence of metastases. If unaffected thyroid tissue was removed, this was not taken into account. The TNM classification system does not take information regarding the completeness of surgery into consideration.

Statistical Analysis

Conditional logistic regression matched for patient age at the time of diagnosis, gender, and calendar period was used to estimate odds ratios (OR) of death from DTC, with 95% confidence intervals (95% CI). Effects were considered to be statistically significant when the 95% CI for the OR did not include 1. In the multivariate analysis, adjustments were made for histopathologic subgroups, grade of differentiation, completeness of surgical excision, and TNM stage when possible, depending on the outcome variable. When interactions were suspected from a clinical standpoint, the effects of such interactions were estimated.

RESULTS

The mean age at the time of diagnosis among the 595 sets of cases and controls was 63.8 years (range, 24–92 yrs). In total, 391 case–control sets were female and 204 sets were male, resulting in a female-to-male ratio of 1.9:1 compared with the ratio of 3:1 in the entire cohort of DTC patients during the study period.[1] The mean follow-up time (i.e., survival) for the cases was 6.7 years.

Histopathology

There was a 70% higher risk of dying from DTC for patients diagnosed with FTC compared with those patients diagnosed with PTC (Table 1). After adjusting for differentiation and TNM stage, this figure was reduced to 40% (Table 1). All but 2% of the cases and controls were subclassified into histopathologic subgroups according to WHO.[11,16] Using unspecified PTC as the reference (Table 1), widely invasive FTC (OR = 2.3; 95% CI, 1.7–3.3) and unspecified FTC (OR = 4.4; 95% CI, 2.7–7.4) were the only histopathologic subgroups found to have a significantly worse prognosis.

Patients with a reported excess of lymphocyte infiltration in the tumor had a significantly more favorable survival (OR = 0.4; 95% CI, 0.2–0.8) (Table 1). This effect remained after adjusting for TNM stage, histopathologic subgroup, and differentiation. Patients with certain thyroid disorders such as Graves disease might have more lymphocyte infiltration in the thyroid and therefore we adjusted for previously diagnosed thyroid disorders in the multivariate analysis; nevertheless, the effect remained the same (data not shown). When the histopathologist reported vascular invasion in the tumor, the risk of death due to DTC was found to increase significantly (OR = 1.7; 95% CI, 1.2–2.8).

Differentiation was found to be a strong determinant of prognosis (Table 1). Patients with poorly differentiated tumors experienced a mortality rate that was nearly three times higher than that of patients with well differentiated tumors, a finding that did not appear to be influenced by adjustment for other tumor characteristics.

TNM Classification

As expected, we observed a strong association between TNM stage and DTC mortality (Table 2). Patients classified as having Stage I disease experienced a mortality rate of only 40% compared with patients classified as having Stage II disease (OR = 0.4; 95% CI, 0.2–0.8), whereas patients classified as having Stage IV disease were estimated to be 9.1 times more likely to die of DTC compared with patients with Stage II disease. Based on an interaction term in the model, there was no evidence that the effect of stage of disease was modified based on whether the tumor was FTC or PTC.

A patient age$>$ 45 years with Stage II disease was considered to have a tumor measuring 2–4 cm with-

TABLE 1
Histopathologic Characteristics of PTC and FTC, Showing Univariate and Multivariate ORs of Dying from Thyroid Carcinoma, with 95% CIs

	Cases		Controls		Univariate analysis[a]		Multivariate analysis[b]	
Histopathologic characteristics	No.	%	No.	%	OR	95% CI	OR	95% CI
FTC, all[c]	281	47	202	34	1.7	1.4–2.2	1.4	1.1–1.9
PTC, all[c]	303	51	384	65	1.0	Reference	1.0	Reference
FTC, unspecified	81	14	25	4	4.4	2.7–7.4	4.5	2.4–8.3
FTC, minimally invasive	51	9	91	16	0.7	0.5–1.1	0.7	0.4–1.1
FTC, widely invasive	149	25	86	15	2.3	1.7–3.3	1.7	1.2–2.6
PTC, unspecified	233	40	308	53	1.0	Reference	1.0	Reference
Papillary carcinoma of follicular type	61	10	60	10	1.3	0.9–2.0	0.7	0.3–2.1
PTC and FTC	9	2	16	3	1.0	0.4–2.4	—	
Well differentiated[d]	237	44	276	57	1.0	Reference	1.0	Reference
Intermediately differentiated	177	32	162	34	1.2	0.9–1.6	1.2	0.9–1.6
Poorly differentiated	124	23	42	9	2.7	1.8–4.0	2.7	1.8–3.9
Lymphocyte infiltration[e]	17	3	38	6	0.4	0.2–0.8	0.3	0.2–0.8
Hurthle cells differentiation[e]	54	9	35	6	1.5	0.9–2.4	1.1	0.6–2.0
Connective tissue[e]	86	14	73	12	1.2	0.8–1.7	1.5	0.9–2.3
Vascular invasion[e]	139	23	88	14	1.7	1.2–2.8	1.2	0.5–2.6

PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; OR: odds ratio; 95% CI: 95% confidence interval.

Percentages were calculated from the total number of cases and controls, including those with incomplete information.

[a] Adjusted for the matching variables (age, gender, and calendar period).

[b] Adjusted for the matching variables (age, gender, and calendar period), histopathologic subgroups (follicular thyroid carcinoma and papillary thyroid carcinoma), and grade of differentiation.

[c] A total of 20 patients lacked information regarding histopathology.

[d] A total of 90 patients lacked information regarding tumor differentiation.

[e] A total of 321 patients lacked detailed information regarding histopathology. Each group was compared independently with the remaining three groups (reference 1.0) by separate analysis.

TABLE 2
TNM Classification of Patients with Differentiated Thyroid Carcinoma, Demonstrating Univariate and Multivariate ORs of Dying from Thyroid Carcinoma, with 95% CIs in Relation to TNM Stage

	Total		Controls		Cases		Univariate analysis[b]		Multivariate analysis[c]	
TNM Stage[a]	No.	%	< 45	≥ 45	< 45	≥ 45	OR	95% CI	OR	95% CI
I	110	9	27	51	27	5	0.4	0.2–0.8	0.3	0.1–0.8
II	319	28	12	206	12	89	1.0	Reference	1.0	Reference
III	519	45	NA	231	NA	288	3.5	2.4–4.9	3.3	2.1–5.1
IIIA (T3 and N0)	279	24	NA	128	NA	151	3.4	2.3–5.0	2.9	1.7–4.6
IIIB (any T and N+0)	240	21	NA	103	NA	137	3.6	2.4–5.6	3.8	2.3–6.5
IV	209	18	NA	48	NA	161	9.1	5.7–14.6	6.0	3.3–10.9

OR: odds ratio; 95% CI: 95% confidence interval; NA: not applicable.

Percentages were calculated from the total number of cases and controls, including those with incomplete information.

[a] A total of 33 patients lacked information regarding TNM stage and were excluded from the analysis.

[b] Adjusted for the matching variables (age, gender, and calendar period).

[c] Adjusted for the matching variables (age, gender, and calendar period), histopathologic subgroups (follicular thyroid carcinoma and papillary thyroid carcinoma), tumor differentiation, and completeness of surgery.

out distant metastases, whereas a patient age < 45 years with a Stage II tumor indicated distant metastasis. We compared the survival of Stage II patients for the two age groups and were unable to identify any significant difference in survival.

TNM Stage III disease is comprised of two clinically distinct subgroups; a patient is diagnosed with either lymph node metastasis and any tumor size (Nx, any T) or with a large tumor (≥ 4 cm) without lymph node metastasis. We were unable to identify any significant difference in prognosis between the two subgroups of patients with Stage III disease (Table 2). Adjustment for histopathologic subgroups or tumor differentiation did not appear to influence this comparison.

TABLE 3
Occurrence of Lymph Node and Distant Metastases in Patients with Differentiated Thyroid Carcinoma, Demonstrating Univariate and Multivariate ORs of Dying from Thyroid Carcinoma with 95% CIs

	Cases		Controls		Univariate analysis[a]		Multivariate analysis[b]		Multivariate analysis[c]	
Metastases	Total	%	Total	%	OR	95% CI	OR	95% CI	OR	95 % CI
Lymph node metastases[d]	196	33	127	21	2.5	1.6–4.1	3.2	1.7–6.0	1.9	1.1–3.6
No lymph node metastases[d]	116	19	179	30	1.0	Reference	1.0	Reference	1.0	Reference
Initial distant metastases[e]	146	25	29	5	6.6	4.1–10.5	5.0	2.9–8.5	2.9	1.2–7.4
No initial distant metastases	427	72	547	92	1.0	Reference	1.0	Reference	1.0	Reference
Late distant metastases[f]	394	66	93	16	15.3	9.8–24.0	14.8	8.5–25.6	14.7	9.0–24.0
No late distant metastases	122	21	456	77	1.0	Reference	1.0	Reference	1.0	Reference

OR: odds ratio; 95% CI: 95% confidence interval.

The percentages were calculated from the total number of cases and controls, including those with incomplete information.

[a] Adjusted for matching variables (age, gender, and calendar period).

[b] Adjusted for histopathologic subgroup (follicular thyroid carcinoma and papillary thyroid carcinoma) and tumor differentiation.

[c] Adjusted for TNM stage.

[d] Included only those patients in whom lymph node surgery was performed; 572 patients lacked information regarding lymph node status or surgery.

[e] A total of 41 patients lacked information regarding distant metastases at the time of diagnosis.

[f] A total of 125 patients lacked information regarding late distant metastases (i.e., > 3 months after diagnosis and no initial distant metastases were detected in the same location).

Metastases

Of the 52% of patients who underwent some form of lymph node resection, locoregional spread of the disease was detected in 27% at the time of initial treatment. Approximately 36% of PTC patients were found to have locoregional spread compared with 16% of the FTC patients. Patients with locoregional spread were more likely to die of DTC (Table 3). The number of lymph node metastases did not appear to influence survival. The effect of local lymph node metastases at the time of diagnosis on mortality from DTC was found to decrease after adjusting for TNM stage but remained statistically significant (OR = 1.9; 95% CI, 1.1–3.6) (Table 3).

Patients age > 45 years with distant metastases were classified as having Stage IV disease (Table 2). At the time of diagnosis, 25% of the cases and 5% of the controls had distant metastases (Table 3). The risk of dying of DTC was found to be 6.6 times higher for patients with distant metastases. Approximately 45% of the distant metastases were diagnosed in the skeleton (n = 95), 80% of which were from FTC. The second most common localization of distant metastases was the lungs (34% [n = 73]), with 60% being FTC metastases. The current study contained too few patients to adequately examine the association between the site of distant metastases and DTC mortality.

A total of 66% of cases (n = 394 cases) were diagnosed with late metastases compared with 16% of the controls (n = 93 controls) (OR = 15.3; 95% CI, 9.8–24.0) (Table 3). Lung metastases (57%) comprised the majority of late metastases and were evenly distributed between PTC and FTC patients. The second most common location for late metastases was the skeleton (26%); this finding was noted predominately in patients with FTC.

Completeness of Surgical Excision

Complete surgical excision was recorded in both the surgical and histopathologic report for 48% of the patients who underwent surgery. The sensitivity of surgeons to predict whether the excision was complete based on the histopathologic report was 91% and the specificity (i.e., the ability of the surgeon to predict an incomplete procedure) was 75%. Approximately 49% of the cases were considered to have undergone a complete surgical excision compared with 77% of the controls (Table 4). The association between the completeness of surgery and mortality was consistent with the basis for classifying the completeness of surgery (surgical or histopathologic reports). Therefore, we decided to report findings based on the surgical reports. The proportion of patients in whom surgical resection was considered complete varied based on the TNM stage and between cases and controls (Table 4). The mortality from DTC was found to be significantly increased when incomplete tumor removal was performed (OR = 4.2; 95% CI, 3.1–5.6; data not shown). The completeness of surgery modified the prognostic effect of TNM stage (Table 4). The effect of complete tumor removal was most obvious in patients with TNM Stage I disease, in whom tumors often are smaller. Many patients with Stage IV disease will have distant metastases at the time of diagnosis and will

TABLE 4
Total Number of Patients who Underwent Surgery and the Number of Patients who Underwent Surgery with CSE, Demonstrating ORs of Dying from Thyroid Carcinoma in Relation to TNM Classification and Performance of CSE, with 95% CIs

TNM stage	Cases			Controls			OR[b]	95% CI
	Total[a]	CSE	%	Total[a]	CSE	%		
I	32	18	56	78	72	92	7.9	2.0–31.0
II	91	66	73	212	182	86	2.9	1.5–5.7
III	267	117	44	223	150	67	3.6	2.3–5.7
IV	118	48	41	35	19	54	1.5	0.7–3.3
All stages	508	249	49	548	423	77		

CSE: complete surgical excision; OR: odds ratio; 95% CI: 95% confidence interval.

The percentages show the proportion of patients treated with complete surgical excision within each TNM group.

[a] Included only those patients for whom information regarding TNM classification and complete surgical excision was available; complete information was missing for 87 cases and 47 controls.

[b] Effect of not undergoing complete surgical excision within each TNM classification (estimated by interaction model).

experience high mortality regardless of whether the primary tumor is excised completely.

DISCUSSION

We found that patients diagnosed with an FTC are more likely to die of their disease than those diagnosed with a PTC. Widely invasive and unspecified FTC confers the least favorable prognosis. FTC tumors have a lower tumor differentiation and are more likely to be of higher TNM stage but these discrepancies do not explain completely the difference in prognosis. Conversely, tumors with signs of lymphocyte infiltration are associated with a better patient prognosis than tumors without this feature. As expected, high tumor differentiation was associated with a good prognosis whereas incomplete surgical excision was found to be associated with poor survival. Metastases at the time of initial diagnosis, regardless of whether they were locoregional or distant, were found to be a marker of worse prognosis. We found no reason to challenge the prognostic value of the latest TNM classification.

Ideally, the effects of treatment should not be evaluated based on observational data. The choice of treatment modality is, to some extent, guided by information we were unable to quantify, thereby hampering the interpretation of our findings. A radical cervical lymph node dissection could have been performed if the surgeon had suspected lymph node metastases and therefore the likelihood of identifying lymph node metastases would increase. Although a randomized trial would minimize such problems, the low incidence and low mortality rate of the disease makes such a trial difficult to conduct in clinical practice. Due to the scarcity of empiric data in this area, we believed an observational study was justified.

The strengths of the current population-based, nested case–control study were the well defined cohort, the comparably long duration of follow-up, and the uniform approach to data retrieval. Virtually all data for both cases and controls (including histopathology reports, clinical variables, and reports of the accuracy of the cause of death) were retrieved. Therefore, we were able to control for the majority of the factors that influence prognosis. Information was gathered from case records, treatment charts, and histopathologic reports in a blinded fashion, thereby making the differential misclassification of exposure unlikely.

We chose to match cases and controls based on gender because the objective of the current study was to identify clinical variables that would provide prognostic information. Females with DTC have a better survival compared with men, as reflected by an overall female-to-male incidence ratio of 3:1[1] compared with the mortality ratio of 1.9:1. Whether this seemingly protective phenomenon of being a female patient with DTC is secondary to beneficial effects of the female sex hormone awaits further study using other approaches.

A potential weakness of the current study is the incomplete information concerning histopathology for some patients. The quality of the histopathologic reports varied greatly during the study period and between different hospitals, which of course could influence our results. However, there is no reason to believe that possible misclassifications would not be distributed evenly among cases and controls. If anything, a nondifferential misclassification would bias our results toward the null. During this study period, the criteria for FTC have changed. Using currently criteria, some of the FTC cases would be classified as atypical follicular adenomas and not as carcinomas.[16] Therefore, all histopathology reports were reevaluated by a specialist blinded to outcome. If the diagnosis of

a DTC was not convincing, the case or control was excluded from the study.

The different subclasses of DTC were found to be of prognostic significance; compared with patients with PTC, patients with widely invasive FTC were found to have a 2.3-times higher risk of death from DTC and a risk of death from unspecified FTC that was 4.4 times higher, a risk that remained after adjusting for tumor grade (Table 1). Patients with well or intermediately differentiated tumors were found to have a significantly better survival compared with patients with poorly differentiated tumors. Therefore, a distinction between histologic subgroup and tumor differentiation grade most likely should be taken into account in a refined scoring system.

It is noteworthy that no difference in survival was observed among patients diagnosed with Hurthle cell differentiation and additive connective tissue in the tumors. Vascular invasion was found to be associated with higher DTC mortality. Lymphocyte infiltration of the tumor appeared to be associated with a lower mortality rate, a finding that merits further investigation (Table 1).

The TNM staging system in its simplicity is a useful scoring system. The TNM classification of DTC is based on the assessment of three components: the extent of the primary tumor (T), the presence of regional lymph node metastases (N), and the identification of distant metastasis (M). The TNM staging system also takes age into consideration because it is believed that a less favorable prognosis is confined to patients age $\geq$ 45 years at the time of diagnosis. Distant metastases do not appear to have the same detrimental effect in younger patients. Other scoring systems such as MACIS,[4] AGES,[3] AMES,[2] and EORTC[2–4,7] also take age at diagnosis, tumor size, extension of the tumor, and distant metastases into consideration. However, lymph node status is not considered because the majority of investigators advocate that locoregional spread of the disease does not influence prognosis. The AGES and MACIS scoring systems were validated only for PTC. The AGES system includes histology grading, EORTC includes histology (all thyroid carcinomas), and MACIS includes the completeness of surgical resection of the primary tumor. To our knowledge, none of the scoring systems takes all factors and both PTC and FTC into consideration.

To our knowledge, only a few studies to date[5,8,17] have identified regional lymph node status as a predictor of a higher disease recurrence rate, in contrast to other findings.[2,4,7] However, the impact on survival as such usually is not considered. The results of the current study demonstrated that patients with lymph node metastases have an increased risk of death from DTC, even after adjusting for TNM stage (Table 3). Although it appears logical to assume that the actual number of lymph node metastases would influence survival, we can only state that the identification of lymph node metastases per se was decisive in the current study. When patients with Stage III disease were separated into two subgroups (Table 2), we did not observe any significant difference with regard to survival. Therefore, the effect of lymph node metastasis would be considered as significant for the patient survival as a large tumor (T $>$ 4 cm) (Table 1). Distant metastases at the time of diagnosis and during the follow-up period still appears to be the most important prognostic factor for older patients with DTC (Table 4).

Data from the current study suggest that complete surgical resection of the tumor is a significant prognostic factor. Incomplete surgical removal of the primary tumor was associated with a significantly higher mortality from DTC. This was evident even in the presence of distant metastasis. Another surprising fact was the large number of patients who were found to have undergone an incomplete surgical excision (Table 4). This is even more intriguing when considering TNM Stage I and Stage II disease, in which the majority of tumors are small and should be easily removed entirely. Therefore, this is due not only to the extent of the tumor, which also is reflected by the results of the multivariate analysis and the use of interaction models (Table 4). In fact, greater than half the cases did not have their tumor radically removed initially, but even more surprising is that approximately 25% of the controls had not undergone a complete surgical excision either. This finding most likely reflects a significant variation in the quality of the surgery between the treating centers and geographic areas. Although many patients survived despite the incomplete surgical procedure, it appears that one of the most significant prognostic factors remains removal of the primary tumor.

The TNM classification system accurately defines subclasses of patients with a less favorable prognosis who are in need of more aggressive therapy. The use of information regarding patient age, tumor size, and metastasis enables the identification of patients who are approximately 15 times more likely to die of their disease. In addition, the TNM system is straightforward, accepted internationally, and easy to understand. The current study data indicate that the system could be expanded by taking postsurgical findings into consideration. Adding information concerning histopathologic subgroups, tumor differentiation, and completeness of surgical excision will better stratify patients according to prognosis.

We believe the results of the current study strongly demonstrate that the TNM classification system robustly determines the prognosis of patients with thyroid carcinoma. Including postsurgical information such as tumor differentiation, histopathology, and completeness of surgery appeared to add to the predictive value of the classifier. There might be other prognostic factors that could increase the quality of a classifier further, but the inherent problems of conducting a randomized trial for evaluating thyroid carcinoma therapy limit the likelihood of identifying additional factors.

In conclusion, the results of the current study demonstrate that postsurgical findings appear to add to the predictive value of the TNM system and complete excision of the tumor decreases the risk of disease recurrence and death from thyroid carcinoma.

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