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ARTICLE

Markov Model-based Estimation of Individual Survival Probability for Medullary Thyroid Cancer Patients*

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The relatively benign, but occasionally rapidly fatal clinical course of medullary thyroid cancer (MTC) has raised the need for individual survival probability estimation. A retrospective study on 91 MTC clinical case histories with a mean follow-up of 6 years indicated prevalences of local, regional and distant residual tumor on primary care completion of 23%, 54% and 54%, respectively. Local, regional and distant relapses during follow-up occurred in 8%, 23% and 26% of the patients, with a cause-specific death in 26% of the cases. Prognostic factors statistically significantly influencing the cause-specific survival were selected by uni- and multivariate analysis. A Markov method-based model was developed for the estimation of individual time-dependent local, regional and distant relapse-free and cause-specific survival probability functions, with parameters numerically determined via a maximum likelihood procedure. These parameters include relative risk factors related to prognosticators, a residual or recurrent local/regional/distant tumor, and combinations of these entities. In multivariate studies, the patient's age and gender, the genetic basis of the disease, lymph node involvement, the existence of a general symptom (diarrhoea) at presentation, and the dosage of external irradiation proved to be prognosticators. The cause-specific survival function of the study population indicated mean 5, 10 and 15-year survival probabilities of 69%, 62% and 58%. Conclusion: Survival probabilities can be predicted for extrastudy cases provided that the same laws and principles govern the clinical course of these cases and those comprising the study. For individual survival probability estimation, a Pascal program (MEDUPRED) was written and is available on the home page of the National Institute of Oncology, Budapest (www.oncol.hu). (Pathology Oncology Research Vol 8, No 2, 93–104, 2002)

Keywords: medullary thyroid carcinoma; prognosis; multivariate analysis; Markov model; individual survival probability; MEDUPRED

Introduction

Medullary thyroid cancer (MTC) is a rare, malignant neuroendocrine tumor originating from the parafollicular C-cells of the thyroid gland. The clinical course may be capricious: it is generally relatively benign, but it may occasionally have a rapidly fatal outcome. These contradictory facts justify the need for individual survival probability estimation, to tailor the therapy in each given clinical case in the awareness of the probable outcome of the different therapeutic decisions. The purpose of this retrospective study was to compile a database for detailed statistical studies and subsequent survival analysis.

Patients and Methods

Patients and therapy

All charts of histologically proven MTC patients were taken from the archived files (1960-1999) at the National Institute of Oncology (NIO) in Budapest. The present study involved 91 Hungarian MTC cases, 1 Afghan

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patient being excluded. All pathological investigations were reviewed for the purpose of this study, and MTC was proved by conventional staining and immunophenotyping.

The variables and their classes for grouping for survival estimation are presented in *Table 1.* Besides age and gender, the inheritance form was determined on clinical grounds, the principles of the International RET Mutation Consortium[14] being taken into account, as the results of genetic screening[26] were not available at the time of the study. For retrospective cancer staging, the UICC definition of the TNM/pTNM system was applied.[40] Locations of distant metastases and the occurrence or not of diarrhoea were also coded.

The different therapeutic measures were classified according to extent or adequacy. Thyroid surgical interventions were defined in terms of extent. The surgical procedures on lymph nodes (LNs) were coded separately in the four (central, right and left lateral, and upper mediastinal) compartments according to their extent. Only the dose was considered a group-forming variable for external irradiation. Cervical irradiation was taken as adequate when the tumor bed and bilateral parajugular LNs were treated with a tumor dose of 50 Gy or more, with a boost of 10 Gy to the proved residual disease.[21] The same dose was classified as adequate for the upper mediastinum if its irradiation was indicated for proved mediastinal LN metastases or advanced primary tumors (pT4). For coding of the adequacy or inadequacy of radiotherapy, the neck and mediastinum were considered together; inadequacy of either of the respective doses therefore entailed classification of the external irradiation dose as inadequate. Patients in whom

Table 1. **Variables and their classes for grouping used for survival estimation**

Variables	*Classes for grouping*
Patient characteristics at primary treatment	
Age (years)	≤19; 20-39; 40-59; 60≤
Gender	male; female
Tumor characteristics at primary treatment	
Genetics on clinical grounds	MEN2a; FMTC; sporadic (including 1 case of *de novo* MEN2b); undetermined
T / pT	1; 2; 3; 4; X
N / pN	0; 1a; 1b; X
M	0; 1
Location of distant metastasis	liver; lung; bone; multiple
Diarrhoea	none; yes
Characteristics of primary treatment	
Extent of thyroid surgery	bilateral total; bilateral subtotal; unilateral; biopsy
Extent of central lymph node surgery	systematic; node picking; none
Extent of right lymph node surgery	radical; modified; node picking; biopsy; none
Extent of left lymph node surgery	radical; modified; node picking; biopsy; none
Extent of mediastinal lymph node surgery	systematic; node picking; biopsy; none
External irradiation dosage	none for a pT1-2 and pN0-X case; adequate dose; insufficient dose; none for a pT3-4 and pN1a-b case
MIBG treatment	yes; none
Chemotherapy	yes; none
Local/regional/distant response to primary treatment	complete remission; partial remission + stable disease; progression; missing
Outcome variables	
Residual local / regional / distant tumor	none; yes; missing
Local / regional / distant relapse	none; yes
Time-related variables (not ranked on groups)	
Date of – primary surgical intervention – first local relapse – first regional relapse – first distant relapse – recent follow-up information	
Latest status of the patient	alive; intercurrent death; cause-specific death

Table 2. **Characteristics of variables at the primary treatment (no. of patients = 91)**

Variables	*No. of patients*	*(%)*	*Variables*	*No. of patients*	*(%)*
Age group (years)			*Type of thyroid surgery*		
≤19	3	(3)	Bilateral total	16	(18)
20-39	21	(23)	Bilateral subtotal	49	(54)
40-59	44	(48)	Unilateral	12	(13)
≥60	23	(25)	None/biopsy only	14	(15)
Gender			*Type of central cervical lymph node dissection*		
Female	50	(55)	Systematic	3	(3)
Male	41	(45)	Node picking	20	(22)
Genetics on clinical grounds			None	68	(75)
MEN2a	24	(26)	*Type of right cervical lymph node dissection*		
FMTC	10	(11)	Radical	5	(5)
Sporadic (including 1 sporadic MEN2b)	28	(31)	Modified	16	(18)
Undetermined	29	(32)	Node picking	7	(8)
Pathological T (pT)			Biopsy	1	(1)
pT1	7	(8)	None	62	(68)
pT2	32	(35)	*Type of left cervical lymph node dissection*		
pT3	24	(26)	Radical	4	(5)
pT4	22	(24)	Modified	13	(14)
pTX	6	(7)	Node picking	9	(10)
Pathological N (pN)			Biopsy	1	(1)
pN0	13	(14)	None	64	(70)
pN1a	18	(20)	*Type of mediastinal lymph node dissection*		
pN1b	18	(20)	None	91	(100)
Data not available	42	(46)	*Dosage of external radiotherapy*		
Distant metastasis at presentation (M)			Not performed (in pT1-2, pN0-X cases)	15	(16)
M0	42	(46)	With adequate dose	14	(16)
M1	49	(54)	With insufficient dose	44	(48)
Location of distant metastases			Not performed (in pT3-4, pN1a-b cases)	18	(20)
Liver	35	(38)	*MIBG therapy*		
Lung	1	(1)	Performed	22	(24)
Bone	1	(1)	Not performed	69	(76)
Multiple	12	(13)	*Chemotherapy*		
Diarrhoea at presentation			Performed	8	(9)
No	70	(77)	Not performed	83	(91)
Yes	21	(23)			

Remark: because of rounding, not all percentages total 100.

external radiotherapy was not performed were subdivided into two categories: patients with a low or a high risk of local/regional relapse (pT1-2/pNX-0 and pT3-4/pN1a-b, respectively). *Meta*-iodobenzylguanidine (MIBG) radionuclide treatment and chemotherapy were classified by performance (yes or no).

The results of primary treatment were assessed separately for local/regional/distant sites. Complete remission (CR) meant a complete disappearance of the tumor; partial remission and stable disease were grouped together; and progression was handled separately. The clinical state following primary treatment was characterized by the presence or absence of post-therapeutic residual local/regional/distant tumor and these were coded separately. The different states can be described by a different set of values of these 3 outcome variables (residual local/regional/distant tumors) with allowed values of no or yes. The states following the appearance of the first local/regional and distant recurrences were regarded as basically different from those just before the appropriate clinical event. The presence or absence of these

baseline clinical features are described by 3 additional outcome variables, again with no or yes as possible values. The relapses were defined only for those patients who achieved CR from the point of view of the corresponding type of clinical state (local/regional/distant tumor) following primary care. It was anticipated that the probability of any process may depend on the values of these 6 outcome parameters (residual tumors and local relapses). Accordingly, during the construction of the model, the outcome variables were considered to have a substantial impact on the clinical course of the disease.

The extent of the tumorous disease was established by regular (6-month intervals) follow-up examinations, including calcitonin determinations, whole-body MIBG scintigraphy (68 patients), CT (66 patients) and MRI (54 patients) examinations of the neck, chest and upper abdomen, whole-body [^{18}F]deoxyglucose (FDG) PET (52 patients), and liver angiography (46 patients). Additional imaging methods were indicated when necessary.

Table 3. **Follow-up data (n=91)**

Clinical event	*No. of patients (%)*		*Elapsed time (years)*		
			Mean	*Median*	*Range*
Residual diseases					
– Local	21	(23)			
– Regional	49	(54)			
– Distant metastasis	49	(54)			
Recurrences					
– Local	7	(8)	3.5	3.0	1-8
– Regional	21	(23)	6.0	5.5	1-29
– Distant	24	(26)	5.0	4.5	1-29
Current status			6.0	5.5	0-30
– Alive	58	(64)			
– Intercurrent death	9	(10)			
– Cause-specific death	24	(26)			
Prevalence of metastases during the whole (6-year) follow-up					
– Lymph node	71	(78)			
– Liver	63	(69)			
– Lung	23	(25)			
– Bone	14	(15)			
– Brain	3	(3)			
– Others	6	(7)			

The first local/regional/distant relapses were confirmed by increased plasma tumor marker (calcitonin) levels and/or pathology/cytology/diagnostic imaging. It should be noted that an increase in the plasma calcitonin level is an extremely sensitive indicator of the appearance of tumorous tissue in this disease. Detection of an increase in the tumor marker level during the investigations was followed by successive diagnostic imaging examinations until the tumor mass was consistent with the plasma calcitonin level.

No patient was lost to follow-up. The cause of death was specified as MTC-related or non-MTC-related, as established by extensive inquiries from the family physicians and hospitals, with the help of death certificates and autopsy reports when available.

Statistics

The basic assumption in the biostatistical modelling was that the general mechanism of the clinical course of the disease is standard and influenced by the same biological processes. Four different, time-dependent survival probabilities were calculated and used in the model: the probabilities of local, regional and distant relapse-free survival, and the probability of cause-specific survival. Uni- and multivariate statistical procedures performed with the BMDP software package, the Kaplan-Meier method and the Cox regression model[6,9,25] identified the prognostic factors for the four survival probabilities. Missing values were handled as if they had a real content and comprised additional subgroups of the variables. A Markov renewal model[1,10,15,31] allowed a more precise estimation of the clinical course. The basic idea of Markov processes is that the probabilities of occurrence of future events are determined in part by the current clinical state, i.e. the outcome variables (residual local, regional and distant tumor on the completion of primary care; and the first local, regional or distant relapse).

It was anticipated that the defined four survival probabilities decay exponentially in time, the exponent depending on the clinical state. This time course is a direct consequence of the presumption of clinical state-dependent constant probabilities which determine the occurrence of the clinical state-altering events (the development of local/regional/distant relapses). Another consequence of this presumption is that these clinical events (whenever one of the outcome variables changes in value) modify the current values of the exponents of all survival probabilities. Thus, survival probabilities are merely transient, valid only between two successive clinical events. To simplify analysis of the relationships of the different outcome variables, the same relative risk factor (a clinical state-dependent constant in the formula describing the exponent in the survival probability functions) was assigned to residual tumor and relapse of the same kind (e.g. residual regional tumor and regional relapse). The time of the first surgical intervention was taken as zero time for cause-specific survival probability estimation; the closing day was the date of cause-specif-

ic death or censoration (intercurrent death or the latest information during follow-up).

Risk factors related to the significant prognosis-influencing predictors selected from multivariate studies, and others related to the basic clinical events (changing the transient survival probabilities as estimated by the Markov method), were applied to calculate the individual survival probability functions for each patient. Averaging of the calculated curves resulted in a mean cause-specific survival function characterizing the investigated population as a whole. Via the Markov model, prediction of the cause-specific survival probability is possible for extrastudy cases if it is assumed that the same laws and principles govern the clinical courses of these cases and those comprising the study. For this purpose, a Pascal program "MEDUPRED" was written and is available on the home page of the NIO, Budapest (www.oncol.hu)[42].

Results

The patients were typically middle-aged (mean age: 47 years, range: 16-76), with a female to male ratio of 1.2:1 and a frequent (38%) genetic background due to systematic screening of the families (*Table 2*). The primary tumor size and extent (T/pT) exhibited a symmetrical and unimodal distribution. The cervical LN status was assessed

Table 4. **Variables with significant effects on the four (local, regional and distant relapse-free and cause-specific) survival probabilities using univariate analysis.**

Variables	*Kaplan-Meier*			*Favourable class****	*Cox regression*		
	*Degree of freedom**	χ^2	*p value (Breslow)***		*Degree of freedom*	χ^2	*p value (Breslow)*
Patient characteristics							
Age group (years)	6	28.67	0.0000	young	2	21.15	0.0000
Gender	2	10.30	0.0058	female	2	10.30	0.0058
Tumor charactersitics							
Genetics on clinical grounds	6	46.03	0.0000	MEN2a/FMTC	4	40.75	0.0000
T	8	48.79	0.0000	T1-2	4	37.63	0.0000
pT	8	52.22	0.0000	pT1-2	4	41.56	0.0000
N	4	22.36	0.0001	negative	2	20.39	0.0000
pN	6	11.99	not sign.	–	4	10.73	0.0298
M	2	33.98	0.0000	negative	2	34.01	0.0000
Location of M	8	39.25	0.0000	liver	4	35.99	0.0000
Diarrhoea	2	17.93	0.0001	absence	2	17.93	0.0000
Treatment characteristics							
Type of thyroid surgery	6	33.00	0.0000	bilat. total	4	26.56	0.0000
Central cervical LN surgery	4	14.44	0.0060	–	2	0.86	not sign.
Right cervical LN surgery	8	22.41	0.0042	adequate	2	7.54	0.0231
Left cervical LN surgery	8	24.03	0.0023	–	2	3.50	not sign.
External irradiation dosage	6	26.24	0.0002	adequate	2	15.07	0.0005
MIBG treatment	2	9.23	0.0099	yes	2	11.80	0.0027
Chemotherapy	2	5.12	not sign.	–	2	5.12	not sign.
Response to primary treatment							
Local response	4	42.97	0.0000	CR	2	37.87	0.0000
Regional response	6	49.19	0.0000	CR	4	42.91	0.0000
Distant response	4	68.71	0.0000	CR	4	61.46	0.0000
Residual local tumor	2	42.45	0.0000	absence	2	42.45	0.0000
Residual regional tumor	4	33.17	0.0000	absence	4	30.50	0.0000
Residual distant metastases	2	33.98	0.0000	absence	4	34.01	0.0000

Remarks:
*The effects of variables on local relapse-free and cause-specific survival as well as regional and distant relapse-free survivals were coupled (this is the reason why the numbers of degrees of freedom contain a multiplier of only 2 instead of 4). For Cox regression, non-missing values (together) and missing values were taken into account.
**Not sign. refers to $p > 0.05$.
***The favourable class is not displayed for the variables whose significance was proved by only one of the two statistical methods applied.
CR = complete remission

Table 5. **Variables with significant effects on the cause-specific survival probability, using multivariate analysis (Cox regression and Markov method). Numerical values of the listed variables were set according to the clinical state at the time of the primary care and were kept constant in time. Outcome variables are not listed.**

Variables	*Degree of freedom*	χ^2	*p value (Breslow)*
Age group (years)	1	13.34	0.0003
Gender	1	8.94	0.0028
Genetics on clinical grounds	6	56.66	0.0000
pN	1	13.97	0.0002
Diarrhoea	1	5.13	0.0235
External irradiation dosage	1	22.32	0.0000

pathologically in 54% of the cases, with 73% positivity (40% of the cohort). Distant metastases were frequent (54%) at primary diagnosis; the only dominant site was the liver (38%). Diarrhoea was a symptom in 23% of the patients at presentation.

The data indicate the heterogeneity of the treatment modalities. A considerable (82%) proportion of the surgical interventions involved bilateral subtotal lobectomy or a more minor intervention; the lymphatic compartments (1-3 per patient) were surgically dissected relatively seldom (0-32% of the patients); external irradiation was performed more frequently (48%) with an insufficient dosage than with an adequate radiation dose (16%); radionuclide treatment and chemotherapy were relatively rare (24% and 9%, respectively). Telecobalt irradiation was the most frequent (22 patients) form of radiotherapy, followed by use of a combined beam (17 patients), 6/9 MV photons (15 patients) and other beam qualities (4 patients). A majority of the patients received only cervical irradiation (60%); mediastinal irradiation was much rarer (19%). The mean dose of MIBG therapy was 4109 MBq (range: 1200-8782 MBq). The variety of the forms of chemotherapy does not allow further comments.

The follow-up data, including outcome variables, are presented in *Table 3*. The proportions of patients with a local or regional residuum or residual distant metastases on completion of primary care were 23%, 54% and 54%, respectively. During a mean follow-up period of 6 years, the proportions of patients experiencing local, regional or distant relapses were 8%, 23% and 26%, respectively. Following primary care, local relapses appeared after the shortest average time, and regional and distant recurrences only after longer periods. The relapses were treated individually; the treatment forms are not considered in this study. At present, 24 subjects (26% of the whole patient group) have died from thyroid cancer, and 9 intercurrent deaths have occurred. The total prevalences of clinically detected metastases (residuum and/or recurrences) in the LNs, liver, lung, bone, brain and other localizations were 78%, 69%, 25%, 15%, 3% and 7%, respectively, as calculated for the entire follow-up period with a mean duration of 6 years.

Univariate cause-specific survival estimation (*Table 4*) revealed a statistically significant impact of several investigated variables on the prognosis. In order to diminish the variance of the estimators, the effects of predictor variables on the local relapse-free and cause-specific survival and on the regional and distant relapse-free survivals were coupled (this is the reason why the numbers of degrees of freedom contain a multiplier of only 2 instead of 4). The favourable classes of these variables were a young age, female gender, a MEN2a or FMTC genetic background, a small primary tumor (T/pT1-2), and the absence of LN involvement, distant metastases and diarrhoea at the initial diagnosis. The liver-only localization of distant metastasis proved a favourable sign in comparison with other metastases from the aspect of the clinical course. Similarly, bilateral total removal of the thyroid lobes, application of external irradiation with an adequate dosage, MIBG treatment, a CR attained by primary treatment, and the lack of residual tumor following primary care had positive impacts on the prognosis.

The multivariate studies included only variables proved to be significant by the preceding univariate analysis. One of each pair of variables with a clear interrelationship (therapeutic responses and residual tumor) and one of each redundant pair of variables (T and pT, and N and pN) were excluded from the model-building. Six (age, gender, genetics, pN, diarrhoea and the external irradiation dosage) of the remaining 11 variables were verified as having significant impacts when extended Cox regression and the Markov method were used (*Table 5*).

These 6 significant prognosticators were used to construct a common cause-specific survival function relating to the whole group. Their impacts on a local/regional/distant residuum, relapses and death were expressed as relative risks by using extended Cox regression (*Table 6a*). The relative risk values of the same clinical status ascribed to the different classes of the same variable are relatively close to each other in almost all cases. Two of the exceptions were the age and external irradiation dosage, as an old age (≥60 years) and the lack of external irradiation for high-risk cases were characterized by very high rates of local relapses.

The relative risks calculated by means of the Markov method to express the transition of different clinical events are given in *Table 6b*. A factor higher than 1 indicates that the incidence of a particular clinical event is usually increased by the occurrence of another clinical event. It is noteworthy that the local residuum/first local relapse constitutes the only exception in this respect: the incidence of

local recurrences diminishes following a regional or distant residuum or relapse.

The mean cause-specific survival probability can be obtained for the group by averaging the individual survival curves (*Figure 1a*). The cause-specific survival probabilities after 5, 10 and 15 years are 69%, 62% and 58%, respectively, with no real trend to plateau formation. *Figures 1b-d* display the individual and mean local, regional and distant relapse-free survival probabilities. It is clear that the time courses of the cause-specific and local relapse-free survival are very close to each other, as are those of the regional and distant relapse–free survival.

Two examples illustrate the use of the MEDUPRED software to estimate the therapy-related individual survival probability. *Figure 2* presents survival curves for the same low-risk patient; here the local/regional/distant relapse-free and cause-specific survival probabilities are practically identical with and without external irradiation, and this type of therapeutic modality has therefore not been indicated. Figure 3 displays analogous curves for the same high-risk case, in which an adequate treatment strategy can increase the survival chance even under critical conditions.

Discussion

Although prospective clinical studies are unquestionably superior to retrospective ones, the published investigations analysing the efficacy of different treatment protocols in

Table 6a. **Relative risks as effects of different variables on clinical events (appearance of first local/regional/distant recurrences and cause-specific death), determined by extended Cox regression using the Markov method. (Statistically significant effect of the LN status on cause-specific death was obtained with the assumption of no effect of this variable on the local, regional and distant relapses.)**

Variables/ Classes	*Relative risks ± confidence intervals*			
	First local relapse	*First regional relapse*	*First distant metastasis*	*Cause-specific death*
Age group (years)				
≤19	0.04 (0.03-0.07)	0.40 (0.13-1.22)	0.54 (0.37-0.79)	0.26 (0.19-0.36)
20-39	0.35 (0.11-1.13)	0.74 (0.48-1.13)	0.81 (0.33-1.99)	0.64 (0.25-1.63)
40-59	2.83 (1.97-4.07)	1.36 (0.52-3.55)	1.23 (0.74-2.04)	1.56 (1.08-2.27)
60≤	22.64 (15.6-32.87)	2.50 (0.64-9.74)	1.86 (0.66-5.25)	3.83 (2.07-7.06)
Gender				
Male	2.50 (1.47-4.25)	1.21 (0.63-2.34)	1.13 (0.65-1.95)	1.61 (0.74-3.49)
Female	0.40 (0.08-2.01)	0.83 (0.59-1.16)	0.89 (0.36-2.17)	0.62 (0.26-1.51)
Genetics on clinical grounds				
MEN2a	0.15 (0.04-0.55)	0.58 (0.39-0.88)	0.69 (0.37-1.31)	0.43 (0.35-0.52)
FMTC	1.21 (0.64-2.29)	2.65 (1.91-3.67)	2.18 (0.73-6.54)	0.41 (0.16-1.10)
Sporadic*	1.68 (0.39-7.32)	1.23 (0.65-2.35)	1.16 (0.39-3.49)	1.18 (0.97-1.43)
Undetermined	3.34 (1.40-7.95)	0.53 (0.30-0.92)	0.57 (0.48-0.68)	4.79 (0.57-40.55)
pN				
0	1.00 (–)	1.00 (–)	1.00 (–)	0.18 (0.13-0.25)
1a	1.00 (–)	1.00 (–)	1.00 (–)	0.52 (0.33-0.82)
1b	1.00 (–)	1.00 (–)	1.00 (–)	1.50 (0.82-2.74)
NA	1.00 (–)	1.00 (–)	1.00 (–)	7.09 (3.75-13.37)
Diarrhoea				
None	0.29 (0.15-0.59)	0.63 (0.13-3.22)	0.73 (0.45-1.18)	0.65 (0.39-1.09)
Yes	3.43 (2.12-5.55)	1.58 (0.73-3.40)	1.38 (1.10-1.73)	1.54 (0.56-4.24)
External irradiation dosage				
None (in pT1-2/pN0-X)	0.03 (0.01-0.09)	0.62 (0.44-0.90)	0.78 (0.67-0.90)	0.13 (0.09-0.20)
Adequate	0.32 (0.13-0.77)	0.85 (0.10-7.02)	0.92 (0.54-1.55)	0.51 (0.24-1.07)
Insufficient	3.11 (2.19-4.41)	1.17 (0.91-1.51)	1.09 (0.31-3.83)	1.96 (0.45-8.55)
None (in pT3-4/pN1a-b)	30.04 (13.46-67.01)	1.60 (0.72-3.57)	1.29 (0.62-2.68)	7.52 (5.45-10.37)

Remarks:
*including sporadic MEN2b
The ratio of the same clinical event-related relative risk factors relating to the successive subclasses of non-dichotomous variables is constant to a first approximation, except for the genetic background.

MTC are all of a retrospective nature. The underlying explanation is the relatively low aggressivity of this disease as compared to a large number of malignant tumors. The fairly long average life expectancy of MTC patients does not allow the closure of a prospective clinical study before a period of 20-30 years has elapsed. Investigations involving data relating to a much shorter time scale are forced to work up case histories from the past.

The statistically relevant characteristics of the cohort

The MTC population at the NIO exhibits certain special features. A large number of patients are referred to the NIO in a relatively advanced stage of the disease, with residual tumor or relapses, for secondary surgery, or for external irradiation and radionuclide treatment, but not for primary surgical treatment. In consequence of the biochemical screening of the relatives of MTC patients, 38% of our cases belong in the MEN2a/FMTC group with a favourable prognosis. Furthermore, the unusually high prevalences of LN and liver metastases diagnosed during the clinical course of the disease (78% and 69%, respectively), can be explained by a systematic and careful search for such dissemination, as all the increased plasma tumor marker level determinations are regularly followed by conventional diagnostic imaging, whole-body FDG PET examination[41] and angiography[16].

An additional feature of the present cohort is that a substantial proportion of the patients underwent non-radical surgery and this commands special interest. Since there is almost total agreement as concerns the superiority of radical surgical intervention, new data on patients who have received less than radical surgical treatment can no longer be expected (there was an abrupt change in the character of surgical interventions at the NIO 3 years ago, in favour of radical surgery). Consequently, earlier data of this kind must also be utilized in order to acquire a more complete understanding of this disease, including its reaction to different treatment strategies.

The useful diversity as concerns tumor, patient and treatment characteristics lead us to anticipate that our database allows meaningful conclusions. The heterogeneity can be explained by the fact that thyroid cancer treatment strategy in Hungary, or even that at the NIO, has not been uniform in recent decades, with the primary decision-making depending on the subjective opinion of the responsible physician. No time-dependent trends could be demonstrated in the treatment variables of the patients included in this study.

Cause-specific survival probability and prognostic factors

The natural history of MTC is characterized by a relatively high cause-specific survival probability. The 5, 10 and 15-year cause-specific survival probabilities in the present series (69%, 62% and 58%, respectively), however, are far below the best results published by the Mayo Clinic (87%, 81% and 78%, respectively)[23]. As explanations for the differences, mention must be made of the considerable proportion of advanced primary tumors (24% pT4, 40% pN positivity and 54% distant metastases at presentation) and the fact that the conservative surgical intervention was not compensated by an adequate level and extent of other therapeutic measures.

With a view to the inclusion of all possible prognosticators, we started with a high number of parameters and, via both uni- and multivariate studies, confirmed the prognostic roles of age, gender, genetic background and diarrhoea in our patients (*Tables 4 and 5*). With either uni- or multivariate analysis, other investigators reached the same conclusion with regard to the favourable prognostic significance of a young age,[5,8,13,18,23,24,34,37,38] female gender,[8,17,18,24,34,37] a MEN2a/FMTC genetic background[13,17,23,34,35] and the initial lack of diarrhoea.[8,34,36]

In contrast, our univariate studies did not confirm the strong prognostic role of LN involvement (Table

Table 6b. **Relative risks characterizing the transition of different clinical events determined by extended Cox regression using the Markov method**

Clinical event	*Relative risks ± confidence intervals*
Local residuum / first local relapse	
following a regional residual sign / regional relapse	0.07 (0.04-0.10)
following a distant residual metastasis / distant relapse	0.10 (0.05-0.20)
Regional residuum / first regional relapse	
following a local residual sign / local relapse	4.42 (2.67-7.33)
following a distant residual metastasis / distant relapse	3.00 (0.86-10.41)
Distant residuum / distant relapse	
following a local residual sign / local relapse	2.07 (0.75-5.70)
following a regional residual sign / regional relapse	1.35 (0.95-1.91)
Death	
following a local residual sign / local relapse	14.04 (12.35-15.96)
following a regional residual sign / regional relapse	63.24 (55.22-72.42)
following a distant residual metastasis / distant relapse	100.28 (41.31-243.45)

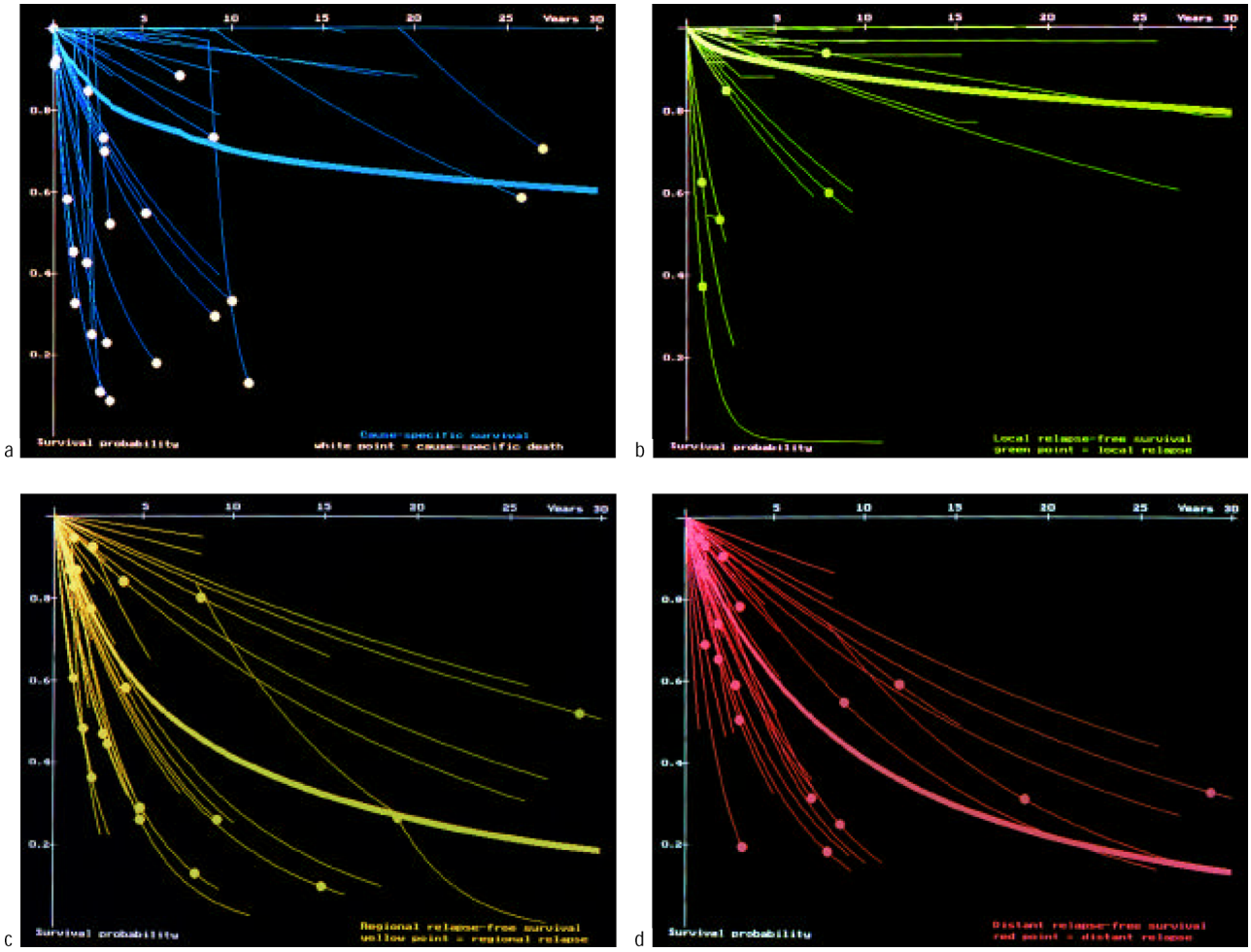

Figure 1. *Estimated individual survival curves (thin lines) of 91 medullary thyroid cancer patients, obtained by using the developed survival prediction method. Blue* ***(a):*** *cause-specific survival; green* ***(b):*** *local relapse-free survival; yellow* ***(c):*** *regional relapse-free survival; red* ***(d):*** *distant relapse-free survival. The curves are drawn for a time-span equal to the follow-up period. The colored circles indicate the time of the occurrence of the real clinical events corresponding to the given panel and case history. Changes in the slope of the curves are due to the altered relative risks related to the occurrence of a non-panel-specific clinical event* ***(see Table 6b).*** *Thick curves represent the average of the individual curves.*

4), whereas the subsequent multivariate studies did (*Table 5*). Previous uni- or multivariate investigations revealed conflicting results concerning the role of LN involvement in the estimation of MTC prognosis: some authors regard it as a significant, unfavourable factor,[20,23,24,33,37,40] whereas others consider it to be insignificant in the prediction of survival probability.[8,32,38] The published differences in the prognostic role of LN involvement may be explained by the different sets of variables in the various multivariate studies, the differences in type of the statistical analysis (uni/multivariate studies), and the possible interpopulation differences.[22] Our careful staging and multivariate analysis lead us to conclude that the pN parameter has a real role in affecting the disease course.

The statistically significant roles observed for pT, M and the extent of surgery in our univariate study could not have been proved by using a multivariate Markov model. A number of previous uni- and multivariate studies have confirmed the prognostic value of pT,[5,7,8,17,23] extracapsular (pT4) tumorous invasion,[8,17,32,33,37,38] M[7,8,17,23,24,32,33,37,38] and stage (TNM together).[5,7,17,18,23,30,34] In contrast, El-Naggar and coworkers found that pT (including pT4) and M do not play a significant role in the determination of the prognosis of MTC,[13] a finding similar to the results of our multivariate study. A strong correlation between the presence of LN involvement, and pT and M (also demonstrated in the correlation matrix) may explain this.

The early lymphatic dissemination of MTC is a fundamental biological characteristic of the disease. The published data document that the LN involvement rate is related to the primary tumor size and extent. Previous pathological examinations of cervical LNs during primary stag-

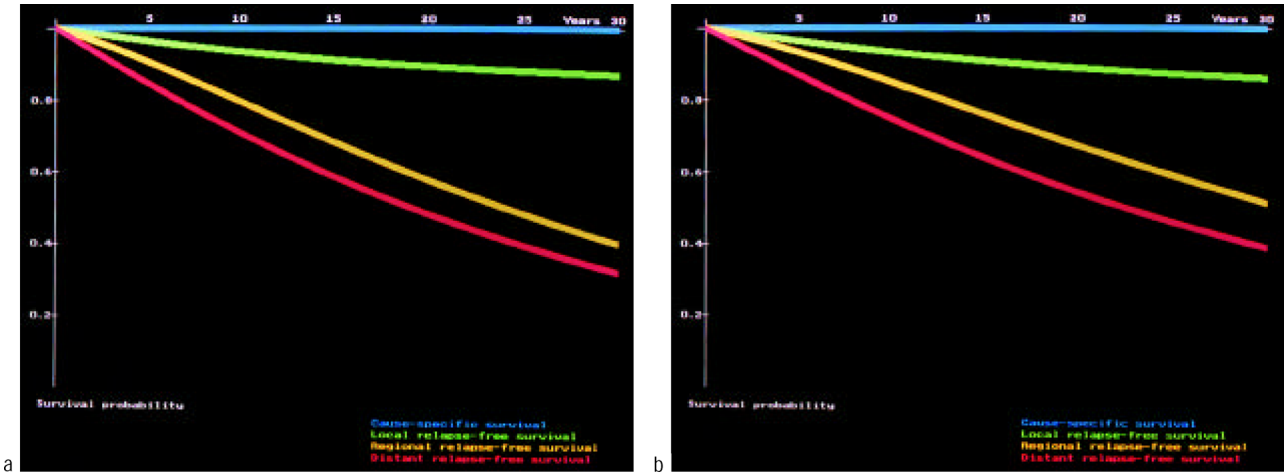

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Figure 2. *Individual survival probability estimation for a 25-year-old female MEN2a patient with a pN1a medullary thyroid cancer, without diarrhoea, without macroscopic residual disease on the completion of primary care, treated without* ***(a)*** *or with an adequate* ***(b)*** *dosage of external irradiation. Blue: cause-specific survival; green: local recurrence-free survival; yellow: regional relapse-free survival; red: distant relapse-free survival.*

ing revealed an involvement in 31-33% of the pT1, 53% of the pT2 and 100% of the pT3-4 cases.[3,19] The rate of overall mediastinal LN involvement was found to be 22-48%.[19] Our present and previous[16] observations indicate that LN involvement may forecast hepatic dissemination. This is clearly seen from the reported data, as the frequencies of LN and hepatic involvements were close throughout the course of the disease: initial pathological LN (40%) and hepatic (38%) involvement (*Table 2*), a regional residue (54%) and residual distant (mainly liver) metastases (54%) following primary care, regional recurrences (23%) and new, distant (mainly liver) metastases (26%), the prevalence of LN (78%) and hepatic metastases (69%) throughout the course of the follow-up (*Table 3*).

Some authors have concluded that the extent of surgery has a prognostic role in MTC,[7,11,13,17,30,32] but, similarly to the finding of Hay,[23] our multivariate study did not confirm this. A partial explanation may be that we introduced 6 outcome variables as presumed prognosticators (this assumption was later proved in the Markov analysis). As local and regional residues relate strongly to the nature of the surgical intervention and we included the two former entities as prognosticators, they may have taken over the role of the extent of surgery. As a result, our multivariate analysis (eliminating extensive redundancy of the variables) did not indicate any prognosis-influencing role of the surgical interventions. Thus, our results do not contradict those ascribing a prognosticator role to the extent of surgery.

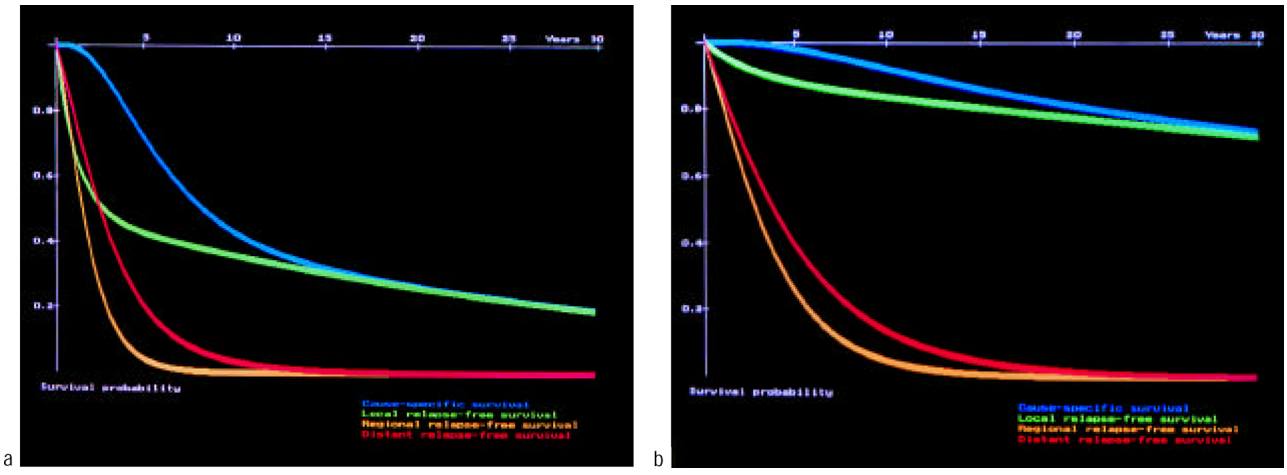

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Figure 3. *Individual survival probability estimation for a 65-year-old male patient with a sporadic pN1b medullary thyroid cancer, without diarrhoea, without macroscopic residual disease on the completion of primary care, treated with an inadequate* ***(a)*** *or an adequate* ***(b)*** *dosage of external irradiation. Blue: cause-specific survival; green: local recurrence-free survival; yellow: regional relapse-free survival; red: distant relapse-free survival.*

Only a few publications report detailed statistical analyses of external irradiation as a predictor in MTC, and with conflicting results. Some argue that this parameter is a significant, favourable factor,[32] others[8,36] claim that external irradiation is insignificant in the prediction of survival probability. Nevertheless, these authors agree that, in cases at high risk of local/regional relapse (thyroid capsule invasion or multiple LN involvement), external irradiation should be considered.[8,32,39] Our data lend support to this strategy.

In consequence of the frequent and early appearance of regional and distant metastases, and the lack of their efficient therapy, residual tumors are very probable in MTC. It is well documented that residual tumorous masses[8,32] and consecutive hypercalcitoninaemia[8,28], are of prognostic significance. Our model is in complete agreement with this. Because of their strong prognostic role, we treated the residual diseases as outcome variables of cause-specific survival. The inclusion of outcome variables in prognosis estimation is supported by the fact that the appearance of the appropriate clinical states is directly related to a set of important (not routinely investigated and not sufficiently well known) prognosis-influencing variables, such as DNA ploidy,[2,4,5,12,13,23] the proportion of S-phase cells,[23] certain pathological features,[4,5,7, 8,13,18,27,29,30,38] oncogen expression, etc.

In the present study, the relative risk values attributed to the different subclasses of a selected variable barely change with the nature of the clinical events (*Table 6a*). There are only two exceptions, those relating to the appearance of the first local relapse for patients aged ≥60 years, and those with locally/regionally advanced tumor and no radiotherapy. This reflects the presumed conservative nature of the biological processes involved in the occurrence of these events. An additional manifestation of the permanency of the biological processes is the fact that the characteristics of the originally diagnosed disease did not change throughout the generation-long clinical course.

Individual survival probability estimation

Previous studies analysing the relation of different factors or variables and the course of the MTC disease investigated merely the existence of the interrelationship, with no attempt to describe how a defined set of variables would affect tumor progression in the individual cases. A search for a detailed interconnection between these entities seems a quite natural ambition.

Evaluation of the prognostic roles of the most determinant variables clearly demonstrates that the prognosis of the individual clinical course of MTC should not be based solely on the TNM/pTNM classification system without inclusion of a set of important variables (e.g. age, genetics, diarrhoea, etc.). Two simple, individual prognostic scoring systems have been elaborated for MTC with the intention of taking additional prognosis-influencing factors into consideration. These systems range the patients into groups on the basis of the stage of the tumor,[17,30] the completeness of surgical resection[17,30] and the amyloid staining positivity.[30] Average survival probabilities were assigned to each group of individual cases, but the increment in the discrete values of the cause-specific survival probabalities for the different risk groups was too large.

For a more detailed prognosis estimation, we developed an algorithm to calculate the time-dependent individual survival probabilities for MTC patients, using all variables proved by the multivariate analysis to be prognosticators. Some of the input parameters of the developed model characterize the biological state of the patient and the disease, while others relate to the treatment. To the best of our knowledge, the outlined model is the first that offers a method of calculating individual survival probabilities that change in a continuous manner, instead of providing merely a few discrete values. In addition to the prediction of cause-specific survival, our method is the first procedure that furnishes probability data for the appearance of local, regional and distant recurrences in the individual cases.

In the current age of individualized treatment approaches, efforts may be made to distinguish prognostically different patient groups requiring different treatment strategies. The present biostatistical model offers a way to calculate individual cause-specific survival probabilities, facilitating the identification of patients at different risks. This information is valuable for the clinician, but it is of the utmost importance for the patient. The present model allows a more accurate determination of the parameters (smaller SD), and therefore permits a more precise estimation of the clinical course as compared to that provided by a Kaplan-Meier model.

As MTC is rather conservative in biological nature, to a first approximation the model is of value for the prediction of patient survival for any type of MTC, patient and treatment characteristics in any geographical area. Ready accessibility to the program is ensured for all medical teams engaged in the treatment of this cancer type. PC-supported survival estimation for a particular case takes about 1 min.

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