Determinants of life expectancy in medullary thyroid cancer: age does not matter

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Summary

Objective In medullary thyroid cancer (MTC) age is considered an important prognostic factor but survival has never been properly adjusted for baseline mortality in the general population. We aimed to identify prognostic factors by analysing patients with MTC regarding life expectancy.

Design We described a retrospective cohort study with a median follow-up of 8 years (range 1–35 years).

Patients We included 120 consecutive patients of whom 66 (55%) had sporadic MTC. Male/female ratio was 1 : 1; median age was 45 years (range 3–83 years).

Measurements Measurements were overall and disease-specific survival and life expectancy expressed as survival adjusted for baseline mortality rate in the general population.

Results Overall and disease-specific 10-year survival was 65% and 73%, respectively. After 10 years, 29% of patients were biochemically and 63% clinically cured. Median overall life expectancy was 0·58 (95%CI 0·37–0·80). Detectable recurrence occurred in 60 patients after a median of 36 months (range 5–518 months). On multivariate regression analysis only stage of disease and extrathyroidal extension predicted recurrence-free life expectancy. Extrathyroidal extension was the only independent predictor of overall life expectancy. Persistent biochemical MTC did not independently affect life expectancy but calcitonin doubling time of less than one year indicated worse prognosis. Patients without detectable recurrences after initial treatment had a life expectancy similar to the general population.

Conclusions In MTC patients, extrathyroidal extension and stage at diagnosis are the only independent predictors of (recurrence-free) life expectancy. Patients diagnosed in an early stage of disease and patients without detectable recurrence have favourable life expectancy independently of biochemical cure.

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Introduction

Approximately 5–10% of all thyroid cancers encompass medullary thyroid carcinoma (MTC). MTC occurs in sporadic and hereditary variants and, although the clinical course varies, it is usually considered relatively indolent. The hereditary forms of MTC occur as part of familial MTC (FMTC) or multiple endocrine neoplasia type 2 (MEN 2A and MEN 2B). These syndromes are caused by germline mutations in the RET gene (Rearranged during Transfection).

MTC is characterized by an early spread to locoregional lymph nodes, often even before the primary tumour is diagnosed. Nevertheless, the overall survival of patients with MTC ranges from 78% to 91% at 5 years follow-up and is about 75% (ranging from 61% to 88%) at 10 years follow-up. Previous studies have suggested a number of factors influencing survival, such as age and sex of the patient, type of MTC (sporadic vs hereditary), tumour stage and extent of the tumour at presentation but their relative importance on life expectancy is not clear. Furthermore, despite the relatively high survival rates, only about 34% to 44% of patients are biochemically cured by surgery as indicated by undetectable serum calcitonin levels. Persistently elevated calcitonin levels indicate occult MTC and can be a source of anxiety in both the patient and the clinician. However, it is unknown whether the high prevalence of persistent hypercalcitoninaemia adversely affects life expectancy since patients can coexist with MTC for many years. In addition, commonly used survival curves express survival in years irrespectively of age. To study life expectancy, age at diagnosis has to be considered as well.

Since disease-specific mortality in MTC is relatively low and age at diagnosis varies considerably, long-term survival should be adjusted for the baseline mortality rate in the general population and statistical analysis on survival ought to include methods of age adjustment. The standard used Kaplan-Meier plots do not give insight in the decline of cumulative proportions of survival, both disease-specific and overall with advancing age at diagnosis. Therefore, we employed a new method to study survival, which combines proper adjustment for age at diagnosis with the capability of graphical presentation of the risk distribution unbiased by age. This method is called standardized survival and depicts the age and gender matched life expectancy of the study population relative to the general population. Aim of this study was to analyse a cohort of 120 patients diagnosed with MTC with respect to their life expectancy.
and to compare this with commonly applied survival analysis. Furthermore, we aimed to address the influence of several prognostic factors, in particular persistent hypercalcitoninaemia regarding life expectancy.

Patients and methods

Patients

We registered data on all patients with MTC from January 1970 onward. To January 2003, 130 patients with MTC were identified. Ten patients were excluded: one patient was lost to follow-up, seven patients only had C-cell hyperplasia and in two patients MTC was detected on postmortem examination. Data on the remaining 120 subjects were used for survival analysis.

The diagnosis of MTC was confirmed by histology of resected specimens. Sporadic MTC was defined as the absence of germline RET mutations or, before the introduction of RET analysis, a negative family history of MEN 2 or MTC. MEN 2A was defined by the presence of a germline RET mutation or a first-degree relative with MEN 2A or the presence of MTC with phaeochromocytoma and/or hyperparathyroidism. MEN 2B was defined by the presence of a germline RET mutation or MTC in combination with typical phenotypic features (e.g. marfanoid body habitus, mucosal neuromas and intestinal ganglioneuromatosis) with or without phaeochromocytoma. Since 1994, we used DNA screening for germline RET mutations in exons 10, 11, 13, 14, 15 and 16.

From 1970 to 1992 serum calcitonin was measured by a home-made radioimmunoassay (RIA). From 1992 to 2000 a commercially available RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) was used. From that time onwards we used an enzyme-linked immunosorbent assay (Biosource Europe SA, Nivelles, Belgium until 2001, and thereafter Sangui Biotech, Inc., Santa Ana CA, USA). CEA (carcino-embryonic antigen) levels were determined by chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Total thyroidectomy was performed in 118 (98%) patients, the two others underwent tumour debulking. In 94 (78%) patients, dissection of the central compartment from the hyoid bone to the innominate vein, and laterally to the jugular veins was also performed. This procedure was combined with an unilateral selective neck dissection of levels II–V according to Robbins et al. in 29 (24%) patients, a bilateral selective neck dissection in 14 (12%) patients and an upper mediastinal dissection in 22 (18%) patients at the time of thyroidectomy. Adjuvant external beam radiotherapy was given to 43 (36%) patients with advanced disease at presentation (100% nodal metastases, 84% invasion of the thyroid capsule).

Within 12 weeks postoperatively, basal serum calcitonin and CEA were measured to assess the outcome of surgery. In case of normal basal calcitonin levels, a pentagastrin stimulation test was performed. In patients with sustained postoperative elevated serum calcitonin and/or CEA levels, various techniques such as \(^{99m}\)Tc(V)dimercapto-succinic acid (DMSA), \(^{111}\)In-octreotide, Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and ultrasonography were utilized to detect residual MTC depending on the protocol used during that specific time period. In case of no anatomical substrate for hypercalcitoninaemia, imaging was performed when calcitonin levels further increased, generally once or twice a year. Since 1998, \(^{18}F\)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was also used in the follow-up.

Pathological findings and stage of disease are depicted according to the tumour node metastasis (TNM)-classification. Briefly, T0 means no cancer; T1, tumour confined to the thyroid, ≤ 1 cm; T2, tumour confined to the thyroid, > 1 but ≤ 4 cm; T3, tumour confined to the thyroid, > 4 cm; T4, extrathyroidal invasion of the tumour. In addition, N0 means node negative; N1, node positive and M0 means no distant metastases, M1 distant metastases. Stage I disease corresponds with T1, stage II with T2–4, stage III with any T, N1 and stage IV any T, any N, M1.

Persistent biochemical MTC refers to patients with postoperative stimulated and/or basal elevated serum calcitonin levels. Persistent clinical MTC refers to detectable macroscopic disease after surgery because of irresectable MTC or distant metastases. Recurrence was defined as the emergence of clinically detectable (by at least one of the imaging methods we used), biopsy proven MTC in patients without persistent clinical MTC after surgery. Patients with undetectable basal and stimulated calcitonin levels were considered cured.

Statistical analysis

In all tests a P-value < 0.05 was considered significant and 95% Confidence Intervals (CI) are given when appropriate. The influence of prognostic variables was assessed from the time of diagnosis to the last follow-up date. The standardized survival (life expectancy) was calculated as described earlier. The median residual lifetime was derived from the reports by the Dutch Central Office of Statistics (www.CBS.nl). Differences in various parameters were evaluated using the Mann–Whitney rank-sum test (for continuous variables), the Fisher exact test and the \(\chi^2\)-test with continuity correction (for categorical data), as appropriate. The Kaplan-Meier method was used to estimate overall and disease specific survival. Differences in (standardized) survival were tested by Cox regression analysis with relative risks calculated as the quotient of the ratio of observed events and extent of exposure. Patients were censored at the end of follow-up, unless an event happened before that date. To examine the impact of clinicopathological variables, we used the following events as end-points: sustained normal serum calcitonin levels (for biochemical disease free interval), clinical disease recurrence (for recurrence free interval), death due to MTC (for disease specific survival) and death (for overall survival). The Cox regression model was used in multivariate analysis to study the different clinicopathological variables as an independent risk factor.

Results

Patient characteristics

Characteristics of 120 patients are listed in Table 1. The life expectancy at age of diagnosis ranged from 7 to 78 years. Median follow-up since diagnosis was 8 years (range 1–35 years).

Of 54 patients with hereditary MTC, 56% were female, whereas 40% of 66 patients with sporadic MTC were female. Patients with
hereditary MTC were younger at diagnosis (median age 28 years, range 3–74 years) than patients with sporadic MTC (median age 57 years, range 20–83 years; $P < 0.0001$). Of 54 patients with hereditary MTC, 40 (74%) were detected by screening (either genetic or biochemical or both). Furthermore, patients with hereditary MTC, which was detected by screening, were significantly younger (median age 23·5 years, range 3–56 years) than patients with MTC not detected by screening (median age 41 years, range 11–74 years; $P < 0.0001$).

Twenty-six (48%) patients with hereditary MTC had stage I disease, 12 (22%) stage II, 15 (28%) stage III and one (2%) had stage IV MTC.

Overall and disease-free survival

Overall 10-year survival in all 120 patients was 65% and the disease specific survival was 73% (Fig. 1a). Median survival in the whole cohort was 20 years. After 10 years, 35 (29%) patients were alive and cured as indicated by undetectable serum calcitonin levels whereas 76 (63%) patients were clinically disease-free as indicated by the absence of detectable MTC. In the remaining nine (8%) patients, MTC could be detected by one or multiple imaging methods.

Life expectancy in medullary thyroid carcinoma

Overall and disease-free life expectancy for the entire cohort is depicted in Fig. 1b. The median standardized survival time was 0·58 (95%CI 0·37–0·80). The cumulative proportion of death at half standardized survival time was 0·42 (95%CI 0·31–0·56), which is above the proportion of maximally 0·10 in the age-matched general population. At a standardized survival of one, three quarters of all patients had died of whom about 60% died from MTC.
Persistent disease after initial treatment

Seventy-nine (66%) patients had persistent MTC after initial surgery (71 only biochemical and eight also clinical). In 29 (24%) patients there was a more than twofold rise in basal serum calcitonin within the first year after initial treatment. Of note, in two patients (one male with hereditary MTC operated at age 16 years and one female with sporadic MTC operated at age 38 years) postoperative basal and stimulated calcitonin was normal, but became elevated again during follow-up (after 185 months and 7 months, respectively). Including these two patients, an anatomical substrate for the serum calcitonin elevation was never found in 19 patients despite an extensive diagnostic approach and long-term follow-up (median 143 months, range 6–339 months).

Clinically detectable recurrence

All patients who developed a clinically detectable recurrence had persistent biochemical MTC after surgery. During follow-up a recurrence was detected in 60 patients. Clinically detectable recurrence occurred after a median of 36 months (range 5–518 months) since initial treatment. Physical examination and/or various imaging techniques detected recurrences in all these patients. In 54 patients locoregional (cervical and/or mediastinal) recurrence was detected and in 38 patients distant metastases were detected. Both locoregional and distant metastases were detected in 23 patients.

In 28 (47%) of 60 patients with clinically detectable recurrence no additional therapy with curative intent was given because of advanced disease or patient refusal. Symptomatic therapy such as EBRT on bone metastases was given when indicated and six patients had palliative experimental chemotherapy without any appreciable effect on tumour volume. Treatment of locoregional recurrence included surgery in all cases. A total of 32 patients underwent 40 re-operations for locoregional recurrence (sometimes patients had more than one re-operation). In two (6%) of 32 patients, cure was achieved by re-operation.

Death of other cause

A total of 54 patients died. Twenty (37%) patients died from a cause other than MTC, six were cured and 14 had evidence of persistent biochemical MTC at the latest visit (12 had also clinical MTC). Five (25%) patients died from a second primary tumour (breast, lung, colon, bladder and sarcoma), eight (40%) died from a cardiovascular cause (three cerebrovascular accidents, five cardiac deaths), three (15%) from pulmonary cause, three (15%) from the haemodynamic consequences of a phaeochromocytoma and one (5%) patient committed suicide. Therefore, of 48 patients who died with persistent biochemical MTC, 14 (29%) did not die from MTC. Eight patients (six that were cured and two with biochemical persistent MTC) died without any clinical evidence of disease.

Prognostic factors

Regarding prognostic factors for failing to achieve biochemical cure, Odds Ratios (ORs) for female gender (P = 0·021), hereditary MTC (P = 0·002), the presence of multifocality (P = 0·91), extrathyroidal growth (P < 0·0001), lymph node metastases (P < 0·0001) and extranodal growth (P < 0·0001) were 0·37 (95%CI 0·12–0·82), 0·27 (95%CI 0·12–0·55), 0·91 (95%CI 0·41–2·02), 12·70 (95%CI 2·84–56·60), 25·50 (95%CI 8·00–81·90) and 24·78 (95%CI 3·53–174·15), respectively.

In univariate analysis, all factors depicted in Table 2 except multifocality of the tumour were found to be significant predictors regarding clinically detectable recurrence-free survival and standardized survival. However on multivariate regression analysis only stage of disease at presentation remained a prognostic factor for standardized survival. However on multivariate regression analysis only stage of disease at presentation remained a prognostic factor for detectable recurrence (Table 2). Plots depicting proportion of clinically detectable recurrence.
detectable recurrence against standardized survival time by stage of disease at presentation are given in Fig. 2. A (more than) twofold rise of calcitonin within the first year after treatment, though parameter of outcome by itself, serves as an additional independent risk factor when added to the model of standardized recurrence free survival \((OR = 1.91; 95\% CI 1.07–3.40; P = 0.028)\). Univariate relative risks for overall survival and standardized survival in the total cohort are provided in Table 3. Only age and the presence of extrathyroidal growth remained an independent predictor of survival. However, when standardized survival was used, correcting for basal mortality in the general population, only extrathyroidal growth remained an independent predictor (Fig. 3). Median standardized survival time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Survival</th>
<th>P-value</th>
<th>Standardized survival</th>
<th>P-value</th>
<th>Multivariate Survival</th>
<th>P-value</th>
<th>Standardized survival</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 (1.05−1.10)</td>
<td>0.000</td>
<td>1.03 (1.01−1.05)</td>
<td>0.001</td>
<td>1.06 (1.04−1.09)</td>
<td>0.001</td>
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<tr>
<td>Sex (male)</td>
<td>1.81 (1.01−3.23)</td>
<td>0.046</td>
<td>1.33 (0.74−2.40)</td>
<td>0.346</td>
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<tr>
<td>Type MTC (Sporadic)</td>
<td>4.61 (2.31−9.20)</td>
<td>0.000</td>
<td>3.31 (1.64−6.68)</td>
<td>0.001</td>
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<td>TNM stage</td>
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<tr>
<td>II</td>
<td>1.31 (0.38−4.50)</td>
<td>0.670</td>
<td>1.40 (0.41−4.80)</td>
<td>0.594</td>
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<tr>
<td>III</td>
<td>5.04 (1.77−14.30)</td>
<td>0.002</td>
<td>4.01 (1.40−11.50)</td>
<td>0.010</td>
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<tr>
<td>IV</td>
<td>20.7 (5.91−72.50)</td>
<td>0.000</td>
<td>11.20 (3.22−38.90)</td>
<td>0.000</td>
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<td>Unifocality</td>
<td>0.90 (0.53−1.54)</td>
<td>0.706</td>
<td>1.05 (0.61−1.82)</td>
<td>0.859</td>
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<td>Capsular invasion (T4)</td>
<td>8.08 (4.36−15.00)</td>
<td>0.000</td>
<td>7.89 (4.21−14.80)</td>
<td>0.000</td>
<td>6.16 (3.18−11.90)</td>
<td>0.000</td>
<td>7.89 (4.21−14.80)</td>
<td>0.000</td>
</tr>
<tr>
<td>Nodal metastases</td>
<td>4.45 (2.25−8.80)</td>
<td>0.000</td>
<td>3.54 (1.78−7.05)</td>
<td>0.000</td>
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<tr>
<td>Extranodal growth</td>
<td>6.74 (3.44−13.20)</td>
<td>0.000</td>
<td>4.72 (2.41−9.24)</td>
<td>0.000</td>
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<td>Persistent disease</td>
<td>4.88 (2.07−11.50)</td>
<td>0.000</td>
<td>4.21 (1.76−10.10)</td>
<td>0.001</td>
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HR, Hazard Ratio; MTC, medullary thyroid cancer; TNM, tumour, node, metastasis.
The good prognosis for patients with clinical MTC is further illustrated in Fig. 4. In Fig. 4, mortality in all patients without clinically detectable MTC is shown. Of eight patients that have died, two patients had persistent disease and six patients were cured but none of these patients died of MTC. Survival pattern was similar to that of the general population indicating no excess mortality during the clinical disease-free period.

Discussion

In the present study we described the influence of several epidemiological and pathological variables on survival in MTC patients corrected for baseline mortality in the general population. In our cohort, 10-year overall and disease-specific survival in MTC was 65% and 73%, respectively, and life expectancy was reduced to a median standardized survival of 0·58. Predictors of persistent biochemical MTC were advanced stage of disease, presence of lymph node metastases and extrathyroidal growth. However, biochemical cure after initial treatment was not an independent predictor of overall and recurrence-free survival (life expectancy) in patients with MTC. The only independent prognostic factor for life expectancy on multivariate analysis was extrathyroidal extension of the primary tumour. On multivariate analysis stage at diagnosis was also significant for detectable recurrence-free life expectancy. These data indicate that both stage of disease and extrathyroidal growth at presentation are the only independent predictors of clinical behaviour and life expectancy in patients with MTC.

The present cohort corresponds well with other cohorts reported. Ten-year overall and disease-specific survival in MTC was slightly better in our series compared to other series. The mean age at diagnosis in our cohort is similar to that in these other studies although we do have a fairly high proportion of hereditary cancers comparable to the number reported by Modigliani et al. and Kebebew et al. This most likely reflects a referral bias and may explain to some extent the better survival in our cohort. However, all patients in our cohort had MTC and type MTC did not affect recurrence-free and overall (standardized) survival, therefore this should not interfere with the identification of prognostic factors. Moreover, the implementation of DNA screening has resulted in earlier identification of patients with hereditary MTC resulting in a higher frequency of hereditary MTC detected at an early stage in contemporary series.

Nevertheless, the results of this study should be interpreted keeping in mind that there are some possibilities for error since the sample size is small.

As we have demonstrated, patients with stage I disease have a detectable recurrence-free life expectancy that is comparable to the general population underscoring the importance of early detection of MTC. These findings confirm the results of a previous study from Sweden in which the authors found that patients with stage I and II MTC have a relative survival (the ratio between observed and expected survival) that does not differ from that of the general population.

In accordance with the results from the study of Bergholm et al., we show that postoperative elevated calcitonin per se probably does not affect long-term prognosis. Hypercalcitoninaemia is not an independent prognostic factor for overall and recurrence-free survival and life expectancy and, especially when no clinical sign of relapse is present, patients may have a normal residual life span. About 30% of deaths in the cases with persistent biochemical disease are not due to MTC and some patients with persistent MTC have a standardized survival time above one. This illustrates the mild clinical course in a subset of these patients. However, a twofold increase in basal calcitonin levels within the first year after initial treatment does implicate a worse prognosis.

Obviously, persistent disease has a very high sensitivity for clinical recurrence. However, the specificity is not very high as 24% of patients with persistent elevated calcitonin remained clinically disease-free even after long-term follow-up and since some patients (around 3%) will develop recurrences when they are considered biochemically cured.

Both stage of disease and extrathyroidal growth independently predicted the occurrence of clinically detectable recurrence in our cohort. Patients with stage III and IV have the highest risk of developing
detectable recurrence and are only rarely cured. Pellegriti et al. found that postoperative basal calcitonin levels and pT were independent prognostic factors for imaging detected relapse. Only stage and extrathyroidal growth remained independent prognostic factors upon multivariate analysis in our study because of a strong interrelation between stage of disease, extrathyroidal growth and elevated postoperative calcitonin levels. In practice, for a male patient diagnosed at the age of 50 with stage III MTC (and a normal life expectancy of 29 years) this would mean that he is most likely to develop a clinical recurrence within 14% of his life expectancy (since 50% of patients with stage III MTC will develop a recurrence within this percentage of their life expectancy, Fig. 2). In this particular case this corresponds with four years.

Similar to most other studies, age at diagnosis affected overall survival in the present study. However the standardized survival time, reflecting life expectancy, was not significantly affected by age on multivariate analysis. This means that the increase in death rate is proportional to the age-dependent death rate in the general population and that older patients do not necessarily have a more aggressive form of MTC as suggested by Hyer et al. Therefore, age should not be used as an independent risk factor in prognostic scoring systems.

It is often difficult to identify the stage of disease appropriately since imaging methods frequently miss microscopic metastases to regional lymph nodes or distant organs. In our cohort, elective lateral lymph node dissection was not performed and therefore the stage of disease may be somewhat underestimated. Lymph node metastases very often occur bilaterally and therefore routine central and bilateral lymph node dissection is warranted. In particular in patients presenting with a palpable neck mass. It is conceivable that the rate of clinically detectable locoregional recurrences would decrease and the cure rate would increase when central and bilateral neck dissections are performed routinely. However, given the results of our multivariate analysis, it remains to be seen whether the improved cure rate actually improves survival. Extensive initial surgery minimizes (but does not exclude) locoregional recurrences and associated morbidity (particularly morbidity associated with re-operations) without an obvious increase in surgical complications. However, the occurrence of detectable distant metastases may not be affected by initial treatment in patients with a high risk for detectable recurrence, probably because micrometastases are already present. Nevertheless, even patients who will eventually develop detectable distant metastases benefit from an aggressive initial surgical approach since locoregional control is optimized by meticulous primary surgery in these patients that may live for many years as already emphasized by Van Heerden et al.

In conclusion, risk factors for occult MTC after initial surgery are stage, lymph node metastases and extrathyroidal growth. Prognostic factors for recurrence-free life expectancy are stage of disease and extrathyroidal growth. The only independent prognostic factor for overall life expectancy is extrathyroidal extension. A (more than) twofold rise of calcitonin within the first year after treatment also implicates a shorter (recurrence-free) life expectancy. Additional therapeutic options are needed for patients with stage III or IV MTC and/or extrathyroidal growth since surgery alone will not be sufficient for this patient group. Furthermore, patients without detectable recurrences after initial treatment for MTC have a favourable prognosis and a life expectancy that seems roughly similar to that of the general population. These findings can be reassuring to patients with persistent hypercalcitoninaemia after apparent curative surgery without a detectable anatomical substrate of MTC and also to their treating physicians.

References


