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ORIGINAL ARTICLE

Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis

Johannes A. A. Meijer*, Saskia le Cessie†, Wilbert B. van den Hout‡, Job Kievit‡, Johannes W. Schoones§, Johannes A. Romijn* and Johannes W. A. Smit*

**Departments of Endocrinology and Metabolic Diseases, †Medical Statistics, ‡Medical Decision Making, and §Walaeus Library, Leiden University Medical Centre, Leiden, the Netherlands*

Summary

Context In the management of patients with medullary thyroid carcinoma (MTC), calcitonin doubling time (dt) has gained interest as an independent predictor of recurrence and survival.

Objective To perform a structured meta-analysis of the diagnostic value of calcitonin dt, carcinoembryonic antigen (CEA) dt and the combination and to define dt strata with the highest predictive power.

Design The study was a meta-analysis using individual data.

Methods Ten studies containing data on the post-operative kinetics of tumour marker(s) and (recurrence free) survival were included.

Results Calcitonin- and CEA-dt are significant indicators for survival (hazard ratios (HR) 21·52 respectively infinite for dt 0–1 year compared to dt >1 year) and recurrence (HR 5·33 respectively 6·80 for dt 0–1 year compared to dt >1 year). The highest predictive power was found for the dt classification 0–1 year *vs.* >1 year. CEA dt has a higher predictive value than calcitonin dt in the subgroup of patients for which both parameters were available.

Conclusion The dts of both calcitonin and CEA are strong prognostic indicators for MTC recurrence and death. CEA dt has a higher predictive value than calcitonin dt and therefore measuring both tumour markers is essential for proper risk stratification.

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Correspondence: Johannes A.A. Meijer, Departments of Endocrinology and Metabolic Diseases, Leiden University Medical Centre, Leiden, the Netherlands. Tel.: +31-71-5263082; Fax: +31-71-5248136; E-mail: j.a.a.meijer@lumc.nl

Introduction

Surgery is the only curative treatment for medullary thyroid carcinoma (MTC). Total thyroidectomy with bilateral central lymphadenectomy is generally accepted as the minimal initial treatment,[1–3] the indication and extent of lateral lymphadenectomy still remaining controversial.[4–7] Patients are considered biochemically cured, when post-surgical serum levels of calcitonin are undetectable. Calcitonin is a highly sensitive marker of persistent or recurrent disease, often indicating MTC long before tumour localizations are visualized by imaging.[8,9] Unfortunately, calcitonin levels remain detectable in a majority of patients with the proportion ranging from 55% to 66% despite adequate surgical intervention.[2,10,11] The second tumour marker used in the follow-up of MTC is carcinoembryonic antigen (CEA), generally considered to have lower diagnostic accuracy than calcitonin.[12–14]

Usually, imaging procedures of different modalities are undertaken to search for tumour recurrence or metastasis when elevated serum calcitonin levels are present. However, despite the advent of elaborate imaging techniques, including 18F-DOPA PET,[15] examinations often remain negative resulting in uncertainties on the disease status of the patient. It is therefore necessary to stratify patients with measurable serum calcitonin levels according to their risk for tumour recurrence or death.

The prognostic value of calcitonin kinetics was shown in 1979 by Stepanas *et al.*,[16] although absolute serum levels of calcitonin do not correlate well with tumour progression or survival.[12] Subsequently, several other studies have investigated the prognostic value of sequential changes of calcitonin concentrations. Recently, Barbet *et al.*[17] showed that calcitonin doubling time (calcitonin dt) is an independent predictor of survival with a higher predictive value than TNM stage classification in multivariate analysis. Since then, calcitonin dt has gained interest to stratify post-operative MTC patients with measurable calcitonin levels. In contrast to calcitonin dt, to our knowledge, only two studies have addressed the relationship between CEA dt and survival.[17,18]

As the concept of calcitonin dt as a prognostic marker for risk of recurrence and death in MTC is attractive, we performed a literature review followed by a structured meta-analysis on individual

data to study the prognostic value of calcitonin dt. As most studies so far did not take into account the prognostic value of dts of calcitonin and CEA together, we included this in our analysis.

Materials and methods

Literature search

A formal literature search was performed in the databases PubMed (Medline), EMBASE, Web of Science and Cochrane Library, using the 'AND' combination of the main concepts 'calcitonin' and 'MTC'.

The strategy was optimized for each consulted database. In PubMed and Cochrane Library, the combination of relevant Medical Subject Headings and free text words was used. In EMBASE, the combination of free text words in the title and official keywords was used, whereas in Web of Science free text words were used. The detailed search strategy is available from the authors upon request. We restricted our search to publications in 'English language' and 'articles containing abstracts'. The last date of data acquisition was September 9th, 2008. All abstracts were screened for information on (post-operative) calcitonin kinetics in relation to survival and/or recurrence, or the suggestion that such information would be present in the article.

Initially, 1818 publications were found related to MTC and calcitonin. Based on abstract reading, 60 publications were selected and read in full text. Publications were included when they contained data on (post-operative) calcitonin dt as a prognostic factor for survival or when they contained detailed information on serial calcitonin values and survival for individual patients to calculate individual calcitonin dt values for each patient. The well known study of Giraudet *et al.*[19] was not included in our analysis because this study did not include data on survival.

For the calculation of calcitonin dt, we required a minimum of five patients per publication and at least three calcitonin values per patient. Another inclusion criterion was that calcitonin measurements had to be performed with one laboratory assay technique in each patient. A total of 50 publications were excluded for different reasons (available from authors upon request). Finally, ten studies fulfilling all criteria were included in our analyses.

Data extraction

Common criteria were used to establish outcome and disease progression in the studies that are included in the meta-analysis. The following parameters were collected: age, gender, proportion of sporadic/hereditary MTC, surgical treatment modalities, lymph node surgery, presence of cervical lymph node metastases, follow up duration, presence and time of clinically or radiologically (by (one of) the used imaging techniques) proven recurrence or metastases, additional therapies, tumour-specific death (all patients included in the meta-analysis died due to MTC), number of patients with serial calcitonin and/or CEA measurements, calcitonin and CEA assay method, number of calcitonin CEA measurements per patient, post-operative calcitonin or CEA serum levels, and calcitonin- or CEA-dt in relation to survival and recurrence. We specifically checked for overlapping data sets.

To compare the post-operative values of calcitonin and CEA between patients from different studies, the original serum calcitonin and CEA levels as given in the text were expressed as number of times above the upper limit of normal for the assay used in the particular study. To calculate dts for studies not explicitly reporting calcitonin- and CEA- dt, individual patient data were extracted from the available originally presented data on calcitonin and CEA values. Exponential growing curves $\alpha \exp(\beta \text{ time})$ were fitted to the data (using standard linear regression of the log-transformed serum levels on time) and dts were then calculated as $\ln(2)/\beta$.

Statistical analysis

SPSS for windows, version 14.0 (SPSS Inc., Chicago, IL, USA) was used to perform all analyses. In all tests, a P-value $<0{\cdot}05$ was considered significant and 95% Confidence Intervals (CI) were given, when appropriate.

Kaplan–Meier and univariate Cox regression survival analyses were used to determine the prognostic value of calcitonin and CEA dt for clinical or radiological recurrence (recurrence free survival) and death. For reasons of limited number of events, the analysis was restricted to univariate analysis. As sometimes the estimated hazard ratios (HR) were infinite, the likelihood ratio test was performed to test for associations with survival.

In the literature, different calcitonin dt stratifications are used.[9,17,20–22] In our analyses, we set out to define calcitonin- and CEA-dt strata that were best associated with recurrence-free and disease-specific survival as given by the stratification with the highest HR and smallest CI.

Results

Characteristics of retrospective studies

All studies included are retrospective studies. These are summarized in Table 1. Only four studies provided quantitative data on the prognostic value of calcitonin dt with regard to survival and recurrence. In the other remaining studies, we calculated calcitonin- and CEA-dt from the individual data, according to the methods as described in Materials and methods. There were only two studies reporting both calcitonin- and CEA-dt.[17,18]

In the meta-analysis, individual clinical parameters could be extracted for 73 patients from six studies. Patient characteristics are shown in Table 2. Median follow-up since diagnosis was 71 months (range 6–312 months). During the period of follow-up, clinical or radiological recurrence was observed in 22 (30%) of the patients and 12 (16%) patients died of MTC. The overall 5- and 10-year survival rates were 88% and 81% respectively. Five- and 10-year recurrence free survival rates in all patients were 68% and 47% respectively.

Prognostic factors

Univariate analysis. Kaplan–Meier and univariate Cox regression survival analyses were used to define the prognostic value of calcitonin- and CEA-dt for clinical or radiological recurrence

Table 1. Studies on the prognostic value of calcitonin

Author (year of publication)	Patients (*n*) total/ with serial calcitonin measurement	Sporadic/ familial (%)	Follow-up mean-(range) (in months)	Method of calcitonin analysis	Number of calcitonin values/ patient	Treatment modalities (*n*)†	Clinical proven local recurrence (*n*)	Clinical proven metastases (*n*)	No. patients died of MTC	Calcitonin doubling time and survival (%)	Calcitonin doubling time and recurrence (%)
Stepanas *et al.* (1979)[16]*	32/20	53/47	43–(6–98)‡	RIA	7·7 ± 3·9§	TT 22; ND 7; CT 6; RT 3	nd	4	3	5/10 year§ ≤2 100/nd >2 100/67	5 year§ <2 0 >2 0
Rougier *et al.* (1983)[14]*	31/31	100/0	66–(9–206)	RIA	7·9 ± 3·6§	TT 11; PT 16; ND ≥18; RT 22	5	10	6	5/10 year§ ≤2 100/100 >2 100/100	5 year§ <2 0 >2 31
Busnardo *et al.* (1984)[12]*	41/38	90/10	≤84‡	RIA	8·7 ± 5·8§	TT 36; PT 4; ND 17; CT 7; RT 22	nd	9	4	5/10 year§ >2 91/nd	3 year§ >2 17
Miyauchi *et al.* (1984)[21]	54/54	56/44	33·3 ± 28·3‡	RIA	6·9 ± 5·6¶	nd	12	7	7	3 year ≤0·5 0 >0·5 100	5 year <0·5 100 0·5–1 80 >1 20
Palmer *et al.* (1984)[27]*	19/19	84/16	≤120‡	RIA	15·6 ± 5·1§	TT 11; PT 8; ND 19; CT ≥2; RT 13	0	2	4	5/10 year§ ≤2 0/0 >2 100/100	5 year§ <2 100 >2 33
Saad *et al.* (1984)[18]*	24/24	50/50	Median 66‡ (18–94)	RIA	6·4 ± 2·4§	TT 24; ND 15; RT 7	3	11	4	5/10 year§ ≤2 78/58 >2 100/100	5 year§ <2 78 >2 20
Miyauchi *et al.* (1988)[22]*	67/35	61/39	52 ± 41‡	RIA	10·7 ± 8·3¶	nd	12††	nd	8	3 year§ ≤2 0 >2 100	5 year§ <2 73 >2 23
Barbet *et al.* (2005)[17]	65/65	82/18	115–(6–354)	IRMA	≥4**	TT 65; ND 65; CT nd; RT nd	nd	nd	20	5 /10 year ≤0·5 25/8 0·5–2 92/37 >2 100/100	nd
Chatal *et al.* (2006)[20]	68/68	nd	Median 121 (34–354)‡	RIA	≥7**	nd	nd	nd	29	5/10 year ≤2 67/35 >2 100/100	nd
de Groot *et al.* (2006)[9]	120/nd	55/45	Median 96 (12–420)	RIA or ELISA	nd	TT 118; PT 2; ND 94; CT 6; RT 43	54	38	34	5/10 year ≤1 nd/52 >1 nd/93	10 year ≤1 58 >1 12

*Study which was included in the meta-analysis; †Information only given for the total amount of patients; ‡Duration of serial calcitonin measurements; §Own calculations based on cases with complete information about survival, recurrence and follow-up; ¶Not specified if the amount of calcitonin measurements includes the pre-operative measurements as well; **Includes only the amount of post-operative calcitonin measurements; ††Amount of recurrences (local or distant) not further specified in the article; TT, total thyroidectomy; PT, partial thyroidectomy; ND, node dissection; CT, chemotherapy; RT, radiotherapy; nd, no data; neg, negative doubling time.

Table 2. Clinical characteristics of the patient population

No. patients	73
Age median (range)	41 (14–74)
≤45 / >45 years/unknown	43/28/2
Gender	
Female/male	39/34
Type of MTC	
Sporadic/hereditary/unknown	40/21/12
Extent of surgery	
TT/less than TT/no surgery/unknown	46/14*/1/12
Lymph node dissection†	
Yes/no/unknown	39/22/12
Cervical lymph node metastases	
Yes/no/unknown	41/17/15
Additional treatment	
RT/CT/RAI	29/7/3
None/unknown	28/12
Follow-up duration median (range)	71·0 (6–312)
Calcitonin dt (n = 73)	
< 0 / 0–0·5 / 0·5–2 / > 2 years	21/5/12/35
< 0 / 0–0·5 / > 0·5 year	21/5/47
< 0 / 0–1 / > 1 year	21/11/41
< 0 / 0–2 / > 2 years	21/17/35
CEA dt (n = 39)	
< 0 / 0–0·5 / 0·5–2 / > 2 years	14/4/7/14
< 0 / 0–0·5 / > 0·5 year	14/4/21
< 0 / 0–1 / > 1 year	14/7/18
< 0 / 0–2 / > 2 years	14/11/14
Post-operative calcitonin level‡ median (range) (n = 53)	3·6 (0·16–1600·7)
Post-operative CEA level‡ median (range) (n = 15)	1·74 (0·16–58·1)

*In two patients because of a palliative setting; †Authors did not differentiate between prophylactic and therapeutic lymph node dissection; ‡expressed as number of times above the upper limit of normal for the assay used in each particular study. TT, total thyroidectomy; CT, chemotherapy; RT, radiotherapy; RAI, radioiodine.

(recurrence free survival) and death. There were no significant differences in survival and recurrence-free survival time between the different studies (data not shown).

The following parameters were found to be significant indicators for survival (Table 3): age (HR 5·06, P = 0·020) and calcitonin- and CEA-dt, which appeared to have the highest prognostic value. We compared the prognostic value of the following four classifications:

- dt: 0–0·5 year/0·5–2 years/>2 years (including negative dt),
- dt: 0–0·5 year/>0·5 year (including negative dt),
- dt: 0–1 year/>1 year (including negative dt) and
- dt: 0–2 years/>2 years (including negative dt).

The best prognostic values were found for classification III (Table 3): calcitonin dt classification III: HR: 21·52, $P \leq 0{\cdot}001$ and CEA dt classification III HR: infinite, $P < 0{\cdot}001$. The 5- and 10-year survival for patients with a calcitonin dt of <1 year were 36% and 18% respectively and for patients with calcitonin dt longer than 1 year 98% and 95% respectively (Fig. 1a). A CEA dt of <1 year corresponded with a 5- and 10-year survival of 43% and 21% respectively and a CEA dt longer than 1 year with 100% and 100% respectively (Fig. 2a).

The following parameters were found to be significant indicators for clinical or radiological recurrence (Table 3): lymph node dissection (HR: 0·38, P = 0·044), cervical lymph node metastases (HR: 4·62, P = 0·012) and post-operative calcitonin level (categorized as above or below the upper limit of normal) (HR: 5·89, P = 0·001). Calcitonin- and CEA-dt again appeared to have the highest prognostic value.

Comparing the prognostic value of the former mentioned classifications, the best prognostic values were found for calcitonin dt classification II (HR: 15·00, P = 0·010) and CEA dt classification III (HR: 6·80, P = 0·009). The 5-year recurrence-free survival rate for patients with a calcitonin dt of <1 year was 20%; for patients with a calcitonin dt longer than 1 year, it was 73% (Fig. 1b). For patients with a CEA dt of <1 year, 5-year recurrence-free survival rate was 0% and for patients with a CEA dt longer than 1 year, it was 69% (Fig. 2b).

CEA

Although calcitonin dt is a prognostic parameter for (recurrence free) survival, some patients have a short (recurrence free) survival in spite of a favourable calcitonin dt (calcitonin dt >1 year) and *vice versa* (Fig. 1a, b). One patient with a negative calcitonin dt (−0·22 years) died of MTC 8 months after the primary intervention. The post-operative CEA level in this patient was 58 times the upper limit of normal and the CEA dt was 0·74 year.

Conversely, two patients with unfavourable calcitonin dt of 0·85 and 0·87 years respectively were alive at the end of the period of follow-up of 84 48 months respectively. CEA dt in those patients were 10·2 and 6·5 years respectively. Therefore, it is worthwhile to use CEA dt in addition to calcitonin dt to improve the predictive values of these plasma markers of MTC. When combining the dt of both tumour markers, the combination of a calcitonin dt and CEA dt of <1 year corresponds to 100% mortality and 100% recurrence rate (Table 4). A favourable calcitonin dt and CEA dt (longer than 1 year) corresponds to 100% survival and 32% recurrence rate during the period of follow-up.

In the subset of 39 patients for whom both calcitonin and CEA were known, the model with CEA dt (<1 years) had a higher predictive value for survival (deviance 15·33, HR: ∞, P = <0·001) compared with calcitonin dt (deviance 24·64, HR: 21·09, P = 0·001). Also, for recurrence, the model with CEA dt (<1 year) had a higher predictive value (deviance 80·80, HR: 6·80, P = 0·009) compared with calcitonin dt (deviance 83·30, HR: 4·11, P = 0·036).

The combination of a favourable calcitonin dt (>1 year) with an unfavourable CEA dt (<1 year) seems to represent a worse prognosis, with 50% mortality and 100% recurrence rate when compared with the combination of an unfavourable calcitonin dt (<1 year) and a favourable CEA dt (>1 year), survival being 100% and recurrence rate 50%.

Discussion

We performed this study to analyse the prognostic value of calcitonin- and CEA-dt in patients with MTC.

Table 3. Clinical and biological prognostic variables, univariate analysis

	Survival		Recurrence	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age: ≤45/>45 years	5·06 (1·21–21·13)	**0·020**	1·35 (0·51–3·57)	0·551
Gender: female/male	2·00 (0·58–6·91)	0·268	1·23 (0·53–2·87)	0·626
Type of MTC: hereditary/sporadic	1·01 (0·25–4·05)	0·990	2·17 (0·80–5·89)	0·108
Extent of surgery: total/less than total	1·26 (0·31–5·08)	0·745	0·72 (0·26–1·97)	0·507
LN dissection: yes/no	0·52 (0·10–2·59)	0·403	0·38 (0·14–1·05)	**0·044**
CLN metastases: no/yes	2·59 (0·32–21·07)	0·318	4·62 (1·08–19·86)	**0·012**
Additional treatment: no/yes	3·30 (0·66–16·57)	0·118	1·47 (0·60–3·61)	0·394
Post-operative calcitonin level (n = 53)				
Above or below upper limit of normal	5·08 (0·59–43·38)	0·081	5·89 (1·70–20·45)	**0·001**
Above or below the median	3·26 (0·61–17·28)	0·142	7·38 (2·37–22·98)	**<0·001**
Above or below the mean	2·82 (0·47–16·90)	0·282	3·91 (1·40–10·93)	**0·016**
Post-operative CEA level (n = 15)				
Above or below upper limit of normal	40·90 (0–∞)	0·355	1·43 (0·14–14·12)	0·753
Above or below the median	65·29 (0–∞)	0·244	5·14 (0·53–49·70)	0·122
Above or below the mean	270·76 (0–∞)	0·115	6·27 (0·64–61·12)	0·083
Calcitonin dt classification (n = 73)				
I*: 0.5–2 *vs.* >2 or <0 year(s)	12·58 (2·43–65·21)	**<0·001**	2·18 (0·78–6·07)	**0·015**
0–0.5 *vs.* >2 or <0 year(s)	34·69 (6·39–188·22)		17·32 (3·38–88·82)	
II*: 0–0·5 *vs.* >0·5 or <0 year	12·24 (3·65–41·06)	**<0·001**	15·00 (3·00–74·87)	**0·010**
III*: 0–1 *vs.* >1 or <0 year	21·52 (5·70–81·32)	**<0·001**	5·33 (1·74–16·36)	**0·013**
IV*: 0–2 *vs.* >2 or <0 year	18·23 (3·97–83·65)	**<0·001**	2·90 (1·16–7·21)	**0·033**
CEA dt classification (n = 38)				
I*: 0.5–2 *vs.* >2 or <0 year(s)	∞	**<0·001**	4·09 (1·14–14·69)	**0·033**
0–0·5 *vs.* >2 or <0 year(s)	∞		7·22 (1·33–39·19)	
II*: 0–0·5 *vs.* >0·5 or <0 year	39·53 (4·37–357·71)	**<0·001**	4·93 (0·99–24·54)	0·093
III*: 0–1 *vs.* >1 or <0 year	∞	**<0·001**	6·80 (1·89–24·44)	**0·009**
IV*: 0–2 *vs.* >2 or <0 year(s)	∞	**<0·001**	4·73 (1·49–14·97)	**0·011**

*Classification I: doubling time: 0–0·5 year/0·5–2 years/>2 years (including negative dt), II: doubling time: 0–0·5 year/>0·5 year (including negative dt), III: doubling time: 0–1 year/>1 year (including negative dt), and IV: doubling time: 0–2 years/>2 years (including negative dt). Bold printed categories in the categorical variables were used as reference category in the Cox regression analysis. Significant *P*-values (obtained by the Likelihood ratio test) are printed in bold. LN, lymph node; CLN, central LN.

Although only four studies reported calcitonin dt, we were able to calculate individual calcitonin- and CEA-dt from all 10 studies selected. In the meta-analysis, individual clinical parameters could be extracted for 73 patients from six studies. We found that both calcitonin- and CEA-dt are strong prognostic indicators for disease-related survival and recurrence-free survival, i.e. they can be interpreted as indicators of aggressive disease. Our finding may add to a better stratification of MTC patients to highlight those patients who may be served best through new chemotherapies or radiopharmaceuticals. Doubling times of <1 year reflected the highest hazard ratio: 21·52 for death and 5·33 for recurrence (calcitonin dt) and infinite for death and 6·80 for recurrence (CEA dt). Although calcitonin dt has gained interest to stratify post-operative MTC patients with measurable calcitonin levels, this study shows that CEA dt has a higher predictive value than calcitonin dt.

Interestingly, we also found that in some patients, a favourable calcitonin dt is associated with a poor outcome, although calcitonin dt is a significant prognostic parameter for death and *vice versa*. The addition of CEA-dt to calcitonin dt partially explains this phenomenon, as subgroups of patients have dissociated dts of these two tumour markers.

The underlying assumption in the calculation of dts is that the rates of calcitonin and CEA production per tumour cell are constant during the course of the disease. However, this is not true in all cases, as during the process of dedifferentiation, calcitonin production can be (relatively) normal[23,24] or even decrease, which can be accompanied by an increase in CEA production.[25] We believe, therefore, that the simultaneous analysis of calcitonin- and CEA-dt is essential for a proper risk stratification of MTC patients. Moreover, this process of dedifferentiation may clarify the higher predictive value of CEA dt compared with calcitonin dt which was found in this study.

Finally, we found that the post-operative level of calcitonin is a significant indicator for recurrence-free survival. As in a considerable number of studies, no post-surgical calcitonin levels were reported, it was not possible to combine post-surgical calcitonin levels and calcitonin dt in a statistical model. One needs therefore to consider that the actual tumour burden at baseline is an important factor in determining outcome. A slow dt on a background of high tumour burden may be associated with worse prognosis than short dt in the context of a low starting tumour burden.

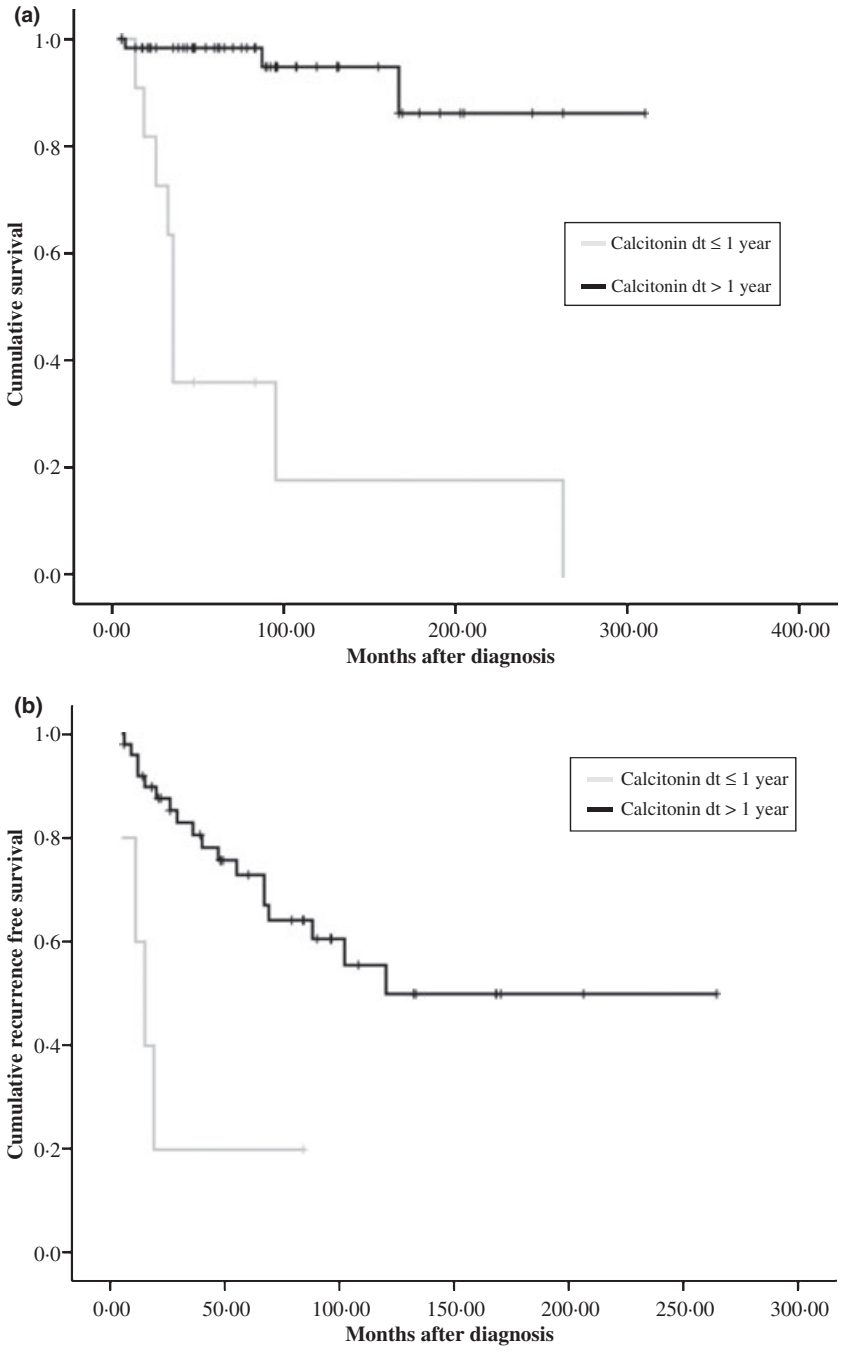

Fig. 1 (a) Disease-specific Kaplan–Meier survival curve of 73 patients with MTC. Patients were grouped according to calcitonin doubling time. Calcitonin dt (0–1 *vs.* >1 year) is a significant prognostic parameter (HR: 21·52, $P = <0{\cdot}001$). The 5- and 10-year survival rates for patients with a calcitonin dt of <1 year were 36% and 18% respectively and for patients with calcitonin dt longer than 1 year, 98% and 95% respectively. (b) Recurrence-free Kaplan–Meier survival curve of 55 patients with MTC. Patients were grouped according to calcitonin doubling time. Calcitonin dt (0–1 *vs.* >1 year) is a significant indicator for clinical or radiological recurrence (HR: 5·33, $P = 0{\cdot}013$). Five-year recurrence-free survival rate for patients with a calcitonin dt of <1 year was 20% and for patients with a calcitonin dt longer than 1 year it was 73%.

Limitations of the current analyses are the retrospective character of the studies and the heterogeneity of the studies involved. Retrospective studies obviously have as a limitation that the outcomes will be affected by changes in surgical procedures, imaging techniques and analytical methods. We were not able to explain the fact that 32% of patients showed a recurrence in spite of favourable dts of both calcitonin and CEA, this being inherent to the retrospective character of the current analysis. In the majority of those patients, information on the post-operative serum level of CEA was missing, which probably is a prognostic indicator as well. Changes in surgical procedures will not affect the biological behaviour of MTC cells (which is the essence of dts), but may have influenced post-surgical calcitonin and CEA levels and may explain the better (recurrence free) survival rates for the unfavourable calcitonin dt in the more recent studies. Nevertheless, there were no significant differences in the calculated survival and recurrence-free survival times among the six studies included in the meta-analysis. We believe that technological developments in imaging devices throughout the follow-up period do not change the general message of our study that calcitonin and CEA dt are important determinants of recurrence, but that the exact cut-off values we found should be interpreted with caution.

The most important aspect in the heterogeneity of the studies are differences in calcitonin and CEA assays. The problem of

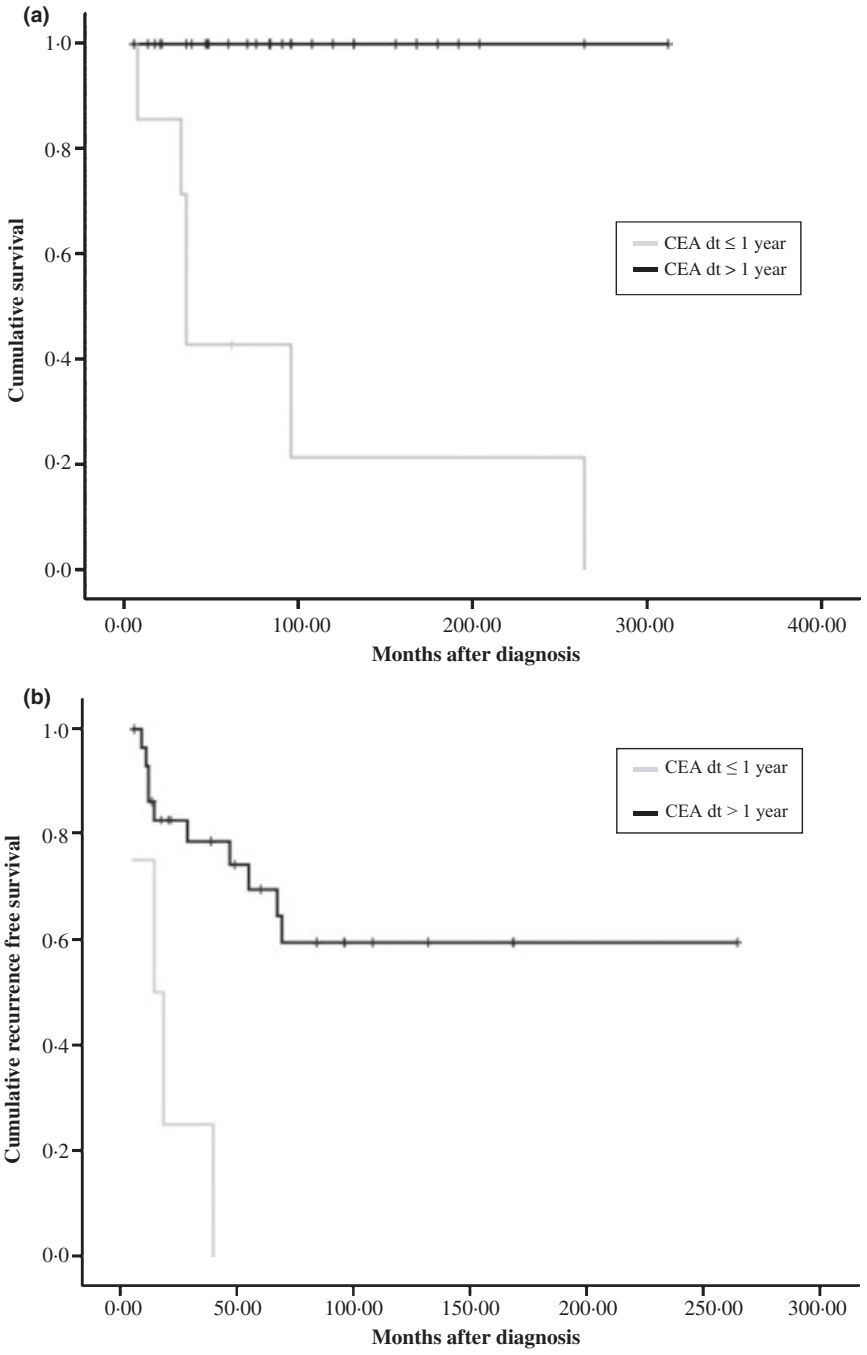

Fig. 2 (a) Disease-specific Kaplan–Meier survival curve of 39 patients with MTC. Patients were grouped according to CEA doubling time. CEA dt (0–1 *vs.* >1 year) is a significant indicator for survival (HR: infinite, $P < 0{\cdot}001$). A CEA dt of <1 year corresponded to a 5- and 10-year survival of 43% and 21% respectively and a CEA dt longer than 1 year to 100% and 100% respectively. (b) Recurrence-free Kaplan–Meier survival curve of 34 patients with MTC. Patients were grouped according to CEA doubling time. CEA dt (0–1 *vs.* >1 year) is a significant indicator for clinical or radiological recurrence (HR: 6·80, $P = 0{\cdot}009$). For patients with a CEA dt of <1 year, 5-year recurrence-free survival rate was 0% and for patients with a CEA dt longer than 1 year, it was 69%.

Table 4. Survival ($n = 39$) and recurrence-free survival ($n = 34$) for the period of follow-up by combination of calcitonin- and CEA-doubling time

	Survival			Recurrence-free survival		
CEA dt	0–1 year	>1 year	Total	0–1 year	>1 year	Total
Ct dt						
0–1 year	0/5	1/2	1/7	0/3	0/1	0/4
>1 year	2/2	30/30	32/32	1/2	19/28	20/30
Total	2/7	31/32		1/5	19/29	

changes in calcitonin assays was overcome by excluding studies in which different assays were used within the same patients. Moreover, as opposed to absolute levels, dts are not affected by the assay. In addition, we normalized absolute calcitonin and CEA levels according to the reference limits of the assays used. Although the 'hook effect' in calcitonin immunoradiometric assay is sporadically described,[26] an effect of this phenomenon on the calcitonin dts as presented in this meta-analysis is theoretically possible. A potential limitation could be overlapping datasets; however, studies conducted by the same group of investigators were not included in the meta-analysis.

Finally, it should be mentioned that in the analysis, we used the Cox regression model of proportional hazards as we assumed that the hazards were proportional. However, it was difficult to test this formally as the number of events was small and several of the estimated HR were infinite. Likewise, the power of the current analysis did not allow a combined quantitative analysis of calcitonin and CEA dt. Therefore, additional studies should be performed with larger numbers of patients.

In conclusion, we found in a structured meta-analysis that both calcitonin- and carcinoembryonic antigen-dt are strong prognostic indicators for medullary thyroid carcinoma recurrence and death. carcinoembryonic antigen-dt has a remarkable higher predictive value than calcitonin dt. The study in part confirms the findings of earlier studies, but extends their findings in the notion that the Carcinoembryonic antigen-dt has a higher predictive value than calcitonin dt.

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Competing interests/financial disclosure

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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