European Thyroid Journal (2026) 15 ETJ250381
https://doi.org/10.1530/ETJ-25-0381

Received 3 December 2025
Accepted 9 February 2026
Available online 10 February 2026
Version of Record published 19 February 2026

RESEARCH

# Clinical presentation and outcomes of medullary thyroid cancer in two European countries: impact of diagnostic strategies

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## Abstract

*Objective:* To evaluate differences in clinical presentation, diagnostic and therapeutic modalities, and outcomes in two cohorts of patients with sporadic medullary thyroid carcinoma (MTC) from reference centres in Italy and the Netherlands. The two centres have different diagnostic approaches, including the use of routine calcitonin (CT) measurement.

*Methods:* A total of 165 patients (106 Italian and 59 Dutch) were retrospectively included. The cohorts were compared overall and according to diagnostic modality. Logistic regression and multivariable Cox proportional hazards models were used, as appropriate, to assess progression-free survival (PFS), disease-specific survival (DSS) and associated risk factors.

*Results:* The Dutch cohort presented with more advanced disease, as per higher TNM, AJCC staging, and significantly higher CT both preoperative and at last visit ($P < 0.001$). Dutch patients received more frequently second operations, radiotherapy, and systemic treatments. PFS and 10-year DSS were significantly lower in the Dutch cohort ($P < 0.001$ and $P$ 0.01). Tumour size, nodal involvement, presence of distant metastases at diagnosis and progression during the follow-up were independent strong predictors of shorter PFS and DSS. Patients diagnosed via routine CT measurement showed a less aggressive presentation and more favourable outcome.

*Conclusion:* We compared for the first time two MTC cohorts from countries with different diagnostic and therapeutic approaches. Our data contribute to highlighting an association between routine CT measurement and MTC presentation and outcome, while suggesting that caution should be exercised when interpreting the differences among countries in MTC prevalence and clinical features.

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*European Thyroid Journal* (2026) **15** ETJ250381
https://doi.org/10.1530/ETJ-25-0381

Keyword: medullary thyroid cancer; outcome; calcitonin screening

## Introduction

Medullary thyroid cancer (MTC) is a rare form of thyroid cancer arising from parafollicular C cells and producing calcitonin (CT). MTC is sporadic in 75% of cases, while hereditary forms, in the context of multiple endocrine neoplasia (MEN) syndromes, represent 25% of cases. MTC disease-specific survival (DSS) is >90% in its early stages (stages I–III), while it dramatically worsens for patients with stage IV tumours (5-year DSS 33%) (1). Consistently, its early detection, mainly based on routine CT measurement in thyroid nodular diseases, leads to earlier and potentially more effective surgical interventions and has been shown to play an important prognostic value (2, 3). Nevertheless, the use of this diagnostic tool is still highly debated at the international scientific level, with the present European and American guidelines not endorsing its routine use in patients without a family history of a hereditary tumour syndrome associated with MTC (4, 5). Although CT determination is highly sensitive and specific in the early detection of MTC, and its cost-effectiveness has been demonstrated in selected healthcare settings, its wide use is limited due to the difficulties in the interpretation of borderline values, to the finding of false-positive results and to substantial heterogeneity among healthcare systems (6). Indeed, mildly elevated CT levels can be due to reactive C-cell hyperplasia related to other thyroid and non-thyroidal diseases and could warrant a further evaluation via calcium stimulation test, whose results often require specific expertise to be correctly interpreted (7, 8). However, the absence of clear clinical practice guidelines for the management of borderline CT values could result in interpretation and management variability. One possible approach to assess the clinical utility of routine CT measurement is to compare different clinical settings, specifically centres that do or do not incorporate this tool into preoperative diagnostics of apparently sporadic thyroid nodules. In particular, in the Netherlands and according to both the previous (9) and the current guidelines (https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom_2024), routine CT measurement is not recommended and the diagnostic work-up of thyroid nodules (e.g. neck ultrasound (US) and fine-needle aspiration cytology (FNAC)) usually starts in clinically symptomatic cases. In Dutch clinical practice, CT levels are often determined preoperatively after cytological (or histological, following diagnostic lobectomy for nodules with indeterminate cytology not suspicious for MTC) confirmation of MTC, to better plan the surgical treatment. On the other hand, neck ultrasound is widely used in Italy, and the finding of incidental thyroid nodules is frequent, especially in females. Moreover, most Italian referral centres apply the routine screening, meaning one CT measurement at the first diagnosis of all thyroid nodule/s. As a possible consequence of these diagnostic differences, MTC incidence is lower in the Netherlands than in Italy (0.24 vs 0.84 per 100,000 women, respectively; period 2008–2012).

The main aim of the present study is to understand if and how different diagnostic approaches applied in two European referral centres (Italy and the Netherlands) can influence the clinical presentation, the treatment burden and the outcome of sporadic MTC patients in a real-life setting.

## Methods

### Study design and population

The study was conducted in accordance with the Ethical Standards of the Institutional Research Committee and with the 2024 Declaration of Helsinki. The Italian cohort includes patients enrolled in a clinical protocol (ClinicalTrials.gov identifier NCT05752604), while Dutch patients consented to the use of their clinical anonymized data for research purposes, being the study approved by the Medical Ethics Review Committee, East Netherlands (file number 2024-17318). Both sites are tertiary referral centres for the diagnosis and treatment of thyroid cancer. Data were retrospectively collected and analysed from medical records at both sites. A total of 165 sporadic MTC patients diagnosed between 01/2000 and 01/2024 (106 from Istituto Auxologico Italiano (IAI) and 59 from Radboud University Medical Centre (RUMC)) with a follow-up (FU) of at least 6 months since primary treatment were included. Median FU time was 111 months for IAI patients and 50 months for RUMC patients. Patients with incomplete FU data were excluded.

### Clinical and pathological evaluation

Diagnostic modalities are mutually exclusive categories and were applied consistently across both centres throughout the analysis. In particular, patients receiving thyroid surgery because of the detection of elevated CT levels in the evaluation of nodular thyroid disease were classified as ‘diagnosed via CT screening’. Patients receiving thyroid surgery upon FNAC suspicion of thyroid cancer were classified as ‘diagnosed via FNAC’. The detection of a MTC in a thyroid removed for other clinical reasons (e.g. multinodular goitre and Graves’ disease) was referred to as ‘incidental MTC’, and patients diagnosed via a biopsy/operation on a

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metastatic site of an initially unknown MTC were referred to as 'metastasis biopsy'.

Throughout the study period, different analytical methods and assays were used across the centres and assay-specific institutional cut-off values were adopted. This applies to both centres in the FU of operated MTC patients and solely to the Italian institution for the interpretation of the basal CT values in the context of the CT screening program. In case of borderline CT levels, patients were further investigated via a calcium gluconate stimulation test (8).

Most patients underwent a total thyroidectomy, while a small proportion underwent a hemithyroidectomy or was considered inoperable at the diagnosis because of the extent of the tumour. Lymphadenectomy was classified as central (level VI), lateral (levels I–V), and central + lateral. Indications for lateral lymphadenectomy were based in both centres based on the presence of clinical suspicious lymph nodes at preoperative US assessment: patients without suspicious nodes at preoperative US did not undergo lateral compartment lymphadenectomy. Tumour staging followed the 8th edition of the AJCC staging system (10). Pathology reports were consulted for each patient to assess tumour size (cm), number of metastatic nodes, presence of extrathyroidal extension (ETE), multifocality and vascular invasion.

All the included patients underwent a germline genetic testing for *RET* gene mutations and only negative patients were included, thus excluding hereditary forms of MTC.

Secondary treatment during FU consisted of one or more of the following: surgery for local and/or distant metastases, palliative/curative radiotherapy (RT), and tyrosine kinase inhibitor (TKI) treatment.

Patients' response to treatment was assessed at the last FU visit and classified as disease remission, biochemical incomplete response and structural incomplete response (11).

Locoregional or distant metastasis progression was assessed according to the RECIST criteria v1.1 (12), and DSS analysis included only TC-related deaths.

### Statistical analysis

Results are expressed as mean for normally distributed continuous variables or as absolute frequencies and percentages for categorical variables. Comparison of continuous variables among the two independent cohorts was performed using one-way ANOVA for normally distributed variables and using non-parametric tests (as Mann–Whitney test) for variables not respecting normality distribution. Categorical variables were compared by chi-square test or Fisher's exact test, as appropriate. DSS and progression-free survival (PFS) analyses were performed using the Kaplan–Meier method, and both populations were compared using the log-rank test. A logistic regression analysis followed by a multivariable Cox proportional hazards analysis with backward stepwise selection was performed to identify factors associated with PFS and DSS. $P < 0.05$ was considered statistically significant. All analyses were carried out using SPSS Statistics for Windows (version 29.0).

### Missing data analysis

Given the retrospective design of the study, some variables contained data not available (NA) (Table 1). They were handled as follows:

- For the comparison via one-way ANOVA/Mann–Whitney test for continuous variables and chi-square test for categorical variables: exclusion of NA data.
- For the multivariable Cox proportional hazards analysis for DSS and PFS: simple imputation method, performed using mean/median for continuous variables and mode for categorical variables. The imputation analysis results were consistent with the studied clinical scenarios, although it may present inherent methodological limitations.

## Results

### Presentation

The differences in clinicopathological features and diagnostic and treatment modalities of the two cohorts are reported in Table 1, highlighting significant differences in diagnostic strategy and disease stage at presentation. In particular, IAI showed a significantly higher proportion of female patients (72 vs 51%, $P = 0.007$), while age was similar between the groups (IAI: 59.3 ± 13.9 vs RUMC: 55.3 ± 15.7, $P = 0.1$). As far as diagnostic modalities are concerned, the two groups showed significant differences ($P < 0.001$): FNAC was used more frequently in the Dutch cohort (90 vs 48%), while no Dutch patient was diagnosed via CT screening (0 vs 47%); incidental MTC and the metastasis biopsy of an initial unknown MTC were infrequent in both cohorts. The median preoperative CT was significantly higher in the Dutch cohort: 5,466 (range: 360–49,761) vs 126 (range: 8–20,538) ng/L, $P < 0.001$. The percentage of patients submitted to central compartment lymphadenectomy was similar in the two series (36 vs 40%), while RUMC patients had higher rates of central + lateral compartment lymphadenectomy (46 vs 26%) and lower rates of patients treated by thyroidectomy without lymphadenectomy (16 vs 32%, $P = 0.055$). In the Dutch cohort, a higher proportion of patients were deemed inoperable due to advanced locoregional disease or did not undergo thyroid surgery because of extensive metastatic disease at the time of

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**Table 1** Comparison of tumour presentation, treatment modalities, and follow-up between the Italian (IAI) and Dutch (RUMC) cohorts. Data are presented as *n* (%) or as median (IQR).

| Variables | IAI | RUMC | *P* |
|---|---|---|---|
| Total *n* | 106 | 59 | |
| Females | 76 (72%) | 30 (51%) | 0.007 |
| Age, years | 59.3 ± 13.9 | 55.3 ± 15.7 | 0.1 |
| Diagnostic modality | | | <0.001 |
| FNAC | 48 (48%) | 52 (90%) | |
| CT screening | 47 (47%) | 0 (0%) | |
| Incidental MTC | 5 (5%) | 3 (5%) | |
| Metastasis biopsy | 0 (0%) | 3 (5%) | |
| NA | 6 | 1 | |
| Preoperative CT, ng/L | 126 (8–20,538) | 5,466 (360–49,761) | <0.001 |
| NA | 43 | 9 | |
| Inoperable disease | 2 (2%) | 9 (15%) | 0.001 |
| Lymphadenectomy | | | 0.055 |
| CC | 40 (40%) | 18 (36%) | |
| CC + LC | 26 (26%) | 23 (46%) | |
| LC | 3 (3%) | 1 (2%) | |
| No | 32 (32%) | 8 (16%) | |
| NA | 5 | 9 | |
| T, cm | 1.2 (0.2–9) | 3.5 (0.7–11) | <0.001 |
| NA | 15 | 12 | |
| T | | | <0.001 |
| T1 | 65 (66%) | 10 (21%) | |
| T2 | 15 (15%) | 20 (42%) | |
| T3 | 17 (17%) | 15 (31%) | |
| T4 | 2 (2%) | 3 (6%) | |
| NA | 7 | 11 | |
| N, *n* | 0 (0–28) | 4 (0–105) | <0.001 |
| NA | 11 | 10 | |
| N | | | <0.001 |
| N0-x | 71 (72%) | 16 (33%) | |
| N1a | 9 (9%) | 11 (22%) | |
| N1b | 19 (19%) | 22 (45%) | |
| NA | 7 | 10 | |
| M1 | 6 (6%) | 15 (25%) | <0.001 |
| AJCC stage | | | <0.001 |
| I | 58 (58%) | 6 (11%) | |
| II | 14 (14%) | 8 (14%) | |
| III | 9 (9%) | 10 (18%) | |
| IVa | 13 (13%) | 18 (32%) | |
| IVc | 6 (6%) | 15 (26%) | |
| NA | 6 | 2 | |
| ETE | | | |
| Yes | 22 (22%) | 14 (30%) | 0.30 |
| NA | 6 | 12 | |
| Multifocality | | | |
| Yes | 14 (15%) | 5 (7%) | 0.48 |
| NA | 10 | 11 | |
| Vascular invasion | | | |
| Yes | 13 (16%) | 11 (24%) | 0.26 |
| NA | 22 | 12 | |
| Other treatment | | | |
| Second operation | 6 (6%) | 20 (34%) | <0.001 |
| RT | 2 (2%) | 9 (15%) | <0.001 |
| TKIs | 11 (10%) | 17 (29%) | 0.002 |
| Last CT, ng/L | 0.5 (0–28,100) | 35 (0–44,330) | <0.001 |

FNAC, fine-needle aspiration cytology; CT, calcitonin; MTC, medullary thyroid cancer; TC, thyroid cancer; CC, central (neck) compartment; LC, lateral (neck) compartment; T, tumour dimension; N, nodes; M, metastasis; TNM and AJCC according to 8th edition; ETE, extrathyroidal extension; TKIs, tyrosine kinase inhibitors; RT, radiotherapy; last CT, calcitonin at the last visit (excluded not operated patients and patients in TKI treatment); and NA, not available for missing data or not applicable data because of operation not performed (and therefore not included in the analysis).

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diagnosis (15 vs 2%, $P$ = 0.001). At histology, the Dutch cases had a larger size (median diameter at histology: 3.5 (range: 0.7–11) vs 1.2 (range: 0.2–9) cm, $P$ < 0.001), were more frequently T3–T4 at TNM classification (37 vs 19%, $P$ < 0.001), and were with a more extensive nodal involvement (median number of nodes at histology: 4 (range: 0–105) vs 0 (range: 0–28) and N1b: 45% vs 19%, for both $P$ < 0.001). Moreover, the Dutch cohort showed a significantly higher proportion of patients presenting with a metastatic disease at diagnosis (25 vs 6%, $P$ < 0.001). Consistent with the above-reported data, the stage at diagnosis was higher in the RUMC cohort: stage III–IVA/C 76 vs 28%, $P$ < 0.001. On the other hand, the differences between RUMC and IAI cohorts did not reach statistical significance as far as ETE (30 vs 22%, $P$ = 0.30), multifocality (7 vs 15%, $P$ = 0.48), and vascular invasion (24 vs 16%, $P$ = 0.26) are concerned. Additional treatments during FU were significantly more frequent in the RUMC cohort: surgery for locoregional disease control (34 vs 6%, $P$ < 0.001), radiotherapy in a palliative and/or curative setting (15 vs 2%, $P$ = 0.002) and TKI therapy (29 vs 10%, $P$ < 0.001). Considering the more advanced disease stages, stage III patients received additional surgeries more frequently in the RUMC cohort (70 vs 11%, $P$ = 0.01), while the rates of stage IV patients receiving additional treatments during FU were comparable (IAI vs RUMC): surgery for locoregional disease control (26 vs 33%, $P$ = 0.31), radiotherapy in a palliative and/or curative setting (10 vs 21%, $P$ = 0.33) and TKI therapy (37 vs 45%, $P$ = 0.54) (data not shown).

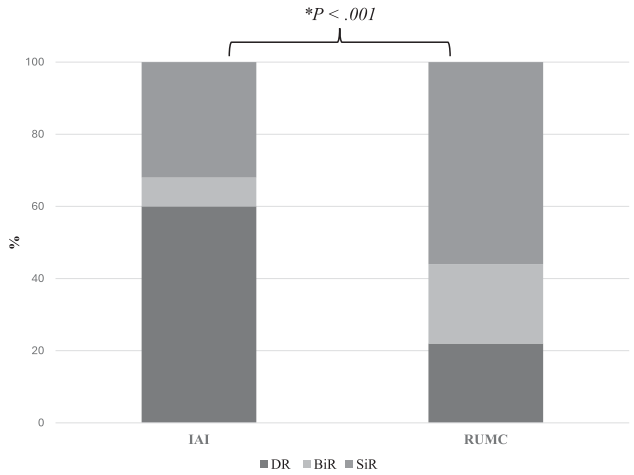


**Figure 1**

Comparison of disease outcomes at the last follow-up visit between the two cohorts. IAI, Istituto Auxologico Italiano (Italian series); RUMC, Radboud University Medical Centre (Dutch series); DR, disease remission; BiR, biochemical incomplete response; SiR, structural incomplete response.

## Outcome

At the last FU visit, IAI cohort had higher rates of disease remission (60 vs 22%) and lower rates of structural incomplete response (32 vs 56%) ($P$ < 0.001) (Fig. 1). Median CT levels at the last follow-up visit were 0.5 (range: 0–28,100) ng/L in the IAI cohort and 35 (range: 0–44,330) ng/L in the RUMC cohort ($P$ < 0.001) (Table 1).

Distant metastatic progression was more frequent in the Dutch cohort (39 vs 12%, $P$ = 0.003), which had a significantly shorter PFS (log-rank: 18.6, $P$ < 0.001, median PFS not reached; 5-year PFS: 71 vs 92%, $P$ = 0.0003; 10-year PFS: 68 vs 88%, $P$ = 0.001) (Fig. 2A). Death from MTC was more frequently recorded in the Dutch cohort (17 vs 6%, $P$ = 0.019), which had a significantly shorter DSS (log-rank: 5.72, $P$ = 0.01, median DSS not reached; 5-year DSS: 86 vs 97%, $P$ = 0.008; 10-year DSS: 85 vs 96%, $P$ = 0.009) (Fig. 2B).

No significant differences in PFS and DSS at the end of FU were found after dividing patients per disease stage. Stage I–II patients showed similar progression and survival outcomes – PFS: 98.5% in IAI vs 92.8% in RUMC, log-rank: 1.61, $P$ = 0.20; DSS: 100% in IAI vs 100% in RUMC, log-rank: 0, $P$ = 1. Similarly, in stage III–IV patients, no statistically significant differences were found in progression and survival outcomes – PFS: 64.3% in IAI vs 51.2% in RUMC, log-rank: 1.43, $P$ = 0.23; DSS: 78.6% in IAI vs 76.7% in RUMC, log-rank: 0.06, $P$ = 0.8 (Fig. 3).

## Risk factor analysis for PFS and DSS for MTC

A univariable analysis was performed including several variables (data not shown). To note, being diagnosed via CT screening trended towards an association to a lower mortality, though not reaching statistical significance ($P$ = 0.1). Moreover, at the multivariable Cox proportional hazards analysis, which included only variables found to be significant at the univariable logistic regression, the median tumour size, the median number of nodes and the presence of distant metastasis at diagnosis were significantly correlated with a shorter PFS (OR: 1.3, CI: 1.12–1.57, $P$ = 0.007; OR: 1.04, CI: 1.03–1.06, $P$ < 0.001; OR: 19.7, CI: 8.96–43.5, $P$ < 0.001, respectively). On the other hand, the presence of T4 tumours, the use of CC + LC lymphadenectomy, the presence at diagnosis and the progression of distant metastasis during FU were independently associated with a shorter DSS (OR: 4.56, CI: 1.13–18.2, $P$ = 0.03; OR: 11.8, CI: 2.48–56.6, $P$ = 0.002; OR: 15.1, CI: 3.57–64, $P$ = 0.0002; OR: 7.5, CI: 1.52–36.7, $P$ = 0.013, respectively).

## Comparison between patients diagnosed via FNAC

In this analysis, we included only patients diagnosed via FNAC (48 in the Italian and 52 in the Dutch cohorts).

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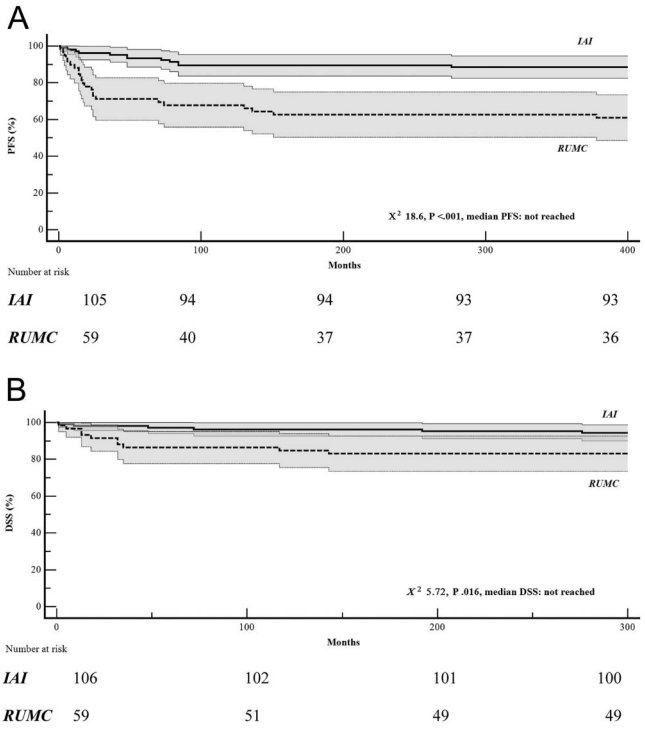


**Figure 2**

(A) Kaplan–Meier analysis for progression-free survival; (B) Kaplan–Meier analysis for DSS. IAI, Istituto Auxologico Italiano (Italian series, continuous line); RUMC, Radboud University Medical Centre (Dutch series, dotted line). The shaded areas represent 95% confidence intervals. Censored events are indicated by marks on the curves.

As far as the Italian cohort is concerned, these patients had a FNAC diagnosis because CT measurement was not required or because cytological data were available before CT measurement. The differences in clinicopathological features and outcome variables of these two subcohorts are reported in Table 2.

The two cohorts had tumours with significantly different median sizes – IAI: 1.4 (range: 0.53–9) vs RUMC: 3.5 cm (range: 0.7–11), $P < 0.001$. T3–T4 tumours and N1b and M involvement were more frequent in the RUMC cohort, though not reaching statistical significance ($P = 0.20$, 0.06 and 0.07, respectively). The median preoperative CT remained significantly higher in the Dutch cohort: 5,037 (360–49,000) vs 306 (8–20,000) ng/L, $P < 0.001$. As a result, the Dutch cohort still showed a more advanced AJCC disease stage (stage III–IVA/C 76 vs 34%, $P < 0.001$), and a higher rate of distant metastasis progression (38% vs 15%, $P = 0.008$). Nevertheless, at the end of the FU, both cohorts showed comparable levels of last CT values (RUMC: 24.4 (0–44,300) vs IAI: 2.8 ng/L (0–14,000), $P = 0.05$), similar rates of structural incomplete response (RUMC: 54% vs IAI: 44%, $P = 0.36$) and similar rates of deaths from MTC (15% vs 6%, $P = 0.14$).

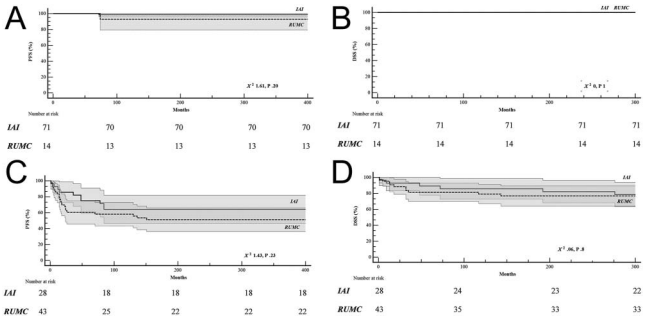


**Figure 3**

(A) Kaplan–Meier analysis for progression-free survival for stage I–II patients; (B) Kaplan–Meier analysis for DSS for stage I–II patients; (C) Kaplan–Meier analysis for progression-free survival for stage III–IV patients; and (D) Kaplan–Meier analysis for DSS for stage III–IV patients. IAI, Istituto Auxologico Italiano (Italian series, continuous line); RUMC, Radboud University Medical Centre (Dutch series, dotted line). The shaded areas represent 95% confidence intervals. Censored events are indicated by marks on the curves.

## Comparison between patients diagnosed via FNAC and CT screening

In this analysis, we compared the clinical presentation and survival outcomes of patients diagnosed via FNAC and CT screening, irrespective of the institution cohort. It is to be noted that the CT screening cohort is composed exclusively of IAI patients, since CT screening is not applied in RUMC. The results are summarized in Table 3.

Patients diagnosed via FNAC presented a more advanced clinical presentation at diagnosis and more severe survival outcomes compared to the one diagnosed via CT screening: preoperative CT levels (2,462 (8–49,761) vs 90 (13–25,380) ng/L, $P < 0.001$), T3–T4 (30% vs 14%, $P = 0.002$), median tumour dimension (cm) (2.2 vs 1.1 ($P = 0.001$)), N1b (39% vs 9%, $P = 0.001$), median number of nodes (1 vs 0 ($P = 0.007$)), AJCC III–IV (54% vs 23%, $P < 0.001$), recurrence of secondary treatments (35% vs 14%, $P = 0.005$), last CT levels (12 (0–44,330) vs 0 (0–28,100) ng/L, $P < 0.001$), structural incomplete response at the last FU visit (49% vs 17%, $P < 0.001$), distant metastasis progression (27% vs 9%, $P = 0.01$) and death from MTC (11% vs 2%, $P = 0.06$).

# Discussion

This study evaluates for the first time two reference cohorts of patients with sporadic MTC treated at tertiary referral centres in two European countries, which differ in the inclusion (Italy) or not (the Netherlands) of the routine CT measurement in the diagnostic work-up of nodular diseases. The comparison of clinical presentation and outcomes between these cohorts holds clinical and socioeconomic implications and represents the best way to get more real-life

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**Table 2** Comparison between the Italian (IAI) and the Dutch (RUMC) patients diagnosed via fine-needle aspiration cytology. Data are presented as *n* (%) or as median (IQR).

| Variable | IAI | RUMC | *P* |
|---|---|---|---|
| Total *n* | 48 | 52 | |
| Females | 32 (66%) | 27 (52%) | 0.13 |
| Age, years | 60.1 ± 13.9 | 55.2 ± 16.4 | 0.27 |
| Preoperative CT, ng/L | 306 (8–20,000) | 5,037 (360–49,000) | <0.001 |
| NA | 18 | 6 | |
| T, cm | 1.4 (0.53–9) | 3.5 (0.7–11) | <0.001 |
| NA | 4 | 7 | |
| T | | | 0.20 |
| T1–T2 | 35 (77%) | 28 (63%) | |
| T3–T4 | 11 (23%) | 16 (37%) | |
| NA | 2 | 8 | |
| N, *n* | 0 (0–17) | 4 (0–105) | 0.005 |
| NA | 3 | 7 | |
| N | | | |
| N1b | 14 (30%) | 22 (49%) | 0.06 |
| NA | 1 | 7 | |
| M | | | |
| M1 | 4 (8%) | 11 (21%) | 0.07 |
| AJCC stage | | | <0.001 |
| I | 23 (49%) | 6 (12%) | |
| II | 8 (17%) | 6 (12%) | |
| III | 3 (6%) | 9 (18%) | |
| IVa | 9 (19%) | 18 (36%) | |
| IVc | 4 (9%) | 11 (22%) | |
| NA | 1 | 2 | |
| Other treatment | | | |
| Second operation | 2 (4%) | 17 (33%) | 0.003 |
| RT | 0 (0%) | 6 (12%) | 0.01 |
| TKIs | 7 (15%) | 14 (27%) | 0.13 |
| Last CT, ng/L | 2.8 (0–14,000) | 24.4 (0–44,300) | 0.05 |
| Response to treatment | | | |
| SiR | 21 (44%) | 28 (54%) | 0.36 |
| Distant metastasis progression | 7 (15%) | 20 (38%) | 0.008 |
| Death from TC | 3 (6%) | 8 (15%) | 0.14 |

T, tumour dimension; N, nodes; M, metastasis; TNM and AJCC according to 8th edition; TKIs, tyrosine kinase inhibitors; RT, radiotherapy; last CT, calcitonin at last visit (excluded not operated patients and patients in TKI treatment); SiR, structural incomplete response; and NA, not available for missing data or not applicable data because of operation not performed (and therefore not included in the analysis).

insights into this highly debated topic. Statistically significant differences in the clinical presentation were observed between the two cohorts. Namely, patients in the Dutch cohort presented with a more advanced disease at diagnosis and during the FU, as per higher TNM, more advanced AJCC staging and higher CT levels both preoperatively and at the last FU visit. These findings are consistent with data from a multicentre Dutch retrospective study on 230 clinically evident MTC cases diagnosed before 2007, in which T3–T4 tumours represented 30% of the cohort (compared to 34% in the present study) and N1b lymph node involvement was observed in 40% of cases (45% in the present study) (13). On the other hand, the current Italian data align with findings from a cohort of 529 sporadic MTC cases from a single academic institution, in which 11.7% of patients had T3–T4 tumours (19% in the present study), 22.9% had N1b involvement (19% in the present study), and 7% had metastatic disease at diagnosis (6% in the present study) (14).

Among the features at presentation, female sex was significantly more represented in the Italian cohort (though not significant at the logistic analysis). This is likely an indicator of the contribution of the widespread use of thyroid ultrasound in Italy with the consequent overdiagnosis of thyroid nodules, particularly in females who are more prone to develop thyroid diseases.

In the present study, we also investigated differences in treatment modalities. The Dutch cohort more frequently underwent lateral neck dissection, surgeries for locoregional disease control during follow-up, radiotherapy (both curative and palliative) and treatment with TKI. These differences likely reflect not only the more advanced disease at diagnosis but also different management protocols. In particular, the

*European Thyroid Journal* (2026) **15** ETJ250381
https://doi.org/10.1530/ETJ-25-0381

**Table 3** Comparison between patients diagnosed via FNAC and 'CT screening' irrespective of institution cohort. Data are presented as *n* (%) or as median (IQR).

| Variables | FNAC | CT screening | *P* |
|---|---|---|---|
| Total *n* | 100 | 47 | |
| Females | 59 (59%) | 35 (75%) | 0.069 |
| Age, years | 59.5 | 58 | 0.38 |
| Preoperative CT, ng/L | 2,462 (8–49,761) | 90 (13–25,380) | <0.001 |
| NA | 25 | 13 | |
| T | | | 0.002 |
| T1 | 37 (41%) | 33 (75%) | |
| T2 | 26 (29%) | 5 (11%) | |
| T3 | 22 (24%) | 6 (14%) | |
| T4 | 5 (6%) | 0 (0%) | |
| NA | 10 | 3 | |
| T, cm | 2.2 (0.5–11) | 1.1 (0.2–4.5) | 0.0001 |
| NA | 10 | 8 | |
| N | | | 0.001 |
| N0-x | 43 (47%) | 33 (77%) | |
| N1a | 13 (14%) | 6 (14%) | |
| N1b | 36 (39%) | 4 (9%) | |
| NA | 8 | 4 | |
| N, *n* | 1 (0–105) | 0 (0–28) | 0.007 |
| NA | 10 | 5 | |
| M | | | |
| M1 | 15 (15%) | 1 (2%) | 0.019 |
| AJCC | | | <0.001 |
| I | 29 (29%) | 30 (65%) | |
| II | 14 (14%) | 3 (7%) | |
| III | 12 (12%) | 6 (14%) | |
| IVa | 27 (27%) | 3 (7%) | |
| IVc | 15 (15%) | 3 (7%) | |
| NA | 3 | 2 | |
| Other treatment needed | 35 (35%) | 6 (14%) | 0.005 |
| Last CT, ng/L | 12 (0–44,330) | 0 (0–28,100) | <0.001 |
| Response to treatment | | | <0.001 |
| DR | 34 (34%) | 38 (81%) | |
| BiR | 17 (17%) | 1 (2%) | |
| SiR | 49 (49%) | 8 (17%) | |
| Distant metastasis progression | 27 (27%) | 4 (9%) | 0.01 |
| Death from TC | 11 (11%) | 1 (2%) | 0.06 |

FNAC, fine-needle aspiration cytology; CT, calcitonin; F, female; T, tumour dimension; N, nodes; M, metastasis; TNM and AJCC according to 8th edition; DR, disease remission; BiR, biochemical incomplete response; SiR, structural incomplete response; last CT, calcitonin at last visit (excluded not operated patients, patients in TKI treatment); and NA, not available for missing data or not applicable data because of operation not performed (and therefore not included in the analysis).

higher frequency of reoperations in the stage III patients of the Dutch cohort could possibly stem for a more aggressive approach to disease persistence or recurrence, while active surveillance behaviour for locoregional persistence seems to be more represented in the Italian cohort. To note, stage IV patients received similar rates of additional treatment between the two cohorts, highlighting that patients with an advanced/life-threatening disease were treated in both cohorts according to the best available therapeutic options.

As far as the outcome is concerned, the Italian cohort had significantly higher rates of disease remission and lower rates of structural disease. Distant metastatic progression was more frequent in the Dutch cohort, which had a significantly shorter PFS and DSS at 10 years (71 vs 92% and 85 vs 96%, respectively). The lack of difference in the outcome when dividing patients by stage likely indicate that those differences are related to a more advanced presentation stage in the Dutch centre rather than to differences in treatment modalities, as underlined by the same frequencies of second operations, RT and TKI treatment in stage IV patients.

Although beyond the scope of our study, we wanted to evaluate the risk factors associated with PFS and DSS in the whole cohort. The multivariable analysis showed that larger tumour size, higher number of metastatic lymph

*European Thyroid Journal* (2026) **15** ETJ250381
https://doi.org/10.1530/ETJ-25-0381

nodes and the presence of distant metastasis at diagnosis were significantly correlated with a shorter PFS, while T4 tumours, CC + LC lymphadenectomy and the presence at diagnosis and the progression of distant metastasis during FU were independently associated with a shorter DSS.

To assess the potential role of CT screening in explaining outcome differences between the two cohorts, we performed a sub-analysis including only those patients, from both cohorts, diagnosed via FNAC of a suspicious thyroid nodule without prior CT determination. Notably, in this comparison, differences in rates of T3–T4 disease, N1b and M involvement at diagnosis, structural disease at the last follow-up and MTC-related mortality were no longer statistically significant, highlighting the role of routine CT measurement in the early diagnosis in the clinical presentation of MTC. Nevertheless, tumour size, AJCC stage and distant metastasis progression were still significantly different. The significantly smaller size of the primary tumour at diagnosis in the Italian cohort reflects the general approach towards diagnosis of thyroid nodules, including the wide use of neck ultrasound. On the other hand, the more restrictive diagnostic approach intended to reduce overdiagnosis and overtreatment likely justifies the worse AJCC stage in the Dutch cohort with a larger tumour size and more extensive locoregional and distant metastatic involvement (with a *P*-value close to the 0.05 threshold). Still, the relatively limited number of cases and events does not allow us to draw a definitive explanation of the higher frequency of metastatic disease progression during the FU in the RUMC cohort compared with FNAC-diagnosed IAI patients.

As an additional tool to study the impact of routine CT measurement, we compared patients diagnosed via FNAC and patients diagnosed via CT screening, irrespective of the institution of origin. Patients diagnosed by FNAC had bigger tumours, a more frequent nodal involvement and a higher frequency of metastatic disease at the diagnosis, resulting in a more advanced AJCC stage at presentation, and a significantly higher frequency of structural disease and metastatic disease progression during the FU. However, it is to be noted that the CT screening cohort was solely composed by IAI patients, and the possible impact of the frequent use of neck US in Italy on top of routine CT program cannot be excluded.

### Study limitations

This study has certain limitations that must be acknowledged. The academic setting of the research may limit the generalizability of the findings to the broader national population. Nevertheless, due to the rarity of this malignancy, patients with MTC are frequently referred to tertiary institutions (15), and these cohorts may thus partially reflect broader national patterns. Moreover, we did not include in our comparative analyses the tumour genetic pattern, and the possibility that one cohort would be enriched by more aggressive mutations cannot be discarded and could partially justify outcome differences in the two cohorts. On the other hand, genetic data were available in a minority of cases and the whole genetic characterization of these two large series goes beyond the scope of the study. In addition, cultural aspects and healthcare system factors have not been considered, although different approaches to the prevention, diagnosis and treatment may partially contribute to the differences found.

Another aspect to be considered is that this is a retrospective study, with a design across 24 years, and inherently, heterogeneity in diagnostics, assays, surgical practice, imaging intensity and systemic therapies may be present. Nevertheless, this heterogeneity applies similarly to both centres and is not expected to have significantly influenced the results obtained.

Finally, it should be underlined that the indication for routine CT measurement cannot probably be applied in all countries. Indeed, the main goal of this tool is to identify small and curable MTCs, by refining the results of ultrasound and cytology, which have a low accuracy in MTC (16, 17). Thus, the benefit is expected to be substantial in countries where neck ultrasonography is routinely performed, leading to the frequent detection of thyroid nodules. However, even in healthcare systems with more restrictive diagnostic policies, CT measurement could provide additional relevant information in thyroid nodules meeting the criteria for FNAC. Finally, it is important to highlight that in some cases, borderline CT values are found, which needs to be evaluated by a dynamic and integrated diagnostic approach. Serial measurements to evaluate the trend, CT assessment in FNA washout and correlation with clinical and US features are essential to guide management, supporting the interpretation of CT as an adjunctive rather than a stand-alone diagnostic tool.

## Conclusion

The data, here reported for the first time, highlight the different presentation and outcome of MTC patients in two European cohorts, likely due to variabilities in diagnostic, therapeutic approaches and in healthcare systems. These findings provide real-life insights into the association between routine CT measurement, earlier diagnosis and improved survival outcomes. Such comparisons can inform guidelines and help determine whether this diagnostic test should be adopted more widely in the preoperative evaluation of thyroid nodules while underscoring that caution should be exercised to the differences existing in different European and non-European countries when defining MTC prevalence and outcome.

**Declaration of interest**

LF is a consultant for Eisai, Ipsen, Lilly and Bayer. The remaining authors have nothing to disclose.

**Funding**

This study was funded by the Italian Ministry of Health, Ricerca Corrente, and by the Erasmus Traineeship Scholarship, which enabled the first author to spend a research period abroad at Radboud University Medical Centre, Nijmegen (NL).

**Author contribution statement**

DC, LF and RTN-M designed the current study. DC, CC, SDeL, HJB, MG, A EvanH and PBO created and/or managed the original databases to collect the clinical data. DC conducted the statistical analyses. DC, LF and RTN-M wrote the initial manuscript. All authors reviewed and revised the manuscript to improve its intellectual and technical content.

## References

1 Roman S, Lin R & Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1,252 cases. *Cancer* 2006 **107** 2134–2142. (https://doi.org/10.1002/cncr.22244)

2 Costante G, Meringolo D, Durante C, *et al.* Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5,817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab* 2007 **92** 450–455. (https://doi.org/10.1210/jc.2006-1590)

3 Elisei R, Bottici V, Luchetti F, *et al.* Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. *J Clin Endocrinol Metab* 2004 **89** 163–168. (https://doi.org/10.1210/jc.2003-030550)

4 Durante C, Hegedüs L, Czarniecka A, *et al.* 2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management. *Eur Thyroid J* 2023 **12** e230067. (https://doi.org/10.1530/ETJ-23-0067)

5 Wells SA Jr, Asa SL, Dralle H, *et al.* Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015 **25** 567–610. (https://doi.org/10.1089/thy.2014.0335)

6 Verbeek HH, de Groot JWB, Sluiter WJ, *et al.* Calcitonin testing for detection of medullary thyroid cancer in people with thyroid nodules. *Cochrane Database Syst Rev* 2020 **3** CD010159. (https://doi.org/10.1002/14651858.CD010159.pub2)

7 Kartal Baykan E & Erdoğan M. Basal and pentagastrin-stimulated calcitonin cut-off values in diagnosis of preoperative medullary thyroid cancer. *Turk J Med Sci* 2021 **51** 650–656. (https://doi.org/10.3906/sag-2003-182)

8 Fugazzola L, Di Stefano M, Censi S, *et al.* Basal and stimulated calcitonin for the diagnosis of medullary thyroid cancer: updated thresholds and safety assessment. *J Endocrinol Investig* 2021 **44** 587–597. (https://doi.org/10.1007/s40618-020-01356-9)

9 Links TP, de Heide LJ, Janssen M, *et al.* Richtlijn schildkliercarcinoom inclusief diagnostiek van de nodus [guideline thyroid cancer including diagnostics of the nodule]. *Ned Tijdschr Geneeskd* 2015 **159** A9413.

10 Amin MB, Greene FL, Edge SB, *et al.* The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017 **67** 93–99. (https://doi.org/10.3322/caac.21388)

11 Filetti S, Durante C, Hartl D, *et al.* Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019 **30** 1856–1883. (https://doi.org/10.1093/annonc/mdz400)

12 Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009 **45** 228–247. (https://doi.org/10.1016/j.ejca.2008.10.026)

13 Meijer JA, Bakker LE, Valk GD, *et al.* Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicentre study. *Eur J Endocrinol* 2013 **168** 779–786. (https://doi.org/10.1530/eje-12-0943)

14 Prete A, Gambale C, Bottici V, *et al.* Body mass index and sporadic medullary thyroid cancer: insights from a large series. *Cancers* 2025 **17** 950. (https://doi.org/10.3390/cancers17060950)

15 Jager EC, Metman MJH, Timmenga IAC, *et al.* Trends in the incidence, organization of care, and surgical treatment of medullary thyroid cancer: a population-based study. *Thyroid* 2025 **35** 87–96. (https://doi.org/10.1089/thy.2024.0433)

16 Matrone A, Gambale C, Biagini M, *et al.* Ultrasound features and risk stratification systems to identify medullary thyroid carcinoma. *Eur J Endocrinol* 2021 **185** 193–200. (https://doi.org/10.1530/eje-21-0313)

17 Trimboli P, Treglia G, Guidobaldi L, *et al.* Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. *Clin Endocrinol* 2015 **82** 280–285. (https://doi.org/10.1111/cen.12563)