

ORIGINAL ARTICLE

## Lymph node metastases and elevated postoperative calcitonin: Predictors of poor survival in medullary thyroid carcinoma

PÄIVI SIIRONEN<sup>1</sup>, JAANA HAGSTRÖM<sup>2</sup>, HANNA O. MÄENPÄÄ<sup>3</sup>,  
JOHANNA LOUHIMO<sup>1</sup>, JOHANNA AROLA<sup>2\*</sup> & CAJ HAGLUND<sup>1,4\*</sup>

<sup>1</sup>Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, <sup>2</sup>Department of Pathology, Haartman Institute and HUSLab, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, <sup>3</sup>Department of Oncology, Helsinki University Hospital, Helsinki, Finland, and <sup>4</sup>Research Programs Unit, Translational Cancer Biology, University of Helsinki, Finland.

### ABSTRACT

**Background.** Total thyroidectomy is the treatment of choice for medullary thyroid carcinoma (MTC), but the extent of neck dissection is controversial. Lymph node metastases, distant metastases, and old age are known predictors of poor survival.

**Patients.** Patients treated for primary MTC at Helsinki University Hospital from 1990 to 2009 were included ( $n = 54$ ). Their clinical characteristics, treatment, and outcome were analysed retrospectively, these patients were followed until death or their last follow-up date.

**Results.** At last follow-up (3.4–23 years), of 54 MTC patients, 19 (35%) were disease-free, 17 (32%) were alive with disease, and 12 (22%) had died of MTC; six patients died of unrelated causes (11%). All disease-free patients were node negative and had normal postoperative calcitonin level. Of 19 disease-free patients, only four (21%) had undergone lymph node dissection. All patients who died of MTC were Stage IV at diagnosis and died with distant metastases. Disease-specific five- and 10-year survival was 84% and 76.2%. Advanced T-stage ( $p = 0.004$ ), lymph node metastases ( $p < 0.001$ ), distant metastases ( $p < 0.001$ ), stage ( $p < 0.001$ ), and elevated postoperative calcitonin ( $p < 0.001$ ) significantly associated with survival.

**Conclusions.** Lymph node metastasis and elevated postoperative calcitonin are important prognostic factors. Patients with lymph node metastasis and/or elevated postoperative calcitonin with present treatments cannot become disease-free, but most of them can live a long life with metastasis.

Medullary thyroid carcinoma (MTC) is a rare malignancy originating from calcitonin secreting parafollicular C-cells. One of four patients with MTC has a hereditary aetiology: either familial MTC or multiple endocrine neoplasia (MEN) type 2A or 2B [1]. MTC has a varying clinical course, but the average 10-year survival is 75–80% [2]. As calcitonin serves as a sensitive tumour marker after primary surgery, normal postoperative calcitonin predicts cure. The clinical course of those with

elevated postoperative calcitonin varies markedly: from rapid progression with survival of only a few years to stable disease lasting decades.

For MTC, the recommend surgery has been total thyroidectomy and central neck dissection [3–5]. The need for lateral neck dissection is controversial, with poor efficacy of non-surgical treatments presenting a problem. MTC cells do not concentrate radioactive iodine, and the effect of chemotherapy is limited [6]. For lymph node recurrence, most

\*These authors contributed equally

Correspondence: P. Siironen, Department of Surgery, Helsinki University Hospital, PO Box 340, 00029 HUCH, Finland. Tel: +35 8400700233. Fax: +35 8947172427. E-mail: paivi.siironen@hus.fi

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family history. Surgical treatment was lobectomy or thyroidectomy. Extent of lymph node dissection was determined as none, limited (central and/or lateral “node picking”) or selective neck dissection [14]. Definition of stage was done according to the UICC TNM classification [15], and primary lymph node status was considered as N1 (pN1) when positive lymph nodes were found in histological examination and, as N0 when no lymph nodes were evident with ultrasound, during surgery, or in histological examination. Only four N0 patients underwent lymph node dissection, therefore, N0, in most cases, represented clinical N0. The diagnosis of local recurrence was made clinically by ultrasound or other imaging techniques, or by elevated calcitonin level.

All patients were followed until death or until the last follow-up date (April 2013). Follow-up time was 3.4–23 years. Survival data came from the Population Register and the cause of death from patient records and from Statistics Finland. The end-points of the study were either death from MTC or tumour status at the time of the last follow-up date (disease-free, alive with disease either biochemically active, or distant metastases). Patients with no clinical or radiological signs of disease and normal calcitonin level at last follow-up were considered to be disease-free. Approval of the study came from the local Ethics Committee and National Supervisory Authority of Welfare and Health (226/E6/2006; revised version approved 17 April 2013).

#### Laboratory assays

During the time period three assays were used for calcitonin measurement: LIAISON immunoanalyser (BYK, Sangtec), commercial immunoluminometric assay (ELISA, Immuno-Biological Laboratories, Ibl, Hamburg, Deutschland) and chemiluminescent assay Immulite 2000 (Immunoluminometric assay, CLIA, Siemens Healthcare Diagnostics, Marburg, Germany). Correlation between the first two is quite good ( $r=0.93$ ) and between the last two good ( $r=0.99$ ). Normal calcitonin values for men were  $<3.3$  pmol/L and for women 1.5 pmol/L (LIAISON), and  $<3.8$  pmol/L and 1.7 pmol/L (ELISA and Immulite 2000).

#### Statistics

Statistical analysis was performed with SPSS software (IBM SPSS Statistics 20.0), with p-values less than 0.05 regarded as statistically significant. Association of patient characteristics with nodal status, extent of lymph node dissection, follow-up status, and postoperative calcitonin level was

assessed with the  $\chi^2$ -test (or Fisher’s exact test when applicable). The Mann-Whitney U-test or Kruskal-Wallis test served to determine the significance of the difference in age, tumour size, and postoperative calcitonin value between patient groups. Life tables and survival curves were calculated by the Kaplan-Meier method. The log-rank test was applied to test the significance of associations between survival and age, gender, nodal metastases, distant metastases, stage, and postoperative calcitonin level. Patients alive at the end of follow-up and those who died from unrelated causes were censored.

## Results

According to the Finnish Cancer Registry, 203 MTCs were diagnosed in Finland (population approx. 5 million) during the 20-year period from 1990 to 2009. Of these, 54 patients were treated at Helsinki University Hospital, and were included in our study. Two autopsy cases were excluded, due to their occult MTC. Median follow-up time was 11.8 years (range 3.4–23.2 years) for patients alive at the end of the study, and 3.9 years (range 0.04–16.9 years) for patients who died of MTC.

#### Symptoms and diagnosis

The most common symptom and finding was thyroid nodule (34/54, 63%), followed by diarrhoea (4/54, 7%).

Fine needle aspiration biopsy (FNAB) of the primary tumour was performed on 44 patients (81%). Of these 44, cytology classified 16 nodules as MTC, six as carcinoma NOS, 11 as neoplastic, nine as non-neoplastic, and two as non-diagnostic. Eleven patients with non-neoplastic/non-diagnostic FNAB underwent surgery for following reasons: solitary nodule (5), diarrhoea with elevated calcitonin (suspicion of MTC) (1), goitre (4), or MTC histology from a lymph-node metastases (1). Final MTC diagnosis was confirmed by histology and calcitonin immunohistochemistry of the surgical specimen.

Ten MTC patients did not undergo FNAB. Of these 10, five patients with MEN syndrome underwent prophylactic thyroidectomy, two patients underwent thyroid surgery for a goitre, and one for Basedow’s disease. In two patients thyroidectomy was performed for a thyroid nodule found at surgery for HPT.

DNA testing was performed on 52 patients; eight were positive for RET proto-oncogene. The two patients without RET testing had metastatic MTC and died soon after the diagnosis. One died of MTC

and the other of intracerebral bleeding. These two were classified as sporadic by a negative family history.

#### Clinical characteristics and follow-up

At the end of the follow-up, 19 patients (35%) were disease-free, and 12 (22%) had died of MTC. Disease-specific five- and 10-year survival was 84% and 76.2%. Mean survival was 18.2 years, and at the end of our study, the final disease-specific survival was 69.3%. Most neck recurrences were detected soon after the primary operation, within a median of one year. In four patients, the neck recurrence was detectable more than five years after the initial operation, even as late as at 18 years. Late distant metastases were detectable within median of three years after the primary operation (range 1.7–5.9 years).

Clinical characteristics of MTC patients are summarised in Tables I and II. Characteristics varied a great deal between the three patient groups (disease-free, alive with disease, died of MTC). In short, 19 (35%) disease-free patients had neither lymph node nor distant metastases, and their postoperative calcitonin levels were normal.

In contrast, all patients who died of MTC had stage IV disease (presence of thyroid capsule invasion, lymph node metastases further than pre- and paratracheal, or distant metastases), and also elevated postoperative calcitonin.

#### Distant metastases

At diagnosis of the 54, nine patients (17%) had distant metastases, and another nine developed them later. The most common sites were liver (83%), bone (56%), and lungs (33%), whereas rare locations were the mediastinum, eye, ovary, brain, adrenal gland, and pancreas.

#### MEN syndrome

Eight patients (15%) had MEN syndrome (7 MEN2a, 1 MEN2b); their mean age was 40 (median 38.9 years); only one of them was female. Their tumours were small (mean 1.6 cm, median 0.7 cm, range 0.3–7 cm) and usually multifocal (7/8, 88%). Only one patient had lymph node metastases and none distant metastases. Moreover, one patient had local recurrence. All MEN patients were alive at the end of follow-up (range 4.2–22.1 years); five

Table I. Clinical characteristics of MTC patients: disease-free (19), alive with disease (17) and dead from medullary thyroid cancer (12). Six patients who died from unrelated causes (pneumonia 2, shooting accident 1, intracerebral haematoma 1, metastatic colon cancer 1, and obstructive bronchitis 1) and were excluded. Tumour-Node-Metastases (TNM) stage was assessed according to the international Union Against Cancer (UICC) TNM classification of 2004.

Patient characteristics	All patients 54	19 disease-free n (%)	17 alive with disease n (%)	12 dead from MTC n (%)	p-Value	6 dead for other reasons
Median age (years)	47	41	47	48	ns	67
Women	27 (50)	14 (74)	8 (47)	4 (33)		1
Men	27 (50)	5 (26)	9 (53)	8 (67)	ns	5
Sporadic	46 (85)	14 (74)	14 (82)	12 (100)	ns	6
Median tumour size (cm)	2.0	1.5	3.0	2.6	ns	2.8
Extent of tumour						
T1	26 (35)	15 (79)	6 (35)	3 (25)		1
T2	8 (15)	3 (16)	2 (12)	1 (8)	<0.001	2
T3	7 (13)	1 (5)	5 (29)	1 (8)		0
T4	13 (24)	0	4 (24)	7 (59)		2
UICC stage						
Stage I	19 (35)	15 (79)	3 (18)	0		1
Stage II	8 (15)	4 (21)	4 (23)	0	<0.001	0
Stage III	3 (6)	0	3 (18)	0		0
Stage IV	24 (44)	0	7 (41)	12 (100)		5
Multifocal tumour	11 (20)	4 (21)	4 (24)	3 (23)	ns	0
Nodal metastases	24 (44)	0	9 (53)	10 (83)	<0.001	5
Neck recurrence	21 (40)	0	13 (76)	7 (58)	<0.001	1
Distant metastases	18 (33)	0	4 (24)	12 (100)		2
– Primary distant metastases	9 (17)	0	1	6	<0.001	2
– Late distant metastases	9 (17)	0	3	6	<0.001	0
Normal post op calcitonin (yes)	21 (39)	19 (100)	2 (12)	0	<0.001	0
Postoperative calcitonin (median)		0	36	1350	<0.001	705
Last calcitonin value (median)		0	47	6779	<0.001	2799
Lymph node dissection						
– No dissection		15	2	1		2
– Limited		4	7	7	<0.001	3
– Selective		0	8	4		1

\*In one MEN patient, MTC focus was very small (0.3 cm) and treatment was lobectomy alone.

Table II. Details of 12 patients who died of medullary thyroid cancer. All were stage IV, with sporadic disease. All underwent thyroidectomy, except Patient 1, who died soon after diagnosis. At the end, all patients had distant metastases. T-classification was assessed according to Union Against Cancer (UICC) TNM classification, 2004.

Patient number	Age/sex	Survival time (years)	Tumour size (cm)	TNM classification	Late treatments	Neck oper. (n)	DM oper	Postop CTN	Last CTN
1	36/F	0.08	X	T4N1M1	none				2195
2	36/F	0.7	3	T2N1M1	RT, T	1	Sternotomy*	96	257
3	69/F	1.4	0.3	T1N0M1	S			4500	35 000
4	53/M	2	2.2	T4N1M1	CH			1350	4412
5	53/M	3.1	0.9	T4N1M1	RT, CH, S			20 362	91 000
6	75/M	3.3	7.5	T4N0M0	RT, S	2		1740	9146
7	55/M	4.5	1.8	T1N1M0	RT, CH	5		26	505
8	47/M	4.7	4	T4N1M1	RT, CH, S			410	1700
9	49/M	5.9	X	T4N1M0	RT, S	6		1400	20 832
10	38/M	6.5	4	T3N1M0	RT, CH, S	5	Sternotomy	106	73 700
11	17/F	9.2	3.7	T4N1M0	RT, CH, S	3	Ovary	1400	144 000
12	45/M	16.9	1.6	T1N1M0	RT, T, S	4	Lung, brain	58	276

CH, chemotherapy; CTN, calcitonin, values pmol/L; DM, distant metastasis; oper, operation; RT, radiotherapy; S, somatostatin; T, tyrosine kinase inhibitor.

\*Mediastinal and cervical lymph nodes operated on.

were disease-free, and three had biochemically active disease. In addition to thyroid surgery, seven patients underwent surgery for pheochromocytoma, and four for hyperparathyroidism.

#### Surgical treatment

Thyroid surgery was performed on 52 patients: total thyroidectomy on 37 patients (71%), and lobectomy at primary operation followed by removal of the other lobe at secondary operation for 14 patients (27%). One microcarcinoma patient underwent lobectomy only. Two patients were inoperable and died soon after the diagnosis.

Of the 52 operated patients, 12 patients (23%) underwent selective neck dissection, and 21 patients (40%) limited neck dissection; in 19 (37%) no neck dissection was performed, and these were clinically N0. Enlarged mediastinal lymph nodes were dissected in two patients. Furthermore, 21 (39%) underwent lymph node dissection for neck recurrence, and five underwent surgery for metastases [mediastinum (2), lung and brain (1), liver (1), ovary (1)].

Thirty patients underwent only surgery and did not receive any other treatments. Of these 30 patients, 24 underwent only primary thyroid surgery ( $\pm$  lymph node excision), and this group included the 19 patients who were disease-free at the end of the follow-up (range 3.4–23.1 years). Six patients underwent primary thyroid surgery and later on re-operation for neck recurrence.

Table I shows the extent of lymph node dissection in MTC patient groups. Most patients (15/19) who were disease-free at the end of the follow-up underwent no dissection. All patients who underwent selective neck dissection were either alive with disease or dead of MTC.

#### Other treatments

Radiotherapy and/or medical treatment was administered to 22 of the 54 patients: 20 patients received radiotherapy (six of them primary radiotherapy), eight chemotherapy, two radionuclide-therapy, eight somatostatin, and five tyrosine-kinase inhibitor treatment. Majority of these 22 patients (19), were at advanced stage of the disease and most of them have died (14).

Of the patients receiving tyrosine-kinase inhibitor (5), two have died of MTC; one had no response and the other partial response for one year. At the end of the follow-up, three were alive with metastases; one was progression-free after two years of treatment with sorafenib, and the other two have had a partial response.

#### Calcitonin level

Of the 54, postoperative calcitonin was normal in 21 (39%), of whom, 19 (90%) were disease-free at the end of the follow-up. Patients with elevated calcitonin level were significantly more often men ( $p=0.011$ ), had lymph node ( $p<0.001$ ) and distant metastases ( $p=0.033$ ), were stage IV ( $p<0.001$ ), and had more neck ( $p<0.001$ ) and distal recurrences ( $p=0.007$ ). Postoperative and latest calcitonin levels differed between the three survival groups (disease-free, alive with metastases, died of MTC); calcitonin level was highest in the last group ( $p<0.001$ ) (Table I).

As to individual postoperative calcitonin levels, these were: in disease-free patients (0), in those alive with disease, a median 36 (range 0–2800), and in patients who died of MTC, a median 1350 (range 26–20 362). Postoperative calcitonin level was significantly higher in patients who died of

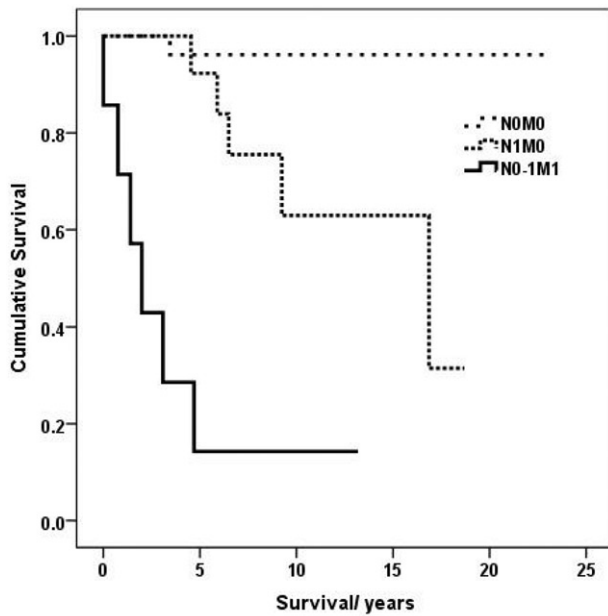


Figure 1. Kaplan-Meier survival curves of 54 MTC patients without metastases (N0M0), with lymph node metastases (N1M0), and with distant metastases (N0-1M1). Differences in survival between groups were significant ( $p < 0.001$ , log-rank test).

MTC than in those alive with disease ( $p = 0.004$ ) (Figure 2).

#### Prognostic factors and survival

Advanced T-stage ( $p = 0.004$ ), lymph node metastases, distant metastases, stage, and elevated postoperative calcitonin (all  $p < 0.001$ ) were factors for worse prognosis. Age, gender, or type of MTC (sporadic MTC, MEN syndrome) lacked significance for prognosis. N1 patients were significantly more often men ( $p = 0.006$ ), had larger tumours ( $p = 0.037$ ), more often neck recurrences ( $p = 0.009$ ) and distant metastases ( $p < 0.001$ ).

The five- and 10-year survival for stage I patients was 100% and 100%, and for stage IV 62.8% and 44.9%. For women the five- and 10-year survival was 88.6% and 83.1%, and for men 78.7% and 68.2%. The corresponding figures for N1 patients were 72.3% and 53.5%, and for M1 patients 16.9% and 16.9%. The Kaplan-Meier survival curves for N0M0, N1M0, and N0-1M1 patients are presented in Figure 1.

#### Discussion

MTC patients in our small consecutive series can roughly be divided into three similar-sized groups: one third cured after initial treatment (disease-free), one third with recurrence or residual disease but surviving (alive with disease), and one third dying

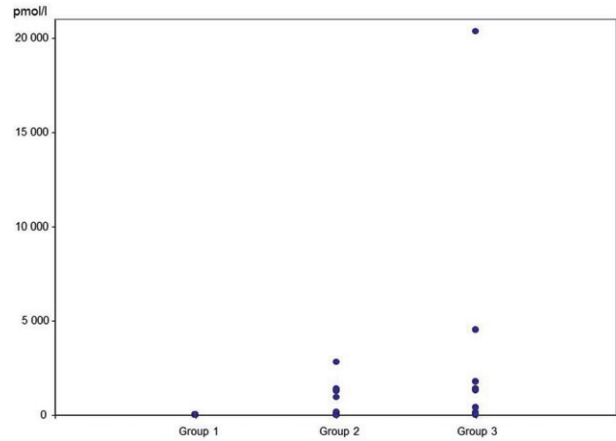


Figure 2. Postoperative calcitonin level (pmol/L) in three groups (1=disease-free, 2=alive with disease, 3=dead from medullary thyroid carcinoma). Postoperative calcitonin levels were significantly higher in patients who died of MTC compared to those alive with disease ( $p = 0.004$ , Mann-Whitney U-test).

of MTC. The cured ones were easy to recognise. They had no lymph node metastases and had normal postoperative calcitonin levels. Moderate- and high-risk patients had either slow progression rate with fairly good survival, or rapid progression fast and lethal disease.

All disease-free patients were clinically N0, with normal postoperative calcitonin level. Postoperative calcitonin level has been shown to be a significant indicator of recurrence-free survival [16,17]. Patients with biochemical remission after primary treatment have an only 3% risk of recurrence [18]. Accordingly, in our study as well, all but two patients with normal postoperative calcitonin (90%) were disease-free at the end of the follow-up. Normal postoperative calcitonin level, however, did not guarantee disease-free survival, nor did N0 stage alone; two N0 patients died of MTC, and eight had recurrence. Postoperative calcitonin was high in both of the N0 patients who died of MTC and was also high in most N0 patients with recurrences (6/8). Clinical N0 in this study, however, is biased, because it was based on a clinical and radiological evaluation of lymph node status, therefore it is likely that some early metastases are missed. Based on our results, negative lymph node status and normal postoperative calcitonin level in combination are best predictors for recurrence-free survival.

The "alive with disease" group was heterogeneous, including patients at all stages. In this particular patient group, predicting tumour behaviour is very difficult. Most patients, 15 of 17, had elevated postoperative calcitonin levels, but their postoperative levels were lower than in those who died of disease. Calcitonin levels, however,

overlapped, making reliable prediction of survival by postoperative calcitonin level impossible, calcitonin surely represents tumour load and thus reflects stage [19,20]. Nevertheless, based on our results, we can only suggest that an extremely high postoperative calcitonin level of 10 000 means fatal disease.

Half of the patients in the "alive-with-disease" group had primary lymph node metastases. These metastases impair survival, but their prognostic significance for long-time survival remains controversial. MTC patients with lymph node metastases have shown more local recurrences and distant metastases [21–23]. Biochemical remission is lower among MTC node-positive than node-negative patients [20,22]. Furthermore, in recurrent MTC, biochemical cure (calcitonin normalisation) is rare, described in only from 0% to 22% of cases [24–26]. In accordance with previous findings, we found that patients with primary lymph node metastases and those with recurrent MTC will not become disease-free despite radical surgery, but they may have a long life expectancy with biochemical disease or even with distant metastases. Four of our patients were alive with distant metastases (follow-up times 5.3, 6.7, 10.0, and 13.1 years), one of them surviving 13 years with primary lung metastases. In rare cases, curative surgical resection of local recurrence or of single distant metastasis may be achieved.

All patients who died of MTC were Stage IV, and their postoperative calcitonin levels were high, probably reflecting tumour load. None of the Stage I–III patients died of MTC. Most of the deceased patients had primary lymph node metastases, and half had primary distant metastases. All of these patients eventually developed distant metastases. M1 patients had shorter survival than the patients who developed metastases later (median survival 1.7 vs. 6.2 years).

Preoperative cytological diagnosing of MTC can be challenging. Serum calcitonin is the most sensitive diagnostic tool to confirm MTC in patients with thyroid nodules [27]. In our series, as many as nine of 44 (20%) FNAs were false negative as diagnosed as non-neoplastic and also only 16/44 (36%) had definitive diagnosis of MTC. In recent meta-analysis, FNA sensitivity in MTC lesions ranged between 12.5% and 88.2% and the key conclusion was that only 56% of histologically proven MTCs are correctly detected by FNA [28]. Elisei et al. confirmed that calcitonin measurement is more sensitive than FNA for the diagnosis of MTC by screening 10 000 patients with nodular thyroid diseases [29].

Primary lymph node status in MTC is an important prognostic factor. The latest ATA guidelines recommend a total thyroidectomy and central lymph node dissection for all MTC patients, and in

cases with MTC confined to the neck and cervical lymph nodes, also resection of involved lateral compartments [27]. If the basal calcitonin level is greater than 200 pg/mL (734 pmol/L), contralateral neck dissection should be considered as well [27].

In our study, disease-free patients had N0 disease, and most of them did not undergo lymph node dissection. However, as mentioned, clinical N0 is rarely definitely N0. Our patient material with dates from 1990 to 2009, and back then, performing lymph node dissection in patients without enlarged nodes with ultrasound or at operation was not routine practice. Of 19 disease-free patients, only four underwent limited lymph node dissection. Thus, based on our small retrospective material, it seems that lymph node dissection has no effect on prognosis in patients without macroscopic lymph node metastases. Furthermore, supporting our findings, the Esfandiari group recently suggested that the extent of lymph node dissection should be tailored to tumour size and distant metastases. When evaluating a cohort of 2968 MTC patients, they found that N0M0 patients with tumours under 2 cm may do well with total thyroidectomy only and no central node dissection [30]. Further studies are warranted to determine the effect of less extensive surgical strategy on survival and on recurrence in low-risk patients. However, because lymph node status predicts cure, central node dissection in such patients is advisable in order to discover microscopical/histological lymph node status.

Lateral neck dissection is recommended for lymph node metastases [27]. Lymph node dissection does not provide complete cure, but patients undergoing less extensive primary surgery require more re-operations than patients undergoing total thyroidectomy with cervical lymph node dissection [6]. In the large patient series reported by Esfandiari, more extensive surgery resulted in a significant improvement in survival if tumours were >2.0 cm and with existing distant metastases [30].

Although our series is small, clinical characteristics are within the reported range. To our credit, our clinical data and follow-up underwent thorough analysis. All histological specimens were re-evaluated by an endocrine pathologist and follow-up information was available for all patients.

Of the MTC patients of our study, 35% were disease-free at the end of the follow-up, in accordance with other findings (33–37.5%) [17,31]. Incidence of lymph node metastasis varies between 27.9% and 63%; in our study it was 43% [2,17, 31–34]. Primary distant metastasis have occurred in 11–27% of cases [17,32,34]; our percentage was 17%. The gender distribution was equal in our material; other studies have showed a small female

predominance [2,19,35]. The mean age has varied between 40 and 51 years [2,35,36]; in our study this was 48. Survival ranges from 56% to 85% at 10 years: 78.4% in [17], 69% [37], 85% [34], 56% [32], 69.2% [35], 73.7% [33]; in our study, 10-year survival rate was 76%. Our MTC patients who died from disease lived an average of 4.7 years (median 3.4 years), in other series from 3.6 to 4.5 years [6,34]. Lymph node metastases, distant metastases, and age over 65 at diagnosis have been shown to be the strongest predictors of survival [2]. In our study, gender did not associate with survival, but advanced T-stage, lymph node metastases, and distant metastases predicted poor survival. All MEN2 patients are alive, but this lacks prognostic significance and can be explained by low number of cases.

### Conclusions

Primary lymph node status is an important prognostic factor. We noticed that MTC patients with lymph node metastasis would not be completely disease-free, but could live a long life. In our small consecutive series, we also found that most patients who were disease-free at the end of the follow-up, did not undergo lymph node dissection. We could not, however, recommend less extensive surgery for N0 patients. Even in cases where postoperative calcitonin is normal, it is difficult to be sure that MTC patient does not have lymph node metastasis. Micrometastasis may still be present, and lymph node dissection may decrease local recurrence and prevent complications from repeated surgery. Normal postoperative calcitonin is a strong indicator of negative lymph nodes, but is it not a guarantee for N0 status.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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