



# Changes in Serum Calcitonin Concentrations, Incidence of Medullary Thyroid Carcinoma, and Impact of Routine Calcitonin Concentration Monitoring in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

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## OBJECTIVE

Increases in serum calcitonin, a tumor marker for medullary thyroid carcinoma (MTC), have been associated with glucagon-like peptide 1 receptor agonist use in some preclinical studies. We report calcitonin changes in exenatide-treated and placebo-administered participants and MTC incidence in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) and consider the impact of within-trial calcitonin monitoring.

## RESEARCH DESIGN AND METHODS

EXSCEL participants were randomized 1:1 to once-weekly exenatide 2 mg or placebo. Serum calcitonin was measured at baseline (with trial medication discontinued if >40 ng/L) and annually thereafter (with trial medication discontinued if ≥50 ng/L). Median calcitonin concentrations were calculated at each time point, and thyroid malignancies were collected prospectively. Data regarding follow-up after an elevated calcitonin were collected retrospectively.

## RESULTS

At baseline, 52 (30 exenatide and 22 placebo) participants had calcitonin >40 ng/L, and during follow-up an additional 23 participants (15 exenatide and 8 placebo) had calcitonin ≥50 ng/L in the intention-to-treat population. Median calcitonin concentrations were similar between treatment groups at baseline with no increase over time. Confirmed MTC occurred in three participants (2 exenatide and 1 placebo), all of whom had significantly elevated baseline calcitonin values (413, 422, and 655 ng/L).

## CONCLUSIONS

During a median 3.2 years' follow-up, no change in serum calcitonin was seen with exenatide therapy. The three confirmed cases of MTC all occurred in participants with markedly elevated baseline calcitonin levels, measured prior to trial medication administration. Regular calcitonin monitoring identified no additional cases of MTC, suggesting no benefit of routine calcitonin monitoring during exenatide treatment.

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Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are effective glucose-lowering treatments for type 2 diabetes that present a low risk of hypoglycemia, a potential for weight loss, and, for some agents, reduced risk of major adverse cardiovascular events (1,2). Preclinical rodent studies of the GLP-1 RAs liraglutide and exenatide demonstrated a dose-dependent increase in serum calcitonin levels, a biomarker for thyroid C-cell diseases such as medullary thyroid carcinoma (MTC), raising concern about potential off-target effects on the thyroid gland (3). Liraglutide use was associated with development of C-cell carcinomas in rats (already predisposed to spontaneous development of C-cell lesions with age) and in female mice exposed to very high doses (~45 times that used in human studies) (4,5). In contrast, preclinical studies with exenatide demonstrated increased incidence of C-cell adenomas (not carcinomas) in female rats at exposures 130 times the clinical dose and no C-cell pathology in mice (6). Neither liraglutide nor exenatide was associated with C-cell pathology in primates (3,6).

Because of these species differences in C-cell response, the relevance to humans of the preclinical carcinogenicity data was unclear at the time that large-scale cardiovascular outcomes trials (CVOTs) with GLP-1 RAs were initiated. As a result, regulatory agencies mandated regular serum calcitonin concentration monitoring during GLP-1 RA CVOTs for safety reasons to assess the potential impact on calcitonin levels over time and to evaluate risks for C-cell hyperplasia or malignancy. We report the results for the calcitonin data collected during the EXenatide Study of Cardiovascular Event Lowering (EXSCEL), as well as the incidence of MTC during the trial, and the impact of routine serum calcitonin concentration monitoring in patients with type 2 diabetes treated with once-weekly exenatide 2 mg.

## RESEARCH DESIGN AND METHODS

### Trial Design

The design and primary results of EXSCEL have previously been described (7,8). The trial was conducted jointly by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor, Amylin Pharmaceuticals, a wholly owned subsidiary of AstraZeneca. The

protocol was approved by the ethics committee at each participating site, and all participants provided written informed consent for trial participation. Briefly, 14,752 adults with type 2 diabetes who either had experienced a prior cardiovascular event (10,782 [73.1%]) or were at any level of risk for a primary cardiovascular event (3,970 [26.9%]) were randomized 1:1 to receive once-weekly exenatide 2 mg or placebo, in addition to usual care, and followed up over a median of 3.2 years. The trial inclusion and exclusion criteria are listed in Supplementary Data. The primary outcome was defined as the first occurrence of a three-component major adverse cardiovascular event outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in a time-to-event analysis. Protocol-specified exclusion criteria related to calcitonin and thyroid tumors included a baseline serum calcitonin concentration >40 ng/L or a personal or family history of MTC or multiple endocrine neoplasia type 2. Randomization and administration of trial medication were permitted prior to knowing the baseline calcitonin value. If an elevated baseline calcitonin value (>40 ng/L) was discovered, trial medication was discontinued immediately, with the participant continuing to be followed until trial cessation. Additionally, the development of a serum calcitonin concentration  $\geq 50$  ng/L during postrandomization necessitated immediate discontinuation of trial medication and notification of the participant's usual care provider, with the participant continuing to be followed until trial cessation.

### Evaluation

#### Safety Outcomes

Serum calcitonin concentrations were measured at baseline, annually throughout follow-up, and at the final study follow-up visit. Samples, which were not required to be taken while fasting, were analyzed at local laboratories until July 2010, after which they were all analyzed at a central laboratory (Quintiles Laboratories Ltd.) using a Siemens Healthcare IMMULITE 2000 assay. The within-run coefficient of variation for the IMMULITE 2000 assay was 2.8–15.7% with acceptance criteria of  $\leq 10\%$ . The earliest recorded elevated calcitonin was collected in September 2010. All assay results were included in the final analysis.

Investigators and participants were blinded to serum calcitonin concentration values unless a protocol-defined elevation was detected. If a serum calcitonin concentration was elevated either at baseline (>40 ng/L) or during follow-up ( $\geq 50$  ng/L), site investigators were given the numeric result, directed to discontinue study medication immediately, and asked to alert the participant's usual care provider to consider additional follow-up investigations. During the trial, unblinded serum calcitonin concentrations were reviewed at regular intervals by the Data and Safety Monitoring Board, which included a thyroid cancer specialist (R.F.G.).

Data on all malignancies, including MTC, were collected prospectively throughout the trial, and all malignancies were adjudicated using prespecified criteria (Supplementary Data) by an independent committee, blinded to treatment assignment.

#### Impact of Routine Serum Calcitonin Concentration Monitoring

Site investigators were asked to complete an ancillary calcitonin case report form (Supplementary Data) for all participants who had an elevated serum calcitonin concentration at baseline (>40 ng/L) or during follow-up ( $\geq 50$  ng/L) retrospectively between July 2016 and May 2017. This form captured additional information about the participants such as referral to specialists, investigations, and procedures performed. Repeat calcitonin measurements were performed outside of the trial following referral to usual care providers or thyroid specialists. Whether or not a repeat measurement was performed in the local health care setting was captured on the ancillary calcitonin case report form, but the results of any such measurements were not collected robustly, as it was not mandatory for site investigators to record them.

#### Statistical Analysis

Baseline characteristics were summarized for participants with and without a serum calcitonin concentration elevation at any time during the trial as median (25th percentile [Q1], 75th percentile [Q3]) for continuous variables and number (percentages) for categorical variables. Median serum calcitonin concentrations for treatment groups were calculated at baseline and then yearly for the overall population and for male and female

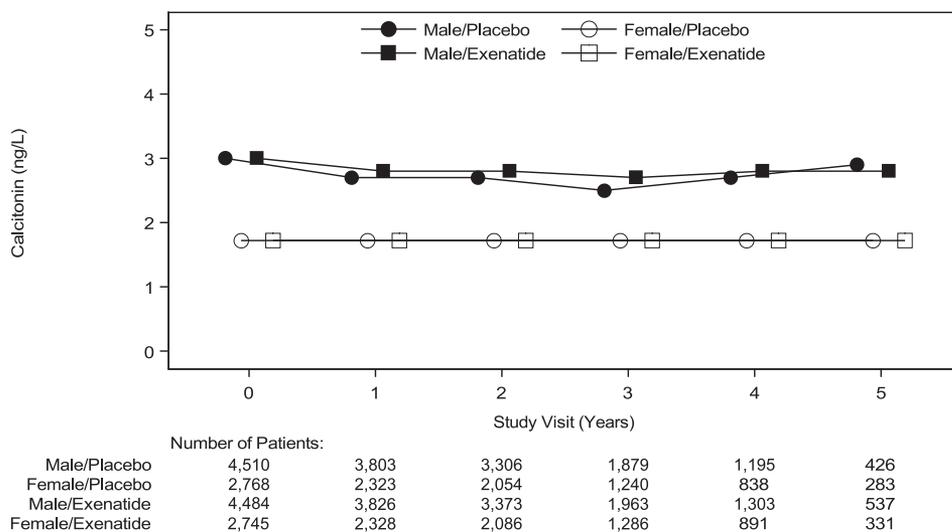


Figure 1—Median serum calcitonin concentrations over time by male and female treatment groups in the intention-to-treat population.

subgroups. Median serum calcitonin concentrations were also calculated for values above the upper 95% range of the assay used (8.4 ng/L for males and 5.0 ng/L for females) at any time during the trial.

Follow-up data for patients with a protocol-specified calcitonin elevation were summarized using descriptive statistics. Costs were estimated for all follow-up activities using Medicare reimbursement rates for procedures, physician visits, and clinical diagnostic laboratory fees derived from Current Procedural

Terminology (CPT) or Diagnosis Related Group (DRG) codes assigned to each follow-up activity (Supplementary Table 1).

RESULTS

Safety Outcomes

A total of 12,831 participants had a baseline and at least one postbaseline serum calcitonin concentration measured and were included in this analysis. In the baseline intention-to-treat population, 52 (30 exenatide and 22 placebo) participants had a serum calcitonin concentration >40 ng/L, and during

follow-up an additional 23 participants (15 exenatide and 8 placebo) had a serum calcitonin concentration ≥50 ng/L. Median baseline serum calcitonin concentration was 1.7 ng/L (Q1 1.7, Q3 4.3) in the exenatide group and 1.7 ng/L (1.7, 4.2) in the placebo group, with no difference between male and female subgroups in each treatment arm and no changes over time (Fig. 1); median differences between baseline and 3 years were 0.0 ng/L (−0.4, 0.0) and 0.0 ng/L (−0.5, 0.0) in the exenatide and placebo groups, respectively.

Table 1—Characteristics of the three participants with confirmed MTC

Age at randomization (years)	Sex	Region	Treatment assignment	Prior smoking history	Baseline serum calcitonin concentration (ng/L)*	Total doses of trial medication prior to discontinuation	Surgical intervention required	Pathology report findings
64	Male	North America	Exenatide	No	413	1	Total thyroidectomy, central neck dissection, and right lateral neck dissection	1.4-cm MTC involving right lobe with all lymph nodes negative, stage pT1b pN0 Mx
59	Female	Latin America	Exenatide	No	665	3	Total thyroidectomy without lymph node dissection	Unknown
75	Male	Europe	Placebo	Yes	422	4	Total thyroidectomy; level 6/7 neck dissection; right selective neck dissection levels 3, 4, and 5; and left level 4 neck dissection	MTC stage pT2pN1bpMx

\*Sample drawn prior to any trial medication administration.

Participants with a calcitonin elevation at any time ( $n = 75$ ) had a median age of 66.0 years (Q1 59.0, Q3 71.0), were predominantly male (78.7%), and were most likely to be from either North America (45.3%) or Europe (42.7%) (Supplementary Table 2). There were 2,502 patients (17.0%: 2,102 male and 400 female) with at least one serum calcitonin concentration above the 95% range of the assay used ( $>8.4$  ng/L for males and  $>5.0$  ng/L for females), with median serum calcitonin concentrations of 12.9 ng/L (10.2, 18.3) for males and 7.8 ng/L (6.2, 12.4) for females in these cohorts. Among those patients with a protocol-defined elevation in calcitonin, either at baseline or during follow-up, the median (IQR) and range were 58.1 ng/L (50.7, 74.8) and 40.4–1003.0, respectively.

A confirmed MTC occurred in three participants (2 exenatide and 1 placebo), all of whom had markedly elevated serum calcitonin concentrations at baseline: 413, 422, and 655 ng/L (Table 1).

### Impact of Routine Serum Calcitonin Concentration Monitoring

Follow-up data were available for 70 of the 75 participants who had an elevated serum calcitonin concentration. Reasons for noncompletion were site closure ( $n = 3$ ) or unknown ( $n = 2$ ). The majority of participants with elevated calcitonin and follow-up data available were referred to their usual care provider (46 of 70 [66%]) or a thyroid specialist (41 of 70 [59%]). Just over half (37 of 70 [53%]) had at least one diagnostic test or procedure performed, with the most common being a thyroid ultrasound (32 of 37 [87%]), fine needle aspiration (9 of 37 [24%]), or surgical intervention (4 of 37 [11%]) (Table 2). Of participants who had a thyroid ultrasound, 75% (24 of 32) had benign findings, most commonly clinically insignificant nodules ( $<1$  cm) or goiter, and required no further clinical evaluation in the opinion of the treating medical team. Nine participants underwent a fine needle aspiration procedure: five had benign or nondiagnostic findings

requiring no further evaluation in the opinion of the treating medical team, and four had findings requiring surgical intervention. Of the four participants requiring surgical intervention, three were those participants with confirmed MTC who underwent a total thyroidectomy, while one participant underwent a partial thyroidectomy for a 4.5-cm left upper lobe solid, hypoechoic benign nodule containing microcalcifications; the final pathology showed a colloid nodule. Estimated overall total costs for follow-up activities undertaken in local healthcare systems following an elevated serum calcitonin concentration are shown in Table 2. Just under half (49%) of the total cost to local health care systems was attributable to the follow-up received by the three participants with MTC.

### CONCLUSIONS

In EXSCEL, treatment with once-weekly exenatide 2 mg had no impact (compared with placebo) on serum calcitonin concentrations over a median 3.2-year follow-up

**Table 2—Follow-up received by participants with elevated serum calcitonin concentrations at any time during EXSCEL by clinical outcome, with associated estimated costs to local health care systems**

	Calcitonin elevation and benign outcome ( $n = 66$ )		Calcitonin elevation and MTC outcome ( $n = 3$ )		Calcitonin elevation and "other" outcome ( $n = 1$ )*	
	Total no.	Estimated cost (USD)†	Total no.	Estimated cost (USD)†	Total no.	Estimated cost (USD)†
Participants with repeat serum calcitonin measurements performed in local health care systems	40		3		1	
Total no. of repeat serum calcitonin sample measurements in local health care systems	90	2,977.20	5	165.40	1	33.08
Participants referred to usual care provider by site investigator‡	42	3,174.36	3	226.74	1	75.58
Participants referred to thyroid specialist by site investigator or usual care provider‡	37	6,289.26	3	509.94	1	169.98
Participants with any diagnostic test/procedure performed in local health care system	33		3		1	
Thyroid ultrasound	28	3,042.76	3	326.01	1	108.67
Fine needle aspiration	5	2,021.20	3	1,212.72	1	404.24
Surgical intervention	0		3		1	
Partial thyroidectomy	0	—	0	—	1	6,677.13
Total thyroidectomy without lymph node dissection	0	—	1	6,897.76	0	—
Total thyroidectomy with lymph node dissection	0	—	2	14,626.52	0	—
Pentagastrin stimulation test	1	231.56	0	—	0	—
Genetic testing for germline RET mutations	1	282.88	0	—	0	—
Estimated total cost by clinical outcome (USD)		18,019.22		23,965.09		7,468.68
Estimated total cost (USD)				49,452.99		
Mean cost per participant (USD)				706.50		

\*"Other" outcome refers to one participant who underwent a partial thyroidectomy for a 4.5-cm hypoechoic benign colloid nodule containing microcalcifications. †Cost calculated by multiplying total number by Medicare reimbursement fee amounts according to CPT or DRG coding (list of CPT/DRG codes and associated fee schedules are shown in Supplementary Table 1). ‡Participants assumed to have had a single appointment if referred to usual care provider or a thyroid specialist.

period. All three confirmed cases of MTC in EXSCEL occurred in participants who had markedly elevated serum calcitonin concentrations at baseline, prior to any trial medication administration.

Our findings are consistent with those from a similar post hoc analysis performed in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (9). In LEADER, no increase in calcitonin concentration was observed in participants randomized to liraglutide versus placebo at 36 months, and there were no episodes of MTC in liraglutide-treated participants.

Determining appropriate protocol-specified calcitonin thresholds for study drug discontinuation in EXSCEL was not straightforward. In routine clinical practice, calcitonin levels are effective tumor markers to monitor treatment and progression but are not recommended as screening or diagnostic tools, especially in unselected populations (10). Markedly elevated serum calcitonin concentrations ( $>100$  ng/L) have a high specificity for MTC (10), but there is no consensus defining a clinically meaningful elevated concentration below this value. The 2009 American Thyroid Association (ATA) guidelines—the most recent at the time of EXSCEL protocol development—did not recommend for or against the routine measurement of serum calcitonin in patients with thyroid nodules but did recommend that an unstimulated calcitonin concentration  $>100$  ng/L was suggestive of MTC in the presence of nodules (10). In comparison, the most recent 2015 ATA guidelines advise that a calcitonin concentration  $>50$ – $100$  ng/L should prompt further investigation for MTC in patients with thyroid nodules. The European perspective differs substantially, with the European Thyroid Association recommending that routine measurement of calcitonin be included in the evaluation of patients with a thyroid nodule or multinodular goiter (11). Both the ATA and European Thyroid Association make no recommendations for calcitonin screening in the wider population (12). In the absence of clear data regarding the positive predictive value of modestly elevated calcitonin values for MTC in a population unselected for thyroid disease and in consultation with thyroid disease experts, a baseline calcitonin threshold of  $>40$  ng/L was chosen for EXSCEL (13). A within-trial

threshold for study drug discontinuation of  $\geq 50$  ng/L was chosen to allow for a variation of  $\sim 20\%$  in assay measurements.

Protocol-mandated routine monitoring of serum calcitonin concentrations in EXSCEL identified a total of 75 participants with an elevated calcitonin concentration and three participants with previously undiagnosed MTC at an estimated cost of  $\sim 8$  million USD to the trial and  $\sim 49,500$  USD to local health care systems. Although these three participants may have benefitted from having their serum calcitonin concentrations measured at the beginning of the trial, the detection and treatment of their cancers was not associated with the use of exenatide therapy. Importantly, no further cases of MTC were identified during the trial follow-up period. In contrast, the imposed calcitonin monitoring program resulted in multiple unnecessary investigations and procedures in those with sporadically or modestly elevated calcitonin levels. Other important unmeasured costs to participants related to receiving an “abnormal” test result are more difficult to quantify and include worry and anxiety over a potential cancer diagnosis and potential loss of productivity because of time away from work to attend follow-up appointments.

Limitations of this analysis include the relatively short median follow-up of 3.2 years in EXSCEL, which may not have been long enough to detect indolent MTC development (14); the retrospective nature of elevated calcitonin follow-up data collection via ancillary case report forms, which may have been subject to recall bias; and lack of follow-up data for five participants who had an elevated serum calcitonin concentration. Furthermore, the method of follow-up of abnormal calcitonin values was not prescribed by the protocol, instead deferring to local referral and practice patterns. Consequently, there was no predefined and unique strategy for follow-up and management of those excluded from the study because of calcitonin elevations. While individual calcitonin values can be impacted by factors such as age, smoking status, and renal function, the impact on absolute calcitonin values is small. No adjustments were made for baseline covariates, as these were equally distributed between treatment groups (8) and therefore unlikely to have confounded

our findings of no impact of exenatide therapy on calcitonin values during follow-up. Strengths include analysis of a data set from a large population in a randomized controlled trial setting and the robust assessment of all reported thyroid malignancies by an independent blinded committee using prespecified adjudication criteria.

In summary, this EXSCEL post hoc analysis shows no evidence that treatment with once-weekly exenatide 2 mg increases serum calcitonin concentrations or increases risk for MTC in humans during  $\sim 3$  years' follow-up. These data, in concert with those from LEADER, provide  $\sim 83,000$  patient-years' follow-up and should provide reassurance that GLP-1 RA therapy does not increase short-term risk for MTC. Calcitonin screening is not recommended in clinical care except in the evaluation of nodular thyroid disease, if a family history of MTC exists, or if multiple endocrine neoplasia type 2 is suspected. Given the trial-related and societal costs of these screening programs, it may be prudent to revisit regulatory requirements for calcitonin screening in future GLP-1 RA trials unless they are likely to contribute novel insights through longer-term follow-up or via enrollment of relevant patient populations.

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**Author Contributions.** M.A.B. designed the study, collected and analyzed data, interpreted data, and reviewed and edited the manuscript. R.A.P. collected and analyzed data and wrote the manuscript. V.P.T. performed statistical analysis. P.M. performed statistical analysis. S.D.R. interpreted data and reviewed and edited the manuscript. Y.L. interpreted data and reviewed and edited the manuscript. S.A. interpreted data and reviewed and edited the manuscript. B.G.K. reviewed and edited the manuscript. S.M.G. contributed to study design and reviewed and edited the manuscript. P.O. contributed to study design and reviewed and edited the manuscript. N.I. reviewed and edited the manuscript. R.F.G. reviewed and edited the manuscript. A.F.H. reviewed and edited the manuscript. J.B.B. interpreted data and reviewed and edited the manuscript. R.R.H. contributed to study design and data interpretation and reviewed and edited the manuscript. M.A.B. and R.R.H. are the guarantors

of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## References

1. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
2. Marso SP, Bain SC, Conso A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
3. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 2010;151:1473–1486
4. Capen CC, Martin SL. The effects of xenobiotics on the structure and function of thyroid follicular and C-cells. *Toxicol Pathol* 1989;17:266–293
5. Martín-Lacave I, Bernab R, Sampedro C, et al. Correlation between gender and spontaneous C-cell tumors in the thyroid gland of the Wistar rat. *Cell Tissue Res* 1999;297:451–457
6. Madsen LW, Knauf JA, Gotfredsen C, et al. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. *Endocrinology* 2012;153:1538–1547
7. Holman RR, Bethel MA, George J, et al. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. *Am Heart J* 2016;174:103–110
8. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228–1239
9. Hegedüs L, Sherman SI, Tuttle RM, et al.; LEADER Publication Committee on behalf of the LEADER Trial Investigators. No evidence of increase in calcitonin concentrations or development of C-cell malignancy in response to liraglutide for up to 5 years in the LEADER trial. *Diabetes Care* 2018;41:620–622
10. Cooper DS, Doherty GM, Haugen BR, et al.; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167–1214
11. Elisei R, Romei C. Calcitonin estimation in patients with nodular goiter and its significance for early detection of MTC: European comments to the guidelines of the American Thyroid Association. *Thyroid Res* 2013;6(Suppl. 1):S2
12. Haugen BR, Alexander EK, Bible KC, et al.; American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1–133
13. Daniels GH. Screening for medullary thyroid carcinoma with serum calcitonin measurements in patients with thyroid nodules in the United States and Canada. *Thyroid* 2011;21:1199–1207
14. Geller G, Laskin J, Cheung WY, Ho C. A retrospective review of the multidisciplinary management of medullary thyroid cancer: eligibility for systemic therapy. *Thyroid Res* 2017;10:6