THEMATIC REVIEW

HEREDITARY ENDOCRINE TUMOURS: CURRENT STATE-OF-THE-ART AND RESEARCH OPPORTUNITIES

Early thyroidectomy in multiple endocrine neoplasia: a four decade experience

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Abstract

Forty years ago, physicians caring for the J-kindred, a 100+ member family with multiple endocrine neoplasia type 2A (MEN2A), hypothesized that early thyroidectomy based on measurement of the biomarker calcitonin could cure patients at risk for development of medullary thyroid carcinoma (MTC). We re-evaluated 22 family members with proven *RET* proto-oncogene mutations (C634G) who underwent thyroidectomy and central lymphadenectomy between 1972 and 1994 based on stimulated calcitonin abnormalities. Current disease status was evaluated by serum calcitonin measurement and neck ultrasound in 18 of the 22 prospectively screened patients. The median age of the cohort at thyroidectomy was 16.5 years (range 9–24). The median duration of follow-up at the time of examination was 40 years (range 21–43) with a median current age of 52 years (range 34–65). Fifteen of the 18 patients had no detectable serum calcitonin (<2 pg/mL). Three had detectable serum calcitonin measurements, inappropriately elevated following total thyroidectomy. None of the 16 patients imaged had an abnormal ultrasound. Survival analysis shows no MTC-related deaths in the prospectively screened patients, whereas there were many in prior generations. Early thyroidectomy based on biomarker testing has rendered 15 of 18 MEN2A patients (83%) calcitonin-free with a median follow-up period of 40 years. There have been no deaths in the prospectively screened and thyroidectomized group. We conclude that early thyroidectomy and central lymph node dissection is an effective prophylactic treatment for hereditary MTC.

Key Words:

- medullary thyroid cancer
- early thyroidectomy
- prophylactic thyroidectomy
- multiple endocrine neoplasia 2A
- J-kindred

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Introduction

Almost 50 years ago, the propositus for the J-kindred set up an appointment in the Endocrine Division of the Tufts-New England Medical Center to discuss concern over a number of deaths in his family from thyroid cancer. The physician he saw very quickly pieced together a history consistent with a recently identified syndrome, multiple endocrine neoplasia type 2A – the association of medullary thyroid carcinoma (MTC), hyperparathyroidism and pheochromocytoma (Steiner *et al.* 1968). He recommended that members of the kindred participate in a prospective screening protocol using a newly developed radioimmunoassay for the biomarker hormone, calcitonin, to identify MTC (Tashjian & Melvin 1968). The physician, Ken Melvin, and the propositus were reunited at the 16th International Workshop on Multiple Endocrine Neoplasia (MEN2019) in Houston, Texas to reflect upon that initial experience and comment upon an update of the impact of treatment intervention in this kindred. As this kindred was the first to undergo prospective screening for MEN2A-related manifestations, their outcomes over the past 40 years continue to provide important insight into the impact of prophylactic thyroidectomy for this disorder.

The kindred may be divided into four groups: the first were individuals of the first and second generations who were diagnosed with MTC at advanced stages and prior to the use of calcitonin or the recognition of a hereditary source; the second were 12 patients identified with MTC by measurement of an elevated serum calcitonin at the initial evaluation (Melvin *et al.* 1971); the third focused on screening children and young adults at genetic risk for MTC annually who had normal pentagastrin-stimulated serum calcitonin values initially and converted to an abnormal test during annual screening (Graze *et al.* 1978, Gagel *et al.* 1988); and the fourth identified individuals with a germline *RET* proto-oncogene mutation after the genetic defect was identified in 1993 (Donis-Keller *et al.* 1993, Mulligan *et al.* 1993). This report will focus on the third group, those who were identified by an interval development of abnormal pentagastrin-stimulated serum calcitonin measurements.

The hypothesis to be tested was whether total thyroidectomy and central lymph node dissection would result in surgical cure with a normal life span in family members who developed an abnormal pentagastrin-stimulated serum calcitonin value. While earlier reports from this family provided an optimistic assessment of outcomes a mean of 11 years following thyroidectomy and the intervention was viewed as successful (Gagel *et al.* 1988), MTC can grow slowly and late recurrence occurs with some frequency. The passage of 45 years since the beginning of screening this third group and the participants' entry into middle age provides the next opportunity to assess the impact of this intervention.

Why is this important? Prophylactic thyroidectomy, which has become the standard therapy for management of hereditary MTC, is based on the premise that the surgery will be curative – that if an early thyroidectomy is performed, a child will, on average, live a normal life span and be free of cancer with all its attendant implications – that is, no need for repeat surgery, radiation or targeted chemotherapy during their lifetime and no worry about cancer recurrence. As the J-kindred was the first to undergo prospective screening and prophylactic thyroidectomy, their experience is relevant and potentially important.

Methods

The J-kindred has multiple endocrine neoplasia type 2A (MEN2A) and is the first kindred to be evaluated prospectively for hereditary MTC by annual serum calcitonin testing. After the initial identification of macroscopic MTC in 12 family members, all members at risk for MEN2A were screened annually with provocative serum calcitonin testing (pentagastrin 0.5 μg/kg injected over 30–60 s with sampling for serum calcitonin at baseline, 2, 5, 10 and 15 min). Children and young adults who converted from a normal to an abnormal test (abnormal calcitonin secretion in response to ≥2 two provocative tests, with either calcium or pentagastrin stimulation, that were not necessarily consecutive) were offered total thyroidectomy (Gagel *et al.* 1988).

This report will describe the long-term outcome of patients evaluated and treated during prospective serum calcitonin testing. Inclusion criteria for this institutional review board-approved study included family members with no clinical evidence of MEN2A who underwent thyroidectomy between the years 1972 and 1994 based upon newly acquired abnormal serum calcitonin values after provocative testing and whose gene carrier status was retrospectively confirmed by the presence of a germline *RET* C634G mutation in a peripheral blood sample. In this current study, evidence of persistent or recurrent MTC was evaluated by: (1) measurement of a basal serum calcitonin (pentagastrin is no longer approved for clinical use in the USA) and (2) evaluation of the neck by comprehensive cervical ultrasound. Serum calcitonin

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was measured by chemiluminescent immunometric methodology (Immulite 2500, Siemens). The sensitivity of this assay is 2 pg/mL. Normal values are ≤8.4 pg/mL for males and ≤5.0 pg/mL for females with an intact thyroid gland; as the thyroid gland produces >95% of circulating serum calcitonin, normal serum calcitonin values for thyroidectomized patients are undetectable (<2 pg/mL). It is important to recognize that multiple generations of radioimmunoassays have been used in this study from 1968 to the present. The most definitive reports for this kindred, including the 11-year follow-up of prospective screening (Gagel *et al.* 1988), used the first-generation assay. Subsequently second (more sensitive radioimmunoassay) and third (2-site immunoradiometric assays or 2-site chemiluminescent immunometric) generation assays have been used. The sensitivity of assays has improved from <100 pg/mL (first generation) to <10 pg/mL (second generation) to the current <2 pg/mL.

Each participant underwent an extensive neck ultrasound by a single senior radiologist (B S E) who was blind to the clinical status of the patient. This radiologist has performed in excess of 80,000 ultrasound examinations of the soft tissue of the neck for thyroid cancer, and the equipment utilized for these studies were high-resolution ultrasounds scanners (Hitachi-Aloka Alpha 10) and the technique previously described. (Morris *et al.* 2013) Clinical detail of additional treatment for MTC beyond initial surgery and need for calcium or vitamin D supplementation was provided by patients and review of medical records, and surgical procedures for pheochromocytoma were documented.

Each participant underwent evaluation of serum calcium and albumin values (Ortho Clinical Diagnostics-Vitros, colorimetric assay). A corrected calcium = the observed serum calcium + 0.8 × (4-serum albumin). A normal calcium range is from 8.4 to 10.2 mg/dL

The surgeries were performed at the New England Medical Center or Boston Floating Hospital by two successive teams of surgeons; the first in the 1970–1980s and a second in the 1990s, and included a total thyroidectomy and a central neck dissection that included 'dissection of the central lymph nodes between the carotid sheaths down to the superior mediastinum that can be reached from the neck above the innominate artery' (Leape *et al.* 1976). Histopathological evaluation has been previously described, briefly the entire thyroid gland was sectioned at intervals of 2–4 mm and alternate sections were examined by histopathology or extracted for calcitonin measurement (Tashjian & Melvin 1968, Wolfe *et al.* 1973, 1975, Gagel *et al.* 1988).

Disease-specific survival was compared among individuals of the first generation diagnosed with MTC prior to the use of calcitonin (Group 1), those identified with MTC by measurement of an elevated serum calcitonin at initial evaluation (Group 2), and those who were detected by prospective screening (Group 3), utilizing a Kaplan Meier curve.

Results

Twenty-two children and young adults underwent thyroidectomy based on abnormal serum calcitonin stimulation tests as described by Gagel *et al.* between 1972 and 1986 (Gagel *et al.* 1988). Nine individuals were excluded from this study; four germline *RET*-positive patients declined participation or did not respond to a request to participate, but are known to be alive and well and five were retrospectively found to be false positives (a normal *RET* proto-oncogene analysis) and thus, ineligible for this study. An additional five family members underwent surgery (1987–1994) after the time of the 1988 publication (Gagel *et al.* 1988) and were identified as meeting study inclusion criteria, for a total of 18 evaluable cohort members. These 18 family members, all with confirmed RET proto-oncogene C634G germline mutations, were prospectively evaluated for evidence of recurrent MTC, and demographic detail of these individuals is provided in Table 1. Their median age at the time of this study was 52.0 years (range 34–65) and the median age at which they underwent thyroidectomy was 15.5 years (range 9–24). The median follow-up since thyroidectomy was 40 years (range 21–43). All eighteen patients underwent a total thyroidectomy and central neck dissection; seven patients had C-cell hyperplasia (CCH) and 11 had microscopic MTC (mMTC). No nodes containing metastatic MTC were reported. Thyroidectomy was performed at a median of 21 years of age (range 9–23) for those diagnosed with CCH on final histopathologic evaluation and 15 years (range 9–24) for those with mMTC. Of note, of the four RET-positive patients who declined participation in the study, one had mMTC (Pedigree #511) and three had CCH (Pedigree #82, #321, #322).

In the current prospective evaluation, 15 of the 18 individuals had serum calcitonin values that were undetectable (<2 pg/mL; Fig. 1). One of these patients (Pedigree #331) was unable to participate in the ultrasound evaluation. Three had measurable serum calcitonin values (Pedigree #221, #415, #441) and are presumed to have residual or recurrent disease (Fig. 1). None of the

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Table 1 Demographics, pathology detail and current disease status of clinically normal members of the J-kindred who underwent thyroidectomy based on abnormal calcitonin values after provocative testing.

Pedigree ID	Gender	Current age (years)	Year (age) of first thyroid surgery	Years of follow-up	Pathology from first surgery[a]	Second surgery (year)	Pathology from second surgery	Current serum calcitonin (pg/mL)	Current corrected serum calcium	Current neck ultrasound: thyroid bed/ soft tissues of the neck	Diagnosis of pheochromocytoma
112	F	61	1973 (21)	42	CCH	--		<2.0	9.4	NED/NED	Bilateral, age 29
1121	M	34	1994 (13)	21	mMTC	--		<2.0	9.4	NED/NED	NA
133	F	58	1974 (17)	41	CCH	--		<2.0	10.0	NED/NED	No
221	M	54	1976 (15)	39	mMTC	--		15.0	9.0	NoUS	NA
331	F	52	1975 (12)	40	mMTC			<2.0	9.6[b]	NoUS	NA
412	M	56	1975 (16)	40	mMTC	--		<2.0	9.2	POC/NED	No
413	M	55	1975 (15)	40	mMTC	--		<2.0	9.1	NED/NED	Left, age 45
415	M	49	1981 (15)	34	mMTC	CND, BLND (1996)	14/50 LN	10.2	9.5	NED/NED	Bilateral, age 29
431	F	52	1975 (12)	40	mMTC	--		<2.0	9.3	POC/NED	Left, age 11; right, age 23
441	F	49	1975 (9)	40	mMTC	--		56.4	9.2	NED/NED	No
443	F	47	1987 (19)	28	mMTC	--		<2.0	9.6	POC/NED	Left, age 26
811	F	53	1975 (13)	40	mMTC	--		<2.0	9.2	POC/NED	Right, age 30
812	M	49	1975 (9)	40	CCH	--		<2.0	7.8	NED/NED	NA
821	F	48	1991 (24)	24	mMTC	--		<2.0	9.3	NED/NED	Left, age 38; right, age 42
822	M	47	1991 (23)	24	CCH	--		<2.0	9.6	POC/NED	No
823	F	45	1991 (21)	24	CCH	--		<2.0	9.3	POC/NED	Left, age 32
84	F	65	1973 (23)	42	CCH	--		<2.0	10.1	NED/NED	Left, age 26; right, age 48
85	F	60	1972 (17)	43	CCH	--		<2.0	8.8	NED/NED	Left, age 20; right age 29

[a]No lymph node removed had the presence of malignancy; [b]not corrected for serum albumin.
BLND, bilateral lateral neck dissection; CCH, C-cell hyperplasia; CND, central neck dissection; LN, lymph node; mMTC, microscopic medullary thyroid carcinoma; NED, no evidence of disease; NoUS, no ultrasound performed; POC, postoperative changes or normal anatomy; TT, total thyroidectomy.

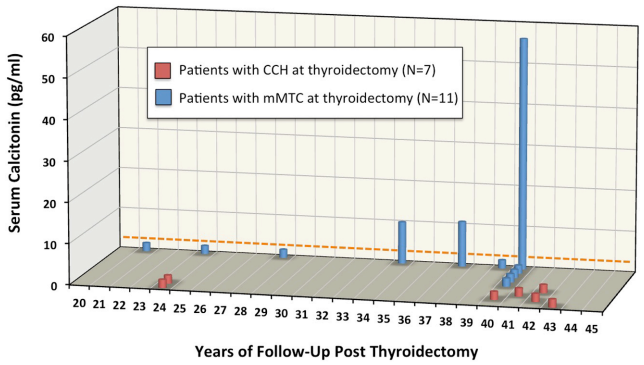

Figure 1
This figure shows individual serum calcitonin values in 18 family members who underwent thyroidectomy and central lymph node dissection between 1972 and 1994. Each cylinder shows the current serum calcitonin value on an individual patient originally found to have either C-cell hyperplasia (red) or microscopic medullary thyroid carcinoma (blue) at the indicated duration of follow-up after surgery (median 40 years). Three individuals who had mMTC at initial diagnosis had elevations of the serum calcitonin and are discussed in the text and in Fig. 2. Values below the lower limit of sensitivity of the assay (2 pg/mL; indicated by dotted line) were assigned a value of 0.5 pg/mL to clarify the display. The data shown utilizes a third generation assay. CCH, C-cell hyperplasia; mMTC, microscopic MTC.

16 patients evaluated by neck ultrasound had radiographic evidence of recurrent disease (Table 1).

Of the three individuals with detectable serum calcitonin, the first (Pedigree #221) had a total thyroidectomy performed in 1976 at 15 years with pathology showing mMTC. Post-thyroidectomy his serum calcitonin values have fluctuated between undetectable and 21 pg/mL with no discernible trend over the past 16 years and a calcitonin doubling time of 15.9 years (Fig. 2, left). He was not able to participate in the ultrasound evaluation. The second (Pedigree #415) had a total thyroidectomy and central neck dissection in 1981 at age 15 years with mMTC and removal of 15 lymph nodes, none abnormal. His basal serum calcitonin was undetectable following surgery, but began to rise over the next decade (Fig. 2, middle), prompting a reoperative central and bilateral lateral neck dissection in 1996 at age 30 years, 15 years after his original surgery. In the second operation, fourteen of 44 nodes in the lateral neck compartments and none of six central compartment nodes were positive for MTC. His current serum calcitonin is 10.2 pg/mL and ultrasound evaluation shows no evidence of disease. His serum calcitonin doubling time since his second surgery is 9.7 years, indicating a low probability of future death from MTC (Laure Giraudet *et al.* 2008). The third (Pedigree #441) underwent thyroidectomy in 1975 at age 9 years for mMTC without lymph node metastasis and has a current serum calcitonin of 56 pg/mL (Fig. 2, right); her basal serum calcitonin value has risen over the past decade with a doubling time of 8.9 years. Ultrasound evaluation shows no evidence of disease.

The median corrected calcium value in the 17 patients for whom we have data was 9.3 mg/dL (range 7.8–10.1) with only one patient's calcium value (7.8 mg/dL) outside of the normal calcium range from 8.4 to 10.2 mg/dLl. No patient has required consistent calcium replacement therapy since the time of original surgery. None of the prospectively screened patients has developed primary hyperparathyroidism before or after thyroidectomy, although one reported in the previous report had nonparathyroid hypercalcemia that resolved following resection of a pheochromocytoma (Gagel *et al.* 1988). As described in Table 1, ten of these patients have developed pheochromocytomas at a median age of first tumour at 29 years of age (range 11–45), and there was no serious morbidity or death related to management of pheochromocytoma.

We performed Kaplan–Meier analysis using MTC-specific death as an end point for Groups 1, 2 and 3 (Fig. 3). Death from MTC was a common event among those in whom the disease was identified when they presented with either a neck mass or metastatic disease (Group 1). Survival is prolonged in patients who underwent thyroidectomy based on initial calcitonin testing (Group 2) and none of the 22 members of Group 3 has died. The differences between these three groups has not reached statistical significance.

Discussion

Does early thyroidectomy in MEN2A have value?

The goal of prophylactic thyroidectomy in MEN2A is to surgically excise all C cells to prevent their subsequent

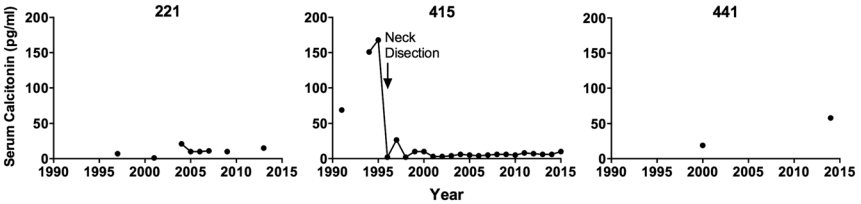

Figure 2
Longitudinal measurements of basal serum calcitonin values in three patients with microscopic MTC with detectable current serum calcitonin values (Pedigree #221, #415, and #441). The data utilized predominately a third-generation assay.

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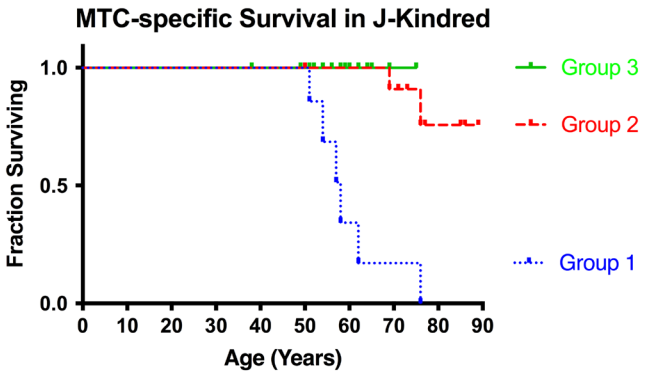

Figure 3
Disease-specific survival among individuals of the first generation diagnosed with MTC prior to use of calcitonin (Kindred #2, 4, 5, 7, 8), those identified with MTC by measurement of an elevated serum calcitonin at initial evaluation (Kindred #1, 3, 11, 13, 22, 31, 32, 33, 41, 43, 44, 51, 81, 83), and those who were detected to have an increase in calcitonin over time (Patient #82, 84, 85, 112, 133, 221, 331, 412, 413, 415, 431, 441, 443, 511, 811, 812, 821, 822, 823, 1121).

malignant transformation. This is particularly true when contemplating prophylactic thyroidectomy in children, where the complications of hypothyroidism, hypoparathyroidism and recurrent laryngeal nerve damage can present a lifelong challenge. The decision to perform a total thyroidectomy in a child, we believe, necessitates setting a high standard – a lifetime free of MTC. To define success in this study, we have applied two sensitive indicators of residual/recurrent disease – measurement of a basal serum calcitonin using a sensitive calcitonin immunoassay and high-resolution neck ultrasonography. As calcitonin is produced predominately by the thyroid gland and is undetectable when measured by 2-site calcitonin immunoassay following total thyroidectomy in normal subjects (Body & Heath 1983), we have applied the criterion of no detectable serum calcitonin as indicative of an absence of C cells. Although MTC is a slowly growing tumour and there are examples of patients with undetectable or normal serum calcitonin values in the immediate postoperative period who subsequently developed metastasis, we reasoned a median 40-year period of observation should provide ample time to detect residual or recurrent disease. Using these criteria, 83% (15/18) of children and young adults who underwent prophylactic thyroidectomy a median of 40 years ago are free of disease. This finding is similar to more recent experiences reporting prophylactic thyroidectomy in individuals with a *RET 634* mutation and suggests that their results may be sustainable with continued follow-up. Skinner *et al.* followed 19 *RET 634* patients over a median of 6.7 years and found 89% free of disease-utilizing stimulated calcitonin at least 5 years after surgery, Machens *et al.* reported 73 *RET 634* individuals with 100% biochemical cure (of those with preoperative elevated calcitonin) as determined by a calcitonin measured at some time after surgery and a median follow-up of 6 years for the larger cohort of 167 patients with any germline *RET* mutation, and Prete *et al.* described 40 individuals with a germline *RET 634* mutation, of whom 73% (27 of 37 with available data) had normal or undetectable basal calcitonin levels after surgery with a a median follow-up of 8.7 years for the larger cohort of 79 individuals (Skinner *et al.* 2005, Machens *et al.* 2018, Prete *et al.* 2018). Given our findings, it is reasonable to postulate that if these studies perform an interval evaluation of calcitonin in three decades, they will find durable results.

A question that could be asked is whether measurement of a basal serum calcitonin and a neck ultrasound is adequate to conclude the absence of disease. We based our decision to limit the image analysis to ultrasound on a prior experience where we performed detailed radiographic evaluations on a sizeable number of patients in preparation for reoperative extensive compartment-oriented lymph node dissection (Yen *et al.* 2003). We never identified imageable disease by computerized tomography, octreotide radionuclide imaging or ultrasound in any patient with a basal serum calcitonin below 250 pg/mL Yen *et al.* 2003). Another interpretation of detectable calcitonin is residual thyroid tissue, including C-cell hyperplasia, as a source, though no thyroid remnant was seen on imaging.

What is the significance of a detectable, but low serum calcitonin concentration four decades after primary surgery?

We consider the three individuals with detectable serum calcitonin values to have recurrent or residual MTC (Fig. 2). The question we have asked is whether these three individuals have derived benefit from their early thyroidectomy. We are heartened by the current absence of identifiable disease in these three patients an average of 38 years later and the lack of an escalating trend in the serum calcitonin for two of three patients. Despite the fact that their prolonged calcitonin doubling times predict that none of these three will die of progressive disease (Laure Giraudet *et al.* 2008), we recognize there are uncommon examples of quiescent MTCs that have changed behaviour and metastasized at later stages of development.

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Indeed, it is important to ask the question of whether the median 40-year period of follow-up for the entire cohort is sufficient to conclude that early thyroidectomy has been successful. We are optimistic when we compare the current median age of these 18 patients (52.0 years) with the median age of death (57.5 years) of the kindred members who died from MTC prior to any screening, though the disease-specific death is not significantly different between these cohorts. Despite these promising results, we are also aware that the 52-year median age for our cohort is still 25–30 years below the average life expectancy. We view the current results as a 'qualified' success story, whose final chapters are yet to be written.

The importance of this study

Perhaps the most important impact of this data set is that it demonstrates the successful use of a biomarker to effect a surgical cure of a genetic malignancy in more than 83% of these children and young adults using 1970–1990 era's screening technology. It also reinforces the point that metastasis can occur in children under the age of 10 years with this *RET* mutation. Thus, a parent (and physician) choosing the appropriate age of thyroidectomy for a child must understand that there is a spectrum of risk and benefit – the earlier the age of a complete thyroidectomy the higher the probability of a lifetime surgical cure, but also a longer and more challenging period during which hypothyroidism and other potential complications of surgery must be managed. Finally, the finding of presumed metastasis in a 9-year old child reinforces the earlier observation that metastasis with this germline mutation can occur as young as 6 years (Gill *et al.* 1996). It provides clear support for the current recommendation to perform a thyroidectomy at the age of 5–6 years in children with a *RET* codon 634 mutation (Eng *et al.* 1996, Wells *et al.* 2015).

As we mingled with family members, many of whom we had not seen for more than 20 years since the last detailed evaluations, there was a single dominant theme that emerged from our discussions – the palpable relief that they and their children did not have to contemplate possible death from metastatic cancer or pheochromocytoma. In the context of having parents and grandparents who died from medullary thyroid carcinoma, their collective survival into the fifth and sixth decades is viewed as a success story.

Note added in proof

Since the submission of this manuscript we have learned that patient 415 (Table 1, Figure 2) had a diagnosis of a skull-based paraganglioma at an outside hospital that was treated with radiation therapy. We were informed that no biopsy was performed, but in view of the patient's prior re-operation for local metastasis of MTC approximately 15 years ago, we suspect this may represent a recurrent focus of MTC. Following the treatment the patient is alive and well.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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