



Long-Term Oncologic Outcomes After Curative Resection of Familial Medullary Thyroid Carcinoma

Philip M. Spanheimer, MD¹, Ian Ganly, MD, PhD¹, Joanne Chou, MS², Marinela Capanu, PhD², Ronald A. Ghossein, MD³, R. Michael Tuttle, MD⁴, Richard J. Wong, MD¹, Ashok R. Shaha, MD¹, and Brian R. Untch, MD¹

¹Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; ²Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; ³Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; ⁴Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Introduction. Long-term outcomes after curative resection in patients with germline RET mutations and medullary thyroid cancer (MTC) are highly variable and mutation-specific oncologic outcomes are not well-described.

Methods. Sixty-six patients identified from 1986 to 2017 from a single-institution cancer database were assessed for recurrence and survival using Kaplan–Meier estimates, and correlated with clinicopathologic features using log-rank or Cox proportional hazards.

Results. Median follow-up was 9.3 years (range 0.3–31.5), median tumor diameter was 1.5 cm (range 0.1–7.5), and preoperative calcitonin was known in 41 patients [median 636 (range 0–9600)]. Overall survival (OS) of the cohort was 94% at 10 years, the cumulative incidence of locoregional recurrence was 38% at 10 years, and 19/24 (79%) patients underwent repeat neck operation. The cumulative incidence of distant recurrence was 27% at 10 years. Predictors of distant recurrence were tumor size, positive lymph nodes, and pre- and postoperative carcinoembryonic antigen, but not calcitonin. M918T mutation-

bearing patients had 10-year distant recurrence-free survival of 0%, compared with 83% in all other patients ($p < 0.001$), and equivalent 10-year OS (100% vs. 92%; $p = 0.49$).

Conclusions. Structural and metastatic recurrence is common in patients with germline RET mutations, and MTC and can occur 20 years after initial treatment, however survival remains high. Management should focus on optimal surveillance strategies and long-term control of structural disease.

The association between germline mutations of the RET proto-oncogene and familial medullary thyroid carcinoma (fMTC) has been established for 25 years.^{1–4} Several studies have investigated long-term oncologic outcomes associated with medullary thyroid cancer (MTC), but there is a paucity of literature in regard to outcomes of patients with familial disease.^{5, 6}

Current American Thyroid Association (ATA) guidelines designate specific mutations within categories of ‘moderate’, ‘high’, and ‘highest’ risk, based primarily on the age of development of MTC^{7–9}. MTC patients with ATA high-risk codon 634 mutations have similar rates of distant metastatic disease and overall survival (OS) compared with patients with MEN2A moderate-risk mutations.¹⁰ These findings indicate that although specific mutations confer differential risk of developing MTC at a young age, the relationship between mutation and tumor behavior, aggressiveness, and long-term oncologic outcomes is unclear, especially with MEN2B patients and the ATA highest-risk M918T mutation.

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B. R. Untch, MD

e-mail: untchb@mskcc.org

We investigated the long-term oncologic outcomes for patients with germline RET mutations and MTC from a single institution, and report the rates of local and distant recurrence (DR), mortality, factors associated with recurrence, and outcome differences in patients with the ATA highest-risk M918T mutation.

METHODS

Following Institutional Review Board approval, we reviewed the cancer registry records at Memorial Sloan Kettering Cancer Center (MSKCC) for patients with MTC, and identified 340 patients who underwent thyroidectomy for MTC between 1986 and 2017. Overall, 316 patients had thyroidectomy with curative intent, with no metastatic or persistent gross disease in the neck. Sixty-six patients were identified as having familial disease based on clinical criteria and/or an identified germline mutation in the RET proto-oncogene. Clinical, pathologic, and follow-up data were obtained by review of the medical record. Postoperative laboratory values were recorded as the first postoperative level within 30 days of surgery. The RET mutation risk category was assigned according to the ATA guidelines.⁸

Lymph node dissections were defined according to levels of the neck recorded in the operative and pathology reports. Levels II–V were classified as the lateral neck and were designated as ipsilateral or contralateral to the primary site in the thyroid. The central neck was defined as levels VI and VII.

All recurrences were defined as structural disease rather than biochemical recurrence. Local recurrence was defined as recurrence in the thyroid bed, nodal recurrence (NR) was defined as recurrence in the neck in any lymph node basin, and DR was defined as recurrence outside of the neck, including the mediastinum. Locoregional recurrences (LRRs) and DRs were recorded independently, and the time to recurrence or death was calculated from the date of surgery.

Patients, disease, and treatment characteristics were summarized using the frequency and percentages for categorical variables and the median and range for continuous variables. OS and recurrence-free survival (RFS) were calculated from the date of the procedure until the date of death, or until the first recurrence or death from any cause, respectively, or censored at the time of the last available follow-up. OS and RFS were estimated using Kaplan–Meier methods and compared between ATA risk (M918T vs. all others) using the log-rank test. The Cox proportional hazards model was used to examine the univariate association between potential risk factors such as age, tumor size, lymph node positivity, and the preoperative and

postoperative biomarkers carcinoembryonic antigen (CEA) and calcitonin, and developed any NR with OS. Preoperative and postoperative biomarkers were transformed using natural logarithm transformation. The development of any LRR was treated as a time-dependent covariate in the Cox regression model.

The cumulative incidence function was used to estimate the probability of any NR and any DR. Patients who experienced another event without the event of interest (death, or developed an LRR or DR) were treated as competing events. Gray's test was used to compare the cumulative incidence of any DR according to ATA risk (M918T vs. all others). Fine and Gray univariate regression methods were used to examine the association between potential risk factors and the risk of LRR or DR. Multivariate analysis was not performed due to the limited number of events in this series.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) or R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All *p* values were two-sided and *p* values < 0.05 were considered to indicate statistical significance.

RESULTS

Clinicopathologic Characteristics

The median age of 66 patients who underwent thyroidectomy with curative intent for MTC and a germline RET mutation was 35.2 years (range 3.4–72.3). The most common RET mutations in our cohort were M918T (*n* = 8), C634X (*n* = 8), and V804 M (*n* = 6); other mutations identified were Y791F, C618X, C611X, T618C, C620R, C786O, and L790F. Nine patients had a family history of MEN2A and two patients had a family history of MEN2B. Additionally, 23 patients had clinically familial disease without a specific mutation identified.

Clinicopathologic variables are listed in Table 1. Median follow-up for survivors was 9.3 years (range 0.3–31.5). Structural disease was defined as known macroscopic disease in the lymph nodes of the neck at the time of thyroidectomy. Ten patients (15%) had structural disease—one in the central compartment, six in the ipsilateral lateral compartment, and three in both the central and ipsilateral lateral compartment. Structural disease was detected by ultrasound in four patients, physical examination in three patients, computed tomography (CT) in two patients, and, in one patient, on positron emission tomography (PET) scan. All patients with known structural disease underwent lymphadenectomy of the involved compartment.

Surgeon preference for prophylactic neck dissection in the absence of structural disease is variable. Of 66 patients,

TABLE 1 Clinicopathologic variables

Variable	Median (range) or <i>n</i> (%)
Age, years	35.2 (3.4–72.3)
Follow-up, years	9.3 (3–31.5)
Sex, female	37 (56)
Prophylactic intent	14 (21)
Known structural disease	10 (15)
Tumor size, cm	1.5 (0.1–7.5)
Node-positive	36 (55)
No. of positive nodes	1 (0–49)
Persistent biochemical disease ^a	36 (55)
Preoperative calcitonin, pg/ml [<i>n</i> = 41]	636 (0–9600)
Preoperative CEA, ng/ml [<i>n</i> = 17]	29.4 (0.9–179)
Postoperative calcitonin, pg/ml [<i>n</i> = 61]	16 (0–9750)
Postoperative CEA, ng/ml [<i>n</i> = 45]	8.4 (0.8–1207)

CEA carcinoembryonic antigen

^aPersistent biochemical disease was defined as an elevation in the first postoperative calcitonin level

including the 10 patients with structural disease, 52 (79%) underwent lymphadenectomy at the time of thyroidectomy. Central lymphadenectomy was performed in 44 patients (67%), ipsilateral lateral was performed in 28 patients (42%), and contralateral lateral was performed in 13 patients (20%). In the entire cohort, 36 (55%) patients had node-positive disease on final pathology, with the number of positive nodes ranging from 1 to 49. The most common positive compartment was the central neck (*n* = 26, 39%), followed by the ipsilateral lateral (*n* = 23, 35%), and contralateral lateral (*n* = 4, 6%). Almost half of the patients with positive nodes had multiple positive compartments (*n* = 17).

Basal serum calcitonin levels were known preoperatively in 41 patients (62%), with a median level of 636 pg/ml (range 0–9750) [normal < 10 pg/ml]. Additionally, preoperative CEA levels were obtained in 17 patients (26%), with a median of 29.4 ng/ml (range 0.8–1207) [normal < 2.5 ng/ml], and postoperative calcitonin levels were known in 61 patients (92%), with a median value of 16 mg/dl (range 0–3750). Persistent biochemical disease was defined as an elevation in the basal calcitonin levels above the upper limit of normal on the first postoperative level. Thirty-six patients (55%) had persistent biochemical disease, including 28 of 36 (78%) patients with positive lymph nodes. Postoperative CEA level was known in 45 patients (68%), with a median level of 8.4 ng/ml (range 0.8–1207).

Recurrence

Twenty-four patients developed an NR (Fig. 1a). Six recurrences were in the central neck, 14 were in the

ipsilateral lateral neck, two were in the contralateral neck, one was in the ipsilateral and contralateral neck, and one was in the central and contralateral neck. The 5- and 10-year cumulative incidence of NR was 26% and 37%, respectively. Of these recurrences, 19 (79%) were managed with reoperation and neck dissection. The factors associated with NR on univariate analysis are listed in Table 2. Age, tumor size, number of positive lymph nodes, preoperative calcitonin, and persistent biochemical disease were associated with NR.

Twenty-one patients (32%) developed a DR (Fig. 1b). Location and management of distant metastasis are detailed in Table 3. The cumulative incidence of DR was 14% and 27% at 5 and 10 years, respectively. Factors associated with DR are listed in Table 2. Statistically significant associations with DR were tumor size, number of positive lymph nodes, preoperative CEA, and postoperative CEA.

Sixteen patients (24%) had both NR and DR. Isolated NRs (without DR) were seen in eight patients (12%) and isolated DRs were seen in five patients (8%). RFS is shown in Fig. 1c. Disease-free survival was 69% and 55% at 5 and 10 years, respectively.

Survival

Six patients (9%) died over the study period (Fig. 1d). Four of these six deaths (67%) were as a result of disease present in the liver, lungs, or both, and two patients died of causes unrelated to MTC. No patients died from invasive disease in the neck. Five- and 10-year OS was 97% and 94%, respectively. Excluding the 14 patients with prophylactic intent thyroidectomy, 5- and 10-year OS was 96% and 93%, respectively, in the 52 patients who underwent thyroidectomy with known MTC. Factors associated with OS were tumor size and postoperative CEA (Table 2). LRR was analyzed as a time-dependent covariate and was not associated with survival (hazard ratio 0.70, 95% confidence interval 0.09–5.41; *p* = 0.74). Of note, persistent biochemical disease and recurrence in the neck were not associated with survival.

Prophylactic Intent Patients

Fourteen patients (21%) underwent thyroidectomy with prophylactic intent and were found to have MTC on pathology. The median age of these patients was 11 years (range 3.4–37), and tumor size was 0.3 cm (range 0.1–1.3). Four patients (29%) had a positive lymph node. Patients were followed for a median of 9.6 years (range 0.8–20.2). One NR was observed at 10.7 years from resection, and two DRs were observed at 10.7 and 12.7 years. Five- and 10-year OS was 100% in prophylactic-intent patients.

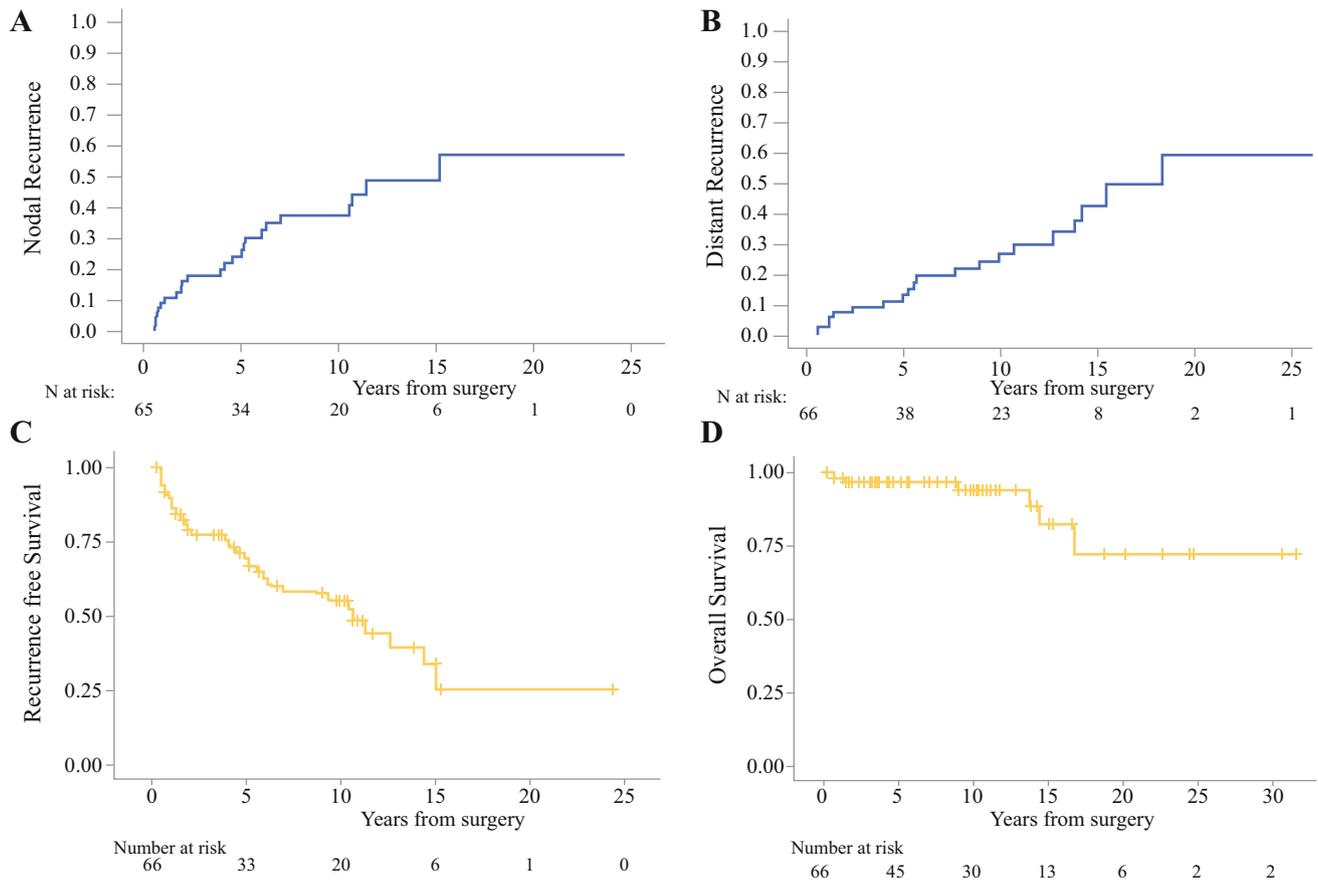


FIG. 1 Cumulative incidence of (a) locoregional recurrence and (b) distant recurrence in 66 patients. (c) Recurrence-free survival and (d) overall survival

TABLE 2 Univariate analysis of factors associated with recurrence and survival

Factor	NR		DR		OS	
	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Age, years	1.03 (1–1.05)	0.03	1.02 (0.99–1.04)	0.16	1.03 (0.98–1.09)	0.18
Sex, male	1.08 (0.48–2.39)	0.86	1.50 (0.65–3.45)	0.34	1.76 (0.32–9.75)	0.52
Tumor size, cm	1.22 (1.04–1.42)	0.01	1.26 (1.06–1.51)	0.01	1.48 (1.03–2.13)	0.03
No. of positive LNs	1.06 (1.02–1.1)	0.001	1.06 (1.02–1.12)	0.008	1.02 (0.93–1.10)	0.70
LN positivity (yes/no)	2.29 (0.98–5.38)	0.06	2.83 (1.13–7.09)	0.03	1.90 (0.34–10.52)	0.46
Ct preoperatively ^{a,b}	1.6 (1.18–2.17)	0.003	1.19 (0.93–1.53)	0.17	2.00 (0.59–6.61)	0.26
CEA preoperatively ^{a,c}	2.13 (0.74–6.17)	0.16	7.57 (2.38–24.13)	0.001	NA	
Ct postoperatively ^{a,d}	1.39 (1.13–1.70)	0.002	1.15 (0.9–1.46)	0.26	1.27 (0.80–2.01)	0.30
CEA postoperatively ^{a,e}	1.17 (0.92–1.5)	0.21	1.71 (1.26,2.33)	0.001	1.85 (1.12,3.09)	0.02
Structural disease	2.93 (1.19–7.2)	0.09	1.89 (0.68,5.25)	0.22	1.38 (0.16, 12.03)	0.77
Persistent biochemical disease	16.34(2.29–116.72)	0.005	4.19 (0.99, 17.59)	0.05	2.34 (0.26, 21.12)	0.45

HR hazard ratio, CI confidence interval, NR nodal recurrence, DR distant recurrence, OS overall survival, LNs lymph nodes, Ct calcitonin, CEA carcinoembryonic antigen, NA not applicable

^aCEA and Ct levels were log-transformed

^b*n* missing = 25

^c*n* missing = 49

^d*n* missing = 5

^e*n* missing = 21

TABLE 3 Management of patients with distant recurrence

Patient	Mutation	Time (months)	Location	Detection	Management
1	M918T	13.5	Bone	CT	Cabozantinib, vandetanib, dacarbazine/5-fluorouracil
2	Positive NOS	169.6	Bone	MRI	Cabozantinib, RT (to symptomatic bone met)
3	M918T	91.6	Liver	PET	Hepatic embolization, LOXO-292
4	C634Y	184.5	Lung, liver	PET	Liver wedge resection, cabozantinib
5	V804 M	62.3	Liver	MRI	LOXO-292
6	Positive NOS	118.8	Liver	CT	RFA liver X2
7	Positive NOS	6.5	Lung, liver, bone	CT	RT (neck, sacrum)
8	M918T	134.7	Lung	CT	RT (lung hilum [hemoptysis]), sorafenib, cabozantinib, vandetanib
9	C618F	67.2	Liver	CT	RT (neck), vandetanib, RT C4, everolimus
10	Positive NOS	13.3	Lung/liver/bone/ breast	CT	RT, imatinib, vandetanib,
11	M918T	99.3	Lung	PET	RT (neck), lung resection, vandetanib
12	Positive NOS	106.2	Lung, liver, bone	CT	RT (neck), vandetanib, LOXO-292
13	M918T	65.8	Liver, lungs	CT	RT (neck), vandetanib, cabozantinib, regorafenib, sunitinib
14	M918T	51.6	Bone	CT	RT (neck), carbo/taxol, RT (rib), vandetanib, LOXO-292
15	V804 M	6.4	Liver, brain	MRI	Vandetanib, temozolomide/capecitabine, RT (brain)
16	MEN2B NOS	356.5	Lung	CT	Vandetanib, RT (neck)
17	M918T	47.0	Liver	MRI	Cabozantinib, LOXO-292
18	C618F	152.1	Liver	MRI	Surveillance
19	Positive NOS	199.6	Bone	CT	Surveillance
20	C620	220.0	Liver, lung	CT	Surveillance
21	C634Y	128.0	Liver	CT	Surveillance

NOS not otherwise specified, RT radiation, RFA radiofrequency ablation, CT computed tomography, MRI magnetic resonance imaging, PET positron emission tomography

Outcomes by RET Mutation

We compared the eight patients with the ATA highest-risk M918T mutation with the remaining 58 patients. Median follow-up for the M918T patients was 8.9 years. The cumulative incidence of DR and OS are shown in Fig. 2. The 10-year distant RFS in patients with M918T mutations was 0% compared with 83% in all other patients ($p < 0.001$). However, this increase in DR did not correspond to increased mortality, with 10-year OS of 100% in patients with M918T mutations compared with 92% in patients with other mutations ($p = 0.49$).

DISCUSSION

In this study, we report the long-term oncologic outcomes for 66 patients with fTMC treated with curative intent thyroidectomy. We report low rates of long-term disease-free survival, with initial recurrences up to 20 years from thyroidectomy. The risk for both LRRs and DRs does not appear to plateau, with a median follow-up of

10 years. These findings indicate that patients with fMTC require lifelong surveillance for recurrent disease. Current ATA guidelines for surveillance involve calcitonin and CEA every 6 months, as well as cross-sectional imaging depending on physical examination findings and calcitonin levels.⁸

There are several limitations to this study. This was a retrospective study spanning a 30-year period in which effective systemic therapy has been developed. Additionally, preoperative and postoperative calcitonin and CEA were missing in a significant number of patients, limiting the analysis of these predictive biomarkers. Finally, the median follow-up of 10 years in this study might be insufficient to characterize true long-term survival in these patients.

Whereas recurrence was common, death was uncommon, with our patients having a 10-year OS of 94%. It is important to note that this study included 14 patients for whom thyroidectomy was performed with prophylactic intent without diagnosis of the underlying MTC prior to surgical pathology. This early treatment could have

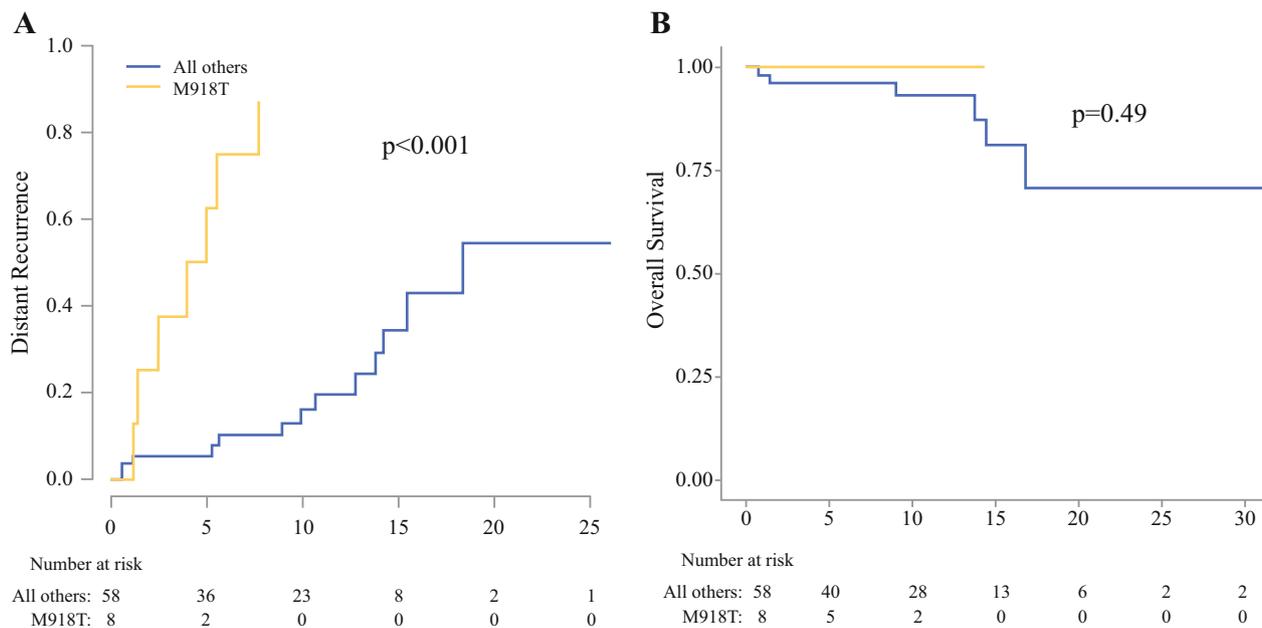


FIG. 2 (a) Cumulative incidence of distant recurrence and (b) overall survival for patients with the M918T mutation compared with all other patients

contributed to both the excellent observed OS and the young median age of 35 years in this study. We did not observe a relationship between age and mortality, which could be due to a low number of events, but older age has previously been reported as a risk factor for death in patients with MTC.^{10–12}

The distinction between recurrence and survival is best illustrated in patients with the ATA highest-risk M918T mutation. All patients with this mutation had a DR by 10 years, but all were still alive at last follow-up. Although we did not demonstrate a difference in survival in patients with M918T mutations, our median follow-up of 8.9 years could be insufficient for a difference to manifest. These findings indicate a disease biology that is difficult to eradicate, but manageable with associated long-term survival. Voss et al. found no difference in distant RFS or OS between patients with high-risk codon 634 mutations and patients with moderate-risk mutations;¹⁰ however, that study was limited to MEN2A patients and did not contain patients with the M918T mutation. Similarly, we found no differences in outcomes between high- and moderate-risk mutations, but did show a significant difference in the incidence of DR in highest-risk M918T patients, which, to our knowledge, is the first report of a cancer-specific outcome affected by a specific mutation.

One active question in the management of MTC is the role of lateral neck dissection for elevated preoperative basal serum calcitonin in the absence of identified structural disease in the lateral neck.¹³ Machens and colleagues investigated ways to predict lymph node metastasis in

different lymph node compartments based on quantifying lymph node involvement in the central compartment, as well as serum calcitonin levels.^{14–16} These studies focused more on rates of identified microscopic disease and postoperative serum calcitonin levels, and less on oncologic outcomes of recurrence and survival. Increased postoperative calcitonin levels have been associated with recurrence and reoperation,^{17–20} and we found that pre- and postoperative calcitonin and persistent biochemical disease were associated with an increased risk of LRR. Interestingly, these associations did not hold for DR and survival, which could be due to a limited number of events.

Thirty-nine years ago, Norton and Brennan reported that in node-positive patients, biochemical ‘cure’ was extremely rare and highly dependent on the method of detection of calcitonin levels. Patients with normal basal peripheral calcitonin frequently had elevated levels of peripheral calcitonin when stimulated with pentagastrin, and, essentially, when undergoing internal jugular catheterization with stimulation, all patients would have residual biochemical disease, despite normal peripheral levels.²¹

The relationship between aggressive surgery, normalization of biochemical levels, and subsequent effects on recurrence and survival has not been well-characterized. Further investigation is needed, both in familial and sporadic MTC, to characterize the differences in oncologic outcomes resulting from lymph node dissection in the absence of structural disease, and to identify patients who might benefit from more aggressive upfront surgery. Our results demonstrate a disease biology with high recurrence

rates, but good long-term survival. With an OS of 94% at 10 years, it is difficult to justify a highly morbid intervention with the goal of improving long-term outcomes.

CONCLUSIONS

fMTC is characterized by high rates of LRR and DR, the risk of which persists for 20 years after diagnosis. However, despite high rates of structural recurrence, mortality is rare. Further studies are needed to determine the impact of aggressive surgery for biochemical disease, particularly in the neck lymph nodes at the time of initial thyroidectomy, although it is unlikely this could improve survival above what was observed in our study. Management strategies for fMTC should focus on optimizing approaches to surveillance and long-term control of structural disease.

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