Long-Term Clinical and Biochemical Follow-up in Medullary Thyroid Carcinoma

A Single Institution's Experience Over 20 Years

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Objective: Many patients with medullary thyroid carcinomas (MTC) have reoperative surgery in different hospitals, which makes their follow-up difficult. To comprehend these complex courses and to find relevant prognostic factors we report a 20-year single center experience of 289 patients with MTC or precursor C-cell-hyperplasias.

Patients and Methods: Between April 1986 and May 2006, 289 consecutive patients with MTC or *MEN2* gene carriers were treated at the Department of Surgery at the University Hospital Düsseldorf. Tumor stages were documented according to the classification of the International Union against Cancer 5th edition, 1997 (Schott. *Endocr Relat Cancer*. 2006;13:779–795). A system to easily comprehend operative procedures is suggested.

Results: There were 159 female and 130 male patients (f/m ratio 1.22). Mean age at time of diagnosis was 32 years (4–77) in the familial cases and 53 years (23–84) years in the sporadic cases. Sixty-six patients (23%) had multifocal disease. Twelve *MEN2*-patients had only C-cell-hyperplasia (pT0). Tumor stage was pT1 in 86 patients, pT2 in 106 patients, pT3 in 25 patients, pT4 in 52 patients and unclear in 8 patients. In the 289 patients 648 operations were performed. One hundred seventy patients had more than 1 operation (59%). Ninety-nine patients (34%) are calcitonin-negative and 91 patients (31%) live with elevated calcitonin. Median follow-up time of the surviving 211 patients was 8.9 years (range, 0.3–30.7 years). The 5- and 10-year survival of all tumor patients was 86% and 68%, respectively.

Conclusion: The chance to achieve biochemical cure in MTC is clearly dependent on the primary tumor size. The chance for long-term biochemical cure in a pT4-tumor is almost nil even after multiple and extended reoperations, whereas a pT1 tumor can be cured in up to 67% of the patients. Long-term survival, however, can be achieved even in pT4 tumor patients in almost 50%.

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Medullary thyroid carcinomas (MTC) are rare tumors, which account for approximately 10% of all thyroid malignancies.[1,2] They occur either sporadically or in a familial form (multiple endocrine neoplasia Type 2a [*MEN2a*], multiple endocrine neoplasia Type 2b [*MEN 2b*], familial medullary thyroid carcinoma [FMTC]). Compared with other thyroid tumors they have unique characteristics:

1. They express calcitonin as a tumor marker of high sensitivity and specificity, which can indicate residual tumor and recurrence even years before clinical or radiologic detection.
2. They do not accumulate radioactive iodine and have only little sensitivity to external beam radiation or chemotherapy. Therefore, the treatment is predominantly surgical even in recurrent cases.
3. Even patients with proven disseminated distant metastases often show a long-term survival with mild symptoms if the neck region is cleared.

Because of these characteristics most of the MTC patients need more than 1 operation and many patients change hospitals. Therefore the course of their illness is often complex and difficult to survey. Although there are well-defined operative standards for newly detected tumors,[3] the procedures in recurrent tumors are often highly individual.[4] Only few publications comprising larger patient groups are available.[2,5–11] But to judge therapeutic strategies and to find prognostic factors a sophisticated documentation and comprehension of a larger patient group is necessary. Therefore, we report a 20-year single center experience of 289 patients with MTC or precursor C-cell-hyperplasias.

PATIENTS AND METHODS

Between April 1986 and May 2006 a total of 289 consecutive patients with MTC or *MEN2* gene carriers with

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C-cell-hyperplasia have been treated at the Department of Surgery of the University Hospital Düsseldorf. All available data of these patients were collected. All resected specimens were examined histopathologically and by immunohistochemistry for calcitonin expression.

Tumor Staging

The tumor staging was documented according to the classification of the International Union against Cancer 5th edition, 1997.[12]

Patients were stratified "lymph node positive" (N1) if there was at least 1 proven lymph node metastasis no matter in which compartment it occurred and no matter in which operation it was removed. A patient was stratified "lymph node negative" (N0) if no lymph node metastasis was present no matter how many lymph nodes had been removed during the operation(s). A patient was stratified as "having distant metastases" (M1) if either distant metastases were proven histologically or there were clear clinical or radiologic signs for metastases while calcitonin was elevated.

Operative Procedures

We applied the following standard neck operations for MTC: thyroidectomy with centrocervical lymph node dissection as prophylactic surgery in *MEN2* gene carriers; thyroidectomy with centrocervical and ipsilateral lymph node dissection in sporadic tumors and thyroidectomy with centrocervical and bilateral lymph node dissection in familial tumors. These procedures are according to the AACE/AAES guidelines 2001.[3] This operative strategy has not been significantly changed during the years of this study. Since 1992 we did not perform a completion thyroidectomy in patients with incidentally diagnosed small sporadic C-cell-carcinomas when the postoperative pentagastrin stimulated calcitonin was negative (this procedure has been published elsewhere[13,14]). All additional extended procedures like trans-sternal mediastinal dissection, reneck dissection or liver resection were performed individually based on radiologic and biochemical findings.

In 289 patients a total of 648 operations were performed. For comparability of treatment results the patients were allocated to 1 of the following operative procedures:

Group a: less than total thyroidectomy (<Tx)
Group b: Total thyroidectomy ± central lymph node dissection, but without dissection of the lateral (levels 2, 3, 4) compartment
Group c: Total thyroidectomy + central lymph node dissection and tumor side lateral lymph node dissection (levels 2, 3, 4)
Group d: Total thryoidectomy + central lymph node dissection + bilateral modified radical neck dissection (levels 2, 3, 4)
Group e: additional mediastinal lymph node dissection via sternotomy
Group f: additional liver resection

For example a patient who underwent 3 consecutive operations: first total thyroidectomy, then bilateral cervical lymph node dissection as second operation and trans-sternal lymph node dissection in the third operation, was cumulatively classed to group e.

Lymph Node Dissection

According to Robbins et al[15] and Clayman and Frank[16] there are 6 levels of lymph nodes in the neck: level 1: submental and submandibular, level 2: upper jugular group, level 3: middle jugular group, level 4: lower jugular group, level 5: posterior triangle and level 6: anterior compartment comprising paratracheal and thyroidal basins. Standard lateral lymph node dissection in our patients contained dissection of levels 2, 3, 4 and 6. Levels 1 and 5 were operated only when there was hint for metastases.

Follow-up

All available patients were reevaluated by direct examination and calcitonin measurement at our institution or by telephone interview. For follow-up a patient was stratified "calcitonin negative" if calcitonin was below the detection limit of 5 pg/mL. A patient was stratified "unclear" if either calcitonin was between 5 and 10 pg/mL or there was no calcitonin measurement available and no other hint for tumor persistence. A patient was stratified "calcitonin elevated" if basal calcitonin was higher than 10 pg/mL.

Statistics

To assess the potential risk factors for survival of MTC-patients, the Kaplan-Meier method was estimated for survival curves and the Log-rank test was applied to test the difference between curves of a factor. Cox regression with stepwise selection method was used in multivariate analysis. The entry testing based on the significance of the score statistic ($P < 0.05$), and removal testing based on the probability of a likelihood-ratio statistic based the maximum partial likelihood estimates ($P > 0.10$). All statistical analyses were used with the statistical program SPSS for Windows (Version: 12.0).

RESULTS

There were 159 female and 130 male patients (f/m ratio 1.22). Mean age at time of diagnosis was 32 years (4–77) in the familial cases and 53 years (23–84) years in the sporadic cases. We had 110 patients from 54 affected families with familial disease (*MEN2a, MEN2b,* FMTC) proven by sequencing of the *RET* proto-oncogene. In the other 179 patients a mutation of the *RET* proto-oncogene was ruled out by genetic sequencing. None of them had a familial history or related endocrine tumors. They were considered sporadic.

Primary Tumor Size, Lymph Node Metastases and Distant Metastases

There were 211 patients with isolated tumors whereas 66 patients (23%) had multifocal disease. Of these 66 patients 50 (76%) had familial disease and 16 (24%) had sporadic disease. Twelve patients from *MEN2* families with prophylactic thyroidectomy had C-cell-hyperplasia but no carcinoma (pT0). There were 86 patients with pT1 tumors, 106 patients with pT2 and 25 patients with pT3 tumors. In 52 patients the primary tumor had spread out through the thyroid capsule

TABLE 1. The Distribution of Tumor Stages for Sporadic and Familial MTC Patients

Primary Tumor	Total	%	Sporadic	%	Familial	%
pT0	12	4	0	0	12	11
pT1	86	30	40	22	46	42
pT2	106	37	74	41	32	29
pT3	25	9	18	10	7	6
pT4	52	18	43	24	9	8
pTx	8	3	4	2	4	4
Total	289		179		110	

TABLE 2. The Number of Patients With Simultaneous or Metachronic Lymph Node (N1) or Distant Metastases (M1) Related to Primary Tumor Size

Primary Tumor	Total	N1	%	M1	%
pT0	12	0	0	0	0
pT1	86	21	24	3	4
pT2	106	70	66	29	27
pT3	25	21	84	7	28
pT4	52	51	98	31	60
pTx	8				
Total	289				

(pT4). The histologic reports were not available in 6 patients and imprecise in 2 patients, which were either pT2 or pT3. These patients were classed as pTx.

Table 1 shows the distribution of tumor stages for sporadic and FMTC patients.

Table 2 shows the number of patients with simultaneous or metachronic lymph node (N1) or distant metastases (M1) related to primary tumor size.

Ten patients had simultaneous papillary thyroid carcinoma (3.5%). One of them had also an additional 5-cm follicular thyroid carcinoma.

Operative Procedures and Lymph Node Dissection

Only 127 patients (44%) had their primary operation at our institution whereas 162 patients (56%) were referred to us after prior surgery at other hospitals.

In the 289 patients 648 operations were performed. Twelve patients had prophylactic surgery, whereas 277 patients had therapeutic surgery. One hundred nineteen patients (41%) had 1 operation, 72 patients (25%) had 2 operations, 48 patients (17%) had 3 operations, 31 patients (11%) had 4 operations, 9 patients had 5 operations, 6 patients had 6 operations, 1 patient had 8 operations, and 3 patients had 9 operations for MTC.

To assess the total number of lymph nodes that were resected in the different groups we have studied all available pathologic reports. Unfortunately, especially before 1993, our pathologists did not always determine the exact number of lymph nodes. In many cases the pathologic reports only say that "multiple lymph node metastases" have been found. So we are unable to provide the exact number in 75 of 289 patients (26%). If "multiple" means at least more than 3, than a total number of at least 4716 lymph nodes have been resected. Of these 1381 lymph nodes contained tumor.

In the 27 patients of group a, a lymph node dissection was not intended. There were only 2 tumor-free lymph nodes incidentally found adjacent to 1 specimen. No patient was unclear.

Among 44 patients of group b, 11 had no lymph node dissection. In 33 patients a centrocervical bilateral lymph node dissection was intended. In these 33 patients 61 lymph nodes were counted. Median number of nodes was 1 lymph node, mean was 1.9 lymph nodes, range was 0 to 8 lymph nodes. Fifty-six lymph nodes were free of tumor. One patient had 4 lymph node metastases and 1 patient had 1 lymph node metastasis. No patient was unclear.

In the 69 patients of group c, 1106 lymph nodes were resected. Among 51 patients with exact data the median number of nodes was 13 and mean was 16 lymph nodes per patient with a wide range from 2 to 42 lymph nodes. Two hundred fifty-seven lymph nodes contained tumor. In 18 patients the exact number was not clear.

Eighty-one patients of group d had 1874 lymph nodes resected. Among 26 patients with exact data the median number of nodes was 22 and mean was 22.8 lymph nodes per patient with a range from 7 to 93. A total of 448 lymph nodes contained tumor. In 26 patients the data were not exactly clear.

The 68 patients of groups e and f had 1673 lymph nodes resected. Among 37 patients with exact data the median was

TABLE 3. The Cumulative Operative Procedures and Number of Resected and Tumor-containing Lymph Nodes

Group	n	%	Total No. Lymph Nodes Removed	Median No. Lymph Nodes Removed	Mean No. Lymph Nodes Removed	Range	Total No. Lymph Nodes Containing Tumor	Patients Without Exact Data
a	27	9	2	0	0	0 to 2	0	0
b	44	15	61	1	2	0 to 8	5	0
c	69	24	1106	13	16	2 to 42	257	18
d	81	28	1874	22	23	7 to 93	448	26
e	56	19	1673*	30*	24*	11 to 96*	671*	31*
f	12	4						
Total	289	100	4716				1381	

*Data for groups e and f combined.

30 and mean was 24 lymph nodes. The range was 11 to 96. 671 lymph nodes contained tumor. In 31 patients the exact number was unclear.

Table 3a, b shows the cumulative operative procedures including the number of resected and tumor containing lymph nodes. All patients with familial disease had at least total thyroidectomy with centrocervical lymph node dissection.

Follow-up

Fifty-eight patients (20%) died of their tumor disease with a median survival time of 4.9 years. Nine patients died of other (non-MTC-related) causes and 11 patients were completely lost to follow-up. Twenty-one patients (7%) were alive and without any clinical signs of tumor recurrence but refused any participation on follow-up examinations and calcitonin measurements (unclear). Ninety-nine patients (34%) are calcitonin negative and 91 patients (31%) live with elevated calcitonin. Median follow-up time of the surviving 211 patients was 8.9 years (range, 0.3–30.7 years) (1 female patient was initially operated 1975 in another hospital and came to us 1988 for cervical reoperation. She is still alive with highly elevated calcitonin and multiple small liver metastases). The 5- and 10-year survival of all tumor patients was 86% and 68%, respectively. Five patients died after more than 10 years (12, 13, 17, 18 and 23 years) of initial diagnosis of their disease. Kaplan-Meier survival functions show survival related to primary tumor size and staging, lymph node spread, distant metastases, and familiarity (Figs. 1–5). The prognosis deteriorated when the primary tumor was larger than 2.5 cm.

Table 4 shows the patient's follow-up related to the primary tumor size and heredity.

DISCUSSION

MTC may be considered the most challenging tumor in thyroid surgery. Therapeutic options other than surgery

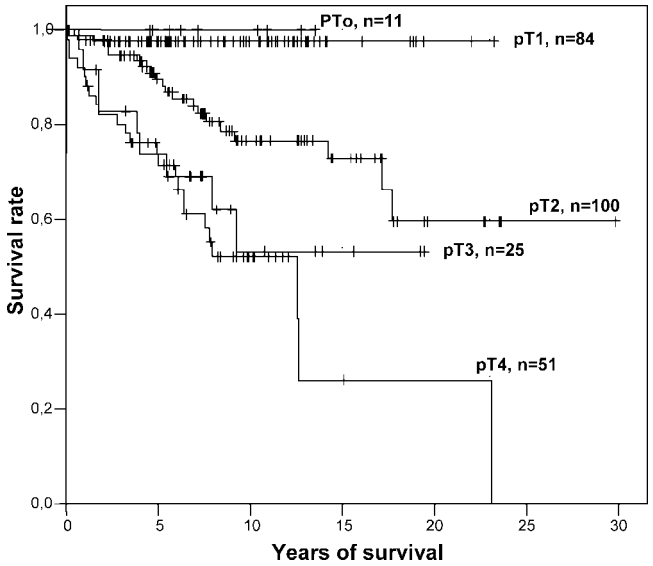

FIGURE 1. Kaplan-Meier survival functions related to primary tumor staging showing that the survival rate depends on size and extent of the primary tumor.

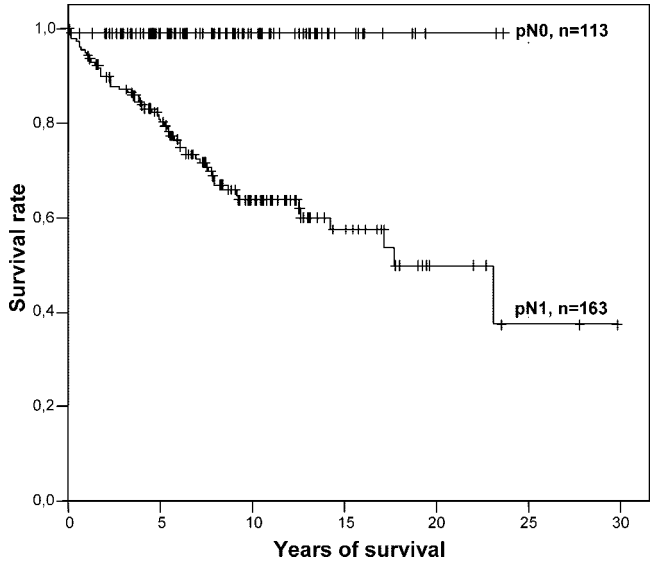

FIGURE 2. Kaplan-Meier survival functions related to lymph node spread.

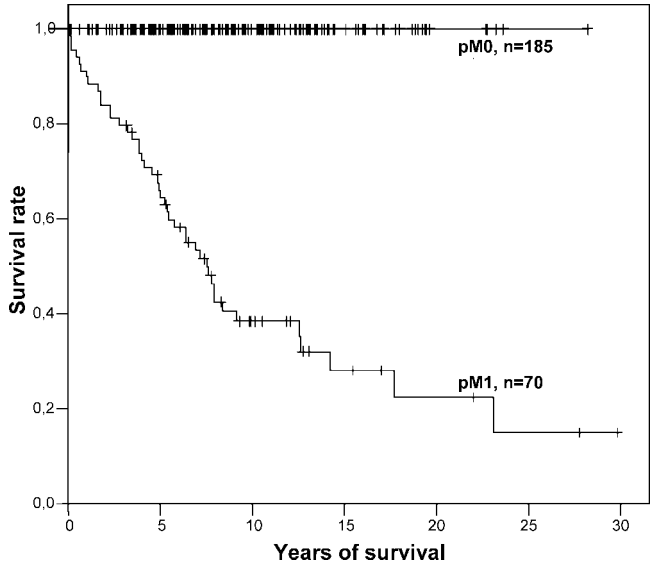

FIGURE 3. Kaplan-Meier survival functions related to distant metastases.

are poor. Many patients undergo various diagnostic procedures for occult persistence and multiple operations for recurrent tumor. The course of their illness is often complex and the value of reoperative surgery sometimes uncertain or speculative.

In a recent retrospective study Ukkat et al[11] found a quite similar distribution of primary tumor stages using the same International Union against Cancer criteria. In both studies the number of pT3 tumors is low [9% (present study) vs. 8% (Ukkat)], the reason being that a tumor is >4 cm, but still completely inside the thyroid capsule is a rare condition. The number of involved lymph node metastases has a widespread reaching from 24% in pT1 (Ukkat 17%) to 98% in pT4 (Ukkat 100%).

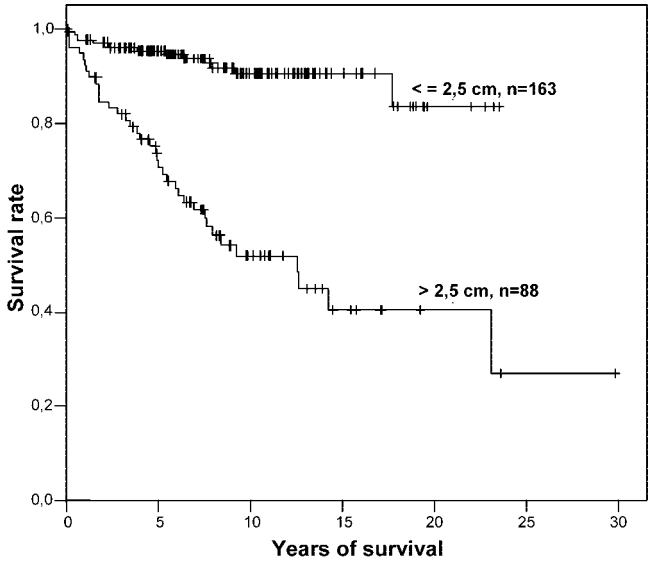

FIGURE 4. Kaplan-Meier survival functions related to primary tumor size (diameter) showing that a tumor-size >2.5 cm may be a critical value for long-term prognosis.

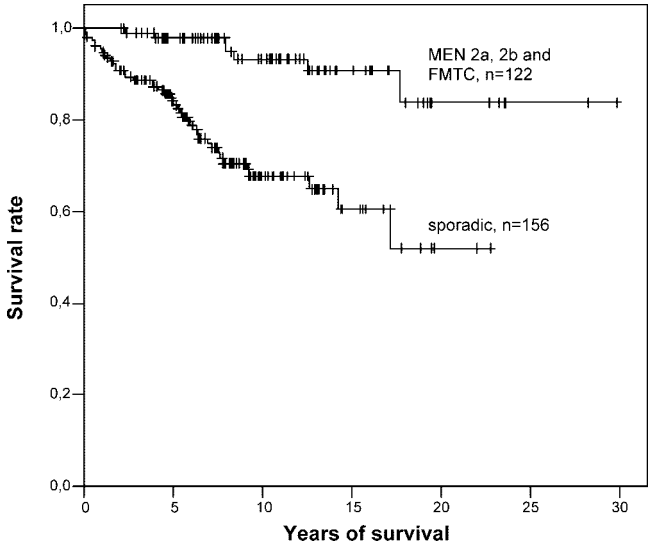

FIGURE 5. Kaplan-Meier survival functions related to heredity. Sporadic tumors have a poorer prognosis.

Patients with familial disease were younger and often presented with lower tumor stages compared with sporadic disease. Whereas 36% of the sporadic patients were pT3 or pT4, only 14% of the inherited MTC-patients were diagnosed in advanced tumor stages, which may account for better outcome of inherited MTC-patients.

Because preoperative calcitonin measurement is not routinely performed in Germany, only 44% of the patients were primarily operated at our institution, dedicated to thyroid surgery, whereas 56% were sent to us from elsewhere for further therapy.

The operative procedures were according to the AACE/AAES guidelines 2001.[3] This operative strategy has not been significantly changed in our hospital during the years of this study. The only change during that time was regarding patients with incidentally diagnosed small sporadic C-cell-carcinomas: Twenty-seven patients with less than thyroidectomy (group a) originally were operated upon benign nodular goiter. There were 18 pT1-tumors and 8 pT2-tumors. In all of them familial background was ruled out by genetic sequencing of the *RET* proto-oncogene and postoperative calcitonin was low and could not be stimulated by pentagastrin injection. None of these patients developed tumor recurrence as reported elsewhere.[13,14] In 1 patient a pT3-tumor was found after hemithyroidectomy. The postoperative tumor staging showed a calcitonin of >9000 pg/mL and multiple distant metastases. He died 21 month later of disease without reoperation. He had no tumor-related local problems in the neck region.

The 5- and 10-year survival rates of patients with MTC in the recent literature are given in Table 5. But even 10 years after initial operation the finding of elevated calcitonin in asymptomatic patients is not unusual.

Table 5 shows 5- and 10-year survival in MTC in the recent literature.

There are no guidelines for reoperative surgery in MTC. But the majority of dedicated endocrine surgeons advocate reoperations in case of positive localization studies and in case of symptomatic disease.[4] In our patients additional procedures like trans-sternal mediastinal dissection, reneck dissection or liver resection were performed individually based on radiologic and biochemical findings. There were different aims of reoperative surgery: in some patients it was an effort to achieve biochemical cure whereas in others the idea was the mere local clearance to avoid local complications.

The most favorable result for the patient is biochemical cure, ie, calcitonin below detection limit. Only few patients may develop tumor recurrence without elevated calcitonin.[17] No patient in our study had clinical or radiologic signs of tumor recurrence without elevated serum calcitonin. But in the literature biochemical cure is reached in only 14% to 38% of patients after reoperation.[18–20] In our study only 24 of 170 patients (14%) with reoperative surgery had a postoperative calcitonin below the detection limit. Nineteen of them had subtotal resection for supposed benign nodular goiter as their first operation.

The most important result of our study is that the likelihood to find lymph node or distant metastases and the chance to achieve biochemical cure is clearly dependent on the primary tumor size. Especially a primary tumor size over 2.5 cm is connected with bad prognosis. The chance to cure a pT4-tumor is small even after multiple reoperations. Only 1 of 52 pT4 patients in our series could be cured biochemically (It was a 58-year-old lady with a 2 cm carcinoma that grew locally beyond the thyroid capsule. The time of follow-up in this patient is 6 years.). And even extended operative procedures rarely lead to biochemical cure. Only 2 of 67 patients (3%) were biochemically cured after trans-sternal mediastinal dissection (Follow-up time 7.6 and 12.5 years).

TABLE 4. The Patient's Follow-up Related to the Primary Tumor Size and Heredity

Primary Tumor	n	Calcitonin Neg.	%	Calcitonin Elevated	%	Unclear	%	d.o.d.	%	d.o.o.c.	%	Lost to Follow Up	%
pT0	12	11	92	0	0	0	0	0	0	0	0	1	8
Sporadic	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
MEN2a	*6*	*5*	*83*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*17*
MEN2b	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
FMTC	*6*	*6*	*100*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
pT1	86	58	67	15	17	8	9	2	2	1	1	2	2
Sporadic	*40*	*24*	*60*	*10*	*25*	*1*	*3*	*2*	*5*	*1*	*3*	*2*	*5*
MEN2a	*19*	*14*	*74*	*3*	*16*	*2*	*11*	*0*	*0*	*0*	*0*	*0*	*0*
MEN2b	*2*	*0*	*0*	*2*	*100*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
FMTC	*25*	*20*	*80*	*0*	*0*	*5*	*20*	*0*	*0*	*0*	*0*	*0*	*0*
pT2	106	25	24	38	36	10	9	21	20	6	6	6	6
Sporadic	*74*	*18*	*24*	*28*	*38*	*5*	*7*	*17*	*23*	*2*	*3*	*4*	*5*
MEN2a	*13*	*2*	*15*	*6*	*46*	*1*	*8*	*2*	*15*	*1*	*8*	*1*	*8*
MEN2b	*3*	*1*	*33*	*0*	*0*	*0*	*0*	*1*	*33*	*1*	*33*	*0*	*0*
FMTC	*16*	*4*	*25*	*4*	*25*	*4*	*25*	*1*	*6*	*2*	*13*	*1*	*6*
pT3	25	4	16	10	40	1	4	9	36	1	4	0	0
Sporadic	*18*	*3*	*17*	*6*	*33*	*1*	*6*	*7*	*39*	*1*	*6*	*0*	*0*
MEN2a	*3*	*1*	*33*	*1*	*33*	*0*	*0*	*1*	*33*	*0*	*0*	*0*	*0*
MEN2b	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
FMTC	*4*	*0*	*0*	*3*	*75*	*0*	*0*	*1*	*25*	*0*	*0*	*0*	*0*
pT4	52	1	2	23	44	2	4	24	46	1	2	1	2
Sporadic	*43*	*1*	*2*	*17*	*40*	*1*	*2*	*22*	*51*	*1*	*2*	*1*	*2*
MEN2a	*5*	*0*	*0*	*2*	*40*	*1*	*20*	*2*	*40*	*0*	*0*	*0*	*0*
MEN2b	*1*	*0*	*0*	*1*	*100*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
FMTC	*3*	*0*	*0*	*3*	*100*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
pTx	8	0	0	5	63	0	0	2	25	0	0	1	13
Sporadic	*4*	*0*	*0*	*1*	*25*	*0*	*0*	*2*	*50*	*0*	*0*	*1*	*25*
MEN2a	*4*	*0*	*0*	*4*	*100*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
MEN2b	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
FMTC	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Total	289	99	34	91	31	21	7	58	20	9	3	11	4
Sporadic	*179*	*46*	*26*	*62*	*35*	*8*	*4*	*50*	*28*	*5*	*3*	*8*	*4*
MEN2a	*50*	*22*	*44*	*16*	*32*	*4*	*8*	*5*	*10*	*1*	*2*	*2*	*4*
MEN2b	*6*	*1*	*17*	*3*	*50*	*0*	*0*	*1*	*17*	*1*	*17*	*0*	*0*
FMTC	*54*	*30*	*56*	*10*	*19*	*9*	*17*	*2*	*4*	*2*	*4*	*1*	*2*

But it is well documented that patients without normalization, but reduction of serum calcitonin benefit from reoperations.[21,22] Local complications are avoided and tumor burden is reduced which may relief symptomatic diarrhea.[23] In a selection of patients a significant reduction of calcitonin levels can be achieved by reoperations.[24]

TABLE 5. Five- and 10-year Survival in MTC in the Recent Literature

Author	Year of Publication	Period	No. Patients	Tumor Type	5-year Survival	10-year Survival
Saad[9]	1984	1944–1983	161	sporadic + familial	78.2	61.4
Brierley[29]	1996	1954–1992	73	sporadic + familial	70	57
Dottorini[30]	1996	1970–1992	53	sporadic + familial	—	71
Bergholm[6]	1997	1959–1981	247	sporadic + familial	—	69.2
Hyer[7]	2000	1949–1998	162	sporadic + familial	72	56
Kebebew[8]	2000	1960–1998	104	sporadic + familial	89.3	86.5
Clark[31]	2005	1969–2000	30	sporadic + familial	97	88
Gülben[28]	2006	1993–2003	32	sporadic	51	—
Present study	2006	1986–2006	277	sporadic + familial	86	68

The future will provide new therapeutic tools and options for MTC especially in disseminated disease like thyrosin kinase inhibitors,[25] radioactive isotopes,[26] immunotherapy[27] and different forms of local liver ablation.[28] Our study may serve as a database with which to compare their therapeutic results.

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