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Original Articles

A Nationwide Clinical Survey of Patients with Multiple Endocrine Neoplasia Type 2 and Familial Medullary Thyroid Carcinoma in Japan

Masatoshi Iihara[1], Tomoyuki Yamashita[1], Takahiro Okamoto[1], Masako Kanbe[1], Kiyomi Yamazaki[1], Shin-ichi Egawa[2], Ken Yamaguchi[2] and Takao Obara[1]

1Department of Endocrine Surgery, Tokyo Women's Medical College, Tokyo and [2]Growth Factor Division, National Cancer Center Research Institute, Tokyo, Japan

MEN (multiple endocrine neoplasia) type 2 syndrome is an inherited disease characterized by medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism and/or developmental anomalies. Germ-line mutations of the RET proto-oncogene have recently been identified as the underlying cause of the syndrome. Accordingly, several investigators have advocated prophylactic total thyroidectomy for medullary thyroid carcinoma at an early age in MEN 2 gene carriers identified by DNA analysis. Before applying this strategy in Japan, the biological behavior of each category of tumor in MEN 2 syndrome, and medullary thyroid carcinoma in particular, should be well understood. We conducted a nationwide questionnaire survey to clarify the clinicopathological features of MEN 2 in Japan, obtaining data for 230 patients diagnosed as having MEN 2. They included 84 males and 146 females, with a median age of 37.5 years (range 5–83). Patients were categorized as 179 with MEN 2A, 17 with MEN 2B, 12 with familial medullary thyroid carcinoma and 22 'other'. Medullary thyroid carcinoma, pheochromocytoma and parathyroid lesions occurred in 224 (97%), 132 (57%) and 25 (11%) patients respectively. Twelve patients (5.2%) died of medullary thyroid carcinoma and 11 patients died of other or unknown causes. Of 163 patients for whom follow-up data were obtained, 82 (50%) experienced recurrences of medullary thyroid carcinoma, including symptomatic recurrent tumors in 24 patients and elevated calcitonin levels alone in 54. In the era of RET mutational analysis for screening relatives of patients with MEN 2, these data provide useful information about surgical management for patients with MEN 2 in Japan.

Key words: multiple endocrine neoplasia – calcitonin – RET proto-oncogene – DNA analysis – medullary thyroid carcinoma

INTRODUCTION

Multiple endocrine neoplasia (MEN) type 2 syndrome is an autosomal dominant inherited disease characterized by the association of medullary thyroid carcinoma (MTC), pheochromocytoma, hyperparathyroidism, and/or developmental anomalies including marfanoid habitus and ganglioneuromatosis. This syndrome is classified into two phenotypes: MEN 2A and MEN 2B. Familial MTC (FMTC) is also included in the MEN 2 syndrome in a broad sense. Recently, germ-line mutations of the RET proto-oncogene have been identified as the underlying causes of MEN 2 and FMTC (1,2). In Europe and the USA, it has been reported that almost all patients with MEN 2 as well as FMTC subsequently develop MTC (3). The prognosis of the disease depends predominantly upon the extent of MTC, so the importance of diagnosis and surgery at an early stage is emphasized. Accordingly, several investigators have shown that prophylactic total thyroidectomy at an early age is a useful intervention for management of MTC in MEN 2 gene carriers who are identified by RET mutational gene analysis (4,5).

Before adopting this surgical strategy for MEN 2 patients in Japan, there is a legitimate need to clarify the clinical characteristics of each component of the MEN 2 symptoms, in particular MTC, and to learn about the natural history and clinical course of this

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For reprints and all correspondence: Takao Obara, Department of Endocrine Surgery, Tokyo Women's Medical College, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162, Japan

Abbreviations: MEN, Multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; FMTC, familial MTC.

syndrome in Japan, since the biological behavior of the tumors may vary with geographical location or race. In order to clarify these issues, we conducted a nationwide questionnaire survey, anticipating that the data obtained would be useful for planning the management of MTC in MEN 2 syndrome.

MATERIALS AND METHODS

We asked 760 physicians working in the fields of endocrinology, surgery and urology in Japan to provide us with the clinical records of patients in their care with MEN 2 or FMTC. For each patient, the following data were obtained: family history, clinical features, biochemical data, location and other clinical characteristics of MTC, pheochromocytoma and parathyroid lesions, operative procedures and treatment outcomes. The survey was completed in September 1995.

The patients with MEN 2 included in this survey were sub-classified into four categories: MEN 2A, MEN 2B, FMTC and 'other'. MEN 2A was defined as one or more members of a family having MTC and pheochromocytoma and/or parathyroid lesions. MEN 2B was characterized by MTC or pheochromocytoma together with typical facies, mucosal neuromas and ganglioneuromatosis of the gut. FMTC was used to describe patients whose families had at least four members with MTC alone, without a family history of either pheochromocytoma or parathyroid disease. Any patients with either MTC or pheochromocytoma alone where screening was not confirmed, or FMTC families with fewer than four cases of MTC, were classified as 'other' (6). The term MEN 2 as used in this article includes patients from all four categories.

The significance of differences among the four groups was assessed using either the χ^2 test or Fisher's exact test. Cause-specific mortality was calculated by means of the Kaplan–Meier product limit method. The log-rank test was used to compare survival rates among the groups.

RESULTS

Data for a total of 230 patients with MEN 2 were assembled from 56 institutions in Japan. Table 1 summarizes the clinical characteristics of the patients. There were 84 males and 146 females, with a median age of 37.5 years (range, 5-83 years). The patients' conditions were categorized as 179 MEN 2A, 17 MEN 2B, 12 FMTC and 22 other.

The primary reasons which led to the diagnosis of MEN 2 were MTC in 128 patients, pheochromocytoma in 46, parathyroid disease in two and family screening in 53. A family history of MEN 2 was positive for 188 patients, negative for 31 and unobtainable for 11.

Of the 230 patients, 224 (97%) with a mean age of 38.0 years (range 5–73) had MTC (Table 1). Patients with MEN 2B developed MTC at a younger age than those in the other three categories. The youngest patient was in the MEN 2B group, whereas the oldest was in the MEN 2A group. In addition, 132 (57%) patients, with a mean age of 40.0 years (range 16–77) had pheochromocytoma. Twenty-four patients, with a mean age of 48.2 years (range 13–71), had parathyroid disease which was confirmed by histopathology. As for the pattern of disease involvement, a combination of MTC and pheochromocytoma was identified in 107 patients, a combination of MTC, pheochromocytoma and parathyroid disease was identified in 19 and 95 patients had MTC alone.

Table 1. Clinical characteristics of patients with MEN 2 and FMTC

	MEN 2A		MEN 2B		FMTC		Other		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
No. of patients (%)	179	(78)	17	(7)	12	(5)	22	(10)	230	(100)
Mean age, yr	40		22		39		38		38	
Males/females (ratio)	69/110	(0.6)	7/10	(0.7)	3/9	(0.3)	5/17	(0.3)	84/146	(0.6)
Basis for detection: n, (%)										
Family screening	47	(26)	2	(12)	0		4	(18)	53	(23)
MTC	88	(49)	10	(59)	12	(100)	18	(82)	128	(55.5)
Pheo	42	(24)	4	(23)	0		0		46	(20)
Para	2	(1)	0		0		0		2	(1)
Unknown	0		1	(6)	0		0		1	(0.5)
Family history: n, (%)										
Present	152	(85)	3	(18)	12	(100)	21	(95)	188	(82)
Absent	21	(21)	10	(59)	0		0		31	(13)
Unknown	6	(3)	4	(23)	0		1	(5)	11	(5)
Lesions: n, (%)										
MTC, Pheo	97	(54)	10	59)	0		0		107	(46.5)
MTC	54	(30)	7	(41)	12	(100)	22	(100)	95	(41)
MTC, Pheo, Para	19	(11)	0		0		0		19	(8)
Pheo	4	(2)	0		0		0		4	(2)
MTC, Para	3	(2)	0		0		0		3	(1.5)
Pheo, Para	2	(1)	0		0		0		2	(1)

MEN, Multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; FMTC, familial MTC; pheo, pheochromocytoma; para, parathyroid lesion.

Table 2. Characteristics of MTC in MEN2 and FMTC

	MEN2A		MEN2B		FMTC		Other		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
MTC occurrence	173	(97)	17	(100)	12	(100)	22	(100)	224	(97)
Tumor distribution										
Bilateral	116	(67)	15	(88)	7	(58.5)	16	(73)	154	(69)
Unilateral, multiple	3	(1.5)	0		0		0		3	(1)
Unilateral, solitary	20	(11.5)	2	(12)	4	(33)	5	(23)	31	(14)
Unknown	34	(20)	0		1	(8.5)	1	(4)	36	(16)
Thyroid resection	164	(100)	16	(100)	12	(100)	22	(100)	214	(100)
Total	114	(70)	11	(69)	7	(58)	13	(59)	145	(68)
Subtotal	11	(7)	1	(6)	1	(8)	7	(32)	20	(9)
Unilateral	15	(9)	2	(13)	2	(17)	2	(9)	21	(10)
Re–operation	20	(12)	1	(6)	2	(17)	0		23	(11)
Unknown	4	(2)	1	(6)	0		0		5	(2)
Lymph node dissection										
Performed	143	(87)	13	(81)	11	(92)	21	(95)	188	(88)
Not performed 1	13	(8)	2	(13)	1	(8)	1	(5)	17	(8)
Unknown	8	(5)	1	(6)	0		0		9	(4)
Lymph node metastasis										
Present	65	(45)	8	(62)	6	(55)	13	(62)	92	(49)
Absent	51	(36)	2	(15)	5	(45)	6	(29)	64	(34)
Unknown	27	(19)	3	(23)	0		2	(9)	32	(17)
Distant metastasis										
Present	2	(1)	2	(12)	0		0		4	(2)
Absent	117	(68)	9	(53)	20	(91)	10	(83)	156	(70)
Unknown	54	(31)	6	(35)	2	(9)	2	(17)	64	(28)

MEN, Multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; FMTC, familial MTC.

Table 3. Characteristics of pheochromocytoma in MEN 2

	MEN2A		MEN2B		Total	
	n	%	*n*	%	*n*	%
Pheochromocytoma occurrence	122	(68)	10	(59)	132	(57)
Tumor distribution						
Bilateral	58	(48)	4	(40)	62	(47)
Unilateral, multiple	3	(2)	0		3	(2)
Unilateral, solitary	32	(26)	3	(30)	35	(26.5)
Ectopic	5	(4)	1	(10)	6	(14.5)
Unknown	24	(20)	2	(20)	26	(20)
Adrenal resection	109	(100)	8	(100)	117	(100)
Total	42	(39)	5	(63)	47	(40)
Subtotal	8	(7)	0		8	(7)
Unilateral	48	(44)	3	(37)	51	(44)
Unknown	11	(10)	0		11	(9)

MEN, Multiple endocrine neoplasia.

Clinical Characteristics and Therapeutic Aspects

MTC

The clinical characteristics and therapeutic aspects of MTC are summarized in Table 2. Among 224 patients who presented with MTC, the diagnosis was confirmed histologically in 214 and was based on clinical evidence of thyroid tumor with an elevated calcitonin (CT) level in 10 patients. Bilateral or multiple tumors were found in 157 (70%) patients, whereas a solitary tumor was found in only 31 (14%). The initial operative procedures employed for MTC were total thyroidectomy, subtotal thyroidectomy and unilateral total or partial lobectomy, being performed in 68%, 9.3% and 9.8% of the patients respectively. Twenty-three patients who had undergone initial hemithyroidectomy required completion thyroidectomy for recurrent MTC in the contralateral thyroid lobe. Cervical lymph node dissection was performed in 188 patients (88%) and lymph node metastases were found in 92 (49%). Distant metastases were found in four patients (1.9%) at the initial operation; two patients had bone involvement and the other two showed metastases to both the lung and the liver.

Table 4. Characteristics of parathyroid lesion in MEN 2A

	MEN2A	
	n	(%)
Parathyroid lesion		
Occurrence	25	(14)
Tumor distribution		
Multiple	5	(20)
Single	13	(52)
Unknown	7	(28)
Parathyroid resection	25	(100)
Total	10	(40)
Subtotal	6	(26)
Simple	8	(32)
Unknown	1	(4)

MEN, Multiple endocrine neoplasia.

Pheochromocytoma

Of 132 patients with pheochromocytoma, the diagnosis was confirmed histologically in 117 (89%) and was established clinically by elevated catecholamine levels and tumor imaging in 15 (11%). The pheochromocytomas were bilateral in 62 patients (47%), unilateral in 38 (29%) and extra-adrenal in six (4.5%). Bilateral total adrenalectomy was performed in 47 patients (40%), unilateral total adrenalectomy along with subtotal resection of the contralateral adrenal gland (subtotal adrenalectomy) was performed in eight (6.8%) and 51 patients (44%) underwent unilateral adrenalectomy alone (Table 3). Eight patients (6.8%) initially underwent unilateral adrenalectomy alone and subsequently required a second operation for recurrent pheochromocytoma in the contralateral adrenal gland. Malignant pheochromocytoma was found in two patients (0.15%).

Parathyroid Disease

Parathyroid lesions were confirmed histologically in 25 patients. Multiple parathyroid lesions were found in five patients and a solitary lesion was found in 13. Total parathyroidectomy with auto-transplantation and subtotal parathyroidectomy (resection of three and a half glands) were performed in 10 and six patients respectively, whereas resection of a single enlarged parathyroid gland was carried out in eight patients (Table 4). Twenty-one patients underwent parathyroid operations at the time of thyroidectomy for MTC. Two patients in whom pheochromocytoma preceded hyperparathyroidism without involvement of MTC underwent parathyroidectomy alone. The other two patients underwent parathyroidectomy either before or after thyroid surgery for MTC.

Follow-up and Outcome

During the follow-up period, which ranged from 2 months to 40 years (median 7 years), 23 patients died. The causes of death were progression of MTC in 12 cases (5.2%), diseases unrelated to MEN 2 in eight cases and unknown causes in three patients. Overall survival rates for MEN 2 patients at 5 years and 10 years after diagnosis were 97.5% and 93.2% respectively. There were no significant differences among the survival rates of the MEN 2 subgroups (Table 5).

Of 214 patients who underwent operations for MTC, follow-up data regarding MTC recurrence were obtained for 163. Eighty-two patients (50%) experienced MTC recurrence, including 16 with distant metastases, eight with local recurrence, 48 with elevated basal CT levels and six with elevated CT levels in provocation tests.

Among the variables including age at initial surgery, sex, MTC tumor size, presence of lymph node metastasis and the surgical procedure used for MTC, only patient age at initial surgery for MTC was statistically significant as a prognostic factor for overall survival in patients with MEN 2A (Table 6).

Table 5. Clinical outcome of patients with MEN2 and FMTC

	MEN2A	MEN2B	FMTC	Other	Total
Death	16	4	1	2	23
MTC	8	3	0	1	12
Other	6	0	1	1	8
Unknown	2	1	0	0	3
Recurrence					
Positive	63	6	9	4	82
Distant metastasis	13	3	0	0	16
Local recurrence	5	1	1	1	8
Calcitonin elevation (basal)	39	2	5	2	48
Calcitonin elevation (stimulated)	4	0	1	1	6
Unknown	2	0	2	0	4
Negative	59	7	3	12	81
Unknown	42	3	0	6	51
Overall survival rate					
5 year	97.6%	91.7%	100%	100%	97.5%
10 year	92.9%	91.7%	100%	92.3%	93.2%

MEN, Multiple endocrine neoplasia; FMTC, familial MTC.

Table 6. Comparison of overall survival in relation to clinical factors in patients with MEN2A

	n	Survival rate (%) 5–yr	10–yr	*P* value
Age at operation				
<40 yr	77	100	98	0.045
.40 yr	71	95	90	
Sex				
Male	57	98	96	0.83
Female	91	97	93	
Tumour size of MTC				
31 cm	17	100	100	
1-4 cm	78	100	96	0.074
>4 cm	14	92	79	
Lymph node metastasis				
Positive	61	96	91	
Negative	46	100	96	0.22
Type of thyroid operation				
Total	102	98	94	
Subtotal	24	95	90	0.87

Survival rates were calculated by the Kaplan–Meier method. Log–rank test was used to compare the survival rates among the groups. MEN, Multiple endocrine neoplasia; MTC, medullary thyroid carcinoma.

DISCUSSION

A similar nationwide questionnaire survey of MEN 2 syndrome was conducted previously in Japan. In this survey of 1984, clinical records of 82 patients with MEN 2 or FMTC were collected (7). In 1990, Oishi *et al.* (8) reported a literature review of 82 Japanese patients with MEN 2. Since the number of patients collected in the present survey was three times higher than in previous reports, we can offer more precise results. The present study, as well as the previous reports, indicated that MTC is the most common manifestation of MEN 2 in Japan. Our results are also consistent with other reports in showing that pheochromocytoma and parathyroid disease develop in approximately 50% and 20% respectively of patients with MEN 2. The four phenotype categories of MEN 2 seem to occur at similar frequencies in Japanese and Caucasian patients (6). Nevertheless, in the present study and in previous reports from Japan, female patients with MEN 2 greatly outnumbered male patients. This trend is not consistent with the genetic nature of the syndrome. The considerably uneven male to female ratio may be due partly to the fact that family screening has not been performed adequately in Japan.

Since the radioimmunological assay for CT was introduced in Japan in the mid 1970s, it has been used to diagnose MTC by family screening. Awareness of the familial occurrence of MEN 2 and FMTC has increased in recent years, and this change is reflected in the fact that a positive family history was recorded more frequently in the present series than in the previous ones. Despite this, the present study revealed that only a small percentage of patients were detected by annual screening for MTC by measuring the stimulated CT level. Presumably, most of the patients detected by family screening already had symptomatic MTC or pheochromocytoma. Indeed, there was no significant difference in patients' ages at initial surgery between the present series and the previous one.

In many published series, MTC has been shown to be the major cause of morbidity and mortality of patients with this syndrome. Lips *et al.* (9) in the Netherlands reported that 16% of patients with MEN 2 died of disseminated MTC. Wells *et al.* (10) in the USA reported that 21 (17%) of 123 patients with MEN 2A and five (50%) of 10 patients with MEN 2B died of MTC, although none of 41 patients with FMTC died of MTC. In Sweden, among patients with hereditary MTC detected as clinically palpable tumors, the survival rates at 5 and 10 years were 78% and 64% respectively (11). Similar survival rates for MEN 2 patients with MTC were reported in Germany (12). Compared with these reports, the present study revealed that the survival rate of MTC patients in Japan is higher than that of Caucasian patients. Even for patients with MEN 2B, which is believed to be associated with aggressive MTC, the clinical course of the Japanese patients was more favorable than that of Caucasians. Yoshimoto *et al.* (13) also pointed out that the clinical course of MTC in Japanese patients with MEN 2B is less aggressive.

However, the present survey demonstrated that the recurrence rate of MTC after thyroidectomy is very high in Japan: 29% of patients with recurrences had clinically evident metastasis and 66% of those showed biochemical recurrence. This may indicate that screening for MTC among families with inherited MTC has been insufficient in Japan, although the value of screening by measurement of the stimulated plasma CT level is well recognized for detecting early MTC or its precursor (C-cell hyperplasia). O'Riordain and associates (14) reported that screening of family members of affected patients accounted for 80% of MEN 2A and 54% of MEN 2B diagnoses in their series, and that a biochemical cure was achieved in 56% of patients with MEN 2A. Gagel *et al.* (15) reported an 85% or higher 15–20 year biochemical cure rate in patients who had been treated surgically for early MTC or C-cell hyperplasia which was detected by annual pentagastrin-stimulation testing.

Currently, RET proto-oncogene testing can be used for diagnosis and to identify asymptomatic family members with the syndrome. Mutations have been identified in 95% of families with MEN 2A, 87% of families with FMTC and 94% of families with MEN 2B (6). Based on this observation, some physicians (4,5,16) advocate prophylactic thyroidectomy for members of families with RET proto-oncogene mutations, although the appropriate age for this prophylactic procedure remains to be determined. Screening for RET mutations in cases of apparently sporadic MTC is also useful for identifying whether or not there is a hereditary component.

Despite support for the role of early diagnosis and prophylactic management for patients with MEN 2, many issues remain to be clarified. In order to reveal the precise clinical course of patients with MEN 2, a central registration system must be established in Japan, otherwise valid assessment of genetic testing will not be possible because of the small number of cases experienced at each institution. Similar registration systems have already been

established in some European countries (12,17–20). It is also important to protect the privacy of people who are registered.

When genetic testing is applied as the standard for the management of MEN 2, concerned family members should be informed about the advantages and disadvantages of testing. Furthermore, clinicians involved in the management of patients with MEN 2 should be aware of the genetic trends of this syndrome. In the present survey it was not possible to obtain follow-up data for pheochromocytoma and parathyroid disease. Although we can exclude family members with a normal RET proto-oncogene test result from further screening, it should be remembered that a MEN 2 gene carrier, even after total thyroidectomy, remains at risk of developing pheochromocytoma, parathyroid disorder or both.

In conclusion, although MTC in Japanese patients with MEN 2 demonstrated a favorable clinical course, the clinical and biochemical recurrence rates were not satisfactory. To improve the cure rate, analysis of RET mutations is warranted in patients with MEN 2 or apparently sporadic MTC. RET mutation-positive relatives of MEN 2 patients should be provided with information about genetic transmission, availability of the screening test and treatment options for each component of MEN 2 syndrome. Establishment of a national registration system is also important.

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