COMMENTARY

Effective Perioperative Management of Multiple Endocrine Neoplasia Type 1–Associated Insulinomas

HEREIN, WE DISCUSS aspects of the recently reported study by Crippa et al, "Surgical Management of Insulinomas: Short- and Long-term Outcomes After Enucleations and Pancreatic Resections,"[1] in terms of effective perioperative management of multiple endocrine neoplasia type 1 (MEN1)–associated insulinomas. Crippa et al concluded that surgical management of insulinomas can provide satisfactory outcomes with no mortality and good functional results.[1] They also revealed that insulinomas associated with MEN1 have a higher risk than those not associated with MEN1 for being malignant and multifocal and that their curative treatment requires pancreatic resection.[1] Multiple endocrine neoplasia type 1 is an autosomal dominantly inherited endocrine tumor syndrome characterized by tumor development in endocrine organs such as the parathyroid, endocrine pancreas, anterior pituitary, and adrenal cortex.[2] A recent multicenter study in Japan reported that primary hyperparathyroidism, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and pituitary tumors were seen in 94.4%, 58.6%, and 49.6% of patients with MEN1, respectively.[2] The presence of GEP-NETs, which includes insulinomas, is one of the most major prognostic factors for patients with MEN1, and surgical resection of these tumors is the most effective therapy to improve long-term prognosis.[3] Despite these findings, the optimal perioperative management of patients with MEN1-associated insulinoma remains unclear. The article by Crippa et al[1] contributes to our understanding of the efficacy of surgical management for MEN1-associated insulinomas; however, there are 3 points that are not fully addressed by this study.[1] These points are: (1) It is not clear how the location of MEN1-associated multifocal insulinomas with malignant potential is identified to achieve curative surgical resection. (2) It is not clear how perioperative glycemic control is achieved in patients with insulinoma. (3) It is not clear if there are differences in tumor location between patients with and without MEN1.

Regarding the first point, Crippa et al reported that multiple insulinomas were found in 8% of patients and 5.5% of patients had MEN1, so insulinomas associated with MEN1 have a higher risk than those not associated with MEN1 for being malignant and multifocal.[1] It is not clear from this study how the locations of MEN1-associated multifocal insulinomas with malignant potential are identified to promote curative surgical resection. It is difficult to accurately detect the location of multiple insulinomas using conventional diagnostic imaging techniques such as percutaneous ultrasonography, computed tomography, and magnetic resonance imaging, especially when tumors are less than 5 mm in diameter. We believe that this issue would be further complicated in cases where there are nonfunctioning tumors, which often appear in MEN1. Although endoscopic ultrasonography and intraoperative ultrasonography are more efficient than the conventional diagnostic imaging techniques mentioned earlier for the detection of microfocal or multifocal insulinomas, they are not able to accurately identify multiple functioning GEP-NETs.[3] To accurately detect the location of MEN1-associated multifocal insulinomas with malignant potential to achieve curative surgical resection, we recommend the selective arterial secretagogue injection (SASI) test with calcium[4,5] because this test can locate functioning GEP-NETs with high sensitivity and specificity, especially in patients with MEN1 with gastrinoma. In support of the SASI test for this purpose, Imamura et al[4,5] showed that identification of functioning NETs (gastrinoma or insulinoma or VIPoma) among multiple GEP-NETs in patients with MEN1 is essentially impossible with imaging techniques alone and that the SASI test was able to localize functioning NETs by assessing whether gut hormones (gastrin or insulin or vasoactive intestinal peptide) were secreted from the GEP-NETs in the area of interest by stimulation with a secretagogue (secretin or calcium). The SASI test appears to be the only technique available that can differentiate functioning NETs among multiple GEP-NETs in patients with MEN1. Furthermore, other reports[6,7] support the application of the SASI test in identifying MEN1-associated insulinomas.

For the second point, Crippa et al clarify how perioperative glycemic control is achieved in patients with insulinoma, which is crucial to effective treatment because most patients with MEN1 with insulinoma have hypoglycemia-related symptoms.[1] Glycemic control in such patients is often difficult because blood glucose concentrations shift from a hypoglycemic state to a hyperglycemic one following removal of the insulinoma. Recently, we reported tight glycemic control (TGC) in surgical patients using an artificial pancreas (AP).[8] Our own prospective randomized clinical trial[9] showed that perioperative TGC using an AP (targeted blood glucose zone of 80-110 mg/dL [to convert to millimoles per liter, multiply by

0.0555]) in patients who underwent pancreatectomy significantly reduced the incidence of surgical site infection compared with conventional insulin therapy (targeted blood glucose zone of 150-200 mg/dL). Using an AP, we achieved TGC without hypoglycemia or hyperglycemia in all patients, including some with insulinomas, with maintenance of blood glucose concentrations compatible with targeted levels. We believe that novel glycemic control using an AP is suitable for patients with insulinoma as an effective approach to achieve TGC.

The final point we raise regarding the study by Crippa et al is that it does not clarify if there are differences in tumor location between patients with and without MEN1.[1] Most pancreatic resections (80.5%) were performed for insulinomas located in the pancreatic body/tail, whereas most insulinomas located in the proximal pancreas (56 of 69; 81%) underwent enucleation.[1] Therefore, we agree with the recommendation by Crippa et al that pancreatic resection be the treatment of choice for patients with MEN1-associated insulinomas.

In conclusion, to improve the surgical management and outcome for patients with MEN1-associated insulinomas, we propose that (1) accurate identification of the location of tumors be carried out preoperatively using the SASI test, (2) stable TGC be achieved by using an AP, and (3) pancreatic resections be the treatment of choice considering the malignant and/or multifocal potential of these tumors.

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Clinical Features, Treatment, and Long-Term Outcome of Papillary Thyroid Cancer in Children and Adolescents Without Radiation Exposure

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Abstract

Background Cancer of the thyroid gland is rare in children and adolescents. A history of neck irradiation is a well-established risk factor for tumor development, and most previous reports focused on cases that were induced by radiation exposure. We present here a retrospective review of the clinical features, treatment, and long-term outcome of children and adolescents with papillary thyroid cancer (PTC) without a history of radiation exposure who were treated at our institution over a period of ~50 years.

Methods We retrospectively investigated 142 PTC patients without an irradiation history who were younger than 20 years of age when treated from 1961 to 2005 (17 males and 125 females; mean age = 16.3 ± 2.7 years; follow-up = 21.8 ± 12.0 years). The clinicopathological results were evaluated using the medical records. Disease-free survival (DFS) and cause-specific survival (CSS) were assessed with the Kaplan-Meier method and compared with the log-rank test. Parametric analyses were performed using Student's *t* test and nonparametric analyses were performed using the Mann–Whitney *U* test.

Results At diagnosis, three patients had distant lung metastasis and 33 had gross neck lymph node (LN) metastasis. All patients were treated with surgery (hemi/partial thyroidectomy in 45 patients, subtotal thyroidectomy in 85, total thyroidectomy in 12, no LN dissection in 50, central compartment dissection in 20, and modified radical neck dissection in 72), and postoperative external beam radiation therapy was administered to 59. Postoperative ablative therapy using I^{131} was not performed in this series. Recurrence was found for regional LN ($n = 25$), lung ($n = 9$), remnant thyroid ($n = 5$), and others ($n = 4$). DFS and CSS at 40 years were 74.1 and 97.5%, respectively. DFS was significantly worse in patients aged <16 years with a family history of thyroid cancer, preoperative neck gross LN metastasis, maximum tumor diameter, and extrathyroidal invasion. Preoperative gross neck LN metastasis and distant metastasis at diagnosis were significant factors for CSS. No other factors contributed to DFS and CSS. When the clinical features of children and adolescents were compared, the incidence of preoperative gross neck LN metastasis and distant metastasis at diagnosis and tumors with a maximum diameter >10 mm were significantly higher in the children group than in the adolescent group. DFS was significantly shorter in the children group than in the adolescent group, but no significant difference was found in CSS between these two groups.

Conclusions The prognosis of PTC in children and adolescents is excellent, regardless of the extent of thyroidectomy and LN dissection. We recommend that only children or adolescents with preoperative gross neck LN metastasis and distant metastasis at diagnosis should be subjected to postoperative ablative therapy.

Introduction

Malignancy of the thyroid gland is rare in children and adolescents, with a reported incidence of 2.6–12.9% of all thyroid malignancy patients [1–6]. Papillary thyroid cancer (PTC) is the most common thyroid malignancy in pediatric and adult patients [1–5]. Radiation exposure in children has been reported to be associated with the occurrence of PTC

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[7–10]. The majority of previous reports focused on the incidence of PTC in children that was induced by radiation exposure, which is associated mainly with the Chernobyl accident [11, 12]. Indeed, only a few studies have focused on the incidence of PTC in children and adolescents in the absence of radiation exposure.

Many studies have reported higher recurrence and survival rates for PTC in children without radiation exposure than in adults [1–6], with recurrence and mortality rates in children of 15–40 and 0–13%, respectively [13–17]. Long-term follow-up periods are needed and the outcome should be discussed in the long-term context, especially for children. The majority of studies had follow-up periods of 10–20 years and only a few studies have provided results for a period longer than 30 years [6, 18, 19].

We present here a retrospective review of the clinical features, treatment, and long-term outcome of PTC in children and adolescents without a history of radiation exposure over a period of 50 years.

Patients and methods

We performed 142 primary surgical resections of PTC in patients younger than 20 years without a history of irradiation who were treated from 1961 to 2005 at the Noguchi Thyroid Clinic and Hospital Foundation. The details of the patients' presentations, family history, radiation history, surgical and pathological findings, adjunctive therapy, and outcome were obtained from our hospital's computerized database, and these data were confirmed using the medical records. The patients were 17 males and 125 females with a median age at initial operation of 16.3 ± 2.7 years (range = 6–19 years). There were 40 patients aged ≤15 years old (children group) and 72 patients aged >15 years (adolescent group). The median follow-up period was 21.8 ± 12.0 years. A familial history of thyroid cancer was seen in 12 patients. We did not include PTC with specific pathology in this study, e.g., poorly differentiated carcinoma and variants of PTC (cribriform-morula, tall cell, and follicular variants).

We analyzed the differences in the following clinical variables between children (≤15 years) and adolescents (>15 years): gender, familial history of thyroid cancer, preoperative gross neck lymph node (LN) metastasis, distant metastasis at initial presentation, maximum tumor diameter, extrathyroidal invasion at primary site, and tumor multiplicity. Statistical analyses were performed using Fisher's exact probability test and Welch's *t* test. Survival rate from the date of initial surgery until death or loss of contact (cause-specific survival; CSS) and tumor recurrence (disease-free survival; DFS) were estimated by the Kaplan-Meier method. Statistical significance for survival was compared using the log-rank test. The candidate risk factors were compared by DFS and CSS in all patients. A p value <0.05 was considered statistically significant. All analyses were performed using JMP 5.1.1 statistical software (SAS Institute, Cary, NC, USA).

Results

The incidence of childhood PTC in patients <20 years was 1.5% (142 of 9,164 PTC patients underwent thyroidectomy between 1961 and 2005). The distribution of patients according to age and sex are shown in Fig. 1. A familial history of thyroid cancer in first-degree relatives was present in 12 of 142 patients (8.5%). At initial presentation, three patients had distant lung metastasis with gross neck LN metastasis and 30 had gross neck LN metastasis without other metastatic organs. All patients were treated with surgery (hemi/partial thyroidectomy in 45 patients, subtotal thyroidectomy in 85, total thyroidectomy in 12, no LN dissection in 50, central compartment dissection in 20, and modified radical neck dissection in 72). Postoperative external beam radiation therapy was administered to 59 patients. Postoperative radioiodine remnant ablation was not performed on any of the patients with a curative resection at the time of the initial surgery. The patients with lung metastasis at initial presentation underwent a total thyroidectomy following radioiodine therapy. Thyroid-stimulating hormone (TSH) suppression therapy was not administrated and the TSH level was maintained at a low normal level with or without L-thyroxine in all patients.

Table 1 gives the surgical procedures and postoperative complications. Hypoparathyroidism, including temporary hypoparathyroidism, was found in 12 patients (9.2%) and permanent hypoparathyroidism was found in 1 (0.7%). Recurrent laryngeal nerve palsy, including temporary

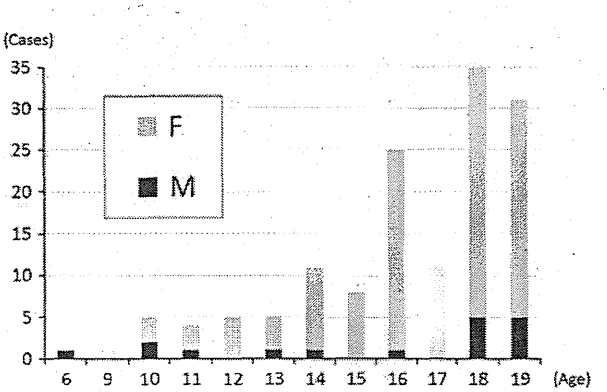

Fig. 1 Age distribution of the childhood PTC patients. The *solid black scale bars* indicate males and the *gray scale bars* indicate females

Table 1 Surgical methods and complications

Surgical complications	Temporary and permanent number	*p* value*	Permanent number	*p* value*
Hypoparathyroidism				
TT (yes/no)	8/4		1/11	
ST (yes/no)	4/81	<0.001	0/85	0.007
Lobectomy and others (yes/no)	0/45	<0.001	0/45	0.051
Laryngeal nerve palsy				
TT (yes/no)	6/6		2/10	
ST (yes/no)	5/80	<0.001	2/83	0.020
Lobectomy and others (yes/no)	6/39	0.006	0/45	0.005

TT total thyroidectomy, *ST* subtotal thyroidectomy

* *p* value compared to TT

recurrent laryngeal nerve palsy, was found in 17 patients (13.6%) and permanent recurrent laryngeal nerve palsy was found in 4 (2.9%). There was a significant increase in the incidence of postoperative hypoparathyroidism following total thyroidectomy compared to subtotal thyroidectomy (temporary, $p < 0.001$; permanent only, $p = 0.007$) and hemi/partial thyroidectomy (temporary, $p < 0.001$; permanent only, $p = 0.051$). Similarly, there was a significant increase in the incidence of postoperative laryngeal nerve palsy following total thyroidectomy compared to subtotal thyroidectomy (temporary, $p < 0.001$; permanent only, $p = 0.020$) and hemi/partial thyroidectomy (temporary, $p = 0.006$; permanent only, $p = 0.005$).

Recurrence was found in 28 (20%) of the 139 patients who underwent a complete operation. The recurrent sites were the neck LN in 25 patients, lung in nine, remnant thyroid in five, mediastinum LN in one, and others in three, including duplication. The patients with recurrence in the neck LN were resected surgically, and the patients with distant metastases in the lung and bone were treated with radioiodine therapy. During follow-up, three patients died of the disease and five patients died of other reasons. DFS and the CSS at 40 years were 74.1 and 97.5%, respectively (Fig. 2).

Significant differences in DFS were observed in patients <16 years ($p = 0.030$) and in those with a familial history of thyroid cancer ($p = 0.041$), preoperative gross LN metastasis ($p = 0.006$), tumor diameter >30 mm ($p = 0.033$), extrathyroidal invasion ($p = 0.004$), and histological LN metastasis ($p = 0.002$) (Fig. 3). Preoperative gross LN metastasis ($p = 0.010$) and distant metastasis at diagnosis ($p < 0.001$) were significant factors for CSS (Fig. 4). No other factors contributed to DFS and CSS (Table 2).

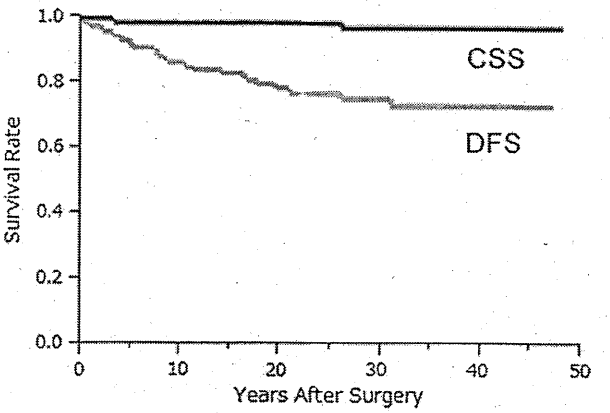

Fig. 2 Overall disease-free survival (DFS) and cause-specific survival (CSS) rates of childhood PTC patients. DFS and CSS at 40 years were 74.1 and 97.5%, respectively

The clinical features of the children and adolescent groups are summarized in Table 3. The male/female ratio was 6/34 (1:5.7) in children and 11/91 (1:8.3) in adolescents. The female ratio tended to be higher in adolescents than in children, although it was not significantly different ($p = 0.567$). Furthermore, this sex difference was not observed in children <11 years (1:1.3). A familial history of thyroid cancer was observed more frequently in children (six patients, 15%) than in adolescents (six patients, 4.2%), but there was no significant difference ($p = 0.097$). Preoperative gross LN metastasis was found in seven children (42.5%) and 16 adolescents (15.7%; $p = 0.002$). Distant lung metastasis at diagnosis was found in three children (7.5%) in contrast to no adolescents ($p = 0.021$). The maximum tumor diameter was significantly larger in children (25.0 ± 2.7 mm) than in adolescents (18.0 ± 1.7 mm; $p = 0.048$). The incidence of a tumor with a maximum diameter >10 mm was significantly higher in children (85%) than in adolescents (55.9%; $p = 0.001$). Extrathyroidal invasion of the tumor was seen in 22 children (55%) and 41 adolescents (40.2%), and multifocal tumors were found in six children (15%) and ten adolescents (9.8%); however, these differences were not significant.

Discussion

Many risk factor analyses of patients with differentiated thyroid cancer have been reported [20–26]. Older age, male gender, familial history of thyroid cancer, tumor size, multifocal tumors, extrathyroidal invasion, LN metastasis, and distant metastasis are well-recognized prognostic risk factors in this field. Various prognostic scoring systems, e.g., TNM Staging System [22], AMES System [23],

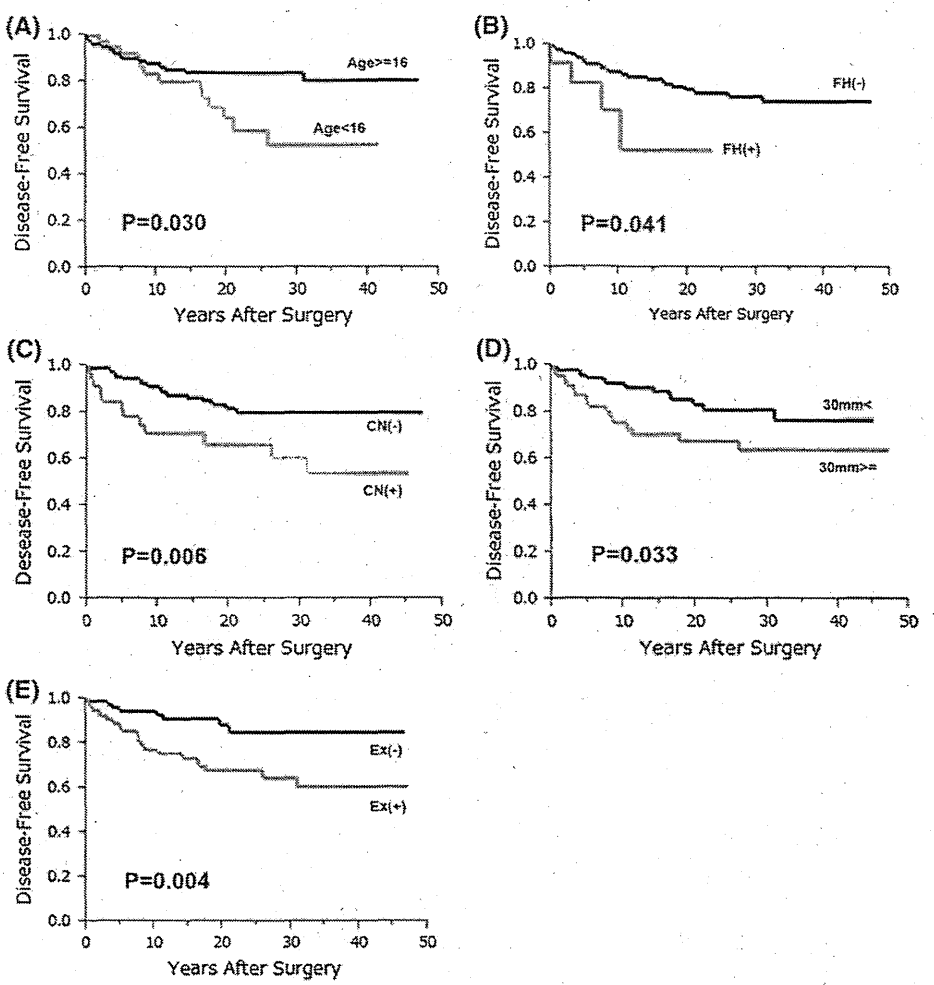

Fig. 3 Postoperative disease-free survival (DFS) rate according to the risk factors: **a** age, **b** familial history (FH) of thyroid cancer, **c** preoperative clinical gross lymph node metastasis (CN), **d** maximum tumor diameter, and **e** extrathyroidal invasion (Ex)

AGES and MACIS System [24, 25], and Ohio State University Scoring System [26], are determined by combining these factors. These risk factors and the scoring systems are based mainly on the results of adult patients with PTC, while childhood PTC accounts for only a small portion of the data. There are many controversies regarding the proper treatment of pediatric patients, and their long-term survival is excellent, but the risk of local recurrence is rather high.

Recent molecular analysis showed that PTC is caused by the activation of the MAP kinase pathway. In young patients, *RET/PTC*, *AKAP9-BRAF*, and *NTRK1* recombination events are the main genetic alterations [27]. In contrast, PTC in adults is the result of predominantly point mutations, e.g., in *BRAF* [27–29]. The difference in oncogenic factor between children and adults may be related to their clinical cause. Identification of the prognostic indicators for PTC that are specific for children and adolescents, which are biologically different, is very important in deciding an appropriate therapeutic strategy.

In this article, we identified age (<16 years), familial history of thyroid cancer, preoperative gross neck LN metastasis, tumor diameter, and extrathyroidal invasion as risk factors for DFS in children and adolescents with PTC without a history of radiation exposure. Furthermore, preoperative gross neck LN metastasis and distant metastasis at diagnosis were significant risk factors for CSS. The patients with these CSS risk factors are considered to belong to a high-risk group and should be treated with total thyroidectomy and radioiodine therapy using I^{131}. The extent of thyroid gland and LN resection was not associated with outcome, while wider resection, especially total thyroidectomy or near-total thyroidectomy, resulted in an increased rate of postoperative hypoparathyroidism. Our sample size may be inadequate to conclude a difference in these variables based on the extent of thyroidectomy. From our long-term survival data, childhood PTC shows a favorable prognosis and we select patients who are indicated for total thyroidectomy with radioiodine therapy from our childhood PTC patients. Our opinion is that stereotypical treatment of total thyroidectomy following radioiodine ablation should not be performed in all childhood patients.

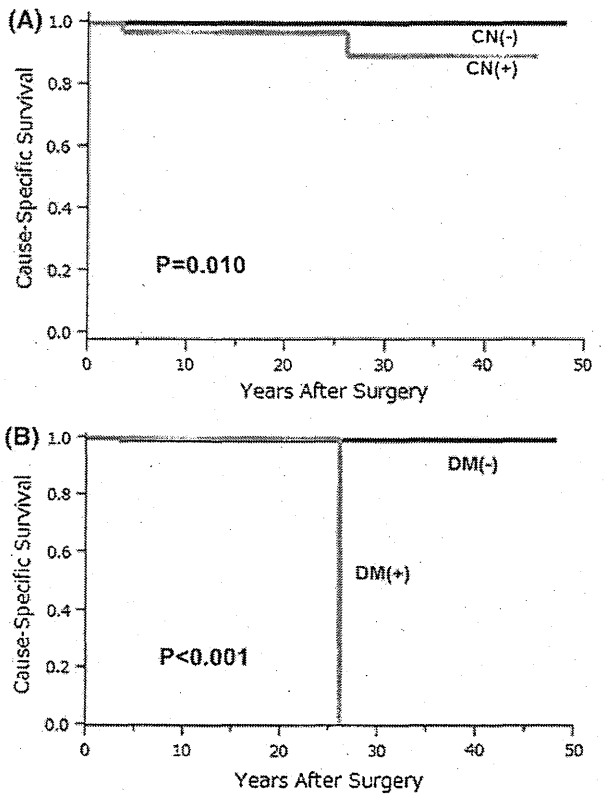

Fig. 4 Postoperative cause-specific survival (CSS) rate according to the risk factors: **a** preoperative clinical gross lymph node metastasis (CN) and **b** distant metastasis at diagnosis (DM)

This is the first report to compare the clinical features of childhood and adolescent PTC directly. A high prevalence of PTC in females was observed in both groups, but it was higher in adolescents. Notably, this sex difference was not seen in patients aged <11 years. Sex-related hormonal factors originating from unknown sex chromosome-related genes may contribute to this female preponderance of PTC.

Robinson and Orr [30] first reported familial nonmedullary thyroid cancer (FNMTC) in 1955. The incidence of FNMTC is reportedly 1.8–10.5% among nonmedullary thyroid cancers, but its incidence in childhood PTC is unknown [31–37]. In this series, a familial history of thyroid cancer was seen in 9.2% of patients and, specifically, the incidence of FNMTC was higher in children compared to adolescents. Genetic factors may be more involved with the occurrence of childhood PTC than adolescent PTC.

Preoperative gross neck LN metastasis, distant metastasis at diagnosis, and tumors with a maximum diameter >10 mm were found significantly more frequently in childhood PTC than in adolescent PTC. The diameter of childhood PTC tumors tended to be larger than that of adolescent PTC tumors. These results suggest that PTC in children may be a distinct clinical entity from PTC in adolescents and adults.

Table 3 Clinical characteristics of the patient groups

	Children ($n = 40$)	Adolescents ($n = 102$)	p
Sex (male/female)	6/34	11/91	0.567
Familial history of thyroid cancer	6 (15%)	6 (4.2%)	0.097
Preoperative lymph node metastasis	17 (42.5%)	16 (15.7%)	0.002
Distant metastasis at diagnosis	3 (7.5%)	0 (0%)	0.021
Tumor with maximum diameter >10 mm	34 (85%)	57 (55.9%)	0.001
Tumor diameter (mm)	25.0 ± 2.7	18.0 ± 1.7	0.048
Extrathyroidal invasion	22 (55%)	41 (40.2%)	0.134
Multiple primary tumor site	6 (15%)	10 (9.8%)	0.387

Conclusion

Children and adolescent PTC patients have an excellent prognosis, regardless of the extent of thyroidectomy and LN dissection. Preoperative neck LN metastasis and distant metastasis at diagnosis emerged as significant risk factors for CSS. We believe that children and adolescents without these risk factors should avoid the extent of thyroidectomy following postoperative ablative therapy.

Table 2 Risk factors for disease-free survival and cause-specific survival in childhood PTC

Factors	Number (%)	p (DFS)	p (CSS)
Sex (male/female)	17 (12%)/125 (88%)	0.2920	0.6073
Age (children: <16/adolescent: ≥16)	40 (28%)/102 (72%)	0.0303	0.4396
Familial history of thyroid cancer (yes/no)	12 (8%)/130 (92%)	0.0143	0.7237
Lymph node metastasis at diagnosis (yes/no)	33 (23%)/109 (77%)	0.0062	0.0062
Distant metastasis at diagnosis (yes/no)	3 (2%)/139 (98%)	–	<0.0001
Tumor size (<30/>30 mm)	96 (68%)/46 (32%)	0.0325	0.0632
Extrathyroidal invasion (yes/no)	63 (44%)/79 (56%)	0.0040	0.1511
Primary tumor site (single/multiple)	126 (89%)/16 (11%)	0.6808	0.6138
Surgery (total or subtotal thyroidectomy/lobectomy, other)	97 (98%)/45 (32%)	0.2193	0.2119
Postoperative radiation therapy (yes/no)	59 (42%)/83 (58%)	0.3633	0.2116

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Thoracoscopic Removal of Mediastinal Parathyroid Lesions: Selection of Surgical Approach and Pitfalls of Preoperative and Intraoperative Localization

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Abstract
Background Thoracoscopic surgery has replaced conventional sternotomy or thoracotomy for resection of mediastinal parathyroid lesions. We review our experience with this type of surgery with reference to selection of the appropriate approach and the pitfalls of lesion localization before and during surgery.
Methods During a 14-year period, we treated 14 patients with hyperparathyroidism, in whom a mediastinal lesion had been localized preoperatively by sestamibi scan. Primary hyperparathyroidism was present in 12 patients (single adenoma in 11, associated with MEN 1 in one) and secondary hyperparathyroidism in 2. Thoracoscopic procedures were performed by the three-port method.
Results The thoracoscopic procedure was successful in eight patients who were shown preoperatively to have a deep-seated (5 anterior, 3 middle) mediastinal lesions. Intraoperative visual confirmation of parathyroid adenoma was difficult only in a 19-year-old patient with a tumor embedded in the thymus, necessitating partial thymectomy. One of the eight mediastinal lesions resected thoracoscopically was a sestamibi-positive thymoma. Secondary hyperparathyroidism recurred 4 years after thoracoscopic mediastinal parathyroidectomy in one patient, necessitating additional thoracoscopic removal of this supernumerary lesion. However, seven patients with mediastinal parathyroid lesions localized at the aortic arch or upper region were treated successfully via a cervical approach. None of the patients suffered any surgical complications.
Conclusions Thoracoscopic surgery is safe and feasible for resection of deep mediastinal parathyroid lesions. Such lesions localized preoperatively at the aortic arch or upper region can be treated via a cervical approach. Preoperative sestamibi scan can sometimes give a false-positive result in cases of concurrent thymoma.

Introduction

For patients with hyperparathyroidism, many of the pathological parathyroid glands are located in the neck and can be resected through standard neck exploration. Up to 20% of parathyroid glands are ectopic, and 2% cannot be accessed by standard cervical surgical approaches because they are located deeply in the mediastinum or high in the neck [1, 2]. Before the advent of effective parathyroid imaging, deep-seated mediastinal parathyroid enlargements were occasionally difficult to localize and remove. However, since the clinical introduction of 99m-TC sestamibi scanning, mediastinal parathyroid lesions can be detected preoperatively.

In the era of minimally invasive surgery, thoracoscopic surgery has replaced conventional sternotomy or thoracotomy for resection of ectopic parathyroid lesions located deep in the mediastinum. Thoracoscopic surgical removal of these lesions offers many of the advantages of median sternotomy, namely the potential for directly visualizing the gland and gaining access to the entire mediastinum. However, because of the rarity of these lesions, reports describing the use of this minimally invasive procedure for their removal have been based mainly on small series or individual cases. Moreover, few reports have addressed the issue of selection of the optimal surgical approach, i.e.,

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transcervical or thoracoscopic. We review our experience of surgical treatment for mediastinal parathyroid lesions with reference to selection of the appropriate surgical approach and the pitfalls of lesion localization before and during surgery.

Patients and methods

Between 1997 and 2010, we treated 994 patients with primary or secondary hyperparathyroidism, among whom a mediastinal lesion was localized preoperatively by 99m-TC sestamibi scintigraphy/single photon emission computed tomography (SPECT) in 14 patients. These 14 patients included 12 with primary hyperparathyroidism (single adenoma in 11, associated with MEN 1 in one) and 2 with secondary hyperparathyroidism. The characteristics of these consecutive patients are shown in Table 1. Three patients (nos. 3, 12, and 13) had a history of previous neck surgery. Patient 12 with recurrent secondary hyperparathyroidism had undergone total parathyroidectomy (4 glands) by bilateral neck exploration accompanied by autografting 6 years before recurrence. Patient 3 with persistent primary hyperparathyroidism had undergone bilateral neck exploration elsewhere. Patient 13 with primary hyperparathyroidism had undergone thyroid lobectomy for papillary thyroid carcinoma. The patients comprised 3 men and 11 women with a median age of 55 (range, 19–78) years. For accurate preoperative localization of mediastinal lesions, CT scan was performed based on the information obtained by 99m-TC sestamibi scintigraphy/SPECT in all patients. MRI was additionally performed if CT scan failed to localize the lesion.

We reviewed the clinicopathologic features of these 14 patients retrospectively. The variables studied were the weight and location of the parathyroid lesion, preoperative localization methods, operative procedure, intraoperative localization, operation time, estimated blood loss, morbidity, and follow-up outcome. Patients were followed for a median of 76 (range, 8–142) months after mediastinal exploration.

Cervical approach for mediastinal parathyroid lesions

A cervical approach was selected for resection of parathyroid lesions localized in the anterior or posterior position of the superior mediastinum before surgery. For anterior superior mediastinal lesions, the anterior mediastinum was entered from beneath the head of the clavicle and sternum by retracting the thymus superiorly. For posterior superior mediastinal parathyroid lesions, dissection was performed medial to the sternocleidomastoid and lateral to the strap muscles. The cervical procedure was performed without any lifting system for the sternum.

Thoracoscopic technique

We selected a thoracoscopic approach for patients whose parathyroid lesions had been localized in the deep mediastinum by preoperative imaging studies. The operations were performed under general anesthesia using a double-lumen endotracheal tube. Patients were placed in the lateral

Table 1 Characteristics of patients with hyperparathyroidism in whom mediastinal lesions were localized preoperatively

Patient	Age at operation (year)	Gender	Diagnosis	Serum Calcium (mg/dl)	Intact PTH (pg/ml)	Previous neck surgery
1	51	M	PHPT	12.8	160	No
2	71	F	PHPT	12.9	320	No
3	73	F	Persistent PHPT	13	364	Yes
4	71	F	PHPT	12.2	212	No
5	78	F	PHPT	13	747	No
6	57	F	PHPT	11.1	201	No
7	48	M	PHPT	11.4	256	No
8	33	F	PHPT with MEN 1	11.9	127	No
9	54	F	SHPT	10.1	1149	No
10	55	F	PHPT	10.8	115	No
11	19	M	PHPT	12.5	142	No
12	61	F	Recurrence of SHPT	10.6	1401	Yes
	66		Repeated recurrence of SHPT*	10.1	2446	
13	53	F	PHPT	11.7	112	Yes
14	55	F	PHPT	12.5	192	No

* Patient 12 developed recurrence again due to another supernumerary gland 4 years after excision of mediastinal supernumerary gland

PHPT primary hyperparathyroidism, *SHPT* secondary hyperparathyroidism

decubitus position, except for two (one with MEN 1 and one with secondary hyperparathyroidism) who underwent cervical exploration concomitantly. All of the thoracoscopic procedures were performed using the three-trocar method. The dissection was performed by using a monopolar hook. After incision of the mediastinal pleura, the location of the lesion was identified on the basis of the findings obtained by preoperative imaging studies.

In all of the patients with primary hyperparathyroidism, intraoperative parathyroid hormone (PTH) levels were monitored with a rapid assay to confirm the success of the procedure 15 min after resecting the lesion. Preoperatively, 99m-TC sestamibi was injected intravenously and intraoperative gamma probe localization was attempted in only one patient (no. 3) with persistent primary hyperparathyroidism.

Results

Location, weight, and histopathology of mediastinal lesions

Fifteen mediastinal lesions localized by preoperative imaging studies included seven located in the superior, five in the anterior, and three in the middle mediastinum (Table 2). Six of the former seven were located in the anterior part (intrathymic) of the superior mediastinum, and the remaining one in the posterior part (on the right side behind the trachea). Two mediastinal lesions located in the aorto-pulmonary window were included. The median weight of the mediastinal parathyroid lesions was 1,188 (range, 260–8,530) mg. The resected mediastinal lesions were histopathologically confirmed to be ten parathyroid

Table 2 Location, weight, histopathology, and preoperative localization results in patients with hyperparathyroidism in whom mediastinal lesions were localized preoperatively

Patient	Location of mediastinal lesion	Weight of mediastinal parathyroid (mg)	Histopathology of mediastinal lesions	99m-TC sestamibi scan	Ultrasonography	CT	MRI
1	Left lower, intrathymic in the superior mediastinum	387	Adenoma	True	Negative	True	ND
2	Right lower, intrathymic in the superior mediastinum	500	Adenoma	True	Negative	True	ND
3	Right lower, intrathymic in the superior mediastinum	738	Adenoma	True	Negative	True	ND
4	Right lower, intrathymic in the superior mediastinum	1,031	Adenoma	True	Negative	True	ND
5	Right upper, right side behind the trachea in the superior mediastinum	8,530	Adenoma	True	Negative	True	ND
6	Right lower, intrathymic in the superior mediastinum	2,568	Adenoma	True	Negative	True	ND
7	Right lower, intrathymic in the superior mediastinum	1,550	Adenoma	True	Negative	True	ND
8	Supernumerary, anterior mediastinum	260	Hyperplasia	True	3 glands positive in the neck	True	ND
9	Supernumerary, anterior mediastinum	2,572	Hyperplasia	True	4 gland positive in the neck	True	ND
10	Thymoma, anterior mediastinum	–	Thymoma	False positive for concurrent thymoma	Negative	Detected	ND
11	Right lower, intrathymic in the anterior mediastinum	520	Adenoma	True	Negative	Negative	True
12	Supernumerary, anterior mediastinum	2,200	Hyperplasia	True	Negative	True	ND
	Supernumerary, middle mediastinum	3,835	Hyperplasia	True	Negative	True	ND
13	Left, aorto-pulmonary window in the middle mediastinum	1,050	Adenoma	True	Negative	True	ND
14	Left, aorto-pulmonary window in the middle mediastinum	1,325	Adenoma	True	Negative	True	ND

ND not done

adenomas, four parathyroid hyperplasias, and one thymoma.

Localization before and during surgery

Abnormal lesion sites and preoperative localization results are shown in Table 2. Although 99m-TC sestamibi scan showed a positive lesion in the mediastinum in all patients, a sestamibi-positive thymoma was included in patient 10 (Fig. 1). For this patient, a sestamibi scan was performed again after thoracoscopic excision of the mediastinal thymoma, and no abnormal RI uptake in the neck could be found. Ultrasonography of the neck showed cervical parathyroid swelling in only two patients (nos. 8 and 9) with multiglandular disease but failed to reveal any mediastinal lesions in any of the patients. CT scan identified all of the mediastinal lesions that had been localized by sestamibi scan, excluding one in a 19-year-old patient (no. 11) whose tumor was embedded in the thymus. MRI was performed only in this CT-negative patient, and this identified the parathyroid adenoma embedded in the thymus. Three-dimensional CT scan provided accurate anatomical information in two patients with parathyroid adenoma located in the aorto-pulmonary window (Fig. 2).

All of the mediastinal lesions treated by using a cervical approach were identified by mediastinal visual inspection. In a cervical approach, intraoperative radio-navigation was not helpful for localization, because it was difficult to differentiate nuclear counts in the parathyroid adenoma from the background activity of the great vessels and the heart. Seven of the eight mediastinal lesions treated by thoracoscopy, except for the one embedded in the thymus of a young patient (no. 11), also were identified by thoracoscopic visual inspection alone. Although the parathyroid adenoma embedded in the thymus could not be identified directly by video view, the region of the thymus where it was embedded was easily identified on the basis of information obtained by preoperative imaging studies. The lesion was removed by partial thymectomy (Fig. 3). One of

Fig. 1 99m-TC sestamibi scan showing abnormal radioisotope uptake in the chest alone. This mediastinal lesion was resected thoracoscopically and was histopathologically proven to be a thymoma

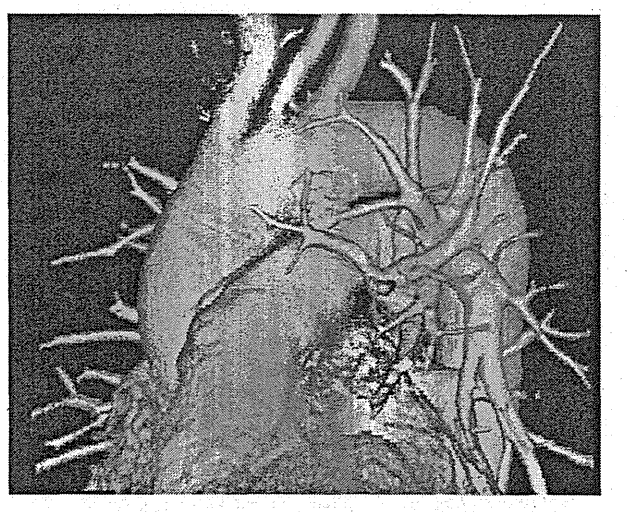

Fig. 2 Parathyroid adenoma localized at the aorto-pulmonary window by 3D-CT before surgery

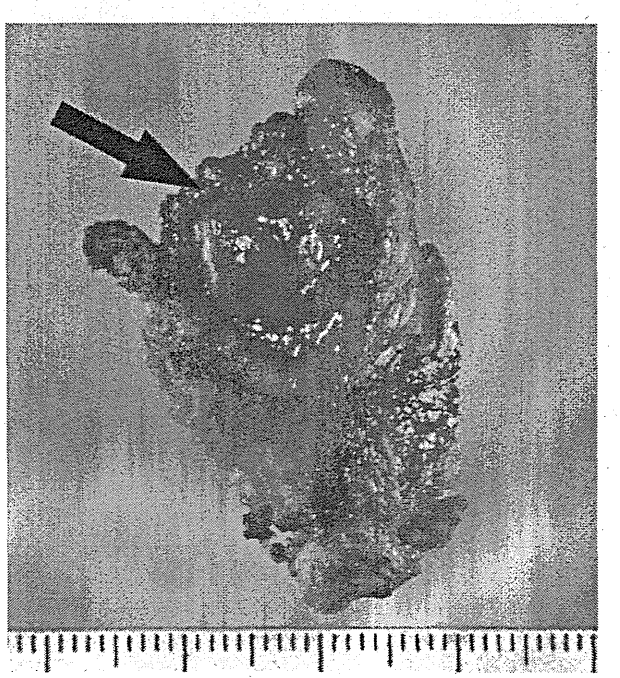

Fig. 3 Macroscopic features of the specimen resected thoracoscopically. A parathyroid adenoma (*arrow*) is deeply embedded in the thymic tissue

Table 3 Surgical method and surgical outcome in patients with hyperparathyroidism in whom mediastinal lesions were localized preoperatively

Patient	Surgical approach	Surgical resection of parathyroid	Postoperative intact PTH* (pg/ml)	Postoperative status of hyperparathyroidism	Operation time (min)	Estimated blood loss (ml)
1	Cervical	Unilateral parathyroidectomy	56	Cured	120	60
2	Cervical	Unilateral parathyroidectomy	21	Cured	110	20
3	Cervical	Removal of single parathyroid adenoma	11	Cured	90	55
4	Cervical	Removal of single parathyroid adenoma	16	Cured	146	40
5	Cervical	Removal of single parathyroid adenoma	19	Cured	174	55
6	Cervical	Removal of single parathyroid adenoma	35	Cured	78	2
7	Cervical	Removal of single parathyroid adenoma	26	Cured	146	35
8	Thoracoscopic and cervical	Resection of 3 glands in the neck and a supernumerary gland in the mediastinum	15	Cured	258	43
9	Thoracoscopic and cervical	Total parathyroidectomy combined with autotransplantation	14	Remission	236	40
10	Thoracoscopic	Partial thymectomy for thymoma, not including parathyroid lesion	115	Persistent	69	5
	Cervical	Removal of single parathyroid adenoma	29	Cured	56	15
11	Thoracoscopic	Removal of single parathyroid adenoma with partial thymectomy	16	Cured	133	5
12	Thoracoscopic	Removal of a supernumerary parathyroid gland	112	Remission	110	10
	Thoracoscopic	Removal of an additional supernumerary parathyroid gland	126	Remission	115	5
13	Thoracoscopic	Removal of single parathyroid adenoma	21	Cured	117	35
14	Thoracoscopic	Removal of single parathyroid adenoma	28	Cured	120	10

* Postoperative intact PTH was measured on the first postoperative day

the mediastinal lesions resected thoracoscopically was a sestamibi-positive thymoma (patient 10). During surgery, we recognized that the mediastinal lesion was not a parathyroid adenoma, and no further explorative procedure was performed at the initial operation. We decided to examine the localization of the parathyroid lesion again to minimize surgical exploration procedure.

Surgical approach and outcome

A cervical approach was selected for resection of parathyroid lesions localized at the 6 anterior and 1 posterior position of the superior mediastinum (Table 3). These parathyroid lesions were successfully resected by cervical incision without any special retractor for the sternum. A thoracoscopic approach was selected for resection of deep mediastinal lesions localized below the level of the aortic arch in seven patients. The thoracoscopic procedure was successful in all these patients in whom a deep (5 anterior, 3 middle) mediastinal lesion was localized preoperatively.

One of the mediastinal lesions resected thoracoscopically was a sestamibi-positive thymoma (patient 10). Postoperative relocalization was required in this patient because of persistent hyperparathyroidism. Although a sestamibi scan was performed again, no abnormal radioisotope uptake was evident. CT scan identified a low-density mass in the neck, and a right lower parathyroid adenoma was successfully removed by focused neck exploration. In patient 12 with recurrence of secondary hyperparathyroidism due to an enlarged supernumerary gland in the anterior mediastinum, the serum PTH level was successfully normalized by the initial thoracoscopic surgery. However, 4 years later, the patient developed recurrence due to enlargement of another supernumerary gland located in the middle mediastinum. The PTH hypersecretion was treated successfully by a repeated thoracoscopic procedure on the same side.

The median operation time and estimated blood loss for the thoracoscopic procedure was 116 (range, 6–133) min and 7.5 (range, 5–35) ml, respectively. No surgical complications were observed in any of the patients. During follow-up after curative resection, none of the patients with primary hyperparathyroidism developed recurrence.

Discussion

The majority of patients with primary or secondary hyperparathyroidism have abnormal parathyroid lesions in the neck, which can be removed through standard neck

exploration. Although up to 20% of patients may have hyperfunctional parathyroid glands extending into the mediastinum, most of these also can be resected through a cervical incision, and direct mediastinal exploration is required in only 2% of cases [1–3]. Traditionally, patients with hyperparathyroidism have a deep mediastinal parathyroid lesion that requires a transsternal or transthoracic approach involving an open technique. The reported complication rate associated with these procedures can be up to 29% [3–5]. In a series of 38 patients treated by using a median sternotomy, Russell et al. [4] reported that chest complications, such as pleural effusion, pneumothorax, and pneumonitis, occurred in 21% and wound complications, such as hematomas, anterior mediastinitis, and sternal dehiscence, occurred in 8%. In another series reported by Conn et al. [5], 4 of 21 patients treated by median sternotomy had complications, including two cases of pleural effusion, one case of left subclavian vein thrombosis, and one case of chondritis of the xiphosternal junction. Because of the high incidence of surgical complications after a transsternal or transthoracic open procedure, many surgeons have evaluated alternative approaches for accessing mediastinal parathyroid glands. Schlinkert et al. [6] reported that anterior mediastinotomy (Chamberlain's approach) was feasible in selected patients, although lesions located deep in the mediastinum required sternotomy. Wells and Cooper [7] described a technique for close anterior mediastinal exploration using a special sternal retractor to achieve thymectomy via a transcervical approach, thereby allowing removal of the parathyroid glands also. However, it is generally believed that parathyroid glands located in the aorto-pulmonary window or posterior mediastinum cannot be safely removed by the transcervical method. As a nonsurgical alternative to standard mediastinal exploration, angiographic ablation also has been reported. Doherty et al. [8] have reported the largest series employing this technique, including 30 angiographic ablations in 27 patients. After these procedures, 3 patients were hypoparathyroid, 14 were normocalcemic, and 10 required subsequent treatment. Three of the patients initially controlled by angioablation developed recurrence. The authors also reported a cohort of 24 patients who underwent sternotomy. In the 1990s, advances in techniques and equipment allowed surgeons to approach such parathyroid lesions located in the deep mediastinum. The first description of successful thoracoscopic resection of mediastinal parathyroid lesions was reported by Prinz et al. [9] in 1994. In their series, all four patients underwent cervical thymectomy as part of their initial neck exploration, but this maneuver did not include removal of their abnormal mediastinal parathyroid glands. Among a series of 16 patients treated using the transsternal/transthoracic approach, Cupisti and coworkers [10] reported three cases of recurrent nerve palsy, one case of chylous fistula, and one case of pleural effusion. In contrast, no complications were observed in the two patients for whom thoracoscopy was successful. This minimally invasive approach for mediastinal parathyroidectomy also has been reported by others [11–21], mainly as case reports or small series because of the rarity of this type of lesion.

With regard to the most suitable surgical approach for resection of mediastinal parathyroid lesions, a few reports have discussed the issue of choosing between a comprehensive approach involving thoracoscopy and a cervical approach. Sukumar et al. [20] recommended a transcervical approach using a special sternal retractor to remove parathyroid glands located within the anterior or superior mediastinum. They demonstrated that a sternal retractor was able to open the thoracic inlet and increase the exposure of the superior mediastinum, allowing the inferior aspect of the left innominate vein to be reached under direct vision. However, the authors also stated that parathyroid adenoma, located even in the anterior mediastinum, was resectable under thoracoscopic vision or that the entire thymus gland could be removed with the adenoma in situ. Liu at al. [18] recommended a cervical "back-door" approach for resection of posterior superior mediastinal parathyroid adenomas. This "back-door" approach was initiated by dissection between the sternocleidomastoid and strap muscles, and then extended down to the spine along a plane medial to the jugular vein and carotid artery, and inferiorly into the posterior superior mediastinum. Both of these reports stated that parathyroid adenomas in the middle or posterior mediastinum were best accessed via a thoracoscopic approach. In our series, we also decided the surgical method according to the location of the mediastinal lesions. All eight mediastinal lesions localized preoperatively below the level of the aortic arch in the deep mediastinum were successfully removed by thoracoscopy. Additionally in this series, a repeat thoracoscopic procedure on the same side of the chest was successful for resection of a hyperfunctional supernumerary parathyroid gland in a patient with recurrent secondary hyperparathyroidism. A thoracoscopic approach can be a feasible option for mediastinal reexploration in such patients. Seven patients whose parathyroid adenomas were localized in the superior mediastinum were treated successfully by a transcervical procedure without having to retract the sternum. The level of the aortic arch on a horizontal chest CT image can be a useful landmark for guiding a suitable surgical approach.

Accurate preoperative localization of mediastinal parathyroid lesions is mandatory for successful mediastinal exploration. Many surgeons have described the importance of preoperative localization using sestamibi scan, CT scan, and/or MRI. In our series, a combination of sestamibi scan

and chest CT scan or MRI not only confirmed the presence of an abnormal mass but also provided valuable information about the surrounding or contiguous structures. It is, however, noteworthy that our series included one mediastinal tumor showing sestamibi false positivity, and this was proven to be a thymoma histopathologically. It has been reported that thyroid disease, including benign nodules and malignancies, and enlarged lymph nodes, can appear false-positive in sestamibi scans for localization of parathyroid lesions [22–24]. Mitochondrial density within a tumor is associated with retention of 99m-TC sestamibi, and it should be borne in mind that some mitochondria-rich mediastinal tumors, such as thymoma, can appear false-positive for this reason. The patient involved underwent sestamibi scan/SPECT for relocalization of an abnormal parathyroid after removal of the thymoma, but no abnormal findings could be identified. On the other hand, a very small mediastinal parathyroid lesion weighing 260 mg associated with MEN 1 was identifiable by sestamibi scan, even though it has been reported that the sensitivity of sestamibi scan in patients with multiglandular parathyroid disease is lower than that in patients with single parathyroid adenoma [25]. This small mediastinal parathyroid lesion was localized by preoperative chest CT. The parathyroid adenoma found to be deeply embedded in the thymus of a 19-year-old male was not revealed as a mediastinal mass by CT scan because the thymus was not atrophic. Only additional MRI was able to localize the lesion in the intrathymic mediastinal parathyroid. Obtaining such anatomic information about tumor location was mandatory not only for selection of the optimal surgical approach but also for dissection and localization during the operation, thus we emphasize the importance of precise localization before surgery.

Another issue in this study was detection of enlarged mediastinal parathyroid glands during surgery. Intraoperative sestamibi gamma probe guidance has been recommended for thoracoscopic mediastinal exploration [15–17], and the use of this radioguided method is able to facilitate identification of parathyroid tissue and may reduce operation time. Recently, however, some reports have cast doubt on the need for intraoperative radio-navigation [18, 21]. Alesina et al. [21] described one case in their personal series that required a longer operation time due to difficulty with dissection and considered that the use of a gamma probe would have been helpful for reducing the operation time. In our series, all the mediastinal lesions localized preoperatively were detected successfully by visual inspection alone during surgery, using not only a cervical but also a thoracoscopic approach. No radioguided technique was necessary for intraoperative detection, even for a small parathyroid lesion weighing only 260 mg. The parathyroid adenoma deeply embedded in the thymus of a young male could not be directly identified by intraoperative visual inspection, but the region of the thymic gland in which the lesion appeared to be located was easily identified based on information from preoperative localization studies. Therefore, we believe that most mediastinal parathyroid lesions can be localized by visual inspection alone during surgery if they are accurately localized beforehand.

Operation time and estimated blood loss in our series were comparable to those reported previously [18, 21]. No morbidities were observed, and the follow-up outcome was favorable. Therefore, thoracoscopic surgery should be the treatment of choice for resection of parathyroid lesions located deep in the mediastinum.

In conclusion, thoracoscopic surgery is safe and feasible for resection of deep mediastinal parathyroid lesions, even in patients undergoing repeat procedures. Mediastinal parathyroid lesions localized preoperatively at the aortic arch or upper region can be treated via a cervical approach without any special sternal retractor. Preoperative sestamibi scan can sometimes give a false-positive result in cases of concurrent thymoma. Most mediastinal parathyroid lesions localized preoperatively can be identified by visual inspection alone.

Conflicts of interest None of the authors have any conflicts of interest for this article.

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特集 消化器神経内分泌腫瘍

11 多発性内分泌腫瘍症1型

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Key words: 遺伝性疾患，遺伝学的検査，発症前診断，SACI 試験

要 旨

多発性内分泌腫瘍症1型(multiple endocrine neoplasia type 1；MEN1)は常染色体優性遺伝性の腫瘍症候群であり，複数の内分泌臓器さらには非内分泌臓器に腫瘍性病変を生じる．MEN1では約60%の患者に膵消化管神経内分泌腫瘍(GEP-NET)を生じ，一方，日本人のデータでは膵神経内分泌腫瘍(P-NET)の10%はMEN1によるものである．MEN1患者を効率的に診断することは，本人のより適切な治療を可能にするのみならず，血縁者の早期診断のためにも重要である．MEN1によるGEPNETは非遺伝性GEPNETに比べて発症年齢や発生部位などに特徴を有しており，これがMEN1を診断するきっかけとなるとともに，治療方針に影響を与える．

表1 MEN1で発生する腫瘍

腫瘍	罹病率
副甲状腺過形成	>95%
下垂体腫瘍：プロラクチノーマ，GH産生腫瘍，ACTH産生腫瘍，非機能性腫瘍	40～60%
GEPNET：ガストリノーマ，インスリノーマ，グルカゴノーマ，ソマトスタチノーマ，非機能性腫瘍	50～70%
胸部腫瘍(カルチノイド)：胸腺神経内分泌腫瘍，気管支腫瘍	5～10%
副腎皮質腫瘍	20～30%
顔面血管線維腫	40～80%
脂肪腫	30%

GH：growth hormone
ACTH：adrenocorticotropic hormone

はじめに

多発性内分泌腫瘍症1型(multiple endocrine neoplasia type 1；MEN1)は原発性副甲状腺機能亢進症，下垂体前葉腺腫，膵消化管神経内分泌腫瘍(gastroenteropancreatic neuroendocrine tumor；GEPNET)を主徴とし，それ以外に副腎皮質，胸腺，気管支，皮膚などに良性・悪性の腫瘍が多発する常染色体優性遺伝性疾患である(**表1**)．臨床的には副甲状腺機能亢進症，下垂体腺腫，GEPNETのうち二つを認める場合にMEN1と診断される．しかしながら副甲状腺病変以外については中高年以降になって発症したり，あるいは生涯発症しなかったりする場合もあるため，この診断基準のみでは患者の早期発見にはあまり有効ではなく，可能性の高い患者に対して臨床医が積極的にMEN1を

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疑って検索を行う必要がある．

本稿では，MEN1 に伴う GEPNET と散発性 GEPNET の臨床的特徴の違いに焦点をあて，MEN1 の診断と治療について述べる．

Ⅰ．臨床診断

この項のポイント
- GEPNET の発症年齢，発症部位が MEN1 診断のヒントになる．
- 多くの例で副甲状腺機能亢進症を伴う．

1．MEN1 の GEPNET の特徴

P-NET のうち 10% は MEN1 によるものである．MEN1 患者に発生する GEPNET では，臨床的に散発性 GEPNET とは異なる特徴を示すものがあり，これが MEN1 診断の契機となりうる．

1）ガストリノーマ

散発例のガストリノーマの多くが膵に単発性に発生するのに対し，MEN1 のガストリノーマではほとんどの例で十二指腸に小腫瘍が多発する．ガストリノーマでは 25% が MEN1 によるため，もともと MEN1 を疑って精査を進める必要があるが，十二指腸原発のガストリノーマではとくにその可能性が高い．個々の腫瘍は小さいため，CT や MRI による検出は難しく，超音波内視鏡が有用である．また MEN1 では非機能性 GEPNET を合併していることが多く，画像検査で腫瘍を確認しても，それがホルモン過剰産生の責任病変とはかぎらない．したがって，ガストリノーマの診断には選択的動脈内カルシウム注入試験（selective arterial calcium injection test；SACI test）が必須である[1]．MEN1 で高率に発症する副甲状腺機能亢進症による高カルシウム血症はガストリン分泌を促進するため，ガストリノーマの診断を難しくする．

2）インスリノーマ

MEN1 においてもインスリノーマの多くは単発性であるが，しばしば腫瘍が小さいために画像検査でとらえることができない．また非機能性腫瘍が同時に存在している場合が多く，この場合はどの腫瘍がインスリノーマかを区別できないので，ガストリノーマと同様，機能性腫瘍を同定し治療方針を決定するためには SACI test が必須となる．MEN1 のインスリノーマはガストリノーマや非機能性 NET に比べてより早い年齢から発症し（診断時平均年齢 34.8 歳），約 25% の症例は 20 歳以前に診断される[2]．20 歳以前の P-NET はまれであり，わが国の疫学統計でも P-NET 全体の 1% を占めるにすぎない[3]．したがって，若年のインスリノーマは単独で MEN1 を疑う必要がある．

3）その他の機能性腫瘍

グルカゴノーマ，ソマトスタチノーマ，vasoative intestinal polypeptide（VIP）産生腫瘍も低頻度ながら MEN1 の膵内分泌腫瘍として発症する．これら腫瘍の診断は特徴的な臨床症状とホルモンの高値の確認によってなされる．これらの腫瘍はガストリノーマやインスリノーマと異なり，腫瘍径は大きく通常の画像検査でとらえることができるが，前述のとおり，MEN1 患者では複数の P-NET が同定されることが多く，個々の腫瘍の機能の評価は容易ではない．

2．原発性副甲状腺機能亢進症

MEN1 ではほぼ全例に原発性副甲状腺機能亢進症を伴い，約半数の症例では高カルシウム血症に関連する症状が初発症状になっている．したがって，GEPNET 患者に対して MEN1 の有無を検索するにあたっては，高カルシウム血症の確認を最初に行うべきである．実際，日本人 MEN1 患者のデータでは，GEPNET を有する患者の約 95% は副甲状腺機能亢進症を合併

している[4]．副甲状腺機能亢進症の診断は高カルシウム血症と高副甲状腺ホルモン(PTH)血症の確認によってなされるが，MEN1の副甲状腺機能亢進症では，これらの上昇がごく軽度にとどまる軽症例も多く，約35%の患者では50歳の時点でも血清カルシウムと血漿PTHのいずれかは正常上限値以下にとどまっている[5]．

3．家族歴

家族歴の情報もきわめて重要である．MEN1の家族歴がある場合は，関連病変の一つを認めるだけでMEN1と診断される．筆者らの研究グループが構築した日本人MEN1患者データベースの解析では，患者の71.8%は家族性，すなわち家系内にMEN1患者が存在していた(11.4%は家族歴の有無について記載がなかった)[4]．海外の知見でも，80%以上の患者で両親の一方が罹患しているとされており，関連病変の既往の有無や疑わしい臨床症状(尿路結石，消化性潰瘍など)の確認が重要である．副甲状腺，下垂体，膵消化管の病変はしばしば甲状腺疾患，脳腫瘍，膵癌などと認識されていることもあるので注意を要する．

Ⅱ．遺伝学的検査

この項のポイント
- MEN1が疑われる症例に対しては遺伝学的検査を考慮する．
- 血縁者に対する発症前診断は推奨されるが，実施にあたっては慎重な対応が求められる．

MEN1の原因遺伝子として11番染色体長腕に存在する腫瘍抑制遺伝子である*MEN1*が知られており，家族歴のあるMEN1患者の90%，家族歴のない患者の50%程度に変異が認められる[4]．*MEN1*遺伝子は腫瘍抑制遺伝子であり，変異は遺伝子の全領域に分布する．また変異と臨床像との間に相関はない．通常のシークエンス解析で変異が見つからない症例のなかには大規模な欠失を生じている場合があり，MLPA法などによる検索を追加する必要がある．

表2　*MEN1*遺伝子解析を考慮すべき病態

- 30歳未満で発症した副甲状腺機能亢進症
- 多腺性副甲状腺機能亢進症
- 副甲状腺機能亢進症の再発
- ガストリノーマ
- 成人以前に発症したインスリノーマ
- 多発性GEPNET
- MEN1関連腫瘍の家族歴

1．発端者の確定診断

MEN1関連腫瘍を1病変のみ発症している症例において，MEN1症例と非遺伝性の散発例を鑑別することはその後の健康管理のためにもきわめて重要であり，*MEN1*遺伝学的検査は確定診断のための非常に有用性の高い情報となる．しかし，すべての患者に遺伝学的検査を実施するのは，変異陽性率も低く効率的ではない．MEN1をより強く疑わせる症例を選択して検査を検討する必要がある．MEN1を疑うべき症例を**表2**にまとめた．

臨床的にすでにMEN1と診断されている症例では，本人の健康管理を目的とした遺伝子診断は必ずしも行う必要がないかもしれない．しかし遺伝情報は血縁者で共有しており，検査によってひとたび情報が得られれば，それは血縁者の発症前診断にも利用することができる．したがって，すでにMEN1と診断されている患者に対しても遺伝子解析を考慮することは妥当である．ただし，その際には検査の意義や限界，血縁者への影響の可能性について十分に説明し，必要な場合は遺伝カウンセリングを提供できる準備を整えておく必要がある[参考URL1)]．

2．発症前診断

MEN1患者が有する遺伝子変異は，子に50%の確率で伝えられる．また変異陽性者の生涯発症率(浸透率)はほぼ100%である．したがって，ひとたび患者に*MEN1*遺伝子変異が同定されれば，患者の兄弟姉妹や子どもが同じ変異を有しているかを診断することができる．発症前診断によって変異保有者を確定することは，綿密な定期検査による健康管理を可能にし，病変の早期発見と早期治療につなげることができる．一方，変異を有していないことがわかれば，たとえ血縁者であっても将来の罹患の心配がなくなる．ただし，健康に不安を抱いていない血縁者に対して一方的に将来の高い罹患確率を宣告することにもなるので，その対応は慎重を要する．発症前診断に際しては，必ず事前の遺伝カウンセリングを行い，適切な情報提供によって被検者が検査の内容や限界，陽性であった場合の対応などを十分理解したうえで実施する必要がある．

子どもに対して発症前診断を行う時期はいつが望ましいのかについてコンセンサスはないが，遅すぎるのが不適切である一方，不必要に早すぎる検査も育児における問題を生じることが危惧されている．海外のMEN診療ガイドラインでは発症前遺伝子検査に関する年齢への言及はないが，筆者は自身で遺伝のことがある程度理解でき，自己判断が可能になる中学生以降に発症前遺伝子検査を受けることを勧める場合が多い．小学生までの年齢でMEN1が発症する例は非常に少ないが，インスリノーマによる低血糖発作と下垂体腫瘍による成長障害は問題となるので，リスクのある子どもの親に対しては，低血糖を疑わせる症状や成長の鈍化について指導し，これらを認めた場合には受診するよう促している．

Ⅲ．治　　療

この項のポイント

- MEN1によるP-NET治療の原則は外科的切除である．
- 腫瘍が多発していることが多いので術式は慎重に検討する．
- 膵全摘はできるだけ回避する．
- 小さい非機能性腫瘍は経過観察を行う．

MEN1に伴うP-NET治療の原則は散発性と同様，外科的切除である．しかしながら，腫瘍が多発すること，小さい非機能性腫瘍は比較的経過が緩徐であることから，散発例とは異なる対応もとられる．

1．ガストリノーマ

MEN1のガストリノーマは個々の腫瘍が小さくかつ多発するため，これまでの外科治療成績は不満足なものであり，そのため外科治療に慎重なグループはプロトンポンプ阻害薬による胃酸分泌を中心に行い，腫瘍径が20～30 mmを超える場合に手術を検討することを提唱している[6),7)]．一方で，積極的な外科治療を行った患者群の肝転移発生率が，保存的治療を行った群より明らかに低いという報告もなされていた[8),9)]．最近は外科手術の良好な治療成績が報告され[1)]，MEN1のガストリノーマの治療は薬物によるホルモン抑制治療からより積極的な外科治療へとシフトしつつある．

2．インスリノーマ

インスリノーマの治療は外科的な腫瘍摘出の絶対適応である．幸いなことにMEN1のインスリノーマの多くは単発性で浸潤傾向はなく，核出術の適応となる場合が多い．ただし高齢で診断された場合はすでに膵に複数のP-NETを生じていることが多いため，膵部分切除が選択される場合が増えてくる[2)]．術後に再びインス