Abstract. While there is no doubt that total thyroidectomy is necessary for medullary thyroid carcinoma (MTC) in multiple endocrine neoplasia type 2A (MEN2A) patients, there is still controversy regarding the management of the parathyroid glands. Although most, but not all, endocrine surgeons leave normal-appearing parathyroid glands in situ during thyroid surgery for MEN2A, we have employed total parathyroidectomy with autotransplantation. Between 1994 and 2006, 12 MEN2A patients underwent therapeutic total or completion thyroidectomy and lymph nodes dissection at least in the central compartment for MTC. Total or completion parathyroidectomy with autotransplantation was performed concurrently with above-mentioned surgery. All patients were over 25 years old, and the median age was 48.5 years. There were 5 males and 7 females from 8 families. The average number of transplanted parathyroid glands was 3. Serum calcium and intact PTH levels have been maintained during the median follow up of 107 months in all patients except for one who died of advanced MTC one year after surgery. Total parathyroidectomy with autotransplantation at the time of primary surgery for MTC, i.e. total thyroidectomy with bilateral central neck dissection, is a feasible approach for managing the risk of hyperparathyroidism.

Key words: MEN2A, Parathyroid transplantation, Medullary thyroid carcinoma, Hyperparathyroidism

MULTIPLE endocrine neoplasia type 2A (MEN2A) is characterized by the occurrence of medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism (HPT). The disease has an autosomal dominant inheritance pattern with near complete penetrance but variable expressivity. All affected patients develop MTC, whereas half of them develop pheochromocytoma and fewer HPT. MTC is uniformly malignant and the most common cause of death in patients with MEN2A. HPT in MEN2A is less common, occurring in 20–30% of patients in Western countries [1-3], and 11% in Japan [4]. A genotype-phenotype correlation has been reported; however, variability among kindreds with the same mutational aberration of the RET gene also exists [5]. The presence of a germ line mutation at codon 634 predicts high risk of the development of HPT in a given MEN2A family [6]. Although conflicting reports exist [7], the clinician should be careful with an increased risk of HPT in patients with a codon 634 mutation, as well as pheochromocytoma in particular kindred.

HPT in MEN2A is mild, often asymptomatic, and many cases have a single enlarged parathyroid although multiglandular disease does occur. In a European multicenter study that included 60 patients
with HPT in MEN2A, cure was achieved in 94% of the patients independent of the extent of resection, including 13% with persistent hypocalcemia, whereas hypercalcemia persisted in 3%, and 3% were lost in follow up. At 8 years of follow up, hypercalcemia recurred in 12% of the patients, which was unrelated to the extent of resection. In a similar multicenter study from France that included 56 HPT patients with MEN2A, persistent HPT occurred in 11%, and 22% had persistent hypocalcemia which was related to more aggressive resection [8]. On the other hand, persistent or recurrent disease was absent after total parathyroidectomy and heterotopic autotransplantation with a mean follow up of 14.7 years without higher rate of persistent hypocalcemia [9]. While there is no doubt that total thyroidectomy is necessary for MTC in MEN2A patients, there is still controversy regarding the management of the parathyroid glands at the time of thyroidectomy. Most, but not all, endocrine surgeons leave normal-appearing parathyroid glands in situ during thyroid surgery for MEN2A [10], whereas autotransplantation to the forearm has been advocated by some [11-13]. Besides European multicenter studies, there have been few long term follow-up reports concerning parathyroid function after thyroid and parathyroid surgery in MEN2A. We report our experience in the treatment of MTC in adult MEN2A patients and describe the results with regard to long-term postoperative parathyroid function.

**Patients and Methods**

Between 1994 and 2006, 12 MEN2A patients, all over 25 years old, underwent surgery for MTC at the Department of Breast and Endocrine Surgery in Nagoya University Hospital (Table 1). None of the surgeries were prophylactic, but 5 patients were diagnosed with MTC during family screening and had a tumor diameter less than 1 cm. There were 5 males and 7 females, from 8 families. Two of the 12 patients showed HPT (high serum calcium and high serum intact PTH level). The other 10 patients had normal parathyroid function preoperatively. Median age was 48.5 years. Preoperative serum calcitonin levels were constitutively high in 6 patients, and the remaining 6 patients showed normal basal calcitonin but a greater than normal elevation of calcitonin when infused with calcium or gastrin.

A total thyroidectomy (including the posterior capsule) or completion thyroidectomy was performed, and lymph nodes in the central zones of the bilateral neck (from the hyoid bone to the thoracic inlet and laterally to the carotid artery) were removed. In selected patients, lymph nodes of the lateral zones were removed, and in 2 patients, those in the mediastinal zone also. The major vessels and nerves were all preserved as were the anterior strap and sternocleidomastoid muscles. The parathyroid glands were all removed and autotransplanted into the brachioradial muscle of the non-dominant forearm (7 patients), or into the sternocleidomastoid muscle (1 patient) or into the major pectoral muscle (4 patients) [14] (Table 1). For transplantation to the forearm, the parathyroids were sliced into slivers measuring approximately 1x1x1 mm, and 16 to 36 of these pieces were implanted intramuscularly, as described by Wells et al. [15]. The extent of transplanted parathyroid tissue (number of glands or number of pieces), methods of transplantation (sliver or mince), and the transplantation sites were determined by each surgeon. The first half of the patients received 2 glands or approximately 20 pieces of transplantation, and the other half of the patients received more glands or pieces. Roughly, most of the normal-appearing parathyroid glands were transplanted. After surgery, the patients were placed on L-thyroxin (100 µg/day), 1α-hydroxyvitamin D3 (2 µg/day), and calcium lactate (7.5 g/day) [16]. Approximately 2 weeks after the operation, oral calcium was stopped and vitamin D was reduced to 1 µg/day. After another 2 weeks, oral vitamin D was discontinued in 10 patients with normal PTH level preoperatively, whereas 2 HPT patients (7-1, 8-1, Table 1) received for prolonged periods. Serum calcium concentration and the serum intact PTH concentration in each antecubital vein were determined in patients with autotransplantation to the forearm to compare concentration of intact PTH in systemic circulation with that in the efflux of the autotransplanted parathyroid [17].

**Results**

Ten of 12 patients received total thyroidectomy, at least bilateral central neck dissection, total parathyroidectomy, and parathyroid autotransplantation as a primary surgical treatment (Table 1). In 9 of these 10 patients the surgery was considered curative for MTC,
PARATHYROID AUTOTRANSPANTATION IN MEN2A

Table 1. Clinical and genetic characteristics of MEN2A patients

<table>
<thead>
<tr>
<th>Family-Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Follow (months)</th>
<th>outcome</th>
<th>primary or completion</th>
<th>transplantation site</th>
<th>HPT</th>
<th>RET mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>M</td>
<td>52</td>
<td>12</td>
<td>Dead</td>
<td>primary</td>
<td>pectoral&lt;sup&gt;a&lt;/sup&gt;</td>
<td>no</td>
<td>634 TGC-TCC</td>
</tr>
<tr>
<td>1-2</td>
<td>M</td>
<td>49</td>
<td>168</td>
<td>Alive</td>
<td>primary</td>
<td>pectoral&lt;sup&gt;a&lt;/sup&gt;</td>
<td>no</td>
<td>634 TGC-TCC</td>
</tr>
<tr>
<td>2-1</td>
<td>F</td>
<td>30</td>
<td>133</td>
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<td>primary</td>
<td>forearm</td>
<td>no</td>
<td>618 TGC-CGC</td>
</tr>
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<td>3-1</td>
<td>F</td>
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<td>152</td>
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<td>primary</td>
<td>forearm</td>
<td>no</td>
<td>634 TGC-GGC</td>
</tr>
<tr>
<td>3-2</td>
<td>F</td>
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<td>107</td>
<td>Alive</td>
<td>primary</td>
<td>forearm</td>
<td>no</td>
<td>634 TGC-GGC</td>
</tr>
<tr>
<td>3-3</td>
<td>F</td>
<td>48</td>
<td>119</td>
<td>Alive</td>
<td>primary</td>
<td>pectoral&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>4-1</td>
<td>M</td>
<td>47</td>
<td>107</td>
<td>Alive</td>
<td>primary</td>
<td>forearm</td>
<td>no</td>
<td>611 TGC-TCT</td>
</tr>
<tr>
<td>5-1</td>
<td>M</td>
<td>47</td>
<td>26</td>
<td>Alive</td>
<td>primary</td>
<td>forearm</td>
<td>no</td>
<td>611 TGC-TCT</td>
</tr>
<tr>
<td>5-2</td>
<td>M</td>
<td>47</td>
<td>22</td>
<td>Alive</td>
<td>primary</td>
<td>sternocleido&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>6-1</td>
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</tr>
<tr>
<td>7-1</td>
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<td>59</td>
<td>26</td>
<td>Alive</td>
<td>primary</td>
<td>pectoral&lt;sup&gt;a&lt;/sup&gt;</td>
<td>yes</td>
<td>634 TGC-TCC</td>
</tr>
</tbody>
</table>

<sup>a</sup>: primary thyroidectomy or completion thyroidectomy for MTC.
<sup>b</sup>: major pectoral muscle
<sup>c</sup>: sternocleidomastoid muscle

Table 2. Isolated and transplanted parathyroids in each patient and parathyroid function

<table>
<thead>
<tr>
<th>Family-Patient</th>
<th>Isolated parathyroids</th>
<th>Transplanted parathyroids</th>
<th>Serum Ca</th>
<th>Systemic PTh&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Forearm PTh&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>2</td>
<td>2 glands&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.2</td>
<td>14.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1-2</td>
<td>4</td>
<td>2 glands&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.7</td>
<td>33</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-1</td>
<td>4</td>
<td>16 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.7</td>
<td>44.4</td>
<td>1408</td>
<td>34.3</td>
</tr>
<tr>
<td>3-1</td>
<td>4</td>
<td>23 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.8</td>
<td>33.1</td>
<td>1022.7</td>
<td>30.9</td>
</tr>
<tr>
<td>3-2</td>
<td>4</td>
<td>20 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.7</td>
<td>52.7</td>
<td>871.6</td>
<td>24.1</td>
</tr>
<tr>
<td>3-3</td>
<td>3</td>
<td>22 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.8</td>
<td>37.1</td>
<td>327.2</td>
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<tr>
<td>5-1</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 glands&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.6</td>
<td>40</td>
<td>732.6</td>
<td>18.3</td>
</tr>
<tr>
<td>5-2</td>
<td>4</td>
<td>32 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.9</td>
<td>38</td>
<td>1550</td>
<td>40.8</td>
</tr>
<tr>
<td>6-1</td>
<td>4</td>
<td>3 glands&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.9</td>
<td>47.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7-1</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36 pieces&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.9</td>
<td>33.9</td>
<td>446.5</td>
<td>13.2</td>
</tr>
<tr>
<td>8-1</td>
<td>4</td>
<td>3 glands&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.9</td>
<td>12</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Two or three parathyroids were resected at the time of previous surgery.
<sup>b</sup>: Two or three parathyroid glands were minced and transplanted in muscle pockets of sternocleidomastoid or major pectoral muscle.
<sup>c</sup>: Sixteen to 36 pieces of fractionated (1x1x1mm) parathyroids glands were transplanted in muscle pockets of forearm.
<sup>d</sup>: Two parathyroid glands were minced and transplanted in muscle pockets of forearm.
<sup>e</sup>: Serum PTh value of opposite side to transplanted arm.
<sup>f</sup>: Serum PTh value of transplanted arm.

while the mediastinal lymph node metastases of MTC could not be removed in one patient (#1-1, see Tables 1 and 2). Two patients (#5-1, #7-1) had undergone partial thyroidectomy previously. Total completion thyroidectomy and parathyroidectomy was performed, and the minced parathyroids were autografted to the forearm. The average number of identified parathyroids was 3.7 glands in patients undergoing primary surgery, and the average number of transplanted parathyroids was 3 glands.

One HPT patient (#7-1) had previously undergone two partial thyroidectomies. The only remaining parathyroid gland, which was hyperplastic, was removed during total completion thyroidectomy and transplanted to the forearm. The other HPT patient (#8-1) received total thyroidectomy with bilateral central neck dissection and total parathyroidectomy. Only one of four parathyroids was enlarged and the three normal parathyroids were transplanted.

The postoperative course of all patients was uneventful, and there was no morbidity such as recurrent nerve palsy or permanent hypoparathyroidism. Patient #1-1, whose surgery was not curative, died of advanced metastatic MTC at one year postopera-
Postoperative parathyroid function

Postoperative trends of serum intact PTH in the patients undergoing autotransplantation show that the function of the autotransplanted parathyroid glands was regained (Fig. 1). The lowest PTH did not drop to an undetectable level in 4 patients (5-1, 5-2, 6-1, 7-1, Fig. 1). Postoperative serum calcium and intact PTH levels at latest examination were normal in all patients except for the one who died of advanced MTC one year after surgery (patient 1-1, Table 2). The intact PTH levels in the forearm of autotransplantation were available in 7 patients. The average value of intact PTH was 36.1 pg/ml in systemic circulation (normal range of PTH: 10-65 pg/ml) and 908 pg/ml proximal to the transplantation site, giving a ratio of 25.2. None of the surviving patients receive oral calcium or vitamin D supplements, except one patient (8-1, Table 2) who has 1α-hydroxyvitamin D3 (1 µg/day).

Discussion

Total thyroidectomy with bilateral central neck dissection is recommended even as a prophylactic measure for MTC in MEN2A patients [18]. However, there is still controversy regarding management of the parathyroid glands at the time of surgery. In this article, we report that total parathyroidectomy with immediate autotransplantation is feasible, and confirm that the transplanted parathyroids have maintained normal function for long periods.

In particular, in the National Comprehensive Cancer Network (NCCN) guidelines, total thyroidectomy with bilateral central neck dissection is recommended [18]. However, management of the parathyroid in
patients with MEN2A and primary hyperparathyroidism is described as follows: during primary operative procedure and parathyroid exploration, “If single adenoma, excise. If multiglandular hyperplasia, leave, or autotransplant the equivalent mass of one normal parathyroid. Consider cryopreservation of parathyroid tissue.” There are no comments regarding cases with normal levels of intact PTH. We have been performing routine total thyroidectomy with bilateral central neck dissection for papillary thyroid carcinoma and sporadic MTC for more than twenty years [14, 16]. In this procedure, the superior parathyroid glands can be left in situ, but the inferior parathyroid glands should be transplanted unless they are located within the thymus. However, thorough dissection as recommended in the NCCN guidelines does not permit preservation of the lower parathyroid glands. Meanwhile, the upper parathyroid glands are left close to the thyroid bed where local recurrence is a matter of concern. Moley and DeBenedetti reported in 1999 that adequate central node dissection is extremely difficult if the parathyroids are left in place with an adequate blood supply, because some nodes are closely associated with the parathyroids and their blood vessels [19]. Attempts to leave the parathyroids in place result in either failure to remove some central nodes, or devascularization of the parathyroids. However, a functioning autograft virtually eliminates the risk of hypoparathyroidism if reoperation of the central compartment becomes necessary.

The EUROMEN study group, which consisted of nine European centers, reported operative procedures and follow-up data from 67 patients with MEN2A and HPT [20]. A single enlarged gland was resected in 42% of patients, 31% of patients underwent subtotal parathyroidectomy, and 16% underwent total parathyroidectomy with autotransplantation. Biochemical cure was achieved in 94% of patients, regardless of the type of operation carried out, and in an 8-year follow up, the recurrence rate was 12%. The authors point out that half of the patients with recurrent disease had in fact undergone subtotal or total parathyroidectomy. They conclude that MEN2A related HPT can be cured in the majority of patients by resection of enlarged parathyroid glands. A French multicentre study evaluating the outcomes of 56 patients with HPT and MEN2A had similar conclusions [21]. These reports have prompted a trend towards a less aggressive approach. Most, but not all, endocrine surgeons leave normal-appearing parathyroid glands in situ during thyroid surgery for MEN2A [10], mainly to avoid postoperative hypoparathyroidism after total parathyroidectomy and autotransplantation. We reported the postoperative parathyroid function after total parathyroidectomy with autotransplantation in patients with papillary thyroid carcinoma [16]. The key to avoid postoperative hypoparathyroidism in this procedure is to find and transplant more than 3 normal parathyroid glands. The lowest PTH did not drop to an undetectable level in 4 patients (5-1, 5-2, 5-1, 6-1, 7-1, Fig 1). Two patients received 4 parathyroidectomy and the other 2 patients received parathyroidectomy of a lesser degree because of previous thyroid surgery. These patients still have their parathyroid glands somewhere, which are either missed or supernumerary parathyroid glands, and the lowest PTH values might reflect this. If those missed or supernumerary parathyroid glands become hyperfunctional in the future, however, they will have to be resected.

As reported previously, HPT occurs in 11-30% of MEN2A patients, and was observed in 2 of 12 patients in our study [1-4]. The majority of MEN2A patients have normal parathyroid function at the time of primary surgery for MTC. However, the lifetime risk of the occurrence of hyperparathyroidism has yet to be clarified in most of RET mutations. Recently, mutation-based risk profiles were reported in patients with C634W RET mutation, the penetrance for HPT for which is 3% by age 30 and 21% by age 50 [22]. Total parathyroidectomy and autotransplantation will be restricted only for the patients who have mutation-based high risk profiles of HPT in the future. In this context, the procedure for parathyroid glands should be prophylactic in most patients with MEN2A.

The patients in this series were rather old; median age was 48.5 years, and 9 of 12 patients were above 47 years old. Quayle et al. reported hereditary MTC in patients greater than 50 years old [23]. Within 39 hereditary MTC patients, 36 were MEN2A, and of these, the clinical stage was higher in the older patients than the younger; however, the survival rates were similar. In the present series, surgery was non-curative in one patient, who died of advanced metastatic MTC at one year postoperative. The other 11 patients have survived without recurrence of MTC with a median follow-up of 107 months, similar to the results reported by Quayle et al.

Preoperative calcitonin level is a good predictive
indicator in MEN2A patients. Total thyroidectomy with aggressive lymph node dissection should be considered with high preoperative calcitonin level, but the occasional adult MEN2A patient with a normal calcitonin level may not require extensive lymph node dissection and parathyroid removal.

On the other hand, parathyroid management in children and infants with MEN2A might be different. Skinner et al. reported a series of 50 children with MEN2A, all of whom had routine parathyroidectomy and autotransplantation, with central neck dissection [12]. Calcium and vitamin D supplements were required to maintain the serum calcium levels in 3 patients. Hypoparathyroidism is more difficult to manage in children, and may have significant long-term sequelae. If the calcitonin level is normal in children, it is not necessary to do a central neck dissection, and therefore not necessary to perform total parathyroidectomy with autotransplantation. If this prophylactic operation is considered for younger patients (for instance; under 15 years old), the permission of ethical committee is needed.

MEN2A patients have two possible risks concerning parathyroid function till the end of life. One is the occurrence of HPT after thyroid operation for MTC. If the parathyroids preserved in situ become enlarged, reoperation in neck will be necessary. If the transplanted parathyroids become hyperfunctional, they can be removed without morbidity such as recurrent laryngeal nerve injury. Another risk is the recurrence of MTC. If the parathyroids are left in situ, they are likely to be removed at the time of reoperation for MTC, and the patients will consequently suffer from permanent hypoparathyroidism. Our surgical goal is to remove all MTC cells in the neck. If total thyroidectomy and bilateral central neck dissection are indicated, the procedure is to excise all glands, whether enlarged or not, and to immediately autotransplant normal, but not hyperplastic, glands. Transplanted parathyroid tissue is functional for long periods.

In this study, we presented that total parathyroidectomy with parathyroid autotransplantation at the time of primary curative surgery for MTC, such as total thyroidectomy with bilateral central neck dissection, is feasible for the management of possible HPT. Transplanted parathyroid tissue retains long-term functionality.

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