Clinical and endocrinological characteristics of adrenal incidentaloma in Osaka region, Japan

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Abstract. The aim of this study was to investigate the clinical and endocrinological characteristics of adrenal incidentalomas in Osaka region, Japan. The study was a multicenter retrospective analysis of 150 patients with adrenal incidentalomas who underwent radiographic and endocrine evaluations between 2005 and 2013. Most adrenal incidentalomas were discovered by computed tomography (77.0%) and the rest were identified by abdominal ultrasonography (14.6%), magnetic resonance imaging (4.2%), or positron emission tomography (4.2%). Adrenal incidentalomas were more frequently localized on the left side than on the right. The average diameter of tumors was 21 ± 11 mm. On endocrinological evaluation, 14 patients were diagnosed with primary aldosteronism (9.3%), 10 with subclinical Cushing’s syndrome (6.7%), 7 with pheochromocytoma (4.7%), 7 with Cushing’s syndrome (4.7%), 2 with both subclinical Cushing’s syndrome and primary aldosteronism (1.3%), and 110 with non-functioning tumors (73.3%). Patients with functioning tumors were significantly younger and had larger tumor diameters than those with non-functioning tumors. Except for hypertension, complications were comparable between patients with functioning and non-functioning tumors, including the presence of glucose intolerance, cardiovascular disease, and dyslipidemia. In conclusion, a higher prevalence of primary aldosteronism was observed compared with a previous report. Complications were comparable between patients with functioning and non-functioning tumors, including the frequencies of glucose intolerance, cardiovascular disease, and dyslipidemia. Long-term follow-up is required in patients with non-functioning tumors because the frequency of complications, such as glucose intolerance, cardiovascular disease, and dyslipidemia, was equal to that in patients with functioning tumors.

Key words: Adrenal incidentaloma, Cushing’s syndrome, Pheochromocytoma, Primary aldosteronism, Non-functioning tumors
20.0% were pheochromocytomas, and 1.6%–10.0% were associated with primary aldosteronism (PA) [5-9]. In Japan, Ueshiba reported the clinical characteristics of 3329 adrenal incidentalomas observed between 1999 and 2002 [10]. In their study, the prevalence of non-functioning adenomas, cortisol-secreting adenomas (including SCS), pheochromocytomas, and PA were 51.0%, 11.7%, 8.7%, and 4.3%, respectively.

The number of medical checkups is increasing in Japan [11], with abdominal imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) widely used every year. Consequently, the detection of adrenal incidentalomas is expected to increase. Furthermore, the Japan Endocrine Society has provided guidelines for the diagnosis and treatment of PA in 2009 [12], and the aldosterone/renin ratio (ARR) has been identified to be a useful tool for endocrinological evaluation of adrenal incidentalomas. However, no reports have characterized adrenal incidentalomas for recent years in Japan.

We conducted a multicenter retrospective analysis of the clinical and endocrinological characteristics of adrenal incidentalomas in Osaka region between 2005 and 2013.

Materials and Methods

Study design

We included 150 adult patients older than 20 years who were diagnosed with adrenal incidentalomas by CT, abdominal US, MRI, or positron emission tomography (PET), and who underwent biochemical and endocrine evaluation. Imaging procedures were performed for gastrointestinal or urogenital symptoms, general checkups, cancer staging, or preoperative evaluation. Patients were identified from April 1, 2005 to March 31, 2013 from the records of 14 participating hospitals. The following hospitals were included: Ikeda Municipal Hospital, Kansai Rosai Hospital, Kawasaki Hospital, National Hospital Organization Osaka Minami Medical Center, Nishinomiya Municipal Central Hospital, Nissay Hospital, NTT West Osaka Hospital, Osaka Police Hospital, Osaka Rosai Hospital, Osaka University Medical Hospital, Sumitomo Hospital, Osaka General Medical Center, Toyonaka Municipal Hospital, and National Hospital Organization Osaka National Hospital. We retrospectively collected the following data for all patients: age, gender, body mass index (BMI), waist circumference, blood pressure, tumor diameter and location, and medical history and the results of the biochemical examination and endocrinological evaluation of the adrenal mass. The study protocol was approved by the Human Ethics Committee of Osaka University (UMIN no. 000003671) and performed according to the principles of the Helsinki declaration.

Diagnostic criteria

Pheochromocytoma was diagnosed based on the combination of clinical signs and symptoms, elevated plasma catecholamine levels (e.g., epinephrine and norepinephrine), elevated 24-h urinary catecholamine metabolites, the presence of an adrenal mass, and a positive 123I- or 131I-metaiodobenzylguanidine scintigraphy result.

The diagnosis of SCS was made using the diagnostic criteria proposed by the Research Committee for Adrenal Diseases supported by Japanese Ministry of Health, Labor and Welfare [13]. This requires the presence of an adrenal incidentaloma, lack of cushingoid features, and specific laboratory findings, including normal basal serum cortisol levels in the morning, lack of serum cortisol suppression following 1-mg and 8-mg dexamethasone suppression tests (>3.0 μg/dL and >1.0 μg/dL, respectively). In addition, it required at least one of the following endocrine criteria to be met: 1) suppressed plasma ACTH (10 pg/mL) and/or decreased ACTH response after CRH stimulation; 2) loss of diurnal cortisol rhythm; 3) decreased serum dehydroepiandrosterone sulfate (DHEA-S) levels; and 4) unilateral uptake of 131I-adosterol on adrenal scintigraphy.

The diagnosis of Cushing’s syndrome (CS) was required the presence of cushingoid features and an adrenal lesion, with normal or higher serum cortisol levels that lack suppression following 1-mg and 8-mg dexamethasone suppression tests (>5.0 μg/dL for both). Regarding serum cortisol measurement, 5 hospitals were used electrochemiluminescent immunoassay (ECLIA, Roche Diagnostics, Tokyo, Japan) (Analytical sensitivity: 0.018 μg/dL), 8 hospitals were used chemiluminescent immunoassay (CLIA, Beckman Coulter, Inc. Tokyo, Japan) (Analytical sensitivity: 0.4 μg/dL), respectively. In addition, at least one of the following endocrine data needed to be met: 1) suppressed plasma ACTH (10 pg/mL) and/or decreased ACTH response after CRH stimulation; 2) loss of diurnal cortisol rhythm; 3) decreased serum DHEA-S levels; and 4) unilateral uptake of 131I-adosterol on adrenal scintigraphy. In this study, we defined CS and SCS as cor-
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cose intolerance, and cardiovascular disease at rates of 66.2%, 48.9%, 37.3%, and 15.9%, respectively. The most frequent indication for abdominal imaging was general check-up (22.2%), but other common reasons included cancer staging (18.1%), abdominal symptoms (14.6%), respiratory symptoms (10.4%), and preoperative evaluation (2.0%) (Table 2). Adrenal masses were detected by CT in 111 cases (77.0%), by abdominal US in 21 cases (14.6%), by MRI in 6 cases (4.2%), and by PET in 6 cases (4.2%) (Table 3). Although adrenal masses were more likely to be left-sided than right-sided on CT (62.2% vs 37.8%, p < 0.001), left-sided masses were less frequent on abdominal US series (33.6% vs 66.4%, p < 0.001). Tumor diameters did not differ among the imaging techniques.

Endocrinological evaluation was performed in all patients with adrenal incidentalomas. Most patients were diagnosed with non-functioning tumors (n = 110; 73.3%). Of the patients with functioning tumors, 14 cases had PA (9.3%), 10 cases had SCS (6.7%), 7 cases had pheochromocytomas (4.7%), and 7 cases had CS (4.7%), while two patients had both SCS and PA (Table 4). Neither adrenocortical carcinoma nor metastatic adrenal tumor was found in this study. Twenty cases were done surgery (4 cases of non-functioning tumor and 16 cases of functioning tumor). Regarding as non-functioning tumor, 3 cases were diagnosed as myelolipoma and 1 case as cortical adenoma histol-producing tumors.

Before 2009, the diagnosis of PA was made according to the following criteria: plasma aldosterone concentration (PAC) (ng/dL) and plasma rennin activity (ng/mL/h) were measured at the same time to calculate the ARR, with values >20 considered positive. In screening-positive patients, we performed the captopril-challenge test, upright furosemide-loading test, and/or saline-loading test to confirm the diagnosis of PA. After 2009, the diagnosis of PA was made using the guidelines of the Japan Endocrine Society [12]. Glucose intolerance was considered present in patients with an established diagnosis of diabetes mellitus and in those classified as being diabetic-type or borderline-type following a 75-g oral glucose-loading test [14]. Hypertension was defined as follows: a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg at clinic; a systolic blood pressure ≥135 mmHg and/or a diastolic blood pressure ≥85 mmHg at home; a systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg by ambulatory blood pressure monitoring [15]; or when patients took antihypertensive medications. Dyslipidemia was defined as a low-density-lipoprotein cholesterol ≥140 mg/dL, and/or a high-density-lipoprotein cholesterol <40 mg/dL, and/or a triglyceride level ≥150 mg/dL [16], or when patients took antilipidemic medications.

**Statistical analysis**

All data were expressed as mean ± SD or as numbers and percentage. Continuous variables were pairwisely compared between groups by using the Student’s t-test. Categorical variables were analyzed by using the chi-square test. A p-value <0.05 denoted the presence of a statistically significant difference.

**Results**

Table 1 shows the clinical characteristics of patients with adrenal incidentalomas. Of the 150 patients, 52.7% (n = 79) were men. The mean age, BMI, and tumor diameter were 61.9 ± 9.3 years, 24.1 ± 4.1, and 21.1 ± 10.6 mm, respectively, and 6.2% of tumors measured <10 mm. Adrenal incidentalomas were more likely to occur in the left than in the right (57.0% vs 33.6%, p < 0.01), but bilateral masses were observed in 9.4%. Serum fasting glucose and triglyceride levels were 103 ± 23 mg/dL and 116 ± 54 mg/dL, respectively. Patients suffered from hypertension, dyslipidemia, glucose intolerance, and cardiovascular disease at rates of 66.2%, 48.9%, 37.3%, and 15.9%, respectively.

The most frequent indication for abdominal imaging was general check-up (22.2%), but other common reasons included cancer staging (18.1%), abdominal symptoms (14.6%), respiratory symptoms (10.4%), and preoperative evaluation (2.0%) (Table 2). Adrenal masses were detected by CT in 111 cases (77.0%), by abdominal US in 21 cases (14.6%), by MRI in 6 cases (4.2%), and by PET in 6 cases (4.2%) (Table 3). Although adrenal masses were more likely to be left-sided than right-sided on CT (62.2% vs 27.0%, p < 0.001), left-sided masses were less frequent on abdominal US series (25.0% vs 70.0%, p < 0.001). Tumor diameters did not differ among the imaging techniques.

Endocrinological evaluation was performed in all patients with adrenal incidentalomas. Most patients were diagnosed with non-functioning tumors (n = 110; 73.3%). Of the patients with functioning tumors, 14 cases had PA (9.3%), 10 cases had SCS (6.7%), 7 cases had pheochromocytomas (4.7%), and 7 cases had CS (4.7%), while two patients had both SCS and PA (Table 4). Neither adrenocortical carcinoma nor metastatic adrenal tumor was found in this study. Twenty cases were done surgery (4 cases of non-functioning tumor and 16 cases of functioning tumor). Regarding as non-functioning tumor, 3 cases were diagnosed as myelolipoma and 1 case as cortical adenoma histol-producing tumors.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of 150 patients with adrenal incidentalomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>79/71</td>
</tr>
<tr>
<td>Age, year</td>
<td>61.9 ± 9.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.7 ± 12.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1 ± 4.1</td>
</tr>
<tr>
<td>Tumor diameter, mm</td>
<td>21.1 ± 10.6</td>
</tr>
<tr>
<td>Location of the tumor</td>
<td>Right/Left/Bilateral, %</td>
</tr>
<tr>
<td>Concomitant disease, n (%)</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Glucose intolerance</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>22 (15.9%)</td>
</tr>
<tr>
<td>Biochemical data</td>
<td>K, mEq/L</td>
</tr>
<tr>
<td></td>
<td>Creatinine, mg/dL</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose, mg/dL</td>
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<td></td>
<td>Triglyceride, mg/dL</td>
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<td></td>
<td>HDL-cholesterol, mg/dL</td>
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</table>

All data were expressed as mean ± SD or as numbers and percentage.
In patients with cortisol-producing tumors, glucose intolerance was more common than in patients with PA and those with pheochromocytomas (Table 5).

**Discussion**

In the current study, we found that left-sided adrenal incidentalomas were significantly more frequent than right-sided ones. This is consistent with recent reports from Cho et al. (2013) and Kim et al. (2013) who reported that left-sided adrenal incidentalomas occurred at rates of 56.0% and 62.0%, respectively (Table 6) [7, 8]. However, it conflicts with the more previous reports by Mantero et al. (2000) and Kim et al. (2005) in which left-sided adrenal incidentalomas were detected at rates of 30.7% and 31.3%, respectively [5, 9]. These discrepancies might be due to advances in medical imaging technology in recent years. Indeed, Mantero et al. showed that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9]. Consistent with this, we also found that abdominal US detected right-sided tumors more often than left-sided ones (65% vs 26%), whereas CT detected them at similar rates (43% vs 43%); they concluded that abdominal US might be able to visualize the right adrenal gland better than the left [9].
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The prevalence of primary aldosteronism (PA) was much higher than the rate of 4.3% reported in a Japanese survey conducted between 1999 and 2002 [10]. However, Comlekci et al., Cho et al., and Kim et al., each conducted studies at a similar time to ours, identifying PA rates of 4.0%, 1.8%, and 4.6%, respectively (Table 6) [6-8]. Although the precise reason for the high prevalence of PA in our study is unknown, it could be explained by the higher rate of hypertensive patients (66.2%) when compared with previous studies (Table 6). Moreover, 14.6% of patients with hypertension had PA, compared with just 4.1% of patients without hypertension (n = 2). Another reason could be the use of the guidelines for the diagnosis and treatment of PA by the Japan Endocrine Society from 2009 [12], the left adrenal gland.

Table 5 Clinical characteristics of patients with adrenal incidentalomas

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>n (%)</th>
<th>Male (%)</th>
<th>Left (%)</th>
<th>Non-functioning tumor (%)</th>
<th>Functioning tumor (%)</th>
<th>Cortisol Producing tumor (%)</th>
<th>Primary Aldosteronism (%)</th>
<th>Pheochromocytoma (%)</th>
<th>Hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantero [1]</td>
<td>1980–1995</td>
<td>Italy</td>
<td>1004</td>
<td>42.5</td>
<td>30.7</td>
<td>85.0</td>
<td>9.2</td>
<td>1.6</td>
<td>4.2</td>
<td>4.2</td>
<td>41.0</td>
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<tr>
<td>Kim [2]</td>
<td>1992–2003</td>
<td>Korea</td>
<td>80</td>
<td>51.3</td>
<td>31.3</td>
<td>58.8</td>
<td>11.3</td>
<td>10.0</td>
<td>20.0</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Comlekci [3]</td>
<td>2002–2010</td>
<td>Turkey</td>
<td>376</td>
<td>29.3</td>
<td>ND</td>
<td>67.4</td>
<td>14.9</td>
<td>4.0</td>
<td>5.3</td>
<td>54.9</td>
<td></td>
</tr>
<tr>
<td>Cho [4]</td>
<td>2004–2011</td>
<td>Korea</td>
<td>282</td>
<td>61.0</td>
<td>56.0</td>
<td>86.2</td>
<td>9.9</td>
<td>1.8</td>
<td>2.1</td>
<td>38.3</td>
<td></td>
</tr>
<tr>
<td>Kim [5]</td>
<td>2005–2012</td>
<td>Korea</td>
<td>348</td>
<td>44.8</td>
<td>62.0</td>
<td>82.2</td>
<td>6.0</td>
<td>4.6</td>
<td>7.2</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Our study</td>
<td>2005–2013</td>
<td>Japan</td>
<td>150</td>
<td>52.7</td>
<td>57.0</td>
<td>72.4</td>
<td>12.5</td>
<td>10.5</td>
<td>4.6</td>
<td>66.2</td>
<td></td>
</tr>
</tbody>
</table>

ND, not described. All data were expressed as numbers or percentage. *p < 0.05, †p < 0.01 vs. Non-functioning tumor, ‡p < 0.05, §p < 0.01 vs. PA; ††p < 0.05, ‡‡p < 0.01 vs. cortisol-producing tumor.

Table 6 Comparison of previous studies of adrenal incidentaloma with our study

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>n (%)</th>
<th>Male (%)</th>
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<th>Non-functioning tumor (%)</th>
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<th>Pheochromocytoma (%)</th>
<th>Hypertension (%)</th>
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<tr>
<td>Comlekci et al.</td>
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<td>14.9</td>
<td>4.0</td>
<td>5.3</td>
<td>54.9</td>
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</table>
which sets the screening criterion for ARR at 20. Given this is lower than the level used in other countries, we might have been more likely to identify candidates for PA, even when the PAC was in the normal range.

Excluding hypertension, complications were comparable between the functioning and non-functioning tumors, including the rates of glucose intolerance, cardiovascular disease, and dyslipidemia (Table 5). Recently, it has been reported that non-functioning tumors are complicated by glucose intolerance, hypertension, and the metabolic syndrome [25, 26]. In addition, Midorikawa et al. [25] documented that several complications of non-functioning tumors could be improved by adrenalectomy and another study reported that blood pressure and carotid intima-media thickness were significantly higher in patients with non-functioning tumors than in age-matched healthy controls [27]. These results indicate that non-functioning tumors warrant long-term clinical follow-up.

The limitation of this study was that the two kinds of serum cortisol assay system which have the different analytical sensitivities were used among the participating hospitals. And only 20 cases were done surgery in this study. This result revealed that most patients were diagnosed by clinical but not pathological evaluation.

In conclusion, we investigated the clinical and endocrinological characteristics of 150 patients with adrenal incidentalomas in Osaka region, Japan. Interestingly, we found a higher prevalence of PA than the previous report on patients with adrenal incidentaloma in Japan by Ueshiba in 2006 [10] and also found that complication rates were comparable between patients with functioning and non-functioning tumors. We propose the need for long-term follow-up of patients with non-functioning tumors.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this study.

**References**

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