ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2024.106.1.38
Annals of Surgical Treatment and Research

# Silent pheochromocytoma in adrenal incidentaloma: unveiling clinical and radiological characteristics

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**Purpose:** Silent pheochromocytoma refers to tumors without signs and symptoms of catecholamine excess. This study aimed to clarify the clinical, radiological characteristics, and perioperative features of silent pheochromocytomas diagnosed after adrenalectomy for adrenal incidentaloma.
**Methods:** Medical records of patients who underwent adrenalectomy for adrenal incidentaloma and were subsequently diagnosed with silent pheochromocytoma between January 2000 and December 2020 were retrospectively reviewed for demographic, diagnostic, surgical, and pathological findings.
**Results:** Of the 130 patients who underwent adrenalectomy for incidentaloma, 8 (6.1%) were diagnosed with silent pheochromocytoma. Almost all patients had no hypertensive symptoms and their baseline hormonal levels remained within normal ranges. All patients exhibited tumor size >4 cm, precontrast Hounsfield unit >10, and absolute washout <60%. Intraoperative hypertensive events were noted in 2 patients (25.0%) in whom antiadrenergic medications were not administered. All patients in the intraoperative hypertensive event group exhibited atypical features on CT, whereas 83.3% of patients in the non-intraoperative hypertensive event group showed atypical features on CT imaging.
**Conclusion:** Silent pheochromocytomas share radiological traits with malignant adrenal tumors. Suspicious features on CT scans warrant surgical consideration for appropriate treatment. Administering alpha-blockers can enhance hemodynamic stability during adrenalectomy in suspected silent pheochromocytoma cases.
**[Ann Surg Treat Res 2024;106(1):38-44]**

**Key Words:** Adrenalectomy, Adrenal incidentaloma, Computed tomography, Hypertensive, Pheochromocytoma

## INTRODUCTION

Pheochromocytoma is a rare tumor originating from chromaffin cells of the adrenal medulla secreting catecholamines [1]. These secretions induce secondary hypertension and account for 0.2%–0.6% of all hypertension cases in the community [2]. Most patients with pheochromocytoma display benign characteristics, with 10%–15% exhibiting malignant features [3].

In more than half of pheochromocytoma cases, elevated blood pressure (BP) is primarily linked to norepinephrine secretion [4,5]. The typical symptoms of pheochromocytoma are headache, heart palpitations, anxiety, and profuse sweating. Diagnosis typically begins when a patient exhibits hemodynamic instability, followed by biochemical testing and abdominal imaging. However, some patients with pheochromocytomas remain asymptomatic. These cases were associated with adrenal incidentalomas. Adrenal incidentalomas may be detected when abdominal imaging is

**Received** October 13, 2023, **Revised** October 28, 2023, **Accepted** November 1, 2023

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performed to evaluate abdominal pain or as a health checkup [6]. These patients may present with atypical tumor features of the adrenal gland detected via CT; in the final diagnosis, pheochromocytoma may occur after surgery [7]. The term silent pheochromocytoma refers to such patients [8]. Therefore, the diagnosis of silent pheochromocytomas is challenging.

Silent pheochromocytoma accounts for approximately 20%–30% of clinically detected adrenal pheochromocytomas [9]. Although patients with silent pheochromocytoma usually remain asymptomatic, a hypertensive crisis can occur. Such a crisis has been reported in several studies in which a patient with an adrenal incidentaloma experienced hemodynamic instability during surgery performed for other abdominal diseases or when a patient underwent adrenalectomy to resect an adrenal incidentaloma [8,10-13]. Furthermore, surgery is the standard therapy for silent pheochromocytomas to achieve the curative treatment [14]. Although silent pheochromocytomas have been reported as individual cases, their clinical and radiological characteristics have not been well described [8,13,15,16].

This study aimed to clarify the clinical, radiological, and perioperative features of silent pheochromocytomas diagnosed after adrenalectomy for adrenal incidentaloma.

## METHODS

This study was approved by the Institutional Review Board of the Asan Medical Center (No. 2022-1603). The need for informed consent from patients was waived owing to the retrospective nature of the study.

### Study design and population

This was a retrospective study involving patients who underwent adrenalectomy for adrenal incidentaloma at a tertiary medical center between January 2000 and December 2020. A total of 744 asymptomatic patients with normal baseline biochemical assessment were diagnosed with nonfunctioning adrenal incidentaloma, of whom 130 underwent adrenalectomy during the study period. In the final pathology, 8 patients (6.1%) were diagnosed with pheochromocytoma postoperatively. Data were collected from a clinical records database. All 8 patients underwent adrenal CT with contrast and baseline hormonal assessments.

### Diagnostic work-up and associated variables

Data regarding patient age, sex, weight, height, body mass index (BMI), preoperative BP, preoperative use of antihypertensive medications, and underlying diseases were collected. We collected CT scan data, including the reason for performing the adrenal CT scan, tumor size, precontrast Hounsfield unit (HU) value, absolute washout, relative washout, and atypical features. Either laparoscopic retroperitoneal or robot-assisted retroperitoneal approach was chosen according to the surgeon's preference. Additionally, the occurrence of intraoperative hypertensive events during surgery, and the highest BP at which the hemodynamic events occurred were recorded. In the postoperative pathology report, the final diagnosis and Pheochromocytoma of the Adrenal gland Scaled Score (PASS) were confirmed [17].

Similar to other studies evaluating the malignant potential of various adrenal tumors, the washout value in CT scans was calculated by measuring the attenuation (HU) of the tumor on precontrast, portal venous phase, and delayed phase images [18-20]. The potential malignant features of CT include precontrast HU >10, absolute washout <60%, and relative washout <40%. The atypical features on CT included calcification, heterogeneous enhancement, fat-containing areas, overall cystic appearance, internal cystic portions, and irregular shape. The PASS was obtained by evaluating various histological features of the tumor, including the cell type, growth pattern, and other characteristics. In cases where the PASS is 4 or higher, it is considered potentially malignant [17]. In addition, the patients were divided into 2 groups according to whether they experienced an intraoperative hypertensive event. An intraoperative hypertensive event was defined as a systolic BP exceeding 160 mmHg at any point during adrenalectomy.

### Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 26 (IBM Corp.). Continuous variables were reported as mean ± standard deviation and compared by the Mann-Whitney U-test. The Fisher exact test and chi-square test were used for categorical variables. Statistical significance was set at $P < 0.05$.

## RESULTS

### Baseline characteristics

The clinical characteristics of the 8 patients with pheochromocytomas are shown in Table 1. Two patients experienced hypertensive events during adrenalectomy. The mean age was 58 years and 5 patients (62.5%) were female. One patient presented with intermittent headaches during the preoperative evaluation, which subsided before the day of the operation. No patients exhibited catecholamine-related clinical symptoms. The mean preoperative systolic and diastolic BP were 112 and 71 mmHg, respectively. However, 3 patients (37.5%) were taking antihypertensive medications at the time of the hospital visit, including calcium channel blockers and/or angiotensin II receptor blockers. Before surgery, the patient who had intermittent headaches received an alpha-1 blocker. There was no significant difference in preoperative BP between the

**Table 1.** Clinical characteristics of patients

| Characteristic | Total | Intraoperative hypertensive event | | P-value |
|---|---|---|---|---|
| | | Yes | No | |
| No. of patients | 8 | 2 | 6 | |
| Age (yr) | 58.3 ± 5.5 | 58.5 ± 3.5 | 58.3 ± 13.6 | >0.999 |
| Sex | | | | 0.673 |
| Male | 3 (37.5) | 1 (50.0) | 2 (33.3) | |
| Female | 5 (62.5) | 1 (50.0) | 4 (66.7) | |
| Weight (kg) | 62.7 ± 12.7 | 75.4 ± 7.9 | 58.4 ± 11.4 | 0.143 |
| Height (cm) | 159.4 ± 6.9 | 158.1 ± 5.5 | 159.9 ± 7.7 | >0.999 |
| Body mass indes (kg/m$^2$) | 26.2 ± 3.3 | 30.3 ± 5.5 | 22.9 ± 3.0 | 0.143 |
| Preoperative symptoms | | | | |
| Headache | 1 (12.5) | 0 (0) | 1 (16.7) | NA |
| Preoperative BP (mmHg) | | | | |
| Systolic | 112.1 ± 18.3 | 117.0 ± 15.5 | 110.5 ± 20.1 | 0.429 |
| Diastolic | 71.5 ± 7.2 | 73.5 ± 2.1 | 70.8 ± 8.3 | 0.286 |
| Underlying hypertension disease with antihypertensive medication | 3 (37.5) | 1 (50.0) | 2 (33.3) | 0.673 |
| Preoperative alpha-1 blocker | | | | >0.999 |
| Yes | 1 (12.5) | 0 (0) | 1 (16.7) | NA |
| Biochemical result | | | | |
| Serum metanephrine (nmol/L)[a] | 0.1 ± 0.0 | 0.2 ± 0.1 | 0.1 ± 0.0 | 0.429 |
| Serum normetanephrine (nmol/L)[b] | 0.5 ± 0.2 | 0.6 ± 0.2 | 0.9 ± 0.3 | 0.429 |
| Reason for CT scan | | | | 0.676 |
| General health checkup | 3 (37.5) | 1 (50.0) | 2 (33.3) | |
| Work-up for other diseases | 5 (62.5) | 1 (50.0) | 4 (66.7) | |
| Side of tumor | | | | 0.206 |
| Right | 3 (37.5) | 0 (0) | 3 (50.0) | |
| Left | 5 (62.5) | 2 (100) | 3 (50.0) | |
| Reason for operation | | | | >0.999 |
| Size ≥ 4cm on CT scan | 8 (100) | 2 (100) | 6 (100) | |
| Atypical features on CT scan | 7 (87.5) | 2 (100) | 5 (83.3) | |
| Operation type | | | | 0.346 |
| Laparoscopic RA | 6 (75.0) | 1 (50.0) | 5 (83.3) | |
| Robot-assisted RA | 2 (25.0) | 1 (50.0) | 1 (16.7) | |
| PASS | 5.6 ± 2.1 | 7.0 ± 2.8 | 5.1 ± 1.9 | 0.286 |

Values are presented as number only, mean ± standard deviation, or number (%).
BMI, body mass index; BP, blood pressure; PASS, pheochromocytoma of the adrenal gland scaled score; NA, not applicable; RA, retroperitoneal adrenalectomy.
[a]Reference range <0.5, [b]reference range <0.9.

intraoperative hypertensive event and no-event groups (P > 0.05).

The mean serum metanephrine and normetanephrine were 0.1 and 0.5 nmol/L, respectively. CT scans were performed in 3 patients (37.5%) as part of a general health checkup, while 5 patients (62.5%) underwent CT scans for workups related to other medical conditions. The tumor was on the right side in 3 patients (37.5%) and on the left side in 5 patients (62.5%), with no bilateral lesions observed.

Size variable was the main reason for performing surgery in patients with adrenal incidentalomas. All patients who underwent adrenalectomy had a tumor size ≥4 cm. Furthermore, all patients in the intraoperative hypertensive event group exhibited atypical features on CT, whereas only 83.3% of patients in the non-intraoperative hypertensive event group showed atypical features on CT scans. Six patients (75.0%) underwent laparoscopic retroperitoneal adrenalectomy and 2 (25.0%) underwent robot-assisted retroperitoneal adrenalectomy.

The mean PASS was 5.6. Although the difference was not statistically significant, the intraoperative hypertensive event group exhibited higher values compared to those of the group without intraoperative hypertensive events (7.0 *vs.* 5.1, respectively; P = 0.286).

## Malignant potential features of CT scan

All patients underwent preoperative adrenal CT. The

**Table 2.** Preoperative adrenal CT scan features

| CT scan features | Total (n = 8) | Intraoperative hypertensive event | | P-value |
|---|---|---|---|---|
| | | Yes (n = 2) | No (n = 6) | |
| Tumor size (cm) | 4.5 ± 2.2 | 4.75 ± 0.0 | 5.6 ± 1.1 | 0.286 |
| ≥4 | 8 (100) | 2 (100) | 6 (100) | |
| Precontrast HU | 24.8 ± 36.8 | 29.6 ± 2.1 | 32.4 ± 11.8 | >0.999 |
| >10 | 8 (100) | 2 (100) | 6 (100) | |
| Absolute washout (%) | 29.0 ± 21.7 | 30.8 ± 38.3 | 28.4 ± 19.1 | >0.999 |
| <60 | 8 (100) | 2 (100) | 6 (100) | |
| Relative washout (%) | 17.7 ± 16.7 | 24.9 ± 31.5 | 15.3 ± 12.8 | 0.857 |
| <40 | 7 (87.5) | 1 (50.0) | 6 (100) | |
| Atypical features | | | | |
| Calcification | 0 (0) | 0 (0) | 0 (0) | |
| Heterogenous enhancement | 4 (50.0) | 2 (100) | 2 (33.3) | 0.429 |
| Fat-containing | 0 (0) | 0 (0) | 0 (0) | |
| Overall cystic | 2 (25.0) | 0 (0) | 2 (33.3) | >0.999 |
| Internal cystic portion | 2 (25.0) | 0 (0) | 2 (33.3) | >0.999 |
| Irregular shape | 3 (37.5) | 2 (100) | 1 (16.7) | 0.035 |

Values are presented as mean ± standard deviation or number (%).
HU, Hounsfield units.

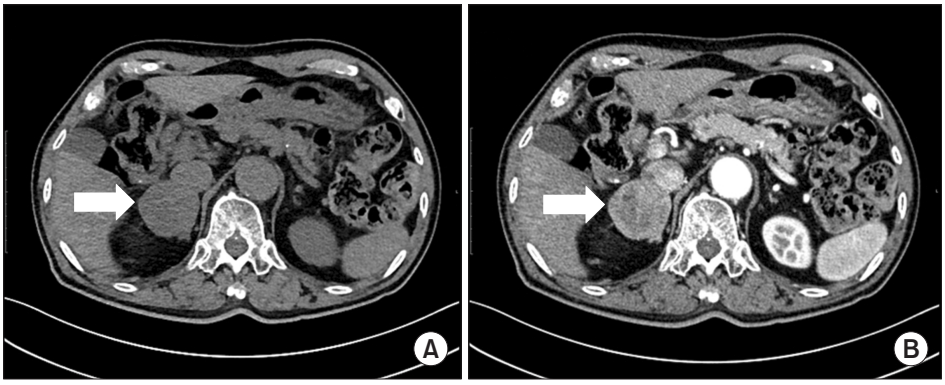


**Fig. 1.** (A) Precontrast image of the adrenal CT presenting the right adrenal tumor (arrow). (B) Postcontrast image of adrenal CT presenting an irregular shape and heterogeneous enhancement (arrow) of the same right adrenal tumor.

characteristics of the CT scan results are shown in Table 2. The mean tumor size was 4.5 cm, and all patients had tumors ≥4 cm. The mean precontrast HU was 24.8, which was above 10 for all patients, and correlated with features of malignant potential. All patients exhibited an absolute washout of <60% (100%), and a relative washout of <40% was observed in 87.5% of patients. Heterogeneous enhancement was observed in 4 patients (50.0%), and all patients in the intraoperative hypertensive event group exhibited this characteristic. Three patients (37.5%) exhibited an irregular shape, and this feature was observed in all patients in the intraoperative hypertensive event group, demonstrating a statistically significant difference compared with the group without intraoperative hypertensive events (100% *vs.* 16.7%, respectively; P = 0.035). The atypical features on the CT scans are shown in Fig. 1.

Among the patients, 1 had intermittent headaches, took alpha-blockers before adrenalectomy, and did not experience an intraoperative hypertensive event. Two patients who experienced an intraoperative hypertensive event had a sudden rise in BP, with peak systolic and diastolic BP reaching 170/90 mmHg and 180/100 mmHg, respectively (Table 3). Hemodynamic instability, with the highest BP increase, was observed when traction was applied to the tumor during periadrenal soft tissue dissection before adrenal vein ligation in patients 4 and 5. One patient who experienced intraoperative hypertensive events had the longest preoperative hypertensive medication duration of 120 months. Overall, age, tumor size, and underlying hypertension with antihypertensive medication were not predictive factors of silent pheochromocytoma. However, CT findings were strongly related to malignant potential features.

**Table 3.** Potential preoperative and intraoperative features of patients for the evaluation of silent pheochromocytomas prior to surgery

| Patient No. | Age (yr) | Tumor size on CT (cm) | Precontrast HU | Absolute washout (%) | Relative washout (%) | Underlying hypertension with antihypertensive medication | Duration of medication (mo) | Preoperative alpha-1 blocker therapy | Intraoperative hypertensive event | Highest SBP/DBP during operation (mmHg) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | 6.5 | 19.3 | 32.1 | 20.7 | × | NA | ○ | × | NA |
| 2 | 59 | 5.2 | 41.8 | 37.7 | 12.6 | CCB | 24 | × | × | NA |
| 3 | 59 | 4.1 | 30.5 | 4.3 | 1.1 | × | NA | × | × | NA |
| 4 | 56 | 4.7 | 28.1 | 3.7 | 2.5 | × | NA | × | ○ | 170/90 |
| 5 | 61 | 4.8 | 31.2 | 57.9 | 47.2 | CCB + ARB | 120 | × | ○ | 180/100 |
| 6 | 60 | 6.0 | 22.7 | 53.8 | 36.6 | × | NA | × | × | NA |
| 7 | 35 | 7.3 | 50.9 | 35.7 | 16.8 | × | NA | × | × | NA |
| 8 | 78 | 4.8 | 29.7 | 7.0 | 3.9 | CCB + ARB | 3 | × | × | NA |

HU, Hounsfield unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker.

## DISCUSSION

In the present study, we confirmed that silent pheochromocytoma was rare among 130 patients who underwent adrenalectomy for adrenal incidentaloma, as it was found in only 8 cases (6.1%). Most patients did not exhibit catecholamine-related symptoms preoperatively and showed normal BP and baseline hormone levels. Three patients had controlled hypertension and were taking antihypertensive medications for an underlying condition. However, this condition was not related to intraoperative hypertensive events, except in 1 patient who had been taking such medication for more than 10 years. The average PASS was 5.6, indicating a potential malignancy. According to the CT scan results, all patients had a tumor size >4 cm, precontrast HU values >10, and absolute washout <60%, indicating a suspicious malignant tumor. Half of the patients had heterogeneous enhancement, 37.5% of the patients had irregular shapes on CT scans, and all patients who experienced intraoperative hypertensive events had these features [19].

Patients with pheochromocytomas usually present with signs and symptoms of sympathetic overstimulation, such as high BP, palpitation, and headaches [21,22]. However, approximately 20%–30% of adrenal pheochromocytomas are asymptomatic, and their baseline hormonal levels are within the normal range [8,10,12,13]. Li et al. [8] and El-Doueihi et al. [13] reported on patients who were diagnosed with pheochromocytoma after adrenalectomy despite the absence of hypertensive symptoms and normal baseline hormonal levels. Similarly, in the present study, baseline hormonal levels were normal in all patients.

Hypertensive crisis has been reported to develop even in cases of silent pheochromocytoma surgery when alpha-blockers are not administrated [13,23]. In the present study, 2 patients (25.0%) who experienced an intraoperative hypertensive event experienced a sudden rise in BP during dissection of the adrenal mass. One patient who had an intermittent headache and was prescribed an alpha-1 blocker before adrenalectomy did not experience intraoperative hypertensive events.

In 2021, a treatment algorithm and imaging features for patients with adrenal incidentalomas were published [19]. On the CT scan, adrenal tumors >4 cm in size, precontrast HU >10, and contrast washout <40%–60% were described as having a suspicious malignant appearance. The imaging features of pheochromocytomas include smooth margins, round or oval shapes, heterogeneous enhancement, precontrast HU >10, and slow washout. In the case of adrenocortical carcinoma or metastasis, the main differences lie in the irregular margin and shape, whereas other features are nearly identical to those of pheochromocytoma. Kota et al. [24] described silent pheochromocytoma as a heterogeneous enhancing mass lesion measuring 7.6 cm in size with an attenuation score of 35 HU without any calcification. In the present study, all patients exhibited a tumor size >4 cm, precontrast HU >10, and absolute washout <60%. Except for 1 patient, the remaining patients had a relative washout of <40%. Furthermore, heterogeneous enhancement and irregular shapes were observed in 50% and 37.5% of the patients, respectively. These imaging features raised the suspicion of malignancy, indicating the possibility of pheochromocytomas, adrenocortical carcinomas, or metastases. This suggests that even if the baseline hormonal levels are normal, the suspicion of malignancy on CT scan should prompt consideration of the possibility of silent pheochromocytoma and provide patients with a chance for curative treatment.

Thompson [17] described the PASS scoring system, relying on different histopathological features, as a tool to distinguish pheochromocytomas with the potential for aggressive behavior. The scoring system distinguishes tumors with a potential for biologically aggressive behavior (PASS, ≥4) from tumors

that behave in a benign manner (PASS, <4). However, there are conflicting studies regarding the ability of the PASS to distinguish aggressive potential [25]. While no patient had tumors invading the surrounding tissues, metastasis, or recurrence, the patient who experienced an intraoperative hypertensive event had a PASS of 9, which was the highest among the patients in the present study.

This study had several limitations. First, this was a retrospective study, and a selection bias may have occurred. Second, the sample size was small, which can reduce the statistical reliability of the findings and make it challenging to generalize the results. Considering these limitations, future studies should aim for larger sample sizes to enhance the generalizability of the results. Third, this study was conducted at a single tertiary center, which may also include selection bias.

In conclusion, asymptomatic silent pheochromocytomas are rare tumors that are difficult to diagnose preoperatively. However, it is associated with the radiological characteristics of malignant adrenal tumors. When an adrenal incidentaloma exhibits suspicious malignant features on a CT scan, surgery should be considered to provide appropriate treatment. When silent pheochromocytoma is suspected, the patient may achieve hemodynamic stability during adrenalectomy if the administration of alpha-blockers is considered. Finally, silent pheochromocytomas should be considered when evaluating adrenal incidentalomas to provide adequate treatment for such patients.

## ACKNOWLEDGEMENTS

### Fund/Grant Support

None.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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