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Isolated Synchronous Adrenal Lesions in Patients with Newly Diagnosed Extra-Adrenal Malignancies

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Background: This study focused on the etiology of patients with extra-adrenal primary malignancy in addition to isolated synchronous adrenal incidentalomas.

Methods: Patients who were diagnosed as extra-adrenal primary malignancy and synchronous adrenal incidentalomas were enrolled from a single tertiary medical center from 2004 to 2014. Those with a history of malignancy or any extra-adrenal metastases at the time of diagnosis were excluded. Statistical analysis was performed to determine possible predictors for adrenal metastases.

Results: The primary malignancies of hepatocellular carcinoma and lung cancer had higher rates of adrenal metastases than colon cancer and renal cell carcinoma. Significant predictors for adrenal metastasis were clinical T stage and adrenal mass diameters. Patients with stage T1/2 primary malignancies were more likely to have benign adrenal tumors than those with stage T3 or T4. The average adrenal mass diameters in the benign and metastatic groups were 2.87 and 4.97 cm, respectively ($P = 0.001$).

Conclusions: Nearly 40% of the isolated synchronous adrenal incidentalomas in patients with newly diagnosed extra-adrenal malignancies proved to be metastases. In patients with large adrenal lesions, high mass density on computed tomography scans, or a primary malignancy at a high clinical T stage, the risk of adrenal metastasis was high.

Key words: Adrenal incidentaloma – Adrenal metastasis – Adrenal tumor – Extra-adrenal malignancy

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Tumors found in the adrenal glands are commonly discovered as incidentalomas, which are defined as previously unsuspected adrenal masses with diameters ≥1 cm discovered during chest or abdomen imaging examinations.[1–4] Adrenal incidentalomas are now being discovered with greater frequency because of the increased use and improved quality of cross-sectional imaging.[5] Indeed, they are discerned in approximately 3.4% of computed tomography (CT) scans.[4]

Adrenal incidentalomas can be classified as benign or malignant on the basis of pathology, or they may be classified as hormonally active or inactive on the basis of endocrine characteristics. In most cases, adrenal incidentalomas are benign adenomas.[6] Benign adenomas and nodular adrenocortical hyperplasia together comprise 80% of adrenal incidentalomas. The incidence rate of adrenocortical carcinoma is estimated to be 5%, and pheochromocytomas constitute approximately 5% and metastases constitute approximately 2%.[7–9]

Because of their rich vascularity, the adrenal glands are a common site of metastases. In 1 autopsy review of 1000 patients with malignancy, metastases to the adrenal glands were discovered in 27% of patients. Among the primary malignancy sites, lung and breast cancers have been found to account for approximately 39% and 35% of adrenal metastases, respectively.[10,11] Because of the high incidence of malignant metastasis from other primary sites, it has been estimated that in patients with a history of previous malignancy, over 50% of newly discovered adrenal lesions are metastatic.[12,13]

After reviewing relevant literature published over the last few decades, we discovered that only a few articles discussed metastasis in the adrenal glands despite the high incidence of adrenal metastasis from other primary malignancies. In addition, most of the articles concerning adrenal metastasis focused on patients with primary malignancy and diagnosed adrenal metastasis or patients with adrenal incidentalomas and a history of extra-adrenal malignancy.[12–14]

To the best of our knowledge, this is the first article to discuss patients who exhibited extra-adrenal primary malignancy and synchronous adrenal incidentalomas and denied any other suspicious metastatic lesion at the time of diagnosis. In this article, we also discuss possible predictors for adrenal metastatic lesions.

Materials and Methods

Study design

A retrospective chart review was conducted that included all patients diagnosed with primary extra-adrenal malignancy and co-existent isolated adrenal incidentalomas in a tertiary urology department from January 2004 through October 2015. All patients were treated with radical resection of the primary malignancy and a simultaneous adrenalectomy for the isolated adrenal mass. The surgeons decided whether to perform an open laparotomy for the adrenalectomy or a laparoscopic adrenalectomy on the basis of the patient's clinical condition. Patients with either a history of malignancy or any metastatic lesion except at the adrenal glands were excluded. Patients in an immunosuppressed condition, such as those receiving an immunosuppressant following organ transplantation or having a hereditary disease related to malignancy, were also excluded. Patients with direct invasion of the adrenal glands by primary malignancies were excluded, and patients with suspicious distant metastatic lesions in addition to adrenal lesions were also excluded.

The Institutional Review Board of Linkou Chang Gung Memorial Hospital approved this retrospective review study.

Variables collected included patient characteristics [age, sex, American Society of Anesthesiologists (ASA) score, body weight, body height, body mass index, and Eastern Cooperative Oncology Group (ECOG) performance status], tumor-related data [primary tumor, adrenal lesion size, Hounsfield units (HUs) on computed tomography (CT) scan, laterality, pathology of primary malignancy and adrenal lesions, and American Joint Committee on Cancer (AJCC) staging], and endocrine-related lab data (electrolyte, cortisol, and aldosterone). We also collected data concerning perioperative complications and steroid replacement therapy after adrenalectomies. All the data were collected retrospectively through review of medical charts. Because it is not routinely used, positron emission tomography (PET) scans were not performed in most of the patients in this study.

Statistical Analysis

Mean and SD were reported for continuous variables and proportions for qualitative and categorical variables. Groups were compared using the chi-square test for discrete variables and the indepen-

dent sample t test for continuous variables. Statistical assessments were considered significant when $P < 0.05$. The statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois).

Results

In total, 49 patients who were diagnosed with extra-adrenal malignancy and co-existent adrenal incidentalomas were included. All patients received radical surgery to remove the primary malignancy and a radical adrenalectomy for incidentalomas simultaneously. Patient characteristics are listed in Table 1.

Study participants included 34 male and 15 female patients for a male to female ratio of 2:3. Mean patient age was 60.5 ± 11.4 years. The ECOG performance status and ASA scores of the patients were usually 0/1 and 2/3, respectively.

Most patients exhibited normal serum sodium, potassium, cortisol, and aldosterone levels in endocrine laboratory data. No patients suffered from clinical symptoms related to adrenal insufficiency. Only 1 patient had hypercortisolemia (serum 8AM cortisol level, 145.0 μg/dL), and the final pathology report concerning the adrenal glands indicated functional macronodular hyperplasia.

Among all the cases, disease stages T1, T2, T3, and T4 (AJCC cancer staging 7th edition) accounted for 12 (24.5%), 12 (24.5%), 18 (36.7%), and 7 (14.3%) of the tumors, respectively, based on the pathological stage of the primary tumor. In the pathologic findings, primary malignancy was defined as adenocarcinoma, carcinoma, and stromal tumor; these 3 pathologic types accounted for 40.8%, 55.1%, and 4.1%, respectively.

Among the patients in this study, a total of 2 perioperative complications occurred. One patient suffered from suture needle migration to the chest cavity, which required a chest surgeon to locate and remove the needle. Another patient developed postoperative sepsis and was admitted to the intensive care unit. No stroke, cardiovascular event, major bleeding, hypertensive crisis, or other complication was noted.

Among the 2 patients who required steroid replacement therapy after the operation because of Addison's disease, one had previously undergone a contralateral adrenalectomy because of a benign tumor and the other had T2 gastric cancer with a left adrenal adenoma.

The kidney, colon, liver, and lung were the four most frequent origin sites for primary malignancy with synchronous adrenal incidentalomas. The ratio of adrenal metastasis was higher in hepatocellular carcinoma and lung cancer than renal cell carcinoma and colon cancer (85.7%, 66.7%, 33.3%, and 36.4%, respectively). The number of patients in each category of primary malignancy sites and the proportions of metastasis are displayed in Fig. 1. The detailed pathologic results for adrenal incidentalomas from various origins of primary malignancy are listed in Table 2. In addition to distant metastasis of primary malignancies, other adrenal benign lesions included cortical adenoma, cortical hyperplasia, ganglioneuroma, and pheochromocytoma.

The metastasis and nonmetastasis groups were compared, and the results are presented in Table 3. The longest diameter of adrenal lesion measured by CT scan was significantly longer in the metastasis

Table 1 Patient characteristics

Total patient number	49
Male	34
Female	15
Mean patient age (range)	60.5 ± 11.0 (26–79) years old
Mean ECOG status	
0	27 (55.1%)
1	21 (42.9%)
2	1 (2.0%)
Mean ASA score	
2	16 (32.7%)
3	33 (67.3%)
Lab data	
Serum sodium	140.2 ± 3.3 (131.0–148.0) mmol/L
Serum potassium	4.1 ± 0.4 (3.4–5.9) mmol/L
Serum aldosterone	139.5 ± 131.8 (13.7–531.0) pg/mL
Primary malignancy T stage	
T1	12 (24.5%)
T2	12 (24.5%)
T3	18 (36.7%)
T4	7 (14.3%)
Pathology of primary tumor	
Adenocarcinoma	20 (40.8%)
Carcinoma	27 (55.1%)
Stroma tumor	2 (4.1%)
Average of largest adrenal diameter	3.8 ± 2.29 (1.0–11.4) centimeter
Pathology of adrenal mass	
Benign lesions	29 (59.2%)
Metastatic tumors	20 (40.8%)
Peri-operative complication	
Postoperative septic shock	1
Needle migration during operation	1
Post-OP steroid replacement treatment	2

ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

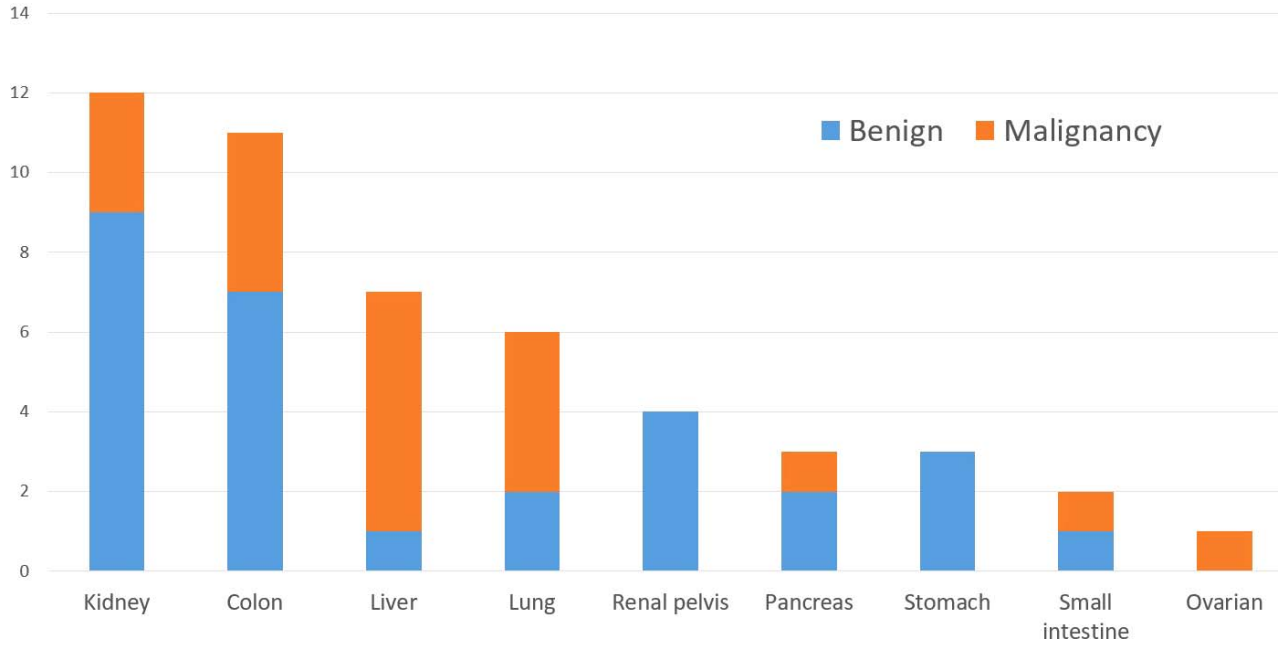

Fig. 1 The number of patients in each category of primary malignancy sites and the proportions of metastasis.

group than in the nonmetastasis group (4.97 ± 2.7 cm versus 2.87 ± 1.4 cm, $P = 0.001$). Additionally, more patients were in the T3 and T4 stages in the metastasis group than in the nonmetastasis group ($P = 0.027$). The HUs of metastatic adrenal lesions on noncontrast phase CT scans were significantly higher than the HUs in the nonmetastasis group (35.2 versus 13.3, P value < 0.001). Metastatic adrenal lesions seemed to have higher HUs in the venous phase and delay phase, and lower relative washout, but did not reach statistical significance. No significant differences existed between the 2 groups with respect to age, sex, or pathologic type of primary cancer.

Discussion

In our study, we analyzed patients with diagnoses of primary extra-adrenal malignancy and a synchronous adrenal incidentaloma who denied a history of malignancy or any extra-adrenal metastasis at the time of diagnosis. Of the 49 patients enrolled in the study, adrenal metastatic malignancy was exhibited in 20 (40.8%) patients. This study only included patients with isolated synchronous adrenal mass lesions, and those with extra-adrenal metastasis or a history of malignancy were excluded; consequently, the adrenal metastasis percentage differs from other studies that did not exclude the same categories of patients.

In another study, the overall adrenal metastasis rate in patients with malignancy was nearly 27%, determined on the basis of an autopsy review.[10] According to other published literature, adrenal metastases occur in up to 40% to 50% of patients with liver or renal cell cancers, and 25% of patients with melanoma or lung cancer may have adrenal metastasis. Lung and breast cancer have the most adrenal metastases compared with other malignancies, accounting for approximately 39% and 35% of adrenal metastases, respectively.[10,11]

One study of patients with a history of—or synchronous—extra-adrenal malignancy determined that 52% of adrenal incidentalomas were adrenal metastases; however, 36% of patients in this study had extra-adrenal distant metastatic disease identified either concurrently or before their adrenal metastasis.[12] One study discovered that up to 71% of adrenal incidentalomas in patients with previous extra-adrenal malignancy were metastatic lesions.[13] This study also reported that 89% of adrenal masses in patients with a current or prior history of renal cell carcinoma were adrenal metastases compared with 40% to 57% of those with a current or prior history of melanoma, colorectal cancer, prostate cancer, or non-small cell lung cancer.

Among the various primary malignancies in our study, patients with hepatocellular carcinomas or lung cancers were the most likely to have metastatic adrenal lesions if synchronous adrenal incidentalo-

Table 2 Pathology of adrenal lesions categorized by primary malignancy site

Colon	11
Cortical adenoma	4 (36.4%)
Cortical hyperplasia	1 (9.1%)
Ganglioneuroma	1 (9.1%)
Pheochromocytoma	1 (9.1%)
Metastatic tumor	4 (36.4%)
Liver	7
Pheochromocytoma	1 (14.3%)
Metastatic tumor	6 (85.7%)
Lung	6
Cortical hyperplasia	1 (16.7%)
Cortical adenoma	1 (16.7%)
Metastatic tumor	4 (66.7%)
Ovarian	1
Metastatic tumor	1 (100.0%)
Pancreas	3
Cortical adenoma	2 (66.7%)
Metastatic tumor	1 (33.3%)
Kidney	12
Cortical adenoma	7 (58.3%)
Cortical hyperplasia	2 (16.7%)
Metastatic tumor	3 (25.0%)
Renal pelvis	4
Cortical adenoma	2 (40%)
Cortical hyperplasia	2 (40%)
Metastatic tumor	0 (0%)
Small intestine	2
Pheochromocytoma	1 (50%)
Metastatic tumor	1 (50%)
Stomach	3
Cortical adenoma	3 (100.0%)

Table 3 Comparison of adrenal metastasis and nonmetastasis group

Age	*P* value = 0.433
Non-metastasis group	61.6 ± 11.9 (years old)
Metastasis group	58.8 ± 9.54 (years old)
Longest diameter of adrenal lesion	*P* value = 0.001
Non-metastasis group	2.87 ± 1.4 (centimeters)
Metastasis group	4.97 ± 2.7 (centimeters)
Gender (non-meta/metastasis)	*P* value = 0.181
Male	18/16
Female	11/4
T stage (non-meta/metastasis)	*P* value = 0.135
T1	10/2
T2	8/4
T3	8/10
T4	3/4
Tumor pathology (non-meta/metastasis)	*P value* = 0.963
Adenocarcinoma	12/8
Carcinoma	16/11
Stroma	1/1
Hounsfield unit in non-contrast phase CT	*P* value < 0.001
Non-metastasis group	13.31 ± 18.7
Metastasis group	35.2 ± 11.5
Hounsfield unit in venous phase CT	*P* value = 0.140
Non-metastasis group	52.9 ± 21.9
Metastasis group	64.7 ± 24.5
RWO [(Relative Wash Out)*100(%)]	*P* value = 0.121
Non-metastasis group	26.19 ± 17.2
Metastasis group	5.82 ± 26.0

CT, computed tomography

mas were found at the time of diagnosis (85.7% and 66.7%, respectively). The percentages of metastatic malignancy of synchronous adrenal mass lesions for pancreatic cancer, small intestine gastrointestinal stromal tumor, colon cancer, and renal cell carcinoma were 33.3%, 50%, 36.4%, and 25%, respectively. The metastatic rates in colon cancers and renal cell carcinomas were lower than hepatocellular carcinomas or lung cancers, even though isolated synchronous adrenal incidentalomas were discovered most frequently in conjunction with these 2 malignancies.

The metastatic adrenal lesions were significantly larger than benign lesions (4.97 ± 2.7 and 2.87 ± 1.4 cm in the metastatic and benign groups, respectively). Only 25% of adrenal lesions <3 cm proved to be metastatic, but 86% of adrenal lesions ≥6 cm were diagnosed as metastatic after surgery.

In addition, patients in either the T3 or T4 clinical T stage were more likely to have adrenal metastasis than patients in either stage T1 or T2. Only 25% of patients (6 out of 24) in clinical stage T1 or T2 had metastatic malignancies, but up to 56% of patients (14 out of 25) in clinical stage T3 or T4 had metastatic adrenal lesions.

In patients with newly diagnosed extra-adrenal malignancies, fewer than half of the isolated synchronous adrenal incidentalomas were diagnosed as metastatic after pathological examination. Thus, management of adrenal lesions must be cautiously undertaken.

Although few patients suffered from adrenal metastasis related to adrenal insufficiency, a standard hormone evaluation that includes serum hormone analysis and a timed urine collection for measuring catecholamines should be conducted before fine needle biopsy or surgical resection. The hormone evaluation can be used to rule out functional adrenal primary tumors and to avoid biopsy- or surgery-related complications such as the release of catecholamines in biopsies for pheochromocytomas.[12]

In addition to examining the diameters of adrenal lesions and taking account of the clinical T stage, imaging studies could provide useful information for distinguishing benign lesions from metastatic

tumors before biopsy or surgical resection. In this study, benign adrenal masses exhibited significantly lower density in noncontrast phase CT scans. The benign group also had a higher enhancement wash out percentage in this study, but only 13 (26.5%) patients had received delay phase CT scans; thus, the result was not statistically significant.

The density of adrenal masses, attenuation coefficients, irregular margins, and invasion of adjacent structures exhibited in CT scans or magnetic resonance imaging (MRI) could be used to distinguish benign from metastatic lesions. If CT scans with a contrast medium are performed, the enhancement washout percentage could be a useful tool for distinguishing lesions.[15,16] However, a substantial portion of patients (20% to 30%) fail to exhibit unmistakable CT or MRI results that clearly distinguish benign from malignant lesions.[17,18] However, MRI and 18-FDG-PET can now provide more accurate differentiation between metastases and benign adenomas.[13]

The overall prognosis for patients with metastatic cancer in the adrenal glands is poor.[19] However, the survival duration in highly selected patients receiving adrenalectomy for metastatic cancer is similar to that in patients who receive resection of metastases in other visceral sites.[20–22] One study reported that adrenalectomy in highly selected patients with isolated adrenal metastases or oligometastases could yield a satisfactory overall survival rate. Minimally invasive adrenalectomy is safe and associated with a low rate of local recurrence, and thus, it should be considered for highly selected patients.[23] An adrenalectomy for a metastatic tumor should not be undertaken unless surgeons are confident in their ability to achieve a favorable surgical outcome (*e.g.*, negative surgical margin and an intact tumor capsule).

The limitations of this study included a small sample size and relatively few cases in each category of primary malignancy. The lack of thorough endocrine surveys and adequate delayed enhancement phase imaging studies for all patients also limits the clinical value.

Conclusions

Roughly 40% of the isolated synchronous adrenal incidentalomas in patients with newly diagnosed extra-adrenal primary malignancies were determined to be adrenal metastases. Adrenal metastasis should be highly suspected in patients diagnosed with a primary malignancy that has a high risk for adrenal metastasis (such as hepatocellular carcinoma or lung cancer), who have an adrenal tumor with a maximum diameter $\geq$6 cm, whose CT scans reveal a relatively high density adrenal mass, or who are in clinical stage T3 or T4. If the results of imaging studies are consistent with metastasis, the primary malignancy should be considered and treated as a malignancy with isolated adrenal metastasis.

Although few patients suffered from metastasis-related adrenal insufficiency, a thorough hormone evaluation must be conducted to rule out functional adrenal lesions; combining this evaluation with an examination of clinical symptoms and imaging could best predict adrenal metastasis and ensure prompt staging and treatment.

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