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Presentation, Disease Progression, and Outcomes of Adrenal Gland Metastases

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Summary

Objective: Data on the presentation and outcomes of patients with adrenal gland metastases are limited. Our objectives were to characterize the prevalence of adrenal metastases subtypes and investigate how varying clinical presentations affect disease progression, development of primary adrenal insufficiency (PAI), and mortality.

Design: Single institution tertiary center, retrospective cohort study from 1997 to 2020.

Patients and Measurements: Adult patients with adrenal metastases. Clinical, radiologic, and biochemical presentations and outcomes were reviewed.

Results: Of 579 patients (62.3% men, median age 67 years [range 25–92]) with adrenal metastases (median tumor size of 30 mm [range 5–200]), 339 (58.5%) were discovered during cancer staging, 210 (36.3%) were found incidentally, and 29 (5.0%) based on symptoms. Tumors originated from the lung (226, 39.0%), genitourinary (GU) (160, 27.6%), gastrointestinal (GI) (79, 13.6%), and other (114, 19.7%) organ systems. Bilateral metastases were found in 140 (24.2%) patients at the time of initial diagnosis, and 249 (43.0%) had bilateral disease throughout the study course. PAI developed in 12.4% of patients with bilateral disease and was associated with larger tumor size. Median follow-up time was 14 months (range 0–232), and 442 (76.3%) patients died. Higher mortality was independently associated with older age, adrenal metastases originating from the lung, bilateral disease, and the absence of adrenalectomy.

Conclusions: Adrenal gland metastases originated most commonly from lung, GU, and GI malignancies. Bilateral adrenal metastases occurred in 43% of patients, and PAI occurred in 12.4% of those with bilateral disease, warranting further case detection strategies.

Keywords

adrenal mass; malignancy; bilateral; adrenal insufficiency; diagnosis; adrenalectomy; mortality

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Conflicts of Interest

Irina Bancos reports advisory board participation with Corcept Therapeutics, ClinCore and HRA Pharma outside the submitted work.

Data Availability Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Introduction

Adrenal tumors are reported in 4.4–7.3% of adults, where most represent benign adenomas.[1–3] Adrenal malignancies represent only 2.8–6.7% of all adrenal tumors, with the prevalence of adrenal cortical carcinomas around 0.6–3.7% and the prevalence of adrenal gland metastases around 0.5–3.8%.[4–6] Patients with a newly discovered adrenal tumor should undergo evaluation to assess if the tumor is malignant and/or hormonally active.[7] The likelihood of a malignant adrenal mass is much higher in certain scenarios such as larger tumor size, suspicious imaging phenotypes, history of an extra-adrenal malignancy, and non-incidental discovery of the adrenal tumor.[8–11] The diagnostic accuracy of individual parameters is suboptimal, especially in diagnosing adrenal metastases.[9] An unenhanced attenuation >10 Hounsfield Units on computed tomography has a 93–100% sensitivity but only a 46–71% specificity in diagnosing adrenal malignancy.[9–11] While tumor size may more accurately diagnose adrenal cortical carcinomas, it is not as good a predictor of adrenal metastases, mainly due to their wide variability in size.[10] Finally, while a history of extra-adrenal malignancy is common in patients with adrenal metastases, nearly 50% of these cases have been previously reported to be discovered incidentally.[10]

Our current understanding of adrenal gland metastases is limited. Data on the mode of discovery, clinical and radiographic presentation, interventions, and prognosis are not well delineated. Data on the types of extra-adrenal malignancy metastasizing to the adrenal glands mainly originate from studies on selected cohorts of patients, resulting in poor characterization of the overall epidemiology of adrenal metastases.[10,12,13] Of special interest is the presentation of bilateral adrenal metastases, as primary adrenal insufficiency (PAI) may occur and negatively contribute to the overall prognosis. While bilateral adrenal involvement has been reported in 20–49% of patients with adrenal metastases, the risk of developing contralateral disease in patients presenting with unilateral metastases is unknown.[12,14] Although PAI has been reported in 2.2–2.4% of patients with bilateral adrenal metastases,[12,14] its association with tumor subtype and size is also unclear. In addition, PAI may go unrecognized as symptoms may overlap with those of the malignancy itself or from the associated side effects of therapy. It is thus unclear what case detection practices are needed to diagnose PAI in patients with adrenal metastases.

In this study, we performed a retrospective investigation of a large consecutive cohort of patients found to have adrenal gland metastases at a single institution tertiary center. Our objectives were to characterize the prevalence of adrenal metastases subtypes and to determine whether the demographic, clinical and radiographic characteristics of patients diagnosed with adrenal metastases are associated with variations in disease progression, development of PAI, and mortality.

Materials and Methods

This was a retrospective study of adult patients (age ≥18 years) diagnosed with and further evaluated for adrenal gland metastases at the Mayo Clinic in Rochester, Minnesota between January 1st, 1997 and March 1st, 2020. This study was approved by the Mayo Clinic Institutional Review Board. A consent waiver was used for this project.

Patients

A longitudinal adrenal mass database within the Mayo Clinic was utilized (7897 patients, onset of electronic medical record, January 1st, 1997, until March 1st, 2020). A computerized search function was used to identify potential study participants, followed by subsequent medical record review to confirm that individuals met inclusion criteria. Patients were identified as having an adrenal gland metastasis based on histopathologic diagnosis (adrenalectomy or adrenal biopsy) or concerning radiographic findings (i.e. suspicious features deemed by the radiologist, increased fluorodeoxyglucose uptake, significant growth of tumor over time, and/or radiologic response to chemotherapy/radiation) in agreement with clinical suspicion and final clinical outcome. Patients with adrenal metastases, or lymphomas or sarcomas with adrenal spread were included. Patients with benign adrenal tumors, pheochromocytomas, adrenal cortical carcinomas, and other primary adrenal malignancies were excluded. Patients with insufficient documentation to support a clear diagnosis of malignancy as described above were also excluded.

Electronic medical records were reviewed for variables of interest including sex, race, age at initial diagnosis of the adrenal tumor based on first radiologic scan, clinical setting in which the tumor was discovered (i.e. mode of discovery), type of imaging modality, maximum tumor size and imaging phenotype at initial diagnosis, unilateral or bilateral disease at initial diagnosis and throughout the study course, presence of PAI in those with bilateral disease, tumor subtype (i.e. primary origin of adrenal metastasis), performance of adrenal biopsy and/or adrenalectomy, date of death or last known follow-up, evaluation of adrenal disease by an endocrinologist at any point of the clinical course, and work-up for catecholamine excess. Of note, patients defined to have “bilateral disease” either had true bilateral metastases or unilateral metastases in the setting of an isolated adrenal gland where the contralateral adrenal gland had been resected. PAI was defined either biochemically (elevated adrenocorticotropic hormone, low cortisol or abnormal cosyntropin stimulation test) or upon clinical suspicion in the setting of bilateral adrenal metastases (i.e. hypotension, orthostasis, hyperpigmentation, hyperkalemia, hyponatremia) followed by glucocorticoid and/or mineralocorticoid replacement therapy.

Statistics

Categorical data were summarized as numbers or percentages, while continuous data were summarized as medians and ranges. Associations between continuous variables were assessed using the Wilcoxon/Kruskal-Wallis test, while associations between categorical variables were assessed using the Pearson chi-square test. Logistic regression was used to assess for independent predictors of PAI and mortality. Statistical significance was defined with a P value <0.05. Data were analyzed using JMP software, version 14 (SAS, Cary, NC).

Results

Within our longitudinal adrenal mass database of 7897 consecutive patients with adrenal tumors diagnosed from January 1st 1997 to March 1st, 2020, we identified a total of 579 (7.3%) patients who met inclusion criteria. Our reference standard for the diagnosis of

adrenal malignancy included histopathology in 439 (75.8%) patients and radiography in 140 (24.2%) patients.

General Presentation and Outcomes

Of the 579 patients (361, 62.3% men; 522, 90% Caucasian) found to have adrenal metastases from extra-adrenal sites, or lymphomas or sarcomas with adrenal involvement, the median age at diagnosis was 67 years (range 25–91). Endocrinologists evaluated only 175 (30.2%) patients with adrenal metastases at either initial diagnosis and/or subsequent follow-up, and work-up for catecholamine excess was performed in a total of 184 (31.8%) patients.

Adrenal tumors were discovered during cancer staging imaging in 339 (58.5%) patients, incidentally found on imaging done for reasons unrelated to an extra-adrenal malignancy in 210 (36.3%), discovered based on B symptoms or mass effect in 29 (5.0%), and was unclear in 1 (0.2%) patient. Median maximum tumor size at initial diagnosis was 30 mm (range 5–200). At diagnosis, 437 (75.5%) patients were found to have unilateral adrenal metastases (179 [30.9%] in the right adrenal gland and 258 [44.6%] in the left adrenal gland), 140 (24.2%) were found to have bilateral disease, and 2 (0.03%) patients did not have documentation of tumor laterality. In addition to the 140 patients with bilateral disease at the time of diagnosis, 109 patients with initial unilateral disease later developed bilateral disease, resulting in a total of 249 (43.0%) cases with bilateral disease due to adrenal gland metastases overall. Adrenal biopsy was performed in 316 (54.6%) patients, and adrenalectomy was performed in 188 (32.5%). Those who underwent adrenalectomy were younger at diagnosis (median age of 63 years, range 26–88) than those who did not undergo adrenalectomy (median age of 68 years, range 25–91), $p<0.0001$.

Tumor Subtypes

Patients were diagnosed with adrenal metastases originating from the lung (226, 39.0%), genitourinary (GU) (160, 27.6%), gastrointestinal (GI) (79, 13.6%), or other (114, 19.7%) organ systems, Table 1. “Other organ systems” comprised of tumor origins from lymphoma (29, 5.0%), skin (23, 4.0%), sarcoma (17, 2.9%), breast (10, 1.7%), neuroendocrine (6, 1.0%), thyroid (4, 0.7%), and miscellaneous/unknown (25, 4.3%).

Median age at diagnosis was similar throughout the four major subtypes. Male predominance was observed in all tumors, more so in those with GU (71.3%) and lung (61.1%) primaries. Incidentally discovered disease was more common in those with lung cancer (46.9%) in comparison to the remaining subtypes (31.9% in GU, 25.3% in GI, 29.0% in other), $p=0.0006$. At initial diagnosis, patients with GI primaries were found to have adrenal tumors of the smallest size (median 21.5 mm, range 5–132), followed by those with lung (median 30 mm, range 5–100), GU (median 30 mm, range 5–200), and other (median 41 mm, range 5–132) primaries, $p=0.0002$. Bilateral disease at initial diagnosis was found to be most prevalent in those with other primaries (29.8%), followed by those with lung (26.6%), GU (21.3%), and GI (15.2%) primaries. In contrast, bilateral disease at any time during follow-up was found to be most prevalent in those with GU primaries (49.4%), followed by those with other (48.3%), lung (38.9%), and GI (34.2%) primaries, $p=0.047$.

Adrenal biopsy was most frequently done in those with lung cancer (149, 65.9%) and least frequently done in those with GU cancer (64, 40.0%), p<0.0001. Adrenalectomy was most commonly performed in those with GU primaries (71.3%), followed by those with GI (27.9%), other (23.7%), and lung (11.1%) primaries, p<0.0001. Mortality was highest in those with lung primaries (88.9%), followed by those with GI (78.5%), other (72.8%), and GU (60.0%) primaries, p<0.0001.

Bilateral Disease and Primary Adrenal Insufficiency

Of the 140 (24.2%) patients with bilateral disease at initial diagnosis, 34 (29.8%) were found to have metastases originating from other primaries, 60 (26.6%) from lung primaries, 34 (21.3%) from GU primaries, and 12 (15.2%) from GI primaries. However, bilateral disease at any time during follow-up was found in 249 (43.0%) patients and was most prevalent in those with GU primaries (79, 49.4%), followed by those with other (55, 48.3%), lung (88, 38.9%), and GI (27, 34.2%) primaries. When compared to patients with unilateral disease, those with bilateral disease were more likely to be evaluated by an endocrinologist (100/249, 40% vs. 76/330, 23%, p<0.0001).

While age did not significantly vary between patients with bilateral disease at any time during follow-up and patients with unilateral disease, maximum tumor size at diagnosis was significantly larger in those with bilateral disease (median 33 mm, range 5–200) than in those with unilateral disease (median 26 mm, range 5–143), p=0.02, Table 2. Adrenalectomy was also performed more frequently in those with bilateral disease (38.2%) compared to those with unilateral disease (28.2%), p=0.01. Mortality in patients with bilateral disease at any time during follow-up was not significantly different from that of those with unilateral disease, (79% vs. 74%, p=0.17). However, after excluding patients who underwent adrenalectomy, mortality in those with bilateral disease was higher (89.6% vs. 82.3%, p=0.046) than in those with unilateral disease.

Of the 249 cases with bilateral metastases at any time during follow-up, 31 (12.4%) developed PAI, Table 3. PAI was most prevalent in patients with other primaries (15, 27.3%), followed by those with GU (7, 8.9%), lung (7, 8.0%), and GI (2, 7.4%) primaries, p=0.003. Larger tumor size was associated with the development of PAI (median tumor size of 46.5 mm, range 13–120 in those with bilateral disease with PAI vs. median tumor size of 30 mm, range 5–200 in those with bilateral disease without PAI), p=0.0006. Only patients with extra-adrenal lymphoma, melanoma, and thyroid malignancy developed PAI from the “other primaries” category, of which the median maximum adrenal tumor sizes from lymphoma and melanoma were notably large at 62.5 mm (range 20–110) and 88 mm (range 43–120), respectively. Multivariate analysis of tumor size and metastases subtype demonstrated that maximum tumor size ≥40 mm (Odds Ratio, OR 2.7 (95% Confidence Interval, CI 1.2–6.1) and “other primaries” subtype (OR 3.8 (95% CI 1.7–8.3) were associated with the development of PAI in patients with bilateral disease. The prevalence of PAI in those with bilateral disease and a maximum tumor size ≥40 mm was 20%.

Follow-up and Mortality

Patients were followed for a median time of 14 months (range 0–232), and 442 (76.3%) died during follow-up. Mortality was higher in those who did not undergo adrenalectomy (85.2%), compared to those who did (58.0%), $p<0.0001$. Of those who died, median time to death was 11 months (range 0–208). Multivariate analysis was performed for mortality as a function of sex, age at diagnosis, maximum tumor size at diagnosis, tumor subtype, bilateral disease at diagnosis or follow-up, and if adrenalectomy was performed. Mortality was associated with older age (OR 4.7, 95% CI 1.3–16.4 per every 5 years), lung primaries (OR 2.7, 95% CI 1.5–4.7), bilateral disease (OR 1.8, 95% CI 1.1–2.8), and the absence of adrenalectomy (OR 3.6, 95% CI 2.2–5.8), but not with sex or tumor size. Adding the presence of PAI to this model revealed that PAI was also not associated with mortality (data not shown).

Discussion

Within our large patient cohort of adrenal gland metastases, or lymphomas or sarcomas with adrenal involvement, the most common primary tumors originated from the lung, followed by the GU and GI organ systems. While the prevalence of bilateral adrenal metastases at diagnosis was estimated to be 24.2%, we found that 18.8% additionally developed bilateral disease during follow-up. The prevalence of PAI in patients with bilateral disease (12.4%) was higher than previously reported[15] and was associated with tumor subtype and size. While the overall mortality in our patient cohort was 76.3%, it was highest in those with lung primaries (88.9%). Mortality was associated with age, lung primaries, presence of bilateral disease, and the absence of adrenalectomy, but not with sex, tumor size, or the presence of PAI.

Demographics and Presentation

Male predominance was observed in our cohort of patients with adrenal metastases. Our reported median age at diagnosis of 67 years was higher than the median age of 62 years in the only other large-scale study of 464 patients with adrenal metastases published in 2002,[14] potentially due to the vast majority (435, 93.4%) of included patients in the earlier study being diagnosed postmortem, suggesting a skewed sample size towards cases with worse prognoses. The discovery of adrenal metastases in our cohort occurred in the setting of cancer staging imaging (58.5%) or incidental imaging performed for reasons unrelated to an extra-adrenal malignancy (36.3%) in the vast majority of patients, while imaging done for preceding symptoms of abdominal mass effect or B symptoms occurred in only 5% of patients. In the previous study by Lam and Lo, 4.3% presented with symptomatic disease (symptoms from adrenal mass/hemorrhage or PAI) and none presented with adrenal incidentalomas. The high proportion of patients incidentally discovered with adrenal metastases in our cohort is representative of the current frequent use of cross-sectional abdominal imaging in clinical practice and emphasizes the need for careful appropriate work-up in any patient with an adrenal incidentaloma. Notably, only 30% of our patients were seen by an endocrinologist, and only 32% underwent work-up for catecholamine excess. As previously reported, pheochromocytomas were discovered in 2% of patients with known extra-adrenal malignancy who were referred for adrenal biopsy, where the diagnosis

could have been made earlier and more safely by following the recommended guidelines for working up catecholamine excess in any indeterminate adrenal mass, even in those with high-risk for adrenal metastases.[12] As lung cancer was found to be the most likely origin of metastases in the setting of an adrenal incidentaloma, chest x-ray or computed tomography may be the next step in evaluating a suspicious nonfunctioning adrenal mass, especially in cases with risk factors.

Bilateral Disease and Adrenal Insufficiency

In our study, bilateral disease was found in 43% of patients. In the prior postmortem study where over 90% of adrenal metastases were confirmed at autopsy, the prevalence of bilateral disease was 49%.[14] We also found that patients with GU primaries had the highest prevalence of bilateral disease throughout the study course (49.4%), as well as the highest risk of developing bilateral disease after initial diagnosis. This may be due to both the proximity and subsequent ease of spread of the primary tumor in anatomic relation to the adrenal gland, as well as the lower mortality of GU cancers, allowing for more time for a contralateral metastasis to develop.

The overall prevalence of PAI in those with bilateral disease was 12.4%, higher than previously reported.[15] Patients with adrenal metastases from “other organ systems” (specifically lymphoma, melanoma, and thyroid) demonstrated the highest prevalence of PAI at 27%. We found no differences in the prevalence of PAI among patients with lung, GU and GI primaries (range 7.4%−8.9%). Tumor size was associated with the development of PAI, supporting the notion that only minimal adrenal tissue is required to maintain normal glucocorticoid and mineralocorticoid production. In fact, of all patients with adrenal tumors ≥40 mm at diagnosis who had or developed bilateral disease, the prevalence of PAI was 20%. These findings differ from a recent systematic review and meta-analysis that had reported that the size of bilateral adrenal metastases was a poor predictor for PAI.[15] However, the quality of the data and the generalizability of the results in the systematic review were low, given the limited number of included studies, small sample size, and older publications not reflective of current clinical practice. Based on our findings, close clinical and biochemical monitoring of PAI should be considered in any patient with bilateral adrenal metastases, especially in those with larger tumor size.

We found that adrenal metastases most commonly originated from the lung, GU, and GI organ systems, and less commonly from other sources such as lymphoma, skin cancer, sarcoma, or breast cancer. Our findings differ from a prior large-scale study where GI adrenal metastases were the second most common subtype.[14] This discrepancy may be explained by selection bias, as the previous study included mostly patients diagnosed postmortem, which likely skewed the distribution towards cases with worse prognoses.[14] As patients with certain metastatic GU cancers (i.e. renal cell carcinoma) present with a far more favorable prognosis if only a solitary intra-adrenal lesion exists as the extent of disease,[16,17] it is likely that fewer cases of GU primaries were included in the former study.

Adrenalectomy was performed in about a third of patients in our study. This intervention was associated with a lower mortality and was more frequently performed in those with GU primaries. In our study, we did not examine the relationship of adrenalectomy to the burden

of disease or the presence of other extra-adrenal metastases. As previously reported in patients with primary renal cell cancer, nephrectomy and concomitant intraoperative adrenalectomy in the setting of a known solitary intra-adrenal lesion was associated with improved prognosis.[16,17] Lam and Lo also reported that aggressive surgical resection of adrenal metastases (as well as other involved sites) was associated with improved survival outcomes overall.[14] Additionally, a recent systematic review on therapeutic interventions for adrenal metastases that had excluded cases with ipsilateral synchronous renal cell carcinoma showed that the 2-year survival of patients who underwent adrenalectomy for adrenal metastases was up to 46%, compared to only 19% in those who underwent stereotactic ablative body radiotherapy, though selection bias was likely present.[18]

Within our cohort, overall mortality was 76.3%. Mortality was highest in those with lung primaries and lowest in those with GU primaries. After excluding cases with adrenalectomy, patients with bilateral adrenal metastases demonstrated a significantly higher mortality compared to those with unilateral adrenal metastases, likely reflective of higher disease burden. Older age and bilateral disease were independently associated with higher mortality on multivariate analysis, while the performance of adrenalectomy was associated with lower mortality. However, tumor size and the presence of PAI were not associated with mortality.

Strengths, Limitations, and Future Directions

This was the largest study to date in characterizing the presentations and outcomes of patients with varying etiologies of adrenal metastases, as well as the first to look at the risks of progression to bilateral disease and PAI over time. Enrollment of a consecutive cohort of cases at a single institution tertiary center allowed for data sampling to occur thoroughly with a degree of standardization in diagnostic evaluation and disease management. In contrast to the results of the prior study on adrenal metastases in largely postmortem patients, our study's findings on prevalence and disease progression also more accurately mirror that within the clinical practice setting. As part of a retrospective cohort study, our conclusions were limited to observed associations and susceptible to selection bias and confounding. Data for certain biochemical or radiographic variables of interest were missing due to a lack of documentation in earlier medical records, and assessments for PAI were heterogeneous, as this condition was allowed to be defined either biochemically or clinically. Maximum tumor sizes were also only recorded at the time of diagnosis and not followed over time in those who developed bilateral disease. Data on concurrent chemotherapy was not available. Finally, extensive subgroup analyses were not performed beyond the 4 metastases subtypes given their smaller sample sizes, especially in those within the "other primaries" category. Longitudinal studies with uniform assessment for PAI are needed for more confident estimates.

Conclusion

In conclusion, adrenal gland metastases originated most frequently from the lung, GU, and GI organ systems. As the vast majority were found during cancer staging or on an incidental scan, careful work-up of adrenal incidentalomas is warranted. We found that patients with GU primaries demonstrated the highest prevalence of bilateral disease overall, as well as the

strongest propensity to develop bilateral disease. PAI developed in 12.4% of all patients with bilateral disease and in 20% of those with a maximum tumor size ≥40 mm, warranting further clinical and/or biochemical case detection strategies in patients with larger tumors.

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Table 1.

Demographic Characteristics, Clinical Presentations, and Management Stratified by Adrenal Metastases Subtype

Variable	Total	Lung[a] primaries	Genitourinary[b] primaries	Gastrointestinal[c] primaries	Other[d] primaries	P value
N (%)	579 (100)	226 (39.0)	160 (27.6)	79 (13.6)	114 (19.7)	
Sex						
Male, N (%)	361 (62.3)	138 (61.1)	114 (71.3)	47 (59.5)	62 (54.4)	0.03*
Age at diagnosis (years), median (range)	67 (25–91)	68.5 (31–91)	66 (27–91)	65 (25–90)	65 (26–89)	0.17
Mode of Discovery						
Cancer staging, N (%)	339 (58.5)	111 (49.1)	104 (65.0)	55 (69.6)	69 (60.5)	0.0006*
Incidental, N (%)	210 (36.3)	106 (46.9)	51 (31.9)	20 (25.3)	33 (29.0)	
Symptoms[e], N (%)	29 (5.0)	8 (3.5)	5 (3.1)	4 (5.1)	12 (10.5)	
Maximum tumor size (mm), median (range)	30 (5–200)	30 (5–100)	30 (5–200)	21.5 (5–132)	41 (5–132)	0.0002*
Tumor location at diagnosis						
Unilateral, N (%)	437 (75.5)	165 (73.0)	126 (78.8)	67 (84.8)	79 (69.3)	0.18
Bilateral, N (%)	140 (24.2)	60 (26.6)	34 (21.3)	12 (15.2)	34 (29.8)	
Bilateral adrenal involvement[f] at diagnosis or follow-up, N (%)	249 (43.0)	88 (38.9)	79 (49.4)	27 (34.2)	55 (48.3)	0.047*
Primary adrenal insufficiency						
Overall, N (%)	31 (5.4)	7 (3.1)	7 (4.4)	2 (2.5)	15 (13.2)	0.0006*
In patients with bilateral adrenal metastases, N (%)	31 (12.4)	7 (8.0)	7 (8.9)	2 (7.4)	15(27.3)	0.003*
Adrenal biopsy, N (%)	316 (54.6)	149 (65.9)	64 (40.0)	39 (49.4)	64 (56.1)	<0.0001*
Adrenalectomy, N (%)	188 (32.5)	25 (11.1)	114 (71.3)	22 (27.9)	27 (23.7)	<0.0001*
Died, N (%)	442 (76.3)	201 (88.9)	96 (60.0)	62 (78.5)	83 (72.8)	<0.0001*

[a]Lung primaries were of the following origins: small cell and non-small cell.

[b]Genitourinary primaries were of the following origins: renal, urothelial, periurethral gland, uterine, ovarian, fallopian tube, cervical, prostate, and testicular.

[c]Gastrointestinal primaries were of the following origins: colorectal, gastric, esophageal, pancreatic, liver, gallbladder and biliary.

[d]Other primaries comprised of lymphoma, skin, sarcoma, breast, neuroendocrine, thyroid, and miscellaneous/unknown.

[e]Symptoms were defined as preceding abdominal mass effect or B symptoms as reason for imaging.

[f] Bilateral adrenal involvement was defined as true bilateral metastases or unilateral metastases in the setting of an isolated adrenal gland.

Table 2.

Presentation and Management of Patients with Unilateral vs. Bilateral Metastases

Variable	Total	Bilateral disease at diagnosis or follow-up	Unilateral disease	P value
N (%)	579 (100)	249 (43.0)	330 (57.0)	
Age at diagnosis (years), median (range)	67 (25–91)	65 (26–89)	68 (25–91)	0.17
Maximum tumor size (mm), median (range)	30 (5–200)	33 (5–200)	26 (5–143)	0.02*
Tumor subtype				
Lung[a], N (%)	226 (39.0)	88 (35.3)	138 (41.8)	0.047*
Genitourinary[b], N (%)	160 (27.6)	79 (31.7)	81 (24.6)	
Gastrointestinal[c], N (%)	79 (13.6)	27 (10.8)	52 (15.8)	
Other[d], N (%)	114 (19.7)	55 (22.1)	59 (17.9)	
Primary adrenal insufficiency in patients with bilateral metastases, N (%)	31 (5.4)	31 (12.4)		
Adrenalectomy, N (%)	188 (32.5)	95 (38.2)	93 (28.2)	0.01*
Died, N (%)	442 (76.3)	197 (79.1)	245 (74.2)	0.17

[a]Lung primaries were of the following origins: small cell and non-small cell.

[b]Genitourinary primaries were of the following origins: renal, urothelial, periurethral gland, uterine, ovarian, fallopian tube, cervical, prostate, and testicular.

[c]Gastrointestinal primaries were of the following origins: colorectal, gastric, esophageal, pancreatic, liver, gallbladder and biliary.

[d]Other primaries comprised of lymphoma, skin, sarcoma, breast, neuroendocrine, thyroid, and miscellaneous/unknown.

Table 3.

Presentation and Management of 31 Patients with Bilateral Disease and Primary Adrenal Insufficiency

N	Tumor subtype	Age[a]	Sex[b]	Tumor laterality at diagnosis	Left tumor size (mm) at diagnosis	Right tumor size (mm) at diagnosis	Modality of primary adrenal insufficiency diagnosis[c]	Underwent Adrenalectomy	Follow-up time (months)	Died
1	Colon adenocarcinoma	68	M	Bilateral	13	12	Biochemical	No	25	Yes
2	Colon adenocarcinoma	69	M	Bilateral	74	56	Biochemical	No	35	Yes
3	Renal cell carcinoma	75	F	Bilateral	33	28	Clinical	Yes	6	Yes
4	Renal cell carcinoma	57	M	Bilateral	37	31	Clinical	Yes	16	Yes
5	Renal cell carcinoma	62	M	Unilateral	55	-	Biochemical	Yes	6	No
6	Renal cell carcinoma	71	M	Bilateral	Unknown	Unknown	Biochemical	Yes	92	Yes
7	Renal cell carcinoma	61	M	Unilateral	23	-	Biochemical	Yes	25	No
8	Renal cell carcinoma	65	F	Bilateral	Unknown	Unknown	Biochemical	Yes	9	Yes
9	Uterine carcinoma	89	F	Unilateral	-	46	Clinical	No	8	Yes
10	Non-small cell lung carcinoma	59	M	Bilateral	55	53	Clinical	No	1	Yes
11	Non-small cell lung carcinoma	53	F	Bilateral	28	17	Clinical	Yes	75	No
12	Non-small cell lung carcinoma	56	M	Bilateral	80	23	Clinical	No	4	Yes
13	Non-small cell lung carcinoma	54	M	Unilateral	30	-	Clinical	Yes	1	Yes
14	Non-small cell lung carcinoma	65	F	Bilateral	24	47	Clinical	No	3	Yes
15	Non-small cell lung carcinoma	64	M	Bilateral	46	15	Biochemical	No	18	Yes
16	Non-small cell lung carcinoma	71	M	Bilateral	35	35	Biochemical	No	24	Yes
17	Lymphoma	72	M	Bilateral	Unknown	Unknown	Biochemical	No	0	No
18	Lymphoma	72	M	Unilateral	20	-	Biochemical	No	16	No
19	Lymphoma	65	F	Bilateral	70	62	Biochemical	No	73	No
20	Lymphoma	74	M	Bilateral	40	40	Biochemical	No	7	Yes
21	Lymphoma	63	M	Bilateral	55	38	Biochemical	No	23	No
22	Lymphoma	77	M	Bilateral	93	75	Biochemical	No	13	Yes
23	Lymphoma	57	M	Bilateral	110	110	Biochemical	No	56	No
24	Lymphoma	78	M	Unilateral	23	-	Biochemical	No	33	Yes
25	Lymphoma	87	F	Bilateral	75	60	Biochemical	No	3	Yes

N	Tumor subtype	Age[a]	Sex[b]	Tumor laterality at diagnosis	Left tumor size (mm) at diagnosis	Right tumor size (mm) at diagnosis	Modality of primary adrenal insufficiency diagnosis[c]	Underwent Adrenalectomy	Follow-up time (months)	Died
26	Melanoma	59	M	Bilateral	79	120	Clinical	No	10	Yes
27	Melanoma	54	M	Unilateral	43	-	Biochemical	No	16	Yes
28	Melanoma	72	M	Bilateral	108	57	Biochemical	No	17	Yes
29	Melanoma	60	M	Unilateral	-	87	Biochemical	No	11	Yes
30	Melanoma	79	M	Bilateral	88	46	Biochemical	No	8	Yes
31	Papillary thyroid carcinoma	45	M	Unilateral	30	-	Biochemical	Yes	52	Yes

[a]Age was defined as age at diagnosis on first radiologic scan of adrenal metastases in years.

[b]Sex was characterized as: M=male, F=female.

[c]Primary adrenal insufficiency was diagnosed either biochemically (elevated adrenocorticotropic hormone, low cortisol or abnormal cosyntropin stimulation test) or upon clinical suspicion in the setting of bilateral adrenal metastases (i.e. hypotension, orthostasis, hyperpigmentation, hyperkalemia, hyponatremia) followed by glucocorticoid and/or mineralocorticoid replacement therapy.

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