Isolated adrenal metastectomy has a low morbidity rate irrespective of performing surgical sub-specialty

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Introduction: *There has been growing use of adrenalectomy as a potentially curative treatment option for patients with oligometastatic disease to the adrenal gland. We sought to compare the perioperative outcomes of patients undergoing isolated adrenalectomy in the setting of disseminated cancer using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. Furthermore, we examined the impact of performing surgical sub-specialty on outcomes.*

Materials and methods: *Data from the ACS-NSQIP database was obtained for patients between 2011 and 2016 who underwent adrenalectomy. Patients were stratified by the presence or absence of disseminated cancer. Univariate and multivariate regression analyses were performed to test for an association between the presence or absence of disseminated cancer and perioperative outcomes. The relationship between performing specialist and outcomes was also compared.*

Results: *A total of 4,207 patients were identified, with 270 (6.4%) in the disseminated cancer group. There was no significant difference in perioperative outcomes between patients with disseminated cancer and without disseminated cancer. On multivariate analysis, neither the presence of disseminated cancer ($p = 0.47$) nor the surgical sub-specialty performing adrenalectomy ($p = 0.52$) were associated with an increased risk postoperative morbidity or mortality. Of note, there was a statistically significant increase in the number of adrenalectomies performed by urologists in the setting of disseminated cancer (19.3% versus 10.4%, $p < 0.01$).*

Conclusions: *Patients undergoing adrenalectomy in the setting of disseminated cancer did not have significantly worse perioperative outcomes compared to patients undergoing adrenalectomy for other indications. The adverse perioperative event rate was similar whether the operation was performed by a urologist or a general surgeon.*

Key Words: adrenalectomy, oligometastasis, metastectomy

Introduction

Incidental adrenal masses are defined as asymptomatic masses > 1cm, and are found in 4%-6% of the population due to the increasing use of cross-sectional imaging for unrelated reasons.[1,2] The majority of these lesions are benign, and primary adrenal cortical carcinomas are an uncommon cancer with an estimated incidence of only 300 cases per year in the United States.[3] In contrast, the adrenal glands are a frequent site of metastasis from other primary tumors including renal cell carcinoma, non-small cell lung cancer, melanoma, breast cancer, and colon cancer.[4] Due to improvements and the more widespread use of radiographic imaging in cancer surveillance, solitary adrenal metastatic

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lesions are more commonly being detected.[5] In this setting, there has been growing use of adrenalectomy as a potentially curative treatment option.[5] Due to the rarity of this clinical scenario, there is currently no level I evidence to suggest that there is a survival benefit to performing adrenalectomy for isolated metastatic disease;[6] however, multiple retrospective reviews have suggested improved survival rates for patients undergoing isolated adrenal metastectomy for a variety of primary tumors.[6]

Depending on practice environment, adrenalectomy is often performed by either a general surgeon, surgical oncologist, and/or a urologist. All three surgical sub-specialties have "claim" to the adrenal gland, and all have the capability to perform the surgical intervention. In particular, urologists are highly familiar with adrenal retroperitoneal anatomy due to its adjacent location to the kidney, and it would be reasonable to expect that they would be performing the majority of these surgeries, yet the literature shows that not to be the case. Previous studies have shown that there is no difference in perioperative outcomes when comparing high-volume general surgeons and high-volume urologists, intimating that in the appropriately trained surgical sub-specialist, adrenalectomy may not need to exclusively reside in the domain of any one specialty.[7,8]

To further explore this question, we sought to examine the use and perioperative outcomes of patients undergoing isolated adrenalectomy using contemporary data from the National Surgical Quality Improvement Program of the American College of Surgeons (NSQIP-ACS). Our specific aims were to determine if isolated adrenal metastatectomy have acceptable morbidity and mortality profiles and whether outcomes and use differed by performing surgical sub-specialty.

Materials and methods

Data for this study was obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). The NSQIP database collects 30-day risk-adjusted perioperative outcome data, which includes patient demographic information, surgical profile variables, preoperative clinical data and lab values, intraoperative variables, and postoperative complications and discharge variables. For this study, patients between 2011 and 2016 were identified by the Current Procedural Terminology (CPT) codes for open adrenalectomy (60540) and minimally-invasive adrenalectomy (60650). Patients were then stratified by the presence or absence of disseminated cancer as the indication for surgery, a likely surrogate for patients undergoing isolated adrenalectomy as a metastatectomy in the setting of stage IV cancer from another organ. In addition, patients who underwent a concomitant procedure at the time of adrenalectomy as well as patients with missing information were excluded from analysis. The total study population analyzed was 4,207 patients with 270 patients undergoing surgery in the setting of disseminated cancer and forming our cohort of interest.

For patients that underwent an adrenalectomy during the study period, information was collected on demographics, comorbidities, smoking history, functional status, surgical approach (open versus laparoscopic), adjuvant treatment, and body mass index (BMI). The age of patients was then divided into different age categories (< 40, 40-49, 50-59, > 60) as well as BMI (< 18.5 = underweight, 18.5-25 = normal weight, 25-30 = overweight, and > 30 = obese). Patient demographic data were then evaluated for significance against presence of disseminated cancer using the Chi-square test of association or Fischer's exact test.

The outcomes of interest for this study were reported complications that occurred within 30 days or less after surgery, length of postsurgical hospital stay, and return to the operating room within 30 days of surgery. Each complication was grouped uniformly into a grade of severity based on the Clavien-Dindo classification as either minor (I-II), major (III- IV), or death (V). Categorical variables were analyzed utilizing the Chi-square test of association and numeric variables were analyzed utilizing the Mann-Whitney U test for non-parametric values.

After adjusting for comorbidity burden, a multivariate ordinal regression analysis was performed to test for an association between the presence or absence of disseminated cancer and severe complications (combination of major complication and death). Additionally, recent operative trends in adrenalectomies performed for disseminated cancer over the 5-year study period were analyzed. The proportion of operations performed by general surgeons versus urologists were also compared.

A p value of less than 0.05 was considered statistically significant. Categorical values were expressed as total (frequency), and numeric values were expressed as median (range). All statistical analysis was performed using SAS version 9.4 software.

Results

There were 4,207 patients included in this study population who underwent adrenalectomy, of whom 270 (6.4%) had disseminated cancer. More patients

in the disseminated cancer group underwent an open adrenalectomy (18.2% versus 10.9%, p < 0.01), and general surgeons performed the majority of adrenalectomies. Interestingly, there was a statistically significant increase in the number of adrenalectomies performed by urologists in the setting of disseminated cancer (19.3% versus 10.4%, p < 0.01).

Table 1 outlines the preoperative characteristics of patients who underwent adrenalectomy, stratified by the presence or absence of disseminated cancer. There were significant differences between the two cohorts of patients undergoing adrenalectomy. Patients undergoing adrenalectomy in the presence of disseminated cancer were more likely to be male (59.0%), Caucasian (82.2%) and older than 60 years of age (63.0%) (p < 0.01 for all). Additionally, there was a statistically significant difference in the incidence of diabetes, hypertension and COPD between the two

TABLE 1. **Preoperative characteristics of study population**

	Disseminated cancer		
	Yes (n = 270) n (%)	**No (n = 3,937) n (%)**	**p value**
Sex			< 0.01‡
Male	159 (58.9)	1,610 (40.9)	
Female	111 (41.1)	2,327 (59.1)	
Age			< 0.01‡
< 40	12 (4.4)	777 (19.7)	
40-49	28 (10.4)	913 (19.5)	
50-59	60 (22.2)	1,068 (27.1)	
≥ 60	170 (63.0)	1,315 (33.4)	
Race			< 0.01‡
Caucasian	222 (82.2)	2,705 (68.7)	
African American	17 (6.3)	552 (14.0)	
Asian	9 (3.3)	166 (4.2)	
Other	22 (8.2)	514 (13.1)	
Diabetes	36 (13.3)	786 (20.0)	0.01‡
COPD	31 (11.5)	186 (4.7)	< 0.01‡
Hypertension	136 (50.4)	2,822 (71.7)	< 0.01‡
Smoking	63 (23.3)	904 (23.0)	0.88
Functional status			0.25
Independent	266 (98.5)	3,890 (98.8)	
Partially dependent	4 (1.5)	25 (0.6)	
Totally dependent	N/A	3 (0.1)	
Unknown	N/A	19 (0.5)	
Body mass index			< 0.01‡
Underweight	4 (1.5)	44 (1.1)	
Normal weight	83 (31.0)	741 (18.9)	
Overweight	89 (33.2)	1,187 (30.3)	
Obese	92 (34.3)	1,944 (49.6)	
Surgical approach			<0.01‡
Open (60540)*	49 (18.2)	427 (10.9)	
Laparoscopic (60650)*	221 (81.9)	3,510 (89.2)	
Surgical specialty			< 0.01‡
General surgery	217 (80.4)	3,516 (89.3)	
Urology	52 (19.3)	410 (10.4)	

‡p value < 0.05; *CPT Code

TABLE 2. **Complications captured by NSQIP**

Complication grade by Calvien-dindo index	Disseminated cancer Yes n (%)	No n (%)
Minor		
Superficial incisional infection	2 (0.7)	26 (0.7)
Pneumonia	6 (2.2)	39 (1.0)
Pulmonary embolus	2 (0.7)	20 (0.5)
Urinary tract infection	7 (2.6)	42 (1.1)
Blood transfusion	9 (3.3)	116 (3.0)
Deep vein thrombosis	2 (0.7)	15 (0.4)
Total	28 (10.4)	258 (6.6)
Major		
Deep incisional infection	N/A	7 (0.2)
Organ space wound infection	1 (0.4)	11 (0.3)
Wound dehiscence	N/A	1 (< 0.5)
Reintubation	1 (0.4)	31 (0.8)
Ventilator > 48 hours	2 (0.7)	19 (0.5)
Acute renal failure	1 (0.4)	6 (0.2)
Cardiovascular accident	N/A	6 (0.2)
Cardiac arrest	N/A	9 (0.2)
Myocardial infarction	2 (0.7)	8 (0.2)
Sepsis	3 (1.1)	20 (0.5)
Total	10 (3.7)	118 (3.0)
Death	N/A	16 (0.4)

Minor = Clavien I-II; Major = Clavien III-IV; Death = Clavien V

groups. In the disseminated cancer group, patients were more likely to have COPD (11.5% versus 4.7%, $p < 0.01$) whereas in the group undergoing adrenalectomy in the absence of disseminated cancer, these patients were more likely to have diabetes (20.0% versus 13.3%, $p = 0.01$) and hypertension (71.7% versus 50.4%, $p < 0.01$). Also, a statistically significant larger number of patients in the not disseminated cancer group were obese ($p < 0.01$). The differences in diabetes, hypertension and obesity are partly likely a reflection of the underlying disease process which necessitated the adrenalectomy. Additionally, patients with disseminated cancer are more likely to have undergone significant weight loss due to their disease process. The higher incidence of COPD in cancer patients may be due to an underlying lung cancer.

Tables 2 and 3 enumerate the complications experienced in each group as well as their severity. Overall, in both groups, there was a low rate of both minor and major complications. In the group with disseminated cancer, only 10.4% and 3.7% of patients experienced a minor or major complication. There were no deaths within 30 days of surgery in this group. Similarly, in the group without disseminated cancer, there was a 6.6% and 3.0% rate of minor and major complications, respectively. In this group, 16 (0.4%) patients died within 30 days of surgery. There was no significant difference in complication or mortality rates between the two groups, Table 3, although higher likelihood of not having any complications approached statistical significance ($p = 0.08$) for the non-disseminated cancer group. The most common minor complication in both groups was the requirement of a blood transfusion, and the most common major complication in both groups was sepsis.

There was no difference between the two groups in the rates of unplanned hospital readmissions or unplanned returns to the operating room ($p = 0.13$ and 0.30, respectively). The median length of stay in the disseminated cancer group was significantly different at 2 (IQR = 1-3) days as compared to 2 (IQR = 1-4) days in the non-disseminated cancer group ($p = 0.03$).

Finally, there was not a statistically significant change in the rate of adrenalectomy in patients with disseminated cancer nor a statistically significant change in the surgical sub-specialty (general surgery versus urology) performing surgery over the 5-year time dataset analyzed.

TABLE 3. **Complication according to cancer dissemination**

Complication grade	Disseminated cancer Yes n (%)	No n (%)	p value
None	244 (90.4)	3,669 (93.2)	0.08
Minor	18 (6.7)	182 (4.6)	0.13
Major	8 (3.0)	70 (1.8)	0.16
Death	N/A	16 (0.4)	N/A

TABLE 4. **Multivariate regression**

	Odds ratio	95% CI	p value
Sex			
Male	1.00		
Female	1.04	0.67-1.62	0.85
Age			
< 40	1.00		
40-49	0.87	0.39-1.92	0.73
50-59	1.09	0.53-2.22	0.81
≥ 60	1.37	0.70-2.70	0.36
Race			
Caucasian	1.00		
African American	0.91	0.47-1.74	0.77
Asian	0.76	0.18-3.26	0.71
Other	1.64	0.90-3.00	0.11
Body mass index			
Normal weight	1.00		
Underweight	3.85	1.17-12.68	0.03‡
Overweight	0.88	0.43-1.83	0.73
Obese	1.70	0.90-3.24	0.10
Diabetes	1.38	0.85-2.25	0.20
COPD	1.47	0.71-3.03	0.30
Hypertension	1.30	0.76-2.25	0.34
Smoking	1.59	0.99-2.55	0.06
Functional status			
Independent	1.00		
Partially independent	11.34	4.35-29.55	< 0.01‡
Disseminated cancer	1.33	0.61-2.90	0.47
Approach/CPT			
Laparoscopic (60650)	1.00		
Open (60540)	3.26	2.02-5.25	< 0.01‡
Surgery specialty			
Urology	1.00		
General surgery	1.26	0.62-2.56	0.52

‡p value < 0.05

Table 4 displays the multivariate logistic regression analysis performed examining the association between pre-operative variables and adverse post-surgical events. Having a decreased functional status (OR = 11.34, 95% CI = 4.35-29.55, p < 0.01), being underweight (OR = 3,85, 95% CI = 1.17-12.68, p = 0.03), and undergoing an open surgical approach (3.26, 95% CI = 2.02-5.25, p < 0.01) were all associated with adverse surgical events. Of note, neither the presence of disseminated cancer at the time of adrenalectomy (1.33, 95% CI = 0.61-2.90, p = 0.47) nor the surgical sub-specialty performing adrenalectomy (1.26, 95% CI = 0.62-2.56, p = 0.52) were independently associated with postoperative morbidity or mortality.

Discussion

In this study, we examined the data obtained from the ACS-NSQIP. A total of 4,207 patients who underwent adrenalectomy from 2011 to 2016 were analyzed of whom 270 patients underwent adrenalectomy in the setting of disseminated cancer, a likely surrogate for

patients who had low-volume metastatic disease for whom surgical metastatectomy was thought to likely benefit. This analysis represents the largest cohort of patients examined in the literature.

In this study, we found that the rates of minor and major complications in both patients undergoing the procedure in the setting of disseminated cancer and for other indications were low. There was no significant difference in the rate of hospital readmissions or returns to the operating room between the two groups. Although this data shows that general surgeons perform the vast majority of adrenalectomies, there was a higher proportion of adrenalectomies performed by urologists in patients who were having the surgery done in the setting of disseminated cancer. Importantly, there was no difference in the rate of complications when comparing the two specialties.

Adrenalectomies are commonly performed in the setting of low-volume stage IV disseminated cancer for isolated metastatic or oligometastatic disease. The adrenal gland is a common site of metastasis for renal cell carcinoma, non-small cell lung cancer, breast cancer, melanoma, and colon cancer.[4,9] As this is a relatively rare clinical scenario, there is currently no level I evidence to suggest that there is a definite survival benefit to metastatectomy; however, in the majority of series,[10-12] there has been shown to be a survival benefit for a variety of primary tumors.[6] Several retrospective series have shown that in patients with NSCLC with an isolated adrenal metastasis, median overall survival ranges from 11 to 31 months with a 5-year survival ranging from 7%-60% following surgical resection.[13,14] In comparison, in a review by Raz et al, these authors concluded that the 5-year overall survival for patients with isolated adrenal metastasis from NSCLC managed non-operatively was 0% compared to 34% for those managed with adrenalectomy ($p = 0.002$).[15] Similarly, a retrospective review by Collinson et al showed that in patients with metastatic melanoma to the adrenal gland, the median overall survival for patients who underwent metastatectomy was 16 months versus 5 months for patients managed without surgery ($p < 0.00001$).[16] Finally, in a retrospective study by Lau et al, they reviewed the case of 11 patients who had metastatic RCC to the contralateral adrenal gland. The mean time to development of metastasis was 5.2 years and all patients were treated with adrenalectomy. There were no reported perioperative complications or mortality. Seven patients died from RCC at a mean of 3.9 years and 2 patients were still alive at last follow up.[17] Further investigation with prospective trials would hopefully provide definitive evidence to confirm this suspected benefit.

Currently, adrenalectomies are being performed by urologists, general surgeons, and surgical oncologists. Previous studies have shown that it is not the specialty, but the frequency of which the surgeon performs the operation that dictates morbidity and mortality rates.[7] Lindeman et al concluded that with respect to adrenalectomies, high volume surgeons had significantly lower mortality (0.56% versus 1.25%, $p = .004$) and complication rates (10.2% versus 16.4%, $p = < .001$) when compared with low volume surgeons. In this study, the authors did note that 46.8% of the operations were performed by a urologist, with the remaining 53.1% being performed by general and endocrine surgeons.[18] In a retrospective review by Park et al, the authors demonstrated that a higher proportion of general surgeons were high volume (34% versus 18%) compared to urologist, and this may be the reason for a larger referral basis. But, there was again no difference in complication rates between the two specialties.[19] In light of the findings of our analysis and prior studies, the evidence does suggest that urologists can and should be more involved in performing adrenalectomies. This is especially true given our finding regarding urologic surgical involvement in patients with disseminated cancer at the time of surgery.

There are several limitations to our study. The NSQIP database collects patient information up to 30 days following surgery. Complications, including deaths, which occur after this period are not collected, potentially under-estimating adverse events. In addition, there is no pathologic variables abstracted thus limiting our ability to comment on the indolence versus aggressiveness or types of tumors seen in this patient population as well as the potential bias associated with who may or may not have undergone surgery. Additionally there is no information on the size of the mass removed, therefore we were unable to account for a potential correlation between mass size and complication rates which has been shown in previous studies.[20,21] Again, patients were assumed to have adrenal metastasis if they had known disseminated cancer; however, it is possible these patients underwent the procedure for benign indications. Finally, there is an inherent limitation in all large, administrative databases in that we are dependent on the accurate and reliable input of the data. Nevertheless, despite these acknowledged limitations of the data, the size of this dataset and the unique clinical variables collected allow for the examination of clinical scenarios as presented in this manuscript.

Conclusions

Patients undergoing adrenalectomy in the setting of disseminated cancer did not have significantly worse perioperative outcomes as compared to patients undergoing adrenalectomy for other indications. Furthermore, the adverse perioperative event rate was similar whether the operation was performed by a urologist or a general surgeon. These data underscore that adrenalectomy appears to have a low complications profile irrespective of indication or performing surgical specialist. □

References

1. Livhits M, Li N, Yeh MW, Harari A. Surgery is associated with improved survival for adrenocortical cancer, even in metastatic disease. *Surgery* 2014;156(6)1531-1540.
2. Thomas AZ, Blute ML, Seitz C et al Management of the incidental adrenal mass. *Eur Urol Focus* 2016;1(3)223-230.
3. Kutikov A, Mallin K, Canter D et al. Effects of increased cross sectional imaging on the diagnosis and prognosis of adrenocortical carcinoma: analysis of the National Cancer Data Base. *J Urol* 2011;186(3):805-810.
4. Adler JT, Mack E, Chen H. Equal oncologic results for laparoscopic and open resection of adrenal metastases. *J Surg Res* 2007;140(2)159-164.
5. Howell GM, Carty SE, Armstrong MJ et al. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Onc* 2013;20(11)3491-3496.
6. Sancho JJ, Triponez F, Montet X, Sitges-Serra A. Surgical management of adrenal metastases. *Langenbecks Arch Surg* 2012; 397(2)179-194.
7. Monn MF, Calaway AC, Mellon MJ et al. Changing USA national trends for adrenalectomy: the influence of surgeon and technique. *BJU Int* 2014;115(2)288-294.
8. Al-Quarayshi Z, Robins R, Buell J, Kandil E. Surgeon volume impact on outcomes and cost of adrenal surgeries. *Eur J Surg Oncol* 2016;42(10):1483-1490
9. Shumarova SY. Management of isolated adrenal metastases. *Khirurgiia (Sogiia)* 2016;82(2):87-96.
10. Kebebew E, Siperstein AE, Clark OH, Duh QY. Results of laparoscopic adrenalectomy for suspected and unsuspected malignant adrenal neoplasms. *Arch Surg* 2002;137(8):948-951.
11. Miccoli P, Materazzi G, Mussi A et al. A reappraisal of the indications for laparoscopic treatment of adrenal metastases. *J Laparoendosc Adv Surg Tech* 2004;14(3):139-145.
12. Silvio Estaba L, Madrazo Gonzalez Z, Pujol Gebelli J et al. Laparoscopic adrenalectomy for suspected isolated adrenal metastasis. *Cir Esp* 2007;81(4):197-201.
13. Villaruz LC, Kubicek GJ, Socinski MA. Management of non-small cell lung cancer with oligometastasis. *Cur Oncol Rep* 2012;14(4):333-341.
14. Mercier O, Fadel E, de Perrot M et al. Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005;130(1):136-140.
15. Raz DJ, Lanuti M, Gaissert HC et al. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. *Ann Thorac Surg* 2011;92(5):1788-1792.
16. Collinson FJ, Lam TK, Bruijn WM. Long-term survival and occasional regression of distant melanoma metastases after adrenal metastasectomy. *Ann Surg Oncol* 2008;15(6):1741-1749.
17. Lau WK, Zincke H, Lohse CM et al. Contralateral adrenal metastasis of renal cell carcinoma: treatment, outcome and a review. *BJU Int* 2003;91(9):775-779.
18. Lindeman B, Hashimoto DA, Bababekov YJ et al. Fifteen years of adrenalectomies: impact of specialty training and operative volume. *Surgery* 2018;163(1):150-156.
19. Park HS, Roman SA, Sosa JA. Outcomes from 3144 adrenalectomies in the United States: Which matters more, surgeon volume or specialty? *Arch Surg* 2009;144(11):1060-1067.
20. Christakis I, Ng CS, Chen C et al. Operation duration and adrenal gland size, but not BMI, are correlated with complication rate for posterior retroperitoneoscopic adrenalectomy for benign diseases. *Surgery* 2019;165(3):637-643.
21. Chen Y, Scholten A, Chomsky-Higgins K et al. Risk factors associated with perioperative complications and prolonged length of stay after laparoscopic adrenalectomy. *JAMA Surg* 2018;153(11):1036-1041.