Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Laparoscopic adrenalectomy for metastatic disease: Retrospective cohort with long-term, comprehensive follow-up

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ARTICLE INFO

Article history:
Accepted 16 November 2018
Available online xxx

ABSTRACT

Background: Several malignancies metastasize to the adrenal gland, especially non-small cell lung cancer, renal cell carcinoma, and melanoma. Adrenalectomy is associated with prolonged survival, but laparoscopic adrenalectomy for this indication is controversial. Our objective was to characterize and quantify outcomes after laparoscopic adrenalectomy for metastases to the adrenal gland.

Methods: A prospectively maintained surgical database and institutional cancer registry were queried for patients who underwent adrenalectomy for metastases. From 1995 to 2016, a total of 62 patients underwent adrenalectomy for metastases, with 59 (95.%) having been performed laparoscopically. Primary end points were cumulative probability of 5-year survival and median survival. Patients in the institutional series were compared with Surveillance, Epidemiology, and End Results patients with metastatic non-small cell lung cancer, renal cell carcinoma, and melanoma.

Results: There were no deaths within a 30-day period, 6 complications, and 2 conversions to open adrenalectomy. Non-small cell lung cancer (N = 20), renal cell carcinoma (N = 14), and melanoma (N = 8) were the 3 most common adrenal metastases. Overall, cumulative probability of 5-year survival was 37% and median survival was 34 months (95% CI 26–53 months). Median survival for non-small cell lung cancer was 26 months, for renal cell carcinoma was 67 months, and for melanoma was 30 months (P = NS). There was no demonstrable survival benefit for metachronous versus synchronous presentations, no association with size or disease-free interval, nor the presence/history of other metastases.

Conclusion: Laparoscopic adrenalectomy for metastases is safe when performed by experienced surgeons. Outcomes are similar or improved compared with series with predominantly open adrenalectomies. Patients selected for laparoscopic adrenalectomy to treat metastatic disease also have prolonged survival compared with Surveillance, Epidemiology, and End Results patients with metastatic non-small cell lung cancer, renal cell carcinoma, or melanoma who do not undergo resection of metastatic disease.

Introduction

In 1982, Clark et al. at the University of California, San Francisco (UCSF) Medical Center published the first report of two successful open adrenal resections for metastatic lesions from non-small cell lung cancers (NSCLC). At the time of publication, both patients were alive at 6 and 14 years postadrenalectomy; whereas contemporary data gave patients with extrathoracic NSCLC a median survival of 3 months with zero survival beyond 1 year.[1] Since then, adrenalectomy for metastatic disease in well-selected patients has become an accepted therapy, and more recently, minimally invasive adrenalectomy has been recommended by some experts as the preferred operative approach.[2,3] As recently as 2017, however, a minimally invasive approach was described as controversial.[4]

Metastases to the adrenal gland are common. A 1950 paper in *Cancer*, based on 1,000 autopsies, found an adrenal metastasis in up to 27% of the autopsies (all patients had died of a nonadrenal carcinoma).[5] Several malignancies in particular are known

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https://doi.org/10.1016/j.surg.2018.11.008
0039-6060/

to metastasize to the adrenal gland, especially NSCLC, renal cell carcinoma (RCC), melanoma, breast cancer, and colorectal cancers. Several case series have investigated both open and laparoscopic adrenalectomy in the management of adrenal metastases, and, among appropriately selected patients, operative management appears to confer a survival benefit compared with nonoperative management alone.[2,6,7] To date, the number of cases of minimally invasive adrenalectomy published by authors at US institutions include 55 (M.D. Anderson, Houston, TX),[8] 41 (University of Pittsburgh, PA),[7] and 31 (Memorial Sloan Kettering, New York NY).[2] The objective of the current study was to elucidate long-term outcomes and, specifically overall survival, for a cohort of patients who primarily underwent laparoscopic adrenalectomy for metastatic disease. Because of a unique resource that is the UCSF Cancer Registry, our long-term follow-up is quite robust. An additional objective was to evaluate other questions of interest to the surgical oncologist and endocrine surgeon in terms of determining whether a patient is a good candidate for laparoscopic adrenalectomy, including the type of primary tumor, history of other nonadrenal metastases, synchronous or metachronous presentation with the primary cancer, and the importance of a disease-free interval (DFI).

Methods

Data sources

Patients who underwent adrenalectomy for metastatic disease were identified from each attending surgeon's prospectively maintained operative log. After appropriate approval by the Institutional Review Board (IRB), a retrospective chart review in the current and previous iterations of the UCSF electronic medical record (EMR)was performed. The UCSF Medical Center maintains a cancer registry that tracks cancer patients treated at the institution and provides long-term follow-up and vital statistics. In addition to the operative logs, we queried the UCSF Cancer Registry for all patients who underwent adrenalectomy for malignancy at our institution from 1995 through 2016. For patients who did not have data in the EMR, either because they were treated before its implementation or their nonoperative care was not at UCSF, the Cancer Registry was able to provide data on vital status, dates of diagnosis, presence or absence of disease at time of death, and other pertinent variables. Because the UCSF Endocrine Surgery faculty also attend at the San Francisco Veterans Administration Medical Center (SF VAMC), we included patients who underwent operations for adrenal metastases at this facility as well. This aspect of the research study received separate approval from the SF VAMC IRB. The series included 9 patients from the SF VAMC and 53 patients from UCSF Medical Center. Both laparoscopic and open adrenalectomy patients were included in the cohort, but the majority of patients ($>$ 95%) underwent minimally invasive operations. To allow complete follow-up, the research team had IRB approval to contact patients or their families. As a secondary analysis, we compared stage 4 NSCLC, RCC, and melanoma patients included in the Surveillance, Epidemiology, and End Results (SEER) program to the relevant group of patients in our cohort. All patients in the SEER analysis were stage 4 patients who had operations for their primary cancer but were not coded as having an operation for their metastatic lesion(s). This study was developed and designed in accordance with the principles outlined in the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) Statement.[9]

Patient inclusion criteria

Patients included in this project were $\geq$18 years of age. Inclusion criteria were a nonadrenal primary malignancy with an adrenal metastasis that was confirmed on final pathology. Adrenal surgery was performed either at the UCSF or SF VAMC between 1995 and 2016 by the General Surgery service or in a few cases by UCSF Urology.

Variables included demographics, primary tumor site, presence or absence of other metastases, DFI and whether it was thought that the patient had active disease other than the adrenal metastasis at the time of adrenalectomy. Whenever possible, we recorded the date that the patient completed treatment for the primary lesion. This was the date of surgery for those patients whose primary was treated with surgery only and this was the date that adjuvant therapy was completed for those who had additional treatment modalities. We defined metachronous adrenal metastases as those that were diagnosed 6 months or more after treatment for the primary lesion. In some cases of synchronous metastases, the adrenal operation was done before definitive treatment of the primary cancer. In each of these cases, the patients were coded as having active disease at the time of adrenal surgery. In other situations, we based the assessment of active disease on what was recorded in the medical oncology or surgical oncology notes. Chart review was extensive. For example, if a radiographic lesion was indeterminate (or believed to be benign) at the time of the adrenal operation, but was later found to be a metastasis in longer term follow-up, this was coded as active disease at the time of the adrenalectomy. All operations were for curative intent, with one possible exception (a patient with melanoma whose operation was for vaccine development). Vital status was able to be confirmed for 61 of 62 patients. The follow-up period ended on August 15, 2016, and all patients known to be alive as of that date were censored.

Statistical analysis

Summary statistics for demographics and clinical characteristics were generated using standard methodologies. Missing data are noted where applicable. Survival analysis was evaluated using univariate and multivariable Kaplan-Meier methodologies and Cox proportional hazard ratios. This enabled us to compare survival outcomes for the three most common primary cancers (NSCLC, RCC, and melanoma), as well as comparisons of metachronous or synchronous presentations and patients with active disease compared with no active disease at the time of adrenal surgery. These survival analyses were performed in a univariate fashion and then were adjusted for age or sex.

For the secondary analysis, we compared stage 4 NSCLC, RCC, and melanoma patients from the SEER database with patients in our cohort with the same primary lesions. All SEER patients had operations for their primary cancer, but were not coded as having had an operation for their metastatic lesion(s), which were not necessarily adrenal metastases. This enabled us to exclude those patients who presented with widely metastatic disease who would not have been operative candidates at all. Survival time in our primary analysis was from adrenalectomy to death or censoring, but this is not comparable with survival times in SEER. Therefore, for this secondary analysis, we utilized survival from the time of diagnosis for SEER patients and survival from treatment of the primary in the UCSF/SF VAMC patients. Time from diagnosis to treatment is generally not prolonged; moreover, this is a conservative limitation (ie, if we were able to evaluate survival time from diagnosis of the primary among the UCSF patients, it would be greater). These adrenalectomy patients are a highly selected group of patients compared with those in the SEER data, but we believed that this comparison provides a useful context for clinicians and the patients they are counseling.

Please cite this article as: F.T. Drake, T. Beninato and M.X. Xiong et al., Laparoscopic adrenalectomy for metastatic disease: Retrospective cohort with long-term, comprehensive follow-up, Surgery, https://doi.org/10.1016/j.surg.2018.11.008

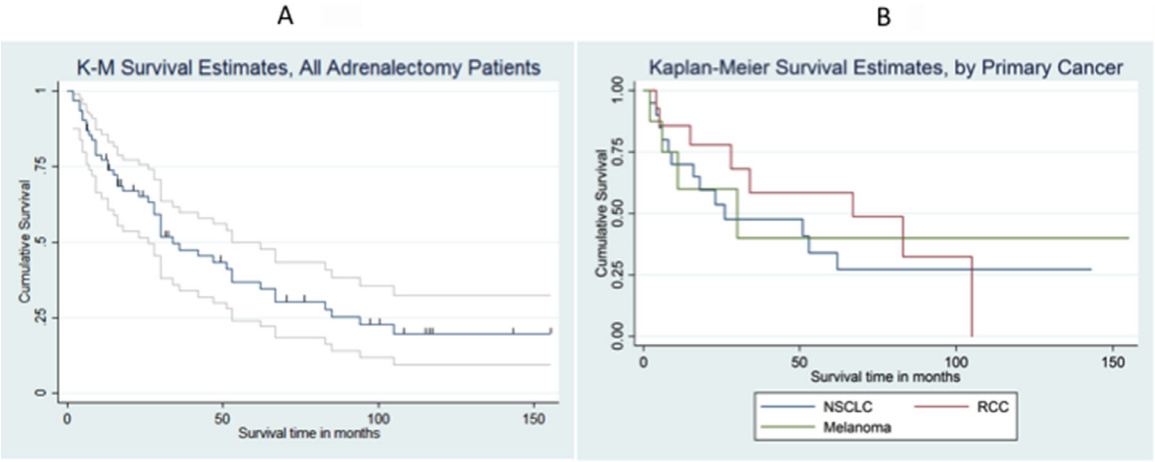

Fig. 1. Kaplan-Meier survival estimates: (*A*) all patients (*light lines* represent the 95% CI for the main KM survival estimate [*dark line*]) and (*B*) stratified by non-small cell lung cancer, renal cell carcinoma, and melanoma.

Human subject approval

This research study was evaluated and approved by both the UCSF and the SF VAMC IRBs.

Results

From 1995 to 2016, a total of 62 patients underwent adrenalectomy for adrenal metastases, with 59 (95.2%) of these performed laparoscopically (2 converted to open). The cohort was predominantly male (69%), and the mean age of patients was 62 years (range 24–89 years). The average size of the lesions was 4.2 cm (standard deviation 2.3 cm). NSCLC was the predominant lesion (33%), followed by RCC (23%) and melanoma (13%). None of the operations were done for palliation. There were no intraoperative deaths, and 30-day mortality was zero. There were 6 complications (10%): 2 pulmonary emboli, and 1 each of aspiration pneumonia, ileus, adrenal insufficiency, and 1 reoperation for retroperitoneal hematoma. Data on the duration of stay were available for 46 patients. The median duration of stay was 2 days. A total of 40 % of patients had a stay of 1 day.

At the time of adrenalectomy, 65% of patients had no known additional sites of active disease detected on preoperative evaluation. Primary lesions were treated either with operation (majority), including adrenalectomy plus adjuvant modalities, and a few patients ($n=6$) underwent radiation with or without chemotherapy of the primary cancer with curative intent. In some instances, the active disease at the time of adrenalectomy was the primary (10% of total patients) and in other cases it was another metastasis (21%). Synchronous presentation of the primary cancer and the adrenal metastases occurred in 27.% of the patients (Table 1). A total of 5 patients underwent bilateral adrenalectomy, but these operations were never concomitant.

Survival was calculated from time of adrenalectomy. Median survival time for the entire patient cohort was 34 months (95% CI 26–53 months). Cumulative probability of survival at 5 years was 37% (95% CI 24–50%; Table 1). A Kaplan-Meier survival curve was generated for the entire patient cohort (Fig. 1, *A*). Among only those 59 patients who underwent LA, median survival was the same at 34 months (95% CI 23–62 months) and cumulative probability of 5-year survival was 37% (95% CI 24–51%). We then stratified the cohort by the 3 most common primary cancers: NSCLC, RCC, and melanoma. RCC patients were older compared with melanoma and NSCLC patients ($P=.003$). There was no difference in size or sex distributions. A total of 42% of patients in the NSCLC group were synchronous at presentation compared with 14% for RCC and 12.4% for melanoma. Median survival for NSCLC was 26 months, for RCC was 67 months, and for melanoma was 30 months. When survival probabilities were compared via Cox proportional hazard testing, differences were not significant, either in univariate comparisons or once adjusted for age and sex (Table 2). Kaplan-Meier survival curves were generated for the 3 most common primary lesions (Fig. 1, *B*).

We compared other potential risk factors for decreased survival, including age, sex, size of adrenal metastasis, synchronous versus metachronous presentation, the presence of other metastases (either active at the time of adrenalectomy or successfully treated before adrenalectomy), DFI, and active disease versus no evidence of active disease. Again, via Cox proportional hazard testing, there were no significant associations among any of these potential risk factors and survival (Table 3). The latter four comparisons were adjusted for sex and age, but did not have an impact on our findings. Kaplan-Meier curves were generated for presence versus absence of active disease and metachronous versus synchronous presentation of the adrenal metastases (Figs. 2*A* and *B*). As Fig. 2 (*A*) illustrates, survival estimates for patients with active disease ($n=19$ [6 primary and 13 nonadrenal metastases]) and without active disease ($n=40$) at the time of adrenalectomy are sharply divergent for at least 5 years after adrenalectomy but converge as follow-up time continues to accrue.

NSCLC, RCC, and melanoma patients in our operative cohort were compared with stage 4 NSCLC, RCC, and melanoma patients in SEER who were treated with an operation for their primary lesion but who did not undergo surgery for their metastatic lesions. A total of 280 SEER patients were included (40 NSCLC, 222 RCC, and 18 melanoma), with 34% women and a mean age of 62.3 years. Between the UCSF/SFVAMC cohort and the SEER group, there was a significant difference in median survival and 5-year survival for all comparisons (Table 2 and Fig. 3).

Discussion

This is the largest single-center series of patients undergoing laparoscopic adrenalectomy for metastatic disease yet published. To our knowledge, other than one small series from two tertiary institutions,[10] there have been no multicenter investigations in the United States. This is in contrast to a large, 317-patient study published in 2013 by a group of authors from across Europe.[11] In that group, less than half of the individuals ($n=146$) underwent laparoscopic operations, and in a notable difference from the US

Table 1
Demographics, clinical characteristics, and unadjusted outcomes.

Age, years (mean [SD]) at the time of adrenalectomy	61.8 (12.7)
Sex	
Male % (n)	69 (43)
Female % (n)	31 (19)
Primary lesion	
NSCLC	33% (20)
RCC	23% (14)
Melanoma	13% (8)
Liver	8% (5)
Colorectal	7% (4)
Breast	(2)
Other*	15% (9)
Timing of adrenal metastasis with primary cancer	
Metachronous†	71% (44)
Synchronous	27% (17)
Unknown	(1)
Other Metastases (prior to adrenal surgery)	
Yes	58% (36)
No	37% (23)
Unknown	5% (3)
Mean Size of Adrenal Metastasis [mean, (SD)]‡	4 (2.3) cm
Active Disease at time of Adrenalectomy	
None	65% (40)
Other metastasis	21% (13)
Primary	10% (6)
Unknown	5% (3)
Mean DFI, years [mean, (SD)] *Prior to adrenalectomy (50 patients)*§	2.5 (3.0)
Operative Approach	
Laparoscopic	92% (57)
Open	5% (3)
Laparoscopic converted to open	(2)
All laparoscopic¶	95% (49)
Bilateral adrenalectomy	8% (5)
Overall Cohort Outcomes	
Median Survival, months (95%CI) (all adrenalectomy patients)	34 (26,53)
KM Probability of survival at 12 months	7% (95% CI 64-86%)
KM Probability of survival at 36 months	50% (95% CI 56-62%)
KM Probability of survival at 60 months	37% (95% CI 24-50%)

* Other includes: esophagus ($n=1$), small cell lung ($n=1$), leiomyosarcoma ($n=2$), prostate ($n=1$), rhabdosarcoma ($n=1$), papillary thyroid cancer ($n=1$).

† Our definition of metachronous adrenal metastases includes all lesions detected within 6 months of treatment of the primary cancer.

‡ Because our operative technique calls for intracorporeal fragmentation of the lesion (within an impermeable bag), this size is based on radiographic measurements.

§ A total of 50 patients had a disease-free interval (DFI) even though only 44 are coded as metachronous, because 6 patients had a <6-month interval between treatment of primary and detection of adrenal metastasis and are thus included in the calculation of DFI.

¶ This includes two operations that were converted to open and one hand-assisted laparoscopic adrenalectomy.

NOTE: This table presents notable demographic and clinical characteristics of the surgical cohort, as well as median survival and probability of survival at 1, 3, and 5 years.

SD, standard deviation; *KM*, Kaplan-Meier; NSCLC, non-small cell lung cancer; *RCC*, renal cell carcinoma.

Table 2
Comparison of non-small cell lung cancer, renal cell carcinoma, and melanoma: UCSF patients and SEER stage 4 patients.

Cohort characteristics and survival results	NSCLC ($n=20$) UCSF only	RCC ($n=14$) UCSF only	Melanoma ($n=8$) UCSF only	
Age	59.3 y	69.5 y	50.7 y	$P=.003$ (ANOVA)
% male	70	86	63	$P=$NS (χ^2)
Size	3.5 cm (SD 2.0)	4.5 cm (SD 1.6)	3.1 cm (SD 1.8)	$P=$NS (ANOVA)
% synchronous	8 (42%)	2 (14%)	1 (12.5%)	$P=$NS (χ^2)
KM probability of survival at 12 mo	70.0% (95% CI 45–85%)	85.7% (95% CI 54–96%)	60.0% (95% CI 20–85%)	
KM probability of survival at 36 months	47.7% (95% CI 24–68%)	58.4% (95% CI 26–81%)	40.0% (95% CI 7–73%)	
KM probability of survival at 60 mo	34.1% (95% CI 13–56%)	58.4% (95%CI 26–81%)	40.0% (95%CI 7–73%)	
Median survival	26 (95% CI 8, 62)	67 (95% CI 12, –)	30 (95% CI 7, –)	$P=$NS (CPHR)
Median survival UCSF patients, measured from *treatment* of primary	51 (95% CI 28, –)	138 (95% CI 78, –)	154 (95%CI 38, –)	
Median survival SEER patients, measured from *diagnosis* of primary	11 (95% CI 5, 23) ($P<.001$)	12 (95% CI 10, 15) ($P<.001$)	14 (95% CI 8,0) ($P<.001$)	

NOTE: Table 2 compares demographic and clinical characteristics of the surgical cohort, as well as median survival and probability of survival at 1, 3, and 5 years. Statistical tests are described in the Methods section but noted here. After adjusting for age, sex, and chronicity of the adrenal metastasis, there was no change in hazard ratio comparing renal cell or melanoma versus NSCLC. There are additional data comparing UCSF patients with SEER stage 4 patients. There was a significant increase in survival for those who underwent an adrenalectomy compared with the SEER stage 4 cohort who had surgery for their primary lesion but no operation for their metastatic disease.

Please cite this article as: F.T. Drake, T. Beninato and M.X. Xiong et al., Laparoscopic adrenalectomy for metastatic disease: Retrospective cohort with long-term, comprehensive follow-up, Surgery, https://doi.org/10.1016/j.surg.2018.11.008

Table 3
Other potential risk factors for decreased survival.

	Cox proportional hazard ratio	95% Confidence interval
Age (years)	1.0	0.99–1.0001
Sex	1.6 (male versus female)	0.82–2.98
Size of adrenal metastasis	1.1	0.95–1.27
Synchronous metastasis	1.3 (versus metachronous)	0.65–2.70
Other metastases (before or concurrent with adrenal met)	1.3 (versus no other metastases)	0.68–2.44
Active disease at time of adrenalectomy	1.6 (versus disease free)	0.83–3.08

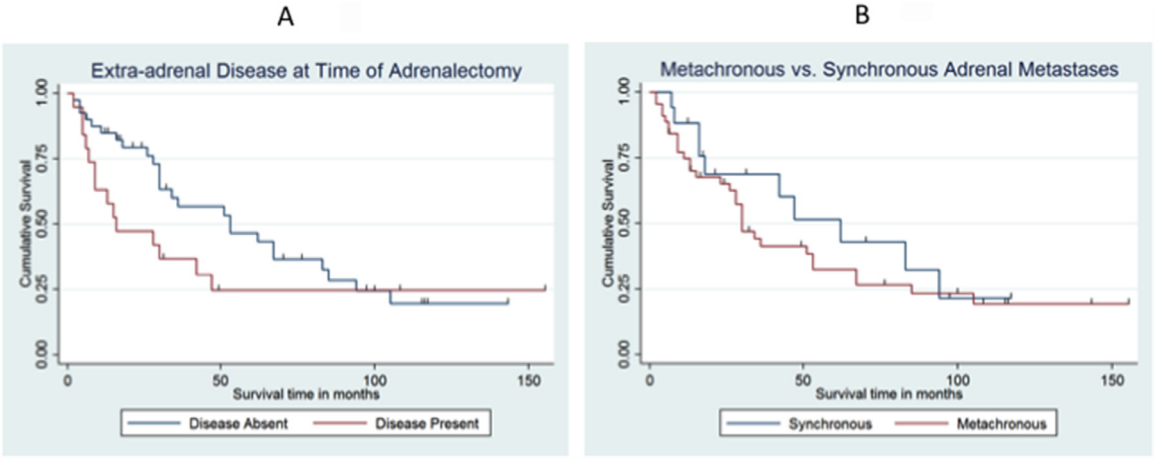

Fig. 2. Kaplan-Meier survival estimates: (*A*) disease free versus active disease present at time of adrenalectomy and (*B*) metachronous versus synchronous adrenal metastases.

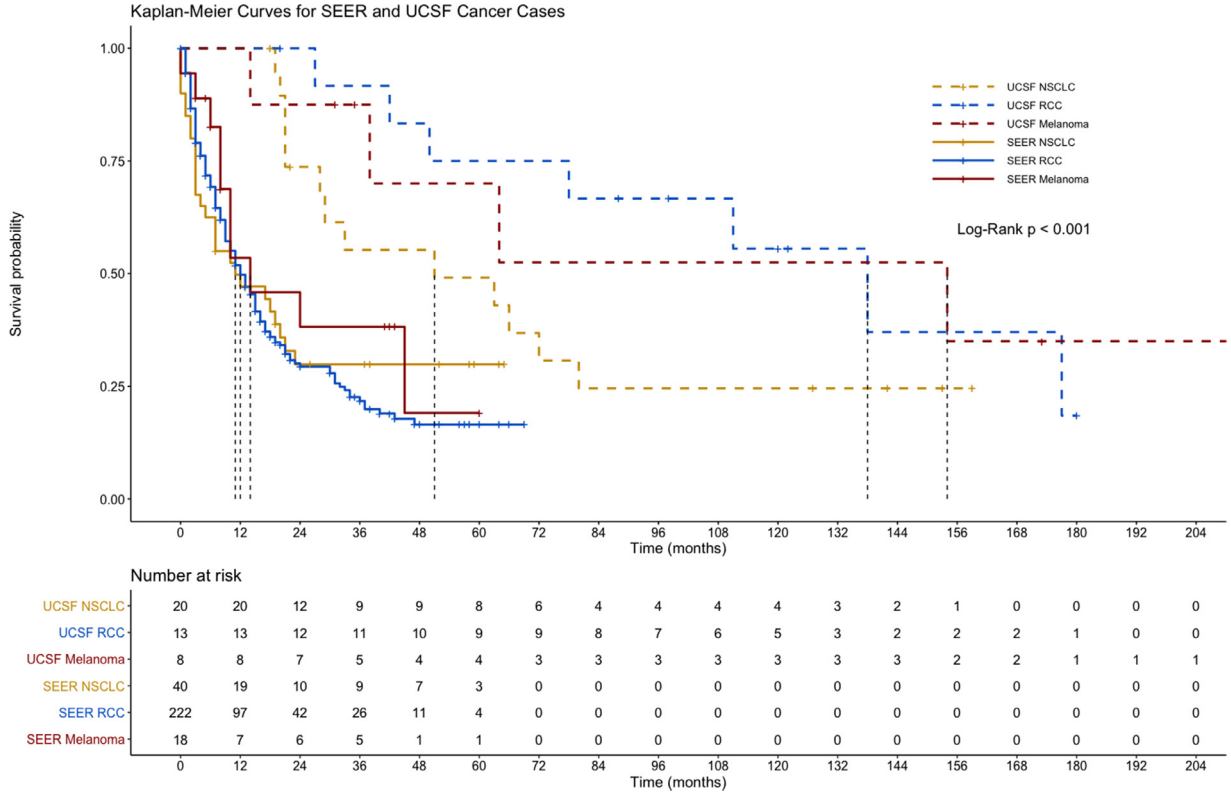

Fig. 3. Kaplan-Meier survival estimates: UCSF adrenalectomy versus SEER stage 4 cohort, NSCLC, RCC, and melanoma *Color of the lines* is the same for NSCLC, RCC, and melanoma. *Dashed lines* represent patients who underwent adrenalectomy for metastatic disease and the *solid lines* represent SEER stage 4 patients who underwent operations for their primary but did not undergo operative treatment of metastatic lesion(s).

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Table 4
Data in context.

	Drake et al. (current study) UCSF - 2018	Romero Arenas et al.[8] MD Anderson - 2014	Howell et al.[7] Pittsburgh - 2013	Strong et al.[7] MSK - 2007	Moreno et al.[11] Europe - 2013
Number of patients	62 (all curative intent)	90 (including 8 palliative operations)	62 (59 with follow-up data, all curative intent)	92 (94 adrenals)	317 multicenter study
Minimally invasive	59 (2 converted to open)	55	41 (3 converted to open)	31 (4 converted to open)	146
Years treated	1995–2016	1990–2012	2000–2012	1995–2006	1999–2011
Percent male	43 (69%)	60 (67%)		54 (59%)	223 (70%)
Age	61.8 y (SD 12.7) (mean)	59 y (median) range (4–84)	60 ± 12 y (mean)	60 ± 2 y (median)	58.9 (SD 10.6 y) (mean)
Metachronous/ synchronous*	44/17 (3 unknown) No difference in survival	74/16 No difference in survival	51/11 Synchronous = worse survival	66/28 No difference in survival	244/73 synchronous = worse survival (univariate)
Size	4.2 (SD = 2.3) cm	Not stated	Not stated	5.6 ± 0.4 cm (median)	0.6 ± 0.3 cm
Median follow-up†	29 mo	14.5 mo	Not stated	Not stated	20 mo
Median survival (all patients)	34 mo (95%CI 26–53)	29.5 mo	30 mo	30 mo	29 mo (95%CI 24.7–33.3)
5-year survival	37% (95%CI 23–50%)	38%	31%	31%	35% (95%CI 29–42%)
NSCLC	20 (33%) median survival = 26 mo	32 (36%) median survival = 19 mo	29 (49%) median survival = 17 mo	39 (42%)	148 (46.7%) median survival = 26 mo
Renal cell cancer	14 (23%) median survival = 67 mo	2	8 (13%)	13 (14%)	37 (11.7%) median survival = 84 mo
Colon cancer	4 (7%)	4 GI cancers	4 (6%)	11 (12%)	43 (13.6%) median survival = 29 mo
Melanoma	8 (13%) median survival = 30 mo	35 (39%) median survival = 24 mo	4 (6%)	7 (8%)	11 (3.5%)
Factors associated with decreased survival	None significant	• Increasing age • Not disease free after adrenalectomy • Increasing operative time (These were significant in multivariate model)	• Lung primary • DFI < 12 mo • Synchronous met	• Size >4.5 cm • Local recurrence	• No chemotherapy • Nonoperative treatment of primary • Incomplete resection of adrenal metastasis (These were significant in multivariate model)

* All studies included here have the same definition of "synchronous," which is diagnosis of the metastasis within 6 months of diagnosis of the primary.
† In our analysis, median follow-up is defined as median time under observation for all participants whether they died or were censored. (Median follow-up time was defined in the other studies.)
NOTE: Table 5 presents an overview of several of the larger US series of patients who have undergone adrenalectomy for metastases and the large European multicenter cohort. Table 5 illustrates similarities and differences in both definitions and outcomes between the various studies.

experience, the lesions in the European multicenter study were considerably smaller (6 mm ± 3 mm on average).

In Table 4, we have generated a cumulative overview of the four largest series from the United States, including our own, which produces a group of 305 patients, nearly the same number as in the European study. Setting aside the size difference between the European and American case series, there are some important commonalities across all of these sets of data. In all cohorts, the average age was around 60 years (range 59–62 years). There was also a strong overall male predominance (59%–70%). In all cohorts, NSCLC was the most common metastasis except for at M.D. Anderson (Houston, TX), where melanoma was the most prevalent (NSCLC was second). In all groups, RCC, melanoma, and GI (or colorectal specifically) made up the next most frequent malignancies with operative metastases to the adrenal gland. Overall median survival was similar for the included cohorts (UCSF = 34 months, M.D. Anderson = 30 months, Pittsburgh = 30 months, Memorial Sloan Kettering = 30 months, European multicenter study = 29 months). Our median follow-up was 29 months compared with 14 months (M.D. Anderson) and 20 months (European multicenter study), which may have contributed to the slightly greater median survival observed in the UCSF patient cohort. In all series where these data were included, RCC had a substantially greater median survival compared with NSCLC. The US reports referenced here each identified various factors associated with decreased survival, such as the presence of active disease at the time of adrenalectomy, lung primary, DFI < 12 months, size of the adrenal metastasis >4.5 cm, and local recurrence of disease in the adrenalectomy bed. Findings were not consistent across the various series. Although our comparisons did not reach statistical significance, several of the trends in our results are similar, particularly our improved survival for RCC compared with NSCLC and the early sharp divergence in Kaplan Meier survival estimates for extra-adrenal disease (Fig. 2, *A*). In our analysis, size of the metastasis was included as a continuous variable, but in the study where size was found to impact survival, the authors created a break point to generate a categorical variable. In the European study, factors associated with decreased survival (in multivariate analysis) included only three factors: no adjuvant chemotherapy, nonoperative treatment of the primary cancer, and incomplete resection of the adrenal metastasis. In their initial univariate analysis, however, additional characteristics associated with decreased survival were synchronous versus metachronous metastases, NSCLC compared with RCC, extra-adrenal disease, extended adrenalectomy versus isolated adrenalectomy, and tumor size. Many of these univariate associations, in particular the influence of tumor size, the presence of additional disease, and improved outcomes for RCC compared with NSCLC are consistent with the other patient series in the literature and with trends in our own data. The fact that these associations were not maintained in multivariable analysis suggests that adjusting for tumor type (among other variables) may diminish the association between some variables and survival and, if a large multicenter cohort is developed in the future, an important analytic strategy would be to stratify the analysis by tumor type then adjust for other variables (such as chronicity, extra-adrenal disease, size of tumor, etc) within each strata.

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To our knowledge, there have been no prospective studies of adrenalectomy for metastatic disease. In addition to the retrospective studies summarized earlier in this report, there has been one study based on a large administrative database and one meta-analysis. The database project was based on the National Inpatient Sample (NIS), with patients selected via ICD-9 codes for adrenalectomy and diagnostic codes for adrenal metastases, yielding a very large cohort of 2,057 patients. The distribution of tumors was relatively similar to other published series, with 50.5% lung, 21.5% renal, 9.6% melanoma, 3.7% colorectal, and 1.9% breast. Because the NIS does not include long-term data, the authors evaluated inhospital mortality. They found that inhospital, postoperative mortality was 2.2% and that age ≥71 years was associated with a greater odds of death. Over time, they saw a steady increase in the use of minimally invasive techniques for these operations and a corresponding decrease in duration of stay. Adrenalectomy for metastatic disease increased from just more than 100 in 1992 to nearly 450 in 2010.[12] The 2008 meta-analysis focused only on NSCLC adrenal metastases and provided pooled data on 114 patients from 10 studies. Median overall survival was less for those with synchronous metastases versus those with metachronous metastases: 12 vs 31 months, which was statistically significant; however, these differences were most notable early on, and, by 5 years, the survival rates were 25% and 26%, respectively.[13] This survival pattern, where clinical variables that tend to portend worse outcomes are influential early and then less influential as time accrues, is similar to trends seen in the Kaplan Meier curves generated by our own data.

Our comparison to SEER data yielded similar findings to those published by Vazquez et al.[6] in 2012, but our comparison suffers from the same limitations, namely that the two patient groups are not directly comparable.[6] In our analysis of SEER patients, median survival was 11 months for NSCLC, 12 for RCC, and 14 for melanoma. Vazquez et al.[6] did not evaluate melanoma in SEER, but they found a 13-month survival for NSCLC and 15.5-month survival for RCC. They chose patients diagnosed 2004-2007, and we chose patients from 2005-2015, but the similarity of results gives external validity to our analysis. Furthermore, in both analyses, patients with adrenalectomy had dramatically prolonged overall survival compared with SEER stage 4 patients (Table 2). Certainly, these data cannot prove that laparoscopic (or open) adrenalectomy for metastatic disease improves survival, but it does demonstrate—at two different high-volume centers—that patients who are chosen carefully for this operation tend to do well. Whether the survival is from control of metastatic disease, from the overall biology of the disease, or from a combination of both, can likely only be determined from a prospective, randomized trial. Because laparoscopic adrenalectomy represents such an advance for this patient population (in terms of patient comfort, low complication rates, short duration of stay, etc), a randomized trial would be a challenging undertaking. Thus, advanced observational methods and prospective patient registries are likely the optimal methods to further our knowledge of this disease and its treatment.

In summary, the most common primary lesions that metastasize to the adrenal gland are NSCLC, RCC, and melanoma, but a wide variety of primary cancers can metastasize to the adrenal gland. NSCLC tends to have a lesser median survival than other lesions. Overall, compared with SEER stage 4 patients who had operations for their primary cancer but not for their metastases, patients who undergo adrenalectomy for metastatic disease tend to do well in terms of survival. Outcome patterns related to size, metachronous versus synchronous presentation, or the presence of other metastatic lesions are not consistent or definitive enough to drive clinical decision-making about operative candidacy; however, the preponderance of data on this topic suggests that synchronous metastases, presence of extra-adrenal disease, and larger tumors may be associated with a lesser survival. This topic should be studied further. A randomized controlled trial seems unlikely, but development of a well-designed, prospective, multicenter patient registry with strictly defined enrollment criteria, variables of interest, and outcomes should be supported.

This is a retrospective, single-center study with all the attendant limitations of retrospective data, including confounders that were unable to be adjusted for in our multivariable models. Furthermore, the outcomes achieved at a single high-volume center are not necessarily applicable outside of that center. Despite our thorough efforts to ascertain outcomes of all patients, one patient was lost to follow-up and censored before the official study end date. As already noted, these highly-selected patients are not directly comparable to stage 4 cancer patients in the SEER database. The former are operative candidates and are deemed to have good control of their primary malignancy or their other sites of disease, but the same cannot be said of all melanoma, NSCLC, and RCC patients who did not have an operation for their metastatic lesion (although we did exclude SEER patients who did not have an operation on the primary). Similarly, this study did not directly compare patients who underwent minimally invasive adrenalectomy with those who underwent conventional open adrenalectomy. Thus, no directly comparative inferences can be made beyond historic comparisons with the literature.

In conclusion, the data presented here demonstrate that laparoscopic adrenalectomy is safe and is associated with prolonged survival in well-selected patients with adrenal metastases. This study and a preponderance of evidence from similar studies support the conclusion that, unless contraindicated by size or other anatomic considerations, minimally invasive adrenalectomy should be the first-line operative modality offered to patients with adrenal metastases.

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Please cite this article as: F.T. Drake, T. Beninato and M.X. Xiong et al., Laparoscopic adrenalectomy for metastatic disease: Retrospective cohort with long-term, comprehensive follow-up, Surgery, https://doi.org/10.1016/j.surg.2018.11.008