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Surgery Is Associated with Improved Survival for Adrenocortical Cancer, Even in Metastatic Disease

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Abstract

Background—Adrenocortical carcinoma (ACC) is a rare but lethal tumor. Predictors of survival include earlier stage at presentation and complete surgical resection. We assessed effect of treatment and demographic variables on survival.

Methods—ACC cases were abstracted from the California Cancer Registry and Office of Statewide Health Planning and Development (1999-2008). Predictors included patient demographics, comorbidities, tumor size, stage, and treatment (none, surgery, chemotherapy and/or radiation (CRT), and surgery plus CRT (S+CRT)).

Results—We studied 367 patients with median tumor size of 10cm. At presentation, 37% had localized, 17% had regional, and 46% had metastatic disease. Median survival was 1.7 years (7.4 years local, 2.6 years regional, and 0.3 years metastatic, $P<0.0001$). One-year and five-year survival was: 92%/62% (local); 73%/39% (regional); 24%/7% (metastatic). Increased age (HR 1.16) and Cushing's syndrome (HR 1.66) worsened survival ($P<0.05$). Low socioeconomic status worsened survival in local and regional disease ($P<0.05$). In multivariable regression, both surgery (regional HR 0.13; metastatic HR 0.52) and S+CRT (regional HR 0.15; metastatic HR 0.31) improved survival compared to no treatment ($P<0.02$).

Conclusion—In ACC, surgery is associated with improved survival, even in metastatic disease. Surgery should be considered for select patients as part of multi-modality treatment.

Keywords

Adrenocortical cancer; adrenalectomy; surgery

Introduction

With increasing use of abdominal cross-sectional imaging, adrenal lesions are more commonly identified, occurring in up to 4 to 6% of the ambulatory population.[1, 2] In contrast, malignant adrenal tumors are extremely rare with an incidence of approximately

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1-2 cases per million.[1-3] Despite its rarity, the consequences of adrenal cancer are significant. Almost all patients present with widely metastatic disease, and these patients die within months of diagnosis.[1-3]

Malignancy in an adrenal nodule cannot be predicted unless it invades into nearby structures or has metastasized.[1, 2, 4] Percutaneous biopsy is not diagnostic except for confirming metastatic tumor of extra-adrenal origin.[5] Tumor size greater than 4-6 cm, heterogeneous patterns and irregular surfaces on imaging, and hormone hypersecretion all increase the likelihood of malignancy. Even after surgical resection, malignant potential is difficult to determine histologically. It can be approximated using the Weiss criteria, but malignancy is only confirmed when the tumor recurs or metastasizes.[6, 7] Therefore, major diagnostic dilemmas arise in the evaluation of patients with solitary adrenal nodules.[5]

Complete surgical resection remains the only curative treatment for ACC, while adjuvant treatment with chemotherapy and/or radiation may have a modest improvement in survival.[8] The major predictor of long-term survival is presentation with either stage I or II disease and the ability to undergo complete resection of the tumor.[2, 9, 10] Five-year survival rates range from 16 to 34% overall and only 32-62% in patients who undergo “curative resection.” The survival is as low as 9% in the case of an incomplete resection.[1] The role of surgery for patients with advanced disease has not yet been elucidated.

It has been difficult to study the optimal treatment of ACC due to its rarity. Most peer-reviewed guidelines focus on evaluation and removal of functioning, non-metastatic adrenal tumors. Unfortunately there is no standardized approach to treating malignant adrenal cancers, especially if they are metastatic at the time of diagnosis. The role of surgical resection is controversial if the goal is not curative intent. If the perioperative risks are felt to be acceptable, it is reasonable to debulk a functional ACC for palliation. Small case series have also shown a possible survival benefit for surgical resection in patients with locally recurrent or metastatic ACC.[11, 12] However, there may be little benefit when complete resection of the primary and all metastases cannot be achieved; this must be weighed against the perioperative risks and delay in systemic treatment.[1]

Given the lack of data on this rare but highly lethal cancer, we evaluated the outcomes of patients diagnosed with ACC using a large population-based cancer registry over a ten-year time span. Our aim was to determine how the following treatments are associated with stage-specific survival in ACC: surgery, chemotherapy, and/or radiation therapy.

Methods

Patient Sample

Newly diagnosed ACC cases were abstracted from the prospectively collected California Cancer Registry (CCR) for the years 1999 to 2008. Records were linked to inpatient and ambulatory hospital records maintained by the California Office of Statewide Health Planning and Development (OSHPD) database using unique patient identifiers. This allowed for longitudinal follow-up for each patient from the time of cancer diagnosis. This study was

approved by the University of California, Los Angeles, and the CCR Institutional Review Boards.

Patients were identified by using the SITE_02 variable in CCR, which codes for the location where the tumor originated. Patients were included if they had a SITE_02 variable that coded for adrenal tumor; International Classification of Disease (ICD)-0-3 codes C74.0, C74.1, and C74.9; as well as the following ICD-0-3 histology codes to ensure that only patients with ACC were captured: 8010 (carcinoma, not otherwise specified), 8020 (carcinoma, undifferentiated type), 8140 (adenocarcinoma, not otherwise specified), and 8370 (adrenal cortical carcinoma). We excluded patients with unknown race (n=7) and those with unknown stage (n=35). An additional 4 patients were diagnosed at death and were also excluded. Median follow-up time was 18.8 months, and 80 patients had at least 5-year follow-up.

Variables

Demographics, clinical characteristics, treatment, and outcomes were analyzed collectively and by disease stage. Demographic data included age, gender, race/ethnicity, socioeconomic status (SES), and patient comorbidities. Race/ethnicity was defined as Non-Hispanic white, Non-Hispanic black, Hispanic, and Asian/Pacific Islander (API). SES score was coded as the quintiles of Yost's index of SES level based on a principal components analysis where the lowest SES score was 1 and the highest SES score was 5.[13] Comorbidity was scored using the Charlson comorbidity scoring system, classified as 0 or >0.[14] Data regarding institution type was stratified into the following categories: private, public, academic, and Health Maintenance organization (HMO) hospitals.

Clinical data included cancer size, stage, and whether the tumor was functional (associated with hormone hypersecretion). Cancer size was classified as <10cm, 10-20cm, 20-30cm, and >30cm. Stage was defined as local, regional (direct extension and/or positive lymph nodes), or metastatic using the CCR variable SUMSTAGE for stage at diagnosis. Treatments were defined as none (no treatment received), surgery alone, chemotherapy and/or radiation alone (CRT), and surgery combined with chemotherapy and/or radiation (S+CRT). The treatment variables were derived from the CCR variables surgdate (surgery), rxdatec (chemotherapy), and rxdater (radiation) as well as OSHPD CPT variables for chemotherapy, radiation, and surgery (supplemental Table 1). If there was no date entered for a given variable in either database, the patient was defined as not having received that treatment. Of the patients in the S+CRT group, the vast majority (93.7%) had surgery as the initial treatment modality. OSPHD database ICD-9 codes were used to identify functional tumors: Cushing's syndrome (255.0), hyperaldosteronism (255.1), virilization (255.2 and 255.3), and feminization (256.0).

Statistical Analysis

Patient data were summarized by means with standard deviations (SDs) for continuous variables and frequencies (%) for categorical variables. The primary outcome was all-cause mortality, calculated as the time from diagnosis until death or last follow-up (censored). The all-cause survival functions were estimated using the Kaplan-Meier method and compared

across stage and treatment groups using the log-rank test. Univariate analyses of demographic and clinical factors were studied by application of Chi-squared test or Fisher's exact test for the association between two categorical variables, and by ANOVA or Kruskal-Wallis test for the association between a continuous variable and a categorical variable. Multivariable analysis was further conducted via Cox regression models with treatment as the primary predictor, adjusting for age, comorbidity score, and any other covariates (sex, race, SES, hospital type, tumor size, and Cushing's syndrome) that showed significant association with all-cause survival in univariate analyses. All tests were two-sided. $P < 0.05$ was regarded as statistically significant. Analyses were performed using SAS, release 9.2 (SAS Institute, Inc; Cary, NC).

Results

Between 1999 and 2008, 367 patients were identified with ACC in California who met inclusion criteria for the study (Table 1). Mean age at diagnosis was 53 years, and 57.8% were female. Most patients were healthy with relatively few comorbidities, with only 22.3% having a Charlson Index score of greater than 1. At presentation, the majority of patients had disease that had spread either regionally (17.4%, n=64) or was metastatic (45.5%, n=167) (Table 2). Median tumor size was 9 cm for local disease (range 0.3 to 34 cm), 12 cm for regional (range 2 to 28 cm) and 12 cm for metastatic disease (range 2 to 34 cm). The mean time from diagnosis to treatment was 18.9 days.

Only 18.0% (n=66) were identified as being functional tumors, and the majority (77.3%, n=51) were associated with Cushing's syndrome. Of patients with metastatic disease, 64.1% of those with functional tumors underwent surgery with or without CRT, 25.6% underwent CRT alone, and only 10.3% had no treatment. Patients with metastatic disease that had non-functional tumors were less likely to have surgery either with or without CRT (34.3%), and more likely to have either CRT alone (31.3%) or no treatment (34.4%) (P=0.0011).

All-cause median survival was 1.7 years, with metastatic patients having significantly worse survival (7.4 years for local disease, 2.6 years for regional, and 0.3 years for metastatic, P<0.0001) (Figure 1). One-year survival was 91.8% for local, 73.4% for regional, and 23.7% for metastatic disease. Five-year survival was 61.7% for local, 39.1% for regional, and 6.7% for metastatic disease. There was no association between tumor size and 5-year survival for patients with local disease (69.7% for <10cm, 62.9% for 10-20cm, and 60.0% for >20cm; P=0.69).

Of 254 patients who underwent surgery, the 30-day postoperative mortality was 2.8% (n=7). In addition to adrenalectomy, procedures involving partial or total resection of other organs performed at the time of original surgery included kidney (20.1%), spleen (8.3%), pancreas (5.1%), and liver (3.1%). Only 9.1% of patients were coded as having lymph node dissection. Only 4.7% (n=12) of patients were coded as having a laparoscopic procedure for their initial surgery. The majority of patients in the local (86.8%, n=118) and regional (75.0%, n=48) groups underwent surgery as the sole treatment (Table 2). In contrast, most patient with metastatic disease underwent CRT either alone (29.9%, n=50) or in combination with surgery (26.3%, n=44). Only a minority of patients with metastatic disease underwent

surgery alone (15.0%, n=25), and the remainder (28.7%, n=48) did not undergo any treatment.

There were some disparities in receipt of care in univariate analysis of the entire patient cohort. There was a trend towards increased time from diagnosis to surgery for black patients (mean 32.6 days) compared to white (20.2 days), Hispanic (16.1 days), or Asian / Pacific Islander patients (12.2 days) (P=0.0506). There was no association between SES and time from diagnosis to surgery. Patients who received no treatment were on average older (mean 67.6 years) compared to those who underwent surgery (mean 51.2 years) or CRT (mean 51.8 years), while those who underwent the most aggressive treatment with S+CRT were younger (mean 42.2 years, P<0.0001). There were no other differences in demographics between the treatment groups.

For all patients, factors associated with decreased survival in univariate analysis included increased age (HR 1.20, P<0.0001), low SES (HR 1.80, P=0.001), and the presence of comorbidities (HR 1.65, P=0.0001). A diagnosis of Cushing's syndrome was also a poor prognostic factor of survival (HR 1.49, P=0.0181). Female gender was associated with improved survival (HR 0.65, P=0.0008). Compared to private hospitals, treatment at either academic (HR 0.68, P=0.0186) or HMO hospitals (HR 0.66, P=0.0091) was associated with improved survival. Tumor size was not associated with outcomes.

Treatment type was a significant predictor of survival in univariate analysis. For all patients, surgery with or without systemic treatment was a significant predictor of improved survival compared to no treatment (surgery: HR 0.13, P<0.0001; S+CRT: HR 0.29, P<0.0001). For patients with local disease, surgery was associated with improved survival over no treatment (HR 0.23, P=0.0021). For patients with regional disease, both surgery (HR 0.20, P=0.0002) and S+CRT (HR 0.19, P=0.0057) were associated with improved survival over no treatment. Patients with metastatic disease had improved survival with surgery (HR 0.42, P=0.0008), CRT (HR 0.56, P=0.0058), and S+CRT (HR 0.24, P<0.0001) over no treatment.

Survival analysis for all patients using the Kaplan-Meier method showed that surgery either alone or in combination with CRT was associated with improved survival (Figure 2a). Median survival for the local disease group was 8.6 years for those treated with surgery, 3.1 years for S+CRT, and 1.0 year for no treatment (P=0.0003). Median survival for the regional disease group was 3.7 years for surgery, 4.7 years for S+CRT, 1.1 years for CRT, and 0.4 years for no treatment (P=0.0003). Median survival for metastatic disease was 0.4 years for those treated with surgery, 0.3 years for CRT, 1.1 years for S+CRT, and 0.1 years for no treatment (P<0.001) (Figure 2b).

In multivariable cox regression analysis of all patients, after adjusting for a number of factors including age, gender, SES, comorbidities, and tumor size, the strongest predictor of mortality was metastatic disease (HR 5.44 compared to local disease, P<0.001) (Table 3). Increasing age (HR 1.17, P=.0008) and the presence of Cushing's syndrome (HR 1.66, P=0.0081) were also associated with decreased survival. In the same regression analysis, surgery either alone (HR 0.40, P=0.0003) or in combination with CRT (HR 0.39, P=0.0002) was a significant predictor of survival over no treatment.

In stage-specific multivariable regression analysis, for patients with regional disease (Table 4a), both surgery (HR 0.13, $P<0.001$) and S+CRT (HR 0.15, $P=0.0079$) were associated with improved survival over no treatment. For patients with metastatic disease. both surgery (HR 0.52, $P<0.02$) and S+CRT (HR 0.31, $P<0.001$) improved survival over no treatment, while CRT was associated with a trend (HR 0.65, $P=0.0928$) towards improved survival (Table 4b). For patients with metastatic disease, multi-modality treatment (S+CRT) was associated with improved survival over CRT alone (HR 0.47, $P=0.0025$) and a trend towards improved survival over surgery alone (HR 0.59, $P=0.08$). Cushing's syndrome was associated with increased mortality for local (HR 4.16, $P=0.0045$) and regional (HR 5.49, $P<0.001$) disease, but was not a significant predictor for metastatic disease.

Discussion

In this contemporary population-based cohort of patients with adrenocortical carcinoma, we have demonstrated that surgery either alone or in combination with CRT is associated with improved survival. Accounting for a number of patient and tumor related characteristics, surgery was predictive of improved survival for patients with regional and metastatic disease. For patients with metastatic disease, multi-modality treatment with S+CRT was more effective than CRT alone. S+CRT may improve survival over surgery alone for metastatic patients, but we could not show a statistically significant relationship in our study likely due to low power. As shown by the low 30-day postoperative mortality in our patient cohort, surgery for ACC can be performed safely for appropriately selected patients.

Previous studies using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) staging system have reported five-year survival of 62% for local (stage I/II) disease and 7% for patients with stage IV disease.[15] A recent study using the SEER database reported that patients with regional disease (stage III or IV) had mean survival of 73 months if treated with surgery compared to 35 months if not treated with surgery ($P=0.007$).[16] They found that surgical resection was associated with a decrease in mortality in multivariate analysis (HR 10.46, $P<0.001$). However, they did not analyze the impact of non-surgical treatment on survival and excluded patients with metastatic disease. To expand on the current literature, our study analyzed the impact of both surgery and systemic therapy on survival. We specifically included metastatic patients, a particularly challenging population.

Since most patients present with advanced disease, there has been considerable interest in adjuvant treatment. Mitotane is the only systemic therapy approved for ACC. It is typically used adjuvantly after resection for high-risk patients, where it has shown some efficacy in prolonging recurrence-free survival.[17] It is also often used for patients who are not resectable (due to local invasion or metastasis) or have recurrent disease, although recent studies have shown a response rate of only 30% in this setting, with even rarer patients achieving complete tumor regression.[8] Mitotane inhibits steroid synthesis and induces hepatic clearance of cortisol, and it can improve symptoms related to Cushing's syndrome. Although there is conflicting data on the efficacy of mitotane, it remains the systemic treatment of choice largely due to the lack of other well-established therapies.

A recent randomized trial compared multi-drug chemotherapy regimens (etoposide, doxorubicin, and cisplatin (EDP) plus mitotane versus streptozocin plus mitotane) for patients with advanced ACC who were deemed to be unresectable.[18] Patients in the EDP group had a longer progression-free interval, but overall survival was not significantly different between the groups and was still poor (14.8 months versus 12.0 months, P=0.07). Radiation can also be considered for high-risk patients following surgical resection or for palliation of metastatic disease not amenable to surgery (e.g. bone and brain). Tumor response rates have been reported of up to 40%, but there has been no proven survival benefit with radiation.

Given the lack of effective systemic therapy, surgical resection has been the mainstay of treatment for ACC. Complete surgical resection with microscopically negative margins and leaving the tumor capsule intact to avoid tumor spillage gives the best chance for a long-term cure.[9] Extensive lymphadenectomy and en bloc resection of adjacent structures should be performed as necessary to achieve complete resection, providing they can be done safely.[19] Surgical debulking for symptoms related to hormone hypersecretion can provide significant palliation and improve the efficacy of additional adjuvant treatment.[20] Studies have also supported repeat operation for local recurrence, with increased overall 5-year survival and decreased pain and symptoms associated with hormone hypersecretion compared to patients who underwent adjuvant systemic therapy or no treatment.[21]

In our opinion, due to the lack of efficacy data and potential side effects of chemoradiation, we cannot say if it currently has a role in patients with local disease who have undergone complete resection, especially in those without high-risk features (e.g. high grade, rapid tumor growth, or intraoperative violation of tumor capsule). Patients with presumed local disease who undergo incomplete resection due to intraoperative findings of local invasion or metastasis should have adjuvant treatment with mitotane or a multi-drug chemotherapy regimen if able to tolerate it. Those who are known to be unresectable preoperatively should be offered neoadjuvant treatment to evaluate primary and distant tumor response. Neoadjuvant treatment allows for observation of tumor biology and response to treatment before offering an extensive operation that can have significant morbidity. The rate of tumor growth, which is not known in this dataset, may reflect how aggressively an individual tumor will behave. This can be a useful prognostic marker that can help to guide treatment. In patients with non-localized disease, surgery should be offered as initial treatment on a case by case basis for patients with: 1) ability to resect the primary and any gross metastasis, 2) low burden of disease, and/or 3) lack of significant comorbid conditions.

In general, for those that present with metastatic disease, we believe non-curative debulking should be considered for patients with a readily resectable primary lesion and low burden of metastatic disease, or for palliation of symptoms related to hormone hypersecretion. Patient selection is critical to ensure that surgery is offered to those who are most likely to benefit either through prolonged survival or improved quality of life. As reflected in the low post-operative mortality and apparent benefit of surgical resection in our study, patients may have been appropriately selected based on their burden of disease and ability to tolerate an extensive operation. The role of adjuvant treatment may evolve as new and potentially more effective chemotherapy becomes available.

As expected, tumors associated with Cushing's syndrome were associated with a worse prognosis for local and regional disease. The negative prognostic implication of Cushing's syndrome in ACC has previously been reported.[22] The etiology is not completely clear but it may be related to either tumor biology or a direct impact of cortisol production on tumor cell growth and host defenses.[22] The low prevalence of hormone hypersecretion (18.0%) associated with ACC is likely under-estimated in our study due to reliance on ICD-9 coding. Most studies report that approximately 60% of patients with ACC have associated hormone hypersecretion, most commonly Cushing's syndrome with or without virilization.[23] The patients that were coded as having a hormonally active tumor were likely the most advanced cases, and would be expected to have worse survival. Despite being undercoded, we included the variable in the analysis because we felt that it was clinically significant and informative to the reader in confirming the negative prognostic relationship between Cushing's syndrome and survival in ACC. We performed the same analysis excluding Cushing's syndrome, and there was no difference in the results.

This study has several limitations. Observational data cannot capture potential sources of bias arising from patient selection factors. There may be a physician referral bias, and some patients may have refused surgery. The extent of disease burden, tumor grade, completeness of resection, and specific chemotherapy and/or radiation regimen are not available in this database. Follow-up for treatments received outside of California was not captured in this data. Due to the small number of patients with local disease treated with CRT either alone (n=0) or in combination with surgery (n=11), we were not able to separately analyze the effect of adjuvant treatment in this subgroup.

Due to the difficulty in defining malignancy in local ACC, patients with benign tumors may have been misdiagnosed as malignant. However, the large median tumor size, confirmation by histology, and use of open rather than laparoscopic surgery all suggest that these tumors were malignant. Additionally, our patient cohort mimics the SEER database, which reported that 40.6% of patients present with local disease, 17.9% with regional, and 34.8% with metastatic disease.[24]

Despite these limitations, our study strengths include a relatively large sample size of this rare cancer from a comprehensive statewide database with longitudinal follow-up, which is representative of real world clinical practice.

Conclusion

In ACC, surgery may be associated with improved survival for patients with regional and metastatic disease. Patients with metastatic disease likely benefit most from multi-modality treatment (surgical resection plus adjuvant chemotherapy and/or radiation). These findings suggest that surgery should be considered for appropriately selected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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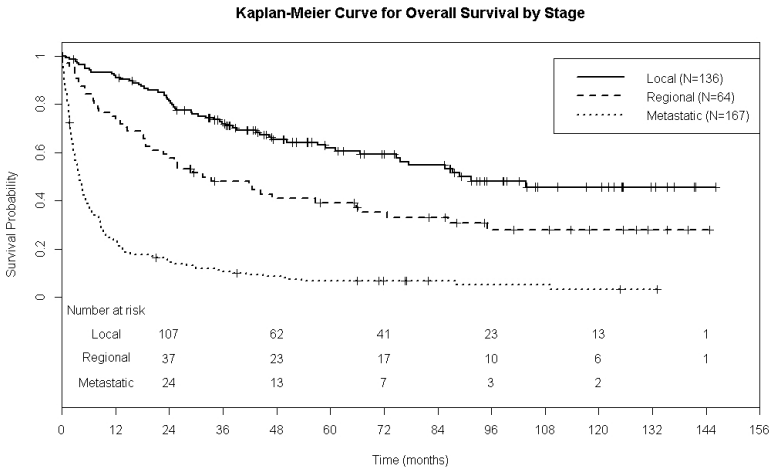

Figure 1.
All-Cause Survival for Patients with Adrenocortical Cancer, by Stage

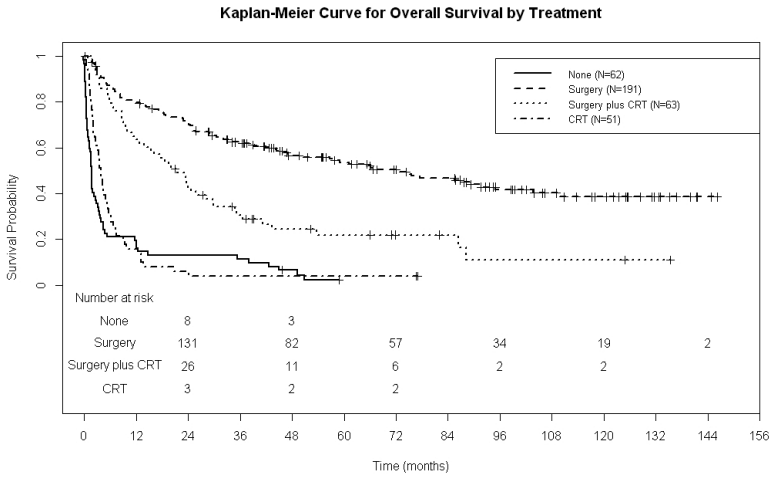

Figure 2a.
All-Cause Survival for All Patients, by Treatment Group

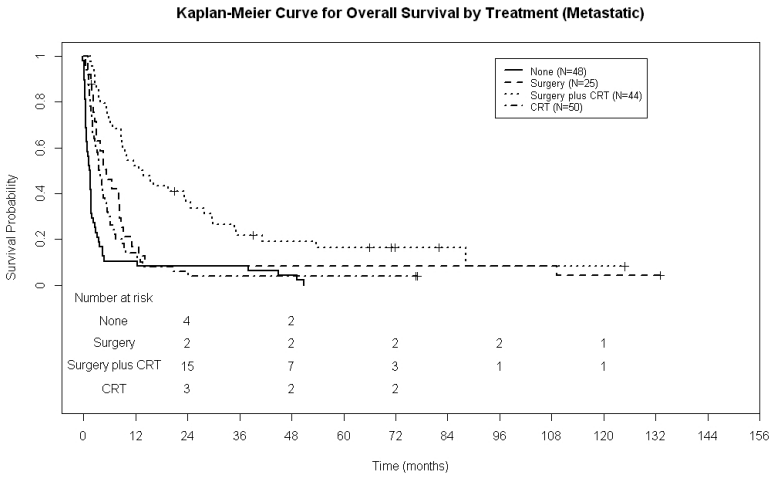

Figure 2b.

All-Cause Survival for Patients with Metastatic Adrenocortical Cancer, by Treatment Group

Table 1

Characteristics of patients with adrenocortical cancer in California (1999-2008)

	Adrenocortical Cancer Patients
Total number of patients	367
Age (years), mean ± SD	52.9 ± 18.5
Male, N (%)	155 (42.2%)
Female, N (%)	212 (57.8%)
Race, N (%)	
Non-Hispanic White	235 (64.0%)
Non-Hispanic Black	15 (4.1%)
Hispanic	91 (24.8%)
Asian/Pacific Islander	26 (7.1%)
Socioeconomic Status (SES),[a] N (%)	
Lowest SES	55 (15.0%)
Lower-Middle and Middle SES	138 (37.6%)
Higher-middle and Highest SES	174 (47.4%)
Comorbidity (Charlson Index)	
0	208 (56.7%)
>0	159 (43.3%)
Hospital type, N (%)	
Public	13 (3.6%)
Academic	84 (23.3%)
HMO	90 (24.9%)
Private	174 (48.2%)

SD, standard deviation

[a]Quintile of YOSTSCL score

Table 2

Tumor characteristics of adrenocortical cancer cases

	All Patients	Local	Regional	Metastatic
Stage, N (%)	367 (100%)	136 (37.1%)	64 (17.4%)	167 (45.5%)
Tumor size (centimeters), N (%)				
<10	188 (51.2%)	81 (59.6%)	24 (37.5%)	83 (49.7%)
10-20	150 (40.9%)	46 (33.8%)	33 (51.6%)	71 (42.5%)
20-30	27 (7.4%)	8 (5.9%)	7 (10.9%)	12 (7.2%)
>30	2 (0.5%)	1 (0.7%)	0 (0%)	1 (0.6%)
Functional tumor, N (%)	66 (18.0%)	17 (12.5%)	10 (15.6%)	39 (23.4%)
Cushing's syndrome	51 (13.9%)	12 (8.8%)	9 (14.1%)	30 (18.0%)
Virilization	17 (4.6%)	4 (2.9%)	1 (1.6%)	12 (7.2%)
Hyperaldosteronism	5 (1.4%)	1 (0.7%)	0 (0%)	4 (2.4%)
Feminization	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)
Treatment, N (%)				
None	62 (16.9%)	7 (5.1%)	7 (10.9%)	48 (28.7%)
Surgery only	191 (52.0%)	118 (86.8%)	48 (75.0%)	25 (15.0%)
Surgery plus CRT	63 (17.2%)	11 (8.1%)	8 (12.5%)	44 (26.3%)
CRT	51 (13.9%)	0	1 (1.6%)	50 (29.9%)

CRT, chemotherapy and/or radiation

Table 3

Cox proportional hazard analysis of factors influencing all-cause mortality for all adrenocortical cancer patients

Predictor	Hazard Ratio	95% Confidence Interval		*P* value
		Lower limit	Upper limit	
Stage				
Local	(reference)	---	---	---
Regional	1.64	1.06	2.55	**0.0270**
Metastatic	5.44	3.46	8.56	**<.0001**
Treatment				
None	(reference)	---	---	---
Surgery	0.40	0.25	0.66	**0.0003**
S + CRT	0.39	0.24	0.64	**0.0002**
CRT	0.78	0.49	1.23	0.2784
Hospital type				
Private	(reference)	---	---	---
Public	0.76	0.31	1.86	0.5431
Academic	0.93	0.65	1.33	0.6786
HMO	0.79	0.55	1.13	0.1973
SES				
High	(reference)	---	---	---
Low	1.16	0.75	1.77	0.5064
Middle	1.12	0.83	1.51	0.4570
Race				
White	(reference)	---	---	---
Black	1.23	0.62	2.45	0.5470
Hispanic	1.14	0.81	1.60	0.4560
Asian	1.07	0.62	1.86	0.8114
Age (in 10 years)	1.17	1.07	1.28	**0.0008**
Sex				
Male	(reference)	---	---	---
Female	0.80	0.61	1.07	0.1294
Tumor size (centimeters)				
<10	(reference)	---	---	---
10-20	0.87	0.65	1.18	0.3711
>20	1.40	0.84	2.31	0.1939
Comorbidity (Charlson Index)				
0	(reference)	---	---	---

Predictor	Hazard Ratio	95% Confidence Interval		*P* value
		Lower limit	Upper limit	
>0	1.15	0.87	1.54	0.3325
Cushing's syndrome				
No	(reference)	---	---	---
Yes	1.66	1.14	2.43	**0.0081**

CRT, chemotherapy and/or radiation treatment; SES, socioeconomic status

Table 4a

Cox proportional hazard analysis of factors influencing all-cause mortality for patients with regional disease

Predictor	Hazard Ratio	95% Confidence Interval		*P* value
		Lower limit	Upper limit	
Treatment				
None	(reference)	---	---	---
Surgery	0.13	0.04	0.37	**0.0002**
S + CRT	0.15	0.04	0.61	**0.0079**
Hospital type				
Private	(reference)	---	---	---
Public	6.26	1.18	33.1	**0.0311**
Academic	0.99	0.41	2.41	0.9881
HMO	0.49	0.20	1.22	0.1234
SES				
High	(reference)	---	---	---
Low	1.05	0.35	3.22	0.9259
Middle	1.37	0.66	2.83	0.3960
Age (in 10 years)	1.32	1.03	1.71	**0.0308**
Sex				
Male	(reference)	---	---	---
Female	0.84	0.43	1.65	0.6169
Comorbidity (Charlson Index)				
0	(reference)	---	---	---
>0	0.66	0.30	1.46	0.3006
Cushing's syndrome				
No	(reference)	---	---	---
Yes	5.49	2.17	13.92	**0.0003**

Table 4b

Cox proportional hazard analysis of factors influencing all-cause mortality for patients with metastatic disease

Predictor	Hazard Ratio	95% Confidence Interval		*P* value
		Lower limit	Upper limit	
Treatment				
None	(reference)	---	---	---
Surgery	0.52	0.28	0.97	**0.0394**
CRT	0.65	0.40	1.07	0.0928
S + CRT	0.31	0.17	0.55	**<.0001**
Hospital type				
Private	(reference)	---	---	---
Public	1.15	0.34	3.84	0.8228
Academic	0.88	0.54	1.42	0.5893
HMO	0.87	0.55	1.37	0.5388
SES				
High	(reference)	---	---	---
Low	0.92	0.53	1.59	0.7709
Middle	1.14	0.78	1.68	0.4920
Age (in 10 years)	1.12	1.00	1.24	0.0511
Sex				
Male	(reference)	---	---	---
Female	0.93	0.65	1.34	0.7092
Comorbidity (Charlson Index)				
0	(reference)	---	---	---
>0	1.02	0.69	1.50	0.9398
Cushing's syndrome				
No	(reference)	---	---	---
Yes	1.42	0.87	2.31	0.1585