Surgery is associated with improved survival for adrenocortical cancer, even in metastatic disease

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Background. *Adrenocortical carcinoma (ACC) is a rare but lethal tumor. Predictors of survival include earlier stage at presentation and complete operative 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).*
Results. *We studied 367 patients with median tumor size of 10 cm. 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 < .0001). One-year and 5-year survival was: 92%/62% (local); 73%/39% (regional); and 24%/7% (metastatic). Increased age (hazard ratio [HR] 1.16) and Cushing's syndrome (HR 1.66) worsened survival (P < .05). Low socioeconomic status worsened survival in local and regional disease (P < .05). In multivariable regression, both surgery (regional HR 0.13; metastatic HR 0.52) and surgery plus CRT (regional HR 0.15; metastatic HR 0.31) improved survival compared with no treatment (P < .02).*
Conclusion. *In ACC, surgery is associated with improved survival, even in metastatic disease. Surgery should be considered for select patients as part of multimodality treatment. (Surgery 2014;156:1531-41.)*

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With increasing use of abdominal cross-sectional imaging, adrenal lesions are more commonly identified, occurring in up to 4–6% of the ambulatory population.[1,2] In contrast, malignant adrenal tumors are extremely rare, with an incidence of approximately 1–2 cases per million.[1-3] Despite its rarity, the consequences of adrenal cancer are substantial. 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 operative 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 operative resection remains the only curative treatment for adrenocortical carcinoma (ACC), whereas 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.

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It has been difficult to study the optimal treatment of ACC because of its rarity. Most peer-reviewed guidelines focus on evaluation and removal of functioning, nonmetastatic 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 operative resection is controversial if the goal is not curative intent. If the perioperative risks are thought to be acceptable, it is reasonable to debulk a functional ACC for palliation. Small case series have also shown a possible survival benefit for operative 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 during a 10-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 1999–2008. Records were linked to inpatient and ambulatory hospital records maintained by the California Office of Statewide Health Planning and Development database via the use of unique patient identifiers, which 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 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 staging (n = 35). An additional 4 patients were diagnosed at death and also were excluded. Median follow-up time was 18.8 months, and 80 patients had at least 5 years of follow-up.

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

Clinical data included cancer size, stage, and whether the tumor was functional (associated with hormone hypersecretion). Cancer size was classified as <10 cm, 10–20 cm, 20–30 cm, and >30 cm. Stage was defined as local, regional (direct extension and/or positive lymph nodes), or metastatic via use of 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 California Office of Statewide Health Planning and Development CPT variables for chemotherapy, radiation, and surgery (Supplementary Table I). 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, 9th Revision 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 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