# *Association of tumor size with metastatic potential and survival in patients with adrenocortical carcinoma: an analysis of the National Cancer Database*

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***Introduction:*** *To assess the impact of size at presentation in patients with adrenocortical carcinoma (ACC) on rates of synchronous metastatic disease and survival following resection using a large administrative dataset.*

***Materials and methods:*** *We queried the National Cancer Database (NCDB) dataset to assemble a cohort of patients with ACC based on SEER staging (1985-2000). Patients were stratified into three groups based on surgical tumor size cutoffs: < 4 cm, 4 cm-6 cm, and > 6 cm. Rates of metastatic disease at presentation in all ACC patients as well as relative survival for patients after resection of localized lesions were calculated and compared among groups.*

***Results:*** *A total of 2248 patients had available staging information for analysis. Tumor size at presentation did not relate to likelihood of non-localized disease at presentation (p = 0.09). A restricted cubic splines analysis revealed a clinically insignificant relationship between tumor size and advanced disease at presentation (OR = 1.02 for each centimeter change in tumor size, p = 0.004, 95% CI 1.01-1.03). On multivariate analysis, only patient age (p < 0.01), and not tumor size, was a significant predictor of overall survival among patients undergoing resection of localized ACCs.*

***Conclusions:*** *Our data suggest that tumor size is imperfect in predicting presence of distant disease at presentation, nor does it consistently correlate with patient survival after resection of localized ACC.*

**Key Words:** adrenocortical carcinoma, adrenal mass, National Cancer Database, tumor size, adrenalectomy

## Introduction

Adrenocortical carcinoma (ACC) is an extremely rare clinical entity, affecting approximately 0.5 to 2.0 per million persons or approximately 300 individuals in the United State per year.[1-3] The mainstay of therapy for ACC is surgical excision, which offers the best chance for cure.[4] Due to the adrenal gland's seclusion in the retroperitoneum, the disease progresses largely in silence, and nearly 50% of patients with ACC present with metastatic disease at the time of detection.[5] As such, 5 year overall survival is poor, ranging from 20%-47%.[6,7]

Although ACC is an infrequent clinical entity, the disease casts a therapeutic shadow on a large number of patients who are diagnosed with an incidental adrenal lesion found at the time of cross-sectional imaging for unrelated symptoms.[8] In fact,

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it is estimated that 4%-6% of the population harbor adrenal incidentalomas.[9-11] Although most of these lesions are small, metabolically silent adenomas, a disproportionate amount of healthcare resources is utilized to evaluate and surveil these lesions due to the concern that these may represent an early-stage ACC.[12,13] Despite this clinical strategy, recent data show that there has been a lack of improved outcomes for patients with ACC despite the "incidental" screening of the adrenal gland in the era of increased cross-sectional imaging.[14,15]

In appropriate surgical candidates, current recommendations advocate the use of adrenalectomy for masses ≥ 4 cm regardless of the lesion's metabolic activity due to the fact that > 5% of these lesions may in fact be malignant.[8,16] A 6 cm cut off is also often mentioned in the adrenal literature.[5] Although the risk of ACC certainly increases with tumor size, the 4 cm or 6 cm cut offs for adrenalectomy are rather arbitrary clinical thresholds that may expose a large number of patients to unnecessary intervention. As such, using the National Cancer Database (NCDB), which maintains the largest cohort of patients with ACC, we sought to evaluate the influence of tumor size on rate of metastatic disease at presentation. Furthermore, we assessed survival of patients with localized ACC treated with surgical excision.

## Materials and methods

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons.[17] Established in 1989 as a comprehensive clinical surveillance resource for cancer care in the United States, the NCDB consists of more than 1400 facility-based tumor registries and contains clinical data on over 25 million cancer cases diagnosed between 1985 and 2007. Presently, the NCBD captures approximately 75% of all newly diagnosed cases of cancer.

Data from the NCDB was used to generate a cohort of patients with adrenocortical carcinoma diagnosed between 1985 and 2000. At present, the NCDB does not yet contain 5 year survival data on patients with ACC in a more contemporary time frame, thus explaining the years examined in this study. Only patients 18 years of age and older, with International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology code 8370, and primary site codes C740 and C749 were included. Importantly, the presence of symptoms at the time of diagnosis or the metabolic functionality of these tumors is not currently captured in the NCDB database. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) staging for ACC was used for this analysis. Using this staging system, we first examined the rates of localized versus regional/metastatic disease stratified by different tumor sizes (< 4 cm, 4 cm-6 cm, and > 6 cm). These tumor sizes were chosen due to their clinical significance. Restricted cubic splines[18] were used to examine the relationship between increasing tumor size and the likelihood of nodal and/or metastatic disease at presentation. We placed knots at 1 cm, 5 cm, 10 cm, 20 cm, 30 cm, 50 cm, and 80 cm to accommodate the wide range of documented tumor sizes (range = 0.2 cm-98.9 cm).

We then identified the patients with localized ACC who underwent resection and evaluated their survival based on the same tumor size groupings. Relative survival rates were calculated by tumor size for cases diagnosed in 1985-2000 for 5 year survival. Relative survival is the ratio of the observed survival rate to the expected survival rate adjusted for age, sex, and race. Expected survival rates were abstracted from the 1990 life expectancy tables created by the National Cancer Institute. Significance of relative survival differences were assessed with the z- test.[19] Median survival curves by tumor size were assessed using Kaplan-Meier estimates and log rank tests. Multivariate Cox regression was used to analyze survival adjusted for demographic and tumor variables. Analyses were conducted using STATA Version 12 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics Version 18.[20] This project was approved by the Fox Chase Cancer Center Institutional Review Board.

## Results

Based on SEER staging, there were 988 cases of localized ACC and 1260 cases with regional/distant disease identified in the NCBD database. Socio-demographic characteristics of patients with localized disease were compared to patients with regional/distant disease, Table 1. Among patients with localized disease, the majority were female (585/988, 59.2%), white (879/988, 89.0%), and were diagnosed and/or treated at a teaching/research (399/988, 40.4%) or comprehensive community hospital (430/988, 43.5%). The median age at diagnosis for localized and regional/distant cases were 54.5 years (mean = 53.7, range = 18-90) and 55.0 years (mean = 53.8, range = 18-100), respectively. There were no significant differences in the socio-demographic variables between patients with localized ACC and regional/distant ACC. Patients with regional/distant ACC were more likely to be treated at a teaching/research institution (p = 0.03).

TABLE 1. **Demographic and clinical variables for patients with localized and regional/distant adrenocortical carcinoma (ACC) 1985-2000 diagnosis years**

| Variables | SEER stage percent distribution | |
|---|---|---|
| | Local (n = 988) | Regional (n = 1263) |
| **Race** | | |
| White | 89.0 (879) | 88.7 (1120) |
| Black | 7.4 (73) | 7.2 (91) |
| Other | 3.6 (36) | 4.1 (52) |
| **Sex** | | |
| Male | 40.8 (403) | 42.1 (532) |
| Female | 59.2 (585) | 57.9 (731) |
| **Age** | | |
| 18-34 | 11.9 (118) | 12.9 (163) |
| 35-44 | 18.0 (178) | 16.7 (211) |
| 45-54 | 20.0 (198) | 19.3 (244) |
| 55-64 | 21.0 (207) | 23.2 (293) |
| 65-74 | 20.9 (206) | 18.5 (234) |
| >= 75 | 8.2 (81) | 9.3 (118) |
| **Hospital type**[1] | | |
| Community | 11.0 (109) | 10.9 (138) |
| Comprehensive community | 43.5 (430) | 37.5 (473) |
| Teaching research | 40.4 (399) | 46.0 (579) |
| Other | 5.1 (50) | 5.6 (70) |

[1]excludes three cases with hospital type unknown

Patients with ACC were stratified into three tumor size groups based on widely accepted clinical tumor size cutoffs(5): < 4 cm, 4 cm-6 cm, and > 6 cm. We first analyzed the ratio of localized to regional/distant cases of ACC stratified by the already mentioned tumor sizes, Table 2. The incidence of metastatic disease at presentation in patients with tumors < 4 cm, 4 cm-6 cm, and > 6 cm was 49.4%, 54.8%, and 46.4%. Comparing among all three groups, there was not a statistically significant difference in the rates of metastatic disease (p = 0.09). Further analysis using restricted cubic splines does show a statistically significant, although extremely weak, relationship between increasing tumor size and the probability of nodal and/or metastatic disease at presentation (OR = 1.02, p = 0.004, 95% CI 1.01-1.03), Figure 1. We then examined the rates of regional/distant disease with each 2 cm increase in tumor size, we found that there was no relationship between the ability of tumor size to predict non-localized disease in tumors < 12 cm, Table 2.

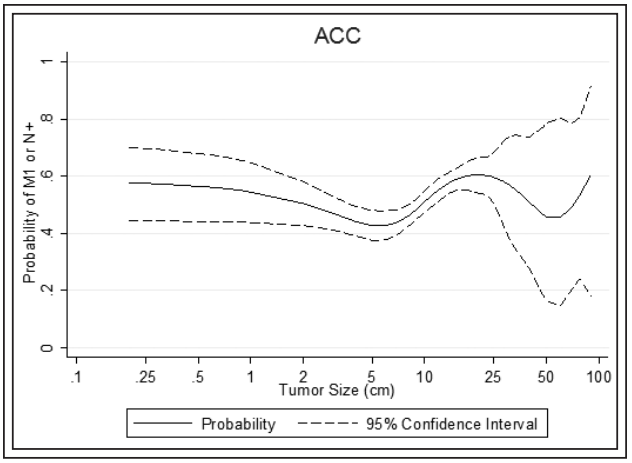


**Figure 1.** Cubic splines analysis assessing relationship between increasing tumor size and the probability of nodal (N+) and/or metastatic (M1) disease at presentation. Tumor size has a weak, and likely clinically insignificant, relationship to the rate of synchronous metastatic disease at presentation (OR = 1.02, 95% CI 1.01-1.03).

Furthermore, in a multivariate logistic regression analysis to determine predictors of regional/distant disease that included tumor size, age, race, sex, diagnosis years, and hospital type, only tumor size was found to be significantly predictive of higher stage disease upon presentation, but with increased odds only observed once tumors were larger than 12 cm: 12 cm-14 cm (OR = 1.18, 95% CI = 0.78-1.80), 14 cm-16 cm (OR = 1.38, 95% CI = 0.89-2.16), and greater than 16 cm (OR = 1.51, 95% CI = 1.03-2.23), Table 3.

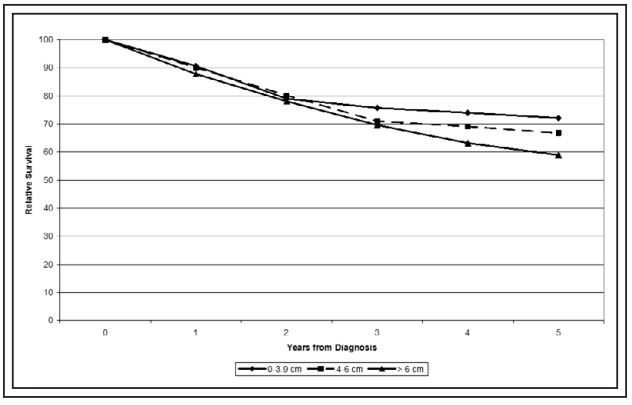


**Figure 2.** Five year relative survival of patients with localized adrenocortical carcinoma (ACC) who underwent surgical resection of ACC stratified by size (< 4 cm, 4 cm-6 cm, and > 6 cm).

TABLE 2. **Distribution by tumor size using SEER staging from 1985-2000 for patients with adrenocortical carcinoma (ACC)**

| Tumor size | SEER stage | | |
|---|---|---|---|
| | Localized | Regional, distant | Total n |
| < 4 cm | 86 (49.4) | 88 (50.6) | 174 |
| 4-6 cm | 102 (54.8) | 84 (45.2) | 186 |
| > 6 cm | 632 (46.4) | 729 (53.6) | 1361 |
| Total n | 820 | 901 | 1721 |

Overall p value = 0.09; two sided p values: < 4 cm v. 4 cm-6 cm, p value=0.31; < 4 cm v. > 6 cm, p value = 0.46; 4 cm-6 cm v. > 6 cm, p value = 0.03

| Tumor size > 6 cm in 2 cm increments | Localized | Regional, distant | Total n |
|---|---|---|---|
| 6.1 cm-8.0 cm | 127 (57.0) | 96 (43.0) | 223 |
| 8.1 cm-10.0 cm | 129 (46.9) | 146 (53.1) | 275 |
| 10.1 cm-12.0 cm | 101 (49.5) | 103 (50.5) | 204 |
| 12.1 cm-14.0 cm | 88 (45.1) | 107 (54.9) | 195 |
| 14.1 cm-16.0 cm | 66 (41.8) | 92 (58.2) | 158 |
| > 16 cm | 121 (39.5) | 185 (60.5) | 306 |

chi square linear trend, p < 0.01
PTV = planning target volume; RFA = radiofrequency ablation

Five year relative survival of patients with localized ACC who underwent surgical resection stratified by size (< 4 cm, 4 cm-6 cm, and > 6 cm) was 72.1, 66.8, and 59.0 months, respectively, Figure 2. There was an absence of a statistically significant survival advantage noted when comparing tumors < 4 cm and 4 cm-6 cm (p = 0.53) and tumors 4 cm-6 cm and > 6 cm (p = 0.22). When the patients with the smallest (< 4 cm) and largest (> 6 cm) localized tumors that underwent resection were compared with regard to relative survival marginal statistical significance was reached (p = 0.04). The small number of cases in the < 4 cm and 4 cm-6 cm tumor size groups (n = 76 and 97) compared to the > 6 cm group (n = 583) must be underscored when interpreting this analysis. In combining the smaller size groups (< 4 cm and 4 cm-6 cm) and then comparing this sum to the > 6 cm group, we again observed a marginally statistically significant relationship between tumor size and survival (survival 69.3 months versus 59.0 months, p value = 0.04). The 6 cm cut point was confirmed upon further survival analysis examining 1 cm tumor size increments. For example, there was no statistical survival difference for tumors ≤ 5 cm and > 5 cm (66.64 months versus 59.84 months, p = 0.25). Nevertheless, when we performed a multivariate Cox regression analysis in patients with resected localized ACC, we found only age to be a statistically significant predictor of survival (p < 0.01). As such, tumor size was not found to be a statistically significant variable in predicting survival in patients with localized ACC that had undergone surgical resection, Table 4.

TABLE 3. **Multivariate logistic regression, odds of regional/distant disease, 1985-2000 diagnosis years, n = 1709**

| Tumor size (cm) | Odds ratio | 95% CI |
|---|---|---|
| < 4 | 1.00 (reference) | |
| 4-6 | 0.78 | 0.51-1.19 |
| 6.1-8.0 | 0.74 | 0.49-1.11 |
| 8.1-10.0 | 1.10 | 0.75-1.62 |
| 10.1-12.0 | 1.01 | 0.67-1.53 |
| 12.1-14.0 | 1.18 | 0.78-1.80 |
| 14.1-16.0 | 1.38 | 0.89-2.16 |
| > 16 | 1.51 | 1.03-2.23 |

other variables in the model include age, race, sex, diagnosis years, hospital type, all p > .05
wald chi square, tumor size, p = .001

TABLE 4. **Multivariate cox regression analysis examining predictors of survival in patients with resected, localized adrenocortical carcinoma (ACC), 1985-2000 diagnosis years (n = 753, 396 deaths)**

| Variable[1] | Hazard ratio | 95% confidence interval | p value |
|---|---|---|---|
| **Age** | | | |
| 18-34 | 1.00 (Reference) | | |
| 35-44 | 1.23 | 0.81-1.86 | 0.33 |
| 45-54 | 1.47 | 1.00-2.18 | 0.05 |
| 55-64 | 1.36 | 0.91-2.03 | 0.13 |
| 65-74 | 2.43 | 1.66-3.57 | < 0.01 |
| >= 75 | 2.81 | 1.77-4.45 | < 0.01 |
| **Diagnosis years** | | | 0.92 |
| 1985-1990 | 1.00 (reference) | | |
| 1991-1995 | 0.95 | 0.74-1.22 | 0.68 |
| 1996-2000 | 0.97 | 0.75-1.26 | 0.82 |
| **Race** | | | 0.65 |
| White | 1.00 (reference) | | |
| Black | 0.86 | 0.58-1.27 | 0.44 |
| Other | 0.85 | 0.49-1.48 | 0.57 |
| **Sex** | | | 0.65 |
| Male | 1.00 (reference) | | |
| Female | 0.95 | 0.78-1.17 | 0.65 |
| **Hospital type** | | | 0.53 |
| Teaching research | 1.00 (reference) | | |
| Community | 0.78 | 0.55-1.12 | 0.19 |
| Comprehensive community | 0.89 | 0.72-1.10 | 0.29 |
| Other | 0.89 | 0.51-1.54 | 0.67 |
| **Tumor size** | | | 0.44 |
| < 4 cm | 1.00 (reference) | | |
| 4 cm-6 cm | 1.09 | 0.72-1.66 | 0.69 |
| > 6 cm | 1.21 | 0.87-1.68 | 0.25 |

## Discussion

ACC, although rare, is an aggressive malignancy with limited treatment options for patients with regional or systemic disease. Early surgical treatment of patients with localized ACC affords the best chance for a durable cure. The prospect of cure for patients with localized ACC largely drives the dictum of early intervention in surgical candidates with adrenal mass greater than 4 cm in diameter regardless of imaging characteristics.[16] Nevertheless, with the increased detection of adrenal incidentalomas, remarkably low incidence of ACC (approximately 300 cases in United States per year), and a non-trivial complication rate associated with adrenal surgery, risks of over-treatment may outweigh the benefits of intervention.[12] Thus, better risk-stratification of patients with an adrenal incidentaloma, through increased understanding of adrenal tumor biology, is necessary in order to improve clinical decision-making.

Harnessing the largest available dataset of patients with ACC from the NCDB, our analysis revealed that tumor size had a complex but weak, and likely clinically insignificant, relationship to the rate of synchronous metastatic disease at presentation (OR = 1.02, 95% CI 1.01-1.03). For each 1 centimeter change in tumor size, chances of metastatic disease appeared to increase only by 2%. This finding is in contrast to the largely linear change in the rate of synchronous metastatic disease with increasing primary tumor size that has been described for tumors of the kidney, an adjacent retroperitoneal organ.[21]

When we assessed the impact of tumor size on survival of patients who underwent resection of localized adrenal lesions, 5 year patient relative survival was 72.1 months, 66.8 months, and 59.0 months for tumors < 4 cm, 4 cm-6 cm, and > 6 cm, respectively. This relationship between tumor size at resection and relative survival was not statistically significant until we condensed the tumor size groupings into ≤ 6 cm and > 6 cm. At this tumor size cut off, we found a statistically significant survival relationship that was durable. Despite this finding, results of a multivariate analysis demonstrated that tumor size at resection was not related to survival. Only patient age was a statistically significant predictor of survival in this cohort of patients who presented with localized disease and underwent adrenalectomy ($p < 0.01$).

Historically, tumor size has driven management of metabolically silent adrenal lesions.[5,8] In fact, differentiating between adenoma and carcinoma both radiographically[22] and on biopsy[5] can be challenging. In a seminal 1991 manuscript, Herrera et al, based on data from a small cohort of patients who underwent adrenalectomy at a single institution (n = 52), proposed that tumors larger than 4 cm should be resected. In this work, the authors compared the radiographic size of adrenal incidentalomas in 342 patients with the surgical pathology available only in 52 patients who underwent resection. Of these 52 resected masses, 42 (80.8%) and 20 (34.5%) were greater than 4 cm and 5 cm, respectively.[16] Furthermore, only 4 (7.7%) adrenal incidentalomas proved to be ACC upon resection, ranging in size from 5.5 cm to17.0 cm.[16] Based on these data, the authors proposed using the 4 cm size cut off as the trigger for intervention, indicating that for every malignant adrenal incidentaloma, eight benign lesions would be removed.[16] These initial data have been supported by large multi-institutional series of incidentally-detected adrenal masses, demonstrating that larger tumors are more likely to harbor malignancy.[23,24] As such, current recommendations suggest resection of all tumors > 6 cm, and strong consideration for resection of tumors greater than 4 cm in otherwise healthy non-comorbid individuals is reasonable.[5,8,24] However, our data suggest that conservative management or radiologic observation that would allow one to assess the growth kinetics of a given adrenal mass before definitive intervention is also a viable option in appropriately selected patients..

Adrenalectomy is not without risk, especially in the elderly. A recent analysis of the Nationwide Inpatient Sample assessing the morbidity and mortality among patients undergoing adrenalectomy revealed an overall 16.5% complication rate.[25] Importantly, the authors found that there was a 41% and 60% increase in complication rates among patients 61-70 and > 70 years old when compared to patients younger than 60 years old.[25] As such, the elderly – who are indeed most likely to harbor incidentalomas[10] – potentially stand to gain the least from a more aggressive approach to treatment. Indeed, despite rising rates of adrenalectomy,[13] centralization of adrenal surgery to high volume centers,[13] and an increase in cross-sectional imaging of the thorax and abdomen over the last several decades, survival rates for adrenocortical carcinoma have remained static.[14] In fact a recent analysis of the NCDB, revealed that "incidental screening" of the adrenal gland with rising rates of cross-sectional imaging has failed to improve patient outcomes.[14] As such, given exceedingly low rates of ACC, high prevalence of benign adrenal masses, and the morbidity of adrenalectomy, especially in the elderly, novel management strategies for adrenal incidentaloma are required. As our data suggest, in contrast to renal cell carcinomas, the relationship between tumor size and metastatic potential of adrenocortical carcinomas is non-linear and complex. Thus, based on data from the NCDB, approximately 22% of patients with localized ACC present with tumors < 6 cm. Thus, if there are an estimated 300 cases of ACC annually in the United States, then thousands of adrenalectomies are being performed in order to potentially impact the clinical outcomes of approximately 70 patients per year. As such, we believe data presented in this manuscript argue for the use of conservative management in elderly or co-morbid patients with adrenal masses smaller than 6 cm.

Nevertheless, this manuscript must be interpreted in the context of its limitations, which include its retrospective nature and inherent shortcomings of large hospital-based administrative dataset. For instance, there are important clinical variables that are either missing (hormone secretion) or poorly captured (tumor grade). Also, more recent years of diagnosis are lacking due to available survival data, however the incidence and survival of ACC has not appreciably changed in recent years. Furthermore, the generalizability of our results are somewhat limited by the absence of cancer-specific mortality and co-morbidity data during the time period of the dataset, restricting our ability to assess the impact of competing risks on overall survival. Despite these limitations, this dataset captures 70%-80% of ACCs diagnosed in the United States, arguably affording the best opportunity to assess outcome measures among patients undergoing treatment for this disease.

Our analysis of the NCDB data suggests that tumor size alone is not a strong predictor of distant disease at presentation. In fact, only patient age was a significant predictor of survival in patients with resected ACC. Thus, a more nuanced approached incorporating clinical variables beyond tumor size alone is required when evaluating patients with an adrenal mass. □

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