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Actual 10-Year Survivors Following Resection of Adrenocortical Carcinoma

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Abstract

Background—Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with limited therapeutic options beyond surgical resection. The characteristics of actual long-term survivors following surgical resection for ACC have not been previously reported.

Method—Patients who underwent resection for ACC at one of 13 academic institutions participating in the US Adrenocortical Carcinoma Group from 1993 to 2014 were analyzed. Patients were stratified into four groups: early mortality (died within 2 years), late mortality (died within 2–5 years), actual 5-year survivor (survived at least 5 years), and actual 10-year survivor (survived at least 10 years). Patients with less than 5 years of follow-up were excluded.

Results—Among the 180 patients available for analysis, there were 49 actual 5-year survivors (27%) and 12 actual 10-year survivors (7%). Patients who experienced early mortality had higher

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rates of cortisol-secreting tumors, nodal metastasis, synchronous distant metastasis, and R1 or R2 resections (all $P < 0.05$). The need for multi-visceral resection, perioperative blood transfusion, and adjuvant therapy correlated with early mortality. However, nodal involvement, distant metastasis, and R1 resection did not preclude patients from becoming actual 10-year survivors. Ten of twelve actual 10-year survivors were women, and of the seven 10-year survivors who experienced disease recurrence, five had undergone repeat surgery to resect the recurrence.

Conclusion—Surgery for ACC can offer a 1 in 4 chance of actual 5-year survival and a 1 in 15 chance of actual 10-year survival. Long-term survival was often achieved with repeat resection for local or distant recurrence, further underscoring the important role of surgery in managing patients with ACC.

Keywords

adrenocortical carcinoma; survival; surgery; adrenal cancer

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of approximately one per million in the United States [1,2]. Approximately 40% of ACC tumors do not secrete hormones and, therefore, may present as large tumors causing local mass effect [3]. As a result, most patients present at an advanced stage of disease and have a median survival time of less than 12 months [2,4]. Even with surgical resection, ACC can still be associated with a poor long-term prognosis, with estimated 5-year survival ranging from 16% to 45% [5–13]. Surgery, however, offers the best chance to achieve long-term survival even if recurrence is common and occurs in as many as 70% of patients following complete resection of ACC [1]. Although several studies have reported survival outcomes following curative-intent surgery for ACC, characteristics of the actual 5- and 10-year survivors have not been previously reported.

In fact, to date, only eight case reports and one small case series of six patients in the literature have reported on patients with ACC who have achieved long-term survival of more than 10 years [10,14–21]. Of note, various clinical and pathologic factors such as tumor size [22,23], lymphadenectomy [24,25], major venous involvement [26], margin status [27], and higher Weiss score [28] have not been consistently associated with long-term survival following resection of ACC. Therefore, the objective of the current study was to use a multi-institutional collaborative database of ACC patients in the United States to identify characteristics of actual 5- and 10-year survivors following resection of ACC.

METHODS

Patient Population and Study Design

Patients who underwent surgical resection for ACC were identified using a multi-institutional database of 13 academic institutions participating in the US Adrenocortical Carcinoma Study Group: Stanford University, Stanford, CA; John Hopkins Hospital, Baltimore, MD; Emory University, Atlanta, GA; Washington University, St. Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The

Ohio State University, Columbus, OH; Medical College of Wisconsin, Milwaukee, WI; New York University, New York, NY; University of California at San Diego, San Diego, CA; University of California at San Francisco, San Francisco, CA; University of Texas Southwestern Medical Center, Dallas, TX; and Vanderbilt University Medical Center, Nashville, TN. Institutional Review Board approval was obtained by each of the participating institutions. Patients were stratified into four groups based on survival: early mortality (died within 2 years), late mortality (died within 2–5 years), actual 5-year survivor (survived at least 5 years) and actual 10-year survivor (survived at least 10 years). Patients alive at the last encounter with less than 5 years of follow-up were excluded.

Data on patient demographics, clinicopathologic characteristics, perioperative outcomes, and overall survival were collected. Preoperative variables included age, race, comorbidities, presence of hormonal excess, and symptoms. Pathologic variables included tumor size, tumor weight, TNM stage, and histologic characteristics. Postoperative morbidity was graded using the modified Clavien-Dindo classification of surgical complications [29]. The seventh edition of the American Joint Commission on Cancer (AJCC) Staging Manual was used to determine TNM classification [30]. Tumors were classified as “atypical ACC” when fewer than 3 Weiss criteria were present on histologic analysis [31].

Statistical Analysis

Continuous variables were reported as median values with interquartile range (IQR) and compared using ANOVA or Kruskal–Wallis test, where appropriate. Categorical variables were presented as frequency and percentages and compared using chi-square or Fisher’s exact test, where applicable. Overall survival was calculated using the Kaplan–Meier method and compared using log-rank test. Clinical and pathologic data were analyzed using univariate and multivariate Cox regression methods. Variables with $P < 0.05$ in the univariate analysis were entered into the Cox’s proportional hazard model to determine predictors of long-term survival. Covariates that did not satisfy the Cox proportional hazard assumption were excluded from the final multivariate model. All statistical analyses were performed using the STATA 13.0 statistical software package (STATA Corp., College Station, TX) and SPSS version 23.0 (IBM, Chicago, IL). Significance was set at a P value of <0.05 (two-tailed).

RESULTS

A total of 265 patients underwent surgery for ACC at one of 13 academic institutions participating in the U.S. Adrenocortical Carcinoma Study Group during the study period (1993–2014). The 5- and 10-year actuarial survival estimates were 44.3% and 31.8%, respectively (Fig. 1). Among the 265 patients, 180 patients met the inclusion criterion of at least 5 years follow-up. Actual 5- and 10-year survival among this subset of patients was 27% and 7%, respectively.

Stratification of these 180 patients into four groups as described in the Methods demonstrated comparable clinical characteristics among the groups with regard to age, sex, race, and comorbidities (Table I). While the proportion of incidental ACC tumors was similar across the four groups, non-secreting tumors were more common among actual 10-

year survivors. On pathological analysis, tumor size and weight were comparable in the four groups. Factors associated with a longer survival included early T-stage, R0 resection, and lack of metastatic disease (Table I). Patients with ACC tumors that did not have lymphovascular invasion (LVI) or capsular invasion were also more likely to have a longer survival. Long-term survivors had a lower incidence of multiorgan resection, intraoperative blood transfusion and lower blood loss (all $P < 0.05$). In contrast, there were no differences in survival among patients with atypical ACC or tumors that had histologic evidence of high mitotic rate, microvascular invasion, or necrosis. The majority of patients did not undergo lymphadenectomy and nodal status was not different among the four groups.

Table II details postoperative variables following initial resection of ACC. Overall morbidity was slightly higher among patients who had a shorter survival, but the incidence of major complications (grade 3 or more) was similar in the four groups. There were no significant differences in rates of specific complications, reoperation, readmission, and length of stay. While the use of adjuvant chemotherapy and radiation were similar in the four groups, mitotane was more commonly used in patients with shorter survival.

Table III shows details on actual 10-year survivors (n¼12, 7%). Most patients were women (83.3%) and had non-secreting tumors (66.7%). The mean tumor size was 12.2-cm (range 4.5–20 cm). Two of the three patients who underwent lymphadenectomy had evidence of lymph node involvement and one patient had synchronous metastatic disease. The absence of IVC tumor thrombus was a universal factor shared by these actual 10-year survivors. None of the patients received adjuvant mitotane after initial resection for adrenocortical carcinoma. Recurrence was eventually observed in 7 of the 12 actual 10-year survivors, and 5 (71%) of these patients underwent repeat resection for recurrent ACC. The longest survivor remains alive 18 years after initial resection and without evidence of recurrence.

DISCUSSION

In one of the largest multi-institutional studies on patients with ACC, we demonstrated that 7% of those who underwent curative intent surgery were actual 10-survivors. To our knowledge, only one small series in the existing literature described actual 10-year survivors in patients with ACC, noting a prevalence of 3% (six patients) over a 28-year period [15]. Thus, our study is the largest series from the United States characterizing factors associated with 10-year actual survival following resection of ACC. Factors associated with early mortality include positive margins, capsular invasion, distant metastasis, and vena cava involvement. The findings of this study underscore the importance of complete resection as well as the prognostic significance of tumor biology and pathology in determining prognosis.

We found several distinct characteristics shared by long-term survivors who underwent curative intent resection for ACC. For example, none of the actual 10-year survivors had Cushing’s syndrome. This finding can be attributed to the negative effects of cortisol production on tumor cell growth and cell immunity [32]. We also observed that long-term survivors universally lacked IVC involvement. Although the benefit of surgery in patients with ACC with vena cava involvement has mostly been limited to case reports, one of the

largest series consisting of 15 patients with ACC extending into the IVC demonstrated a median survival of only 8 months following curative intention resection and no 5-year survivors [26]. These data suggest that although tumors with caval involvement may be technically resectable using surgical techniques such as total hepatic vascular exclusion with or without venovenous or cardiopulmonary bypass, the anticipated limited survival benefit should weigh carefully into the decision to offer surgery in light of the risk of serious postoperative complications. Therefore, while ACC with vena cava involvement should not be considered an absolute contraindication for curative intent resection, it should be considered an indicator of a highly aggressive tumor biology and a limited chance of cure should be anticipated.

In the current study, we observed a high recurrence rate (58%) after resection of primary ACC even within the 10-year survivors group. Several studies have suggested that surgery for recurrent disease can provide a survival benefit [33–36], a second recurrence should be universally anticipated as 94% of patients who had undergone any intervention for recurrent disease eventually experienced repeat recurrence [34]. In our study, 7 of the 12 10-year survivors experienced disease recurrence after the 10-year mark, a finding that underscores the fact that 10-year survival does not equal cure for this disease. Surveillance for recurrence should continue even among those who have reached the 10-year milestone, as these patients should not be considered cured of their disease, especially if they have recurred previously, but underwent successful treatment for this.

A common dilemma faced by clinicians is whether adjuvant therapy is merited after complete macroscopic resection of ACC. The benefit of mitotane after resection of ACC remains controversial given the limited data on long-term outcomes. One promising retrospective study consisting of 177 patients demonstrated prolonged recurrence-free survival, but equivocal overall survival benefit when compared to one of the control groups in the study [37]. Other studies on the efficacy of adjuvant mitotane have revealed no benefit in terms of disease-free or overall survival. One study from M.D. Anderson Cancer Center consisting of 19 patients who underwent resection of ACC demonstrated no survival advantage in patients who received mitotane indefinitely compared to those who received mitotane for a short period (2–12 months) and those who did not receive mitotane after resection [38]. Similarly, a recent study published from our collaborative group did not identify a significant impact in survival even after adjusting for tumor and treatment related factors [39]. In the current study, we found a significant proportion of patients (51.7%) who died within 2 years were treated with adjuvant mitotane (likely prompted by unfavorable pathologic characteristics of the tumor) whereas none of the actual 10-year survivors received adjuvant mitotane. This difference may partly be a function of selection bias, as patients who received mitotane were likely those with the greatest risk of recurrence.

There are several major limitations in this study. First, despite the multi-institutional nature of the study consisting of 13 major academic hospitals in the United States, the sample size is still small, with each institution performing on average about one resection for primary ACC per year. Second, specific data on the Weiss criteria was not universally available due to variation in pathology reporting by each of the participating institutions. Nevertheless, the

heterogeneous population in this multi-institutional study allows for generalizable results for a very rare malignancy.

In conclusion, actual 10-year survival is possible in 7% of patients undergoing surgery for adrenocortical carcinoma. Vena cava involvement, R2 resection, and glucocorticoid secretion are factors precluding 10-year survival. On the other hand, long-term survival beyond the 10-year milestone can still be achieved in the presence of lymph node or even distant metastasis and R1 resection. The vast majority (83%) of 10-year survivors were women and a substantial portion of them (42%) had undergone repeat resection for recurrence. Until more effective systemic therapies become available, these data can help clinicians counsel patients on the long-term outcomes of surgery for this challenging malignancy.

REFERENCES

1. Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: Treatment utilization and prognostic factors. Cancer. 2008; 113:3130–3136. [PubMed: 18973179]
2. Kebebew E, Reiff E, Duh QY, et al. Extent of disease at presentation and outcome for adrenocortical carcinoma: Have we made progress? World J Surg. 2006; 30:872–878. [PubMed: 16680602]
3. Przytulska J, Rogala N, Bednarek-Tupikowska G. Current and emerging therapies for adrenocortical carcinoma—Review. Adv Clin Exp Med. 2015; 24:185–193. [PubMed: 25931348]
4. Sidhu S, Sywak M, Robinson B, et al. Adrenocortical cancer: Recent clinical and molecular advances. Curr Opin Oncol. 2004; 16:13–18. [PubMed: 14685087]
5. Crucitti F, Bellantone R, Ferrante A, et al. The Italian registry for adrenal cortical carcinoma: Analysis of a multiinstitutional series of 129 patients. the ACC Italian registry study group. Surgery. 1996; 119:161–170. [PubMed: 8571201]
6. Haak HR, Hermans J, van de Velde CJ, et al. Optimal treatment of adrenocortical carcinoma with mitotane: Results in a consecutive series of 96 patients. Br J Cancer. 1994; 69:947–951. [PubMed: 8180029]
7. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: Surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg. 2001; 25:891–897. [PubMed: 11572030]
8. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med. 1990; 322:1195–1201. [PubMed: 2325710]
9. Pommier RF, Brennan MF. An eleven-year experience with adrenocortical carcinoma. Surgery. 1992; 112:963–970. discussion 970–961. [PubMed: 1455321]
10. Sakamoto K, Ariyoshi A, Okazaki M. Metastatic adrenocortical carcinoma treated by repeated resection: A case report of long-term survival over 18 years. Int J Urol. 1995; 2:50–52. [PubMed: 7614407]
11. Schulick RD, Brennan MF. Adrenocortical carcinoma. World J Urol. 1999; 17:26–34. [PubMed: 10096148]
12. Vassilopoulou-Sellin R, Schultz PN. Adrenocortical carcinoma. Clinical outcome at the end of the 20th century. Cancer. 2001; 92:1113–1121. [PubMed: 11571723]
13. Venkatesh S, Hickey RC, Sellin RV, et al. Adrenal cortical carcinoma. Cancer. 1989; 64:765–769. [PubMed: 2743269]
14. De Leon DD, Lange BJ, Walterhouse D, et al. Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol Metab. 2002; 87:4452–4456. [PubMed: 12364417]
15. Hermsen IG, Gelderblom H, Kievit J, et al. Extremely long survival in six patients despite recurrent and metastatic adrenal carcinoma. Eur J Endocrinol. 2008; 158:911–919. [PubMed: 18505909]

16. Ilias I, Alevizaki M, Philippou G, et al. Sustained remission of metastatic adrenal carcinoma during long-term administration of low-dose mitotane. J Endocrinol Invest. 2001; 24:532–535. [PubMed: 11508789]
17. Meyer A, Behrend M. 32-year survival with metastatic adrenal cortical carcinoma—Update of a case report. Anticancer Res. 2007; 27:1045–1046. [PubMed: 17465241]
18. Orlando R, Pelizzo MR, Lirussi F. Adrenocortical carcinoma: A 15-year survival after complete resection and repeated resection. A retrospective study in a patient with an expected poor prognosis. Anticancer Res. 2003; 23:2929–2931. [PubMed: 12926137]
19. van Aalderen W, van Seters AP, Backer ET, et al. A case of recurrent adrenocortical carcinoma, with observations on long-term o,p'-DDD therapy and complications. Neth J Med. 1992; 41:161–170. [PubMed: 1470288]
20. Bergeat D, Rayar M, Beuzit L, et al. An unusual case of adrenocortical carcinoma with liver metastasis that occurred at 23 years after surgery. Hepatobiliary Surg Nutr. 2016; 5:265–268. [PubMed: 27275470]
21. Mawardi M, Al-Judaibi B, Marotta P. Hepatic metastasis from adrenocortical carcinoma fifteen years after primary resection. Saudi J Gastroenterol. 2012; 18:140–142. [PubMed: 22421721]
22. Berruti A, Baudin E, Gelderblom H, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23:vii131–vii138. [PubMed: 22997446]
23. Canter DJ, Mallin K, Uzzo RG, et al. Association of tumor size with metastatic potential and survival in patients with adrenocortical carcinoma: An analysis of the National Cancer Database. Can J Urol. 2013; 20:6915–6921. [PubMed: 24128829]
24. Nilubol N, Patel D, Kebebew E. Does lymphadenectomy improve survival in patients with adrenocortical carcinoma? A population-Based study. World J Surg. 2016; 40:697–705. [PubMed: 26510563]
25. Reibetanz J, Jurowich C, Erdogan I, et al. Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. Ann Surg. 2012; 255:363–369. [PubMed: 22143204]
26. Chiche L, Dousset B, Kieffer E, et al. Adrenocortical carcinoma extending into the inferior vena cava: Presentation of a 15-patient series and review of the literature. Surgery. 2006; 139:15–27. [PubMed: 16364713]
27. Margonis GA, Kim Y, Prescott JD, et al. Adrenocortical carcinoma: Impact of surgical margin status on long-Term outcomes. Ann Surg Oncol. 2016; 23:134–141. [PubMed: 26286195]
28. Bulzico D, de Faria PA, de Paula MP, et al. Recurrence and mortality prognostic factors in childhood adrenocortical tumors: Analysis from the Brazilian National Institute of Cancer experience. Pediatr Hematol Oncol. 2016; 33:248–258. [PubMed: 27246903]
29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg. 2009; 250:187–196. [PubMed: 19638912]
30. Edge, SB. American Joint Committee on Cancer American Cancer Society: AJCC cancer staging manual. New York, London: Springer; 2010.
31. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol. 1984; 8:163–169. [PubMed: 6703192]
32. Abiven G, Coste J, Groussin L, et al. Clinical and biological features in the prognosis of adrenocortical cancer: Poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab. 2006; 91:2650–2655. [PubMed: 16670169]
33. Jensen JC, Pass HI, Sindelar WF, et al. Recurrent or metastatic disease in select patients with adrenocortical carcinoma. Aggressive resection vs chemotherapy. Arch Surg. 1991; 126:457–461. [PubMed: 1706914]
34. Erdogan I, Deutschbein T, Jurowich C, et al. The role of surgery in the management of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab. 2013; 98:181–191. [PubMed: 23150691]
35. Dy BM, Wise KB, Richards ML, et al. Operative intervention for recurrent adrenocortical cancer. Surgery. 2013; 154:1292–1299. discussion 1299. [PubMed: 24238048]
36. Gaujoux S, Al-Ahmadie H, Allen PJ, et al. Resection of adrenocortical carcinoma liver metastasis: Is it justified? Ann Surg Oncol. 2012; 19:2643–2651. [PubMed: 22526905]
37. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med. 2007; 356:2372–2380. [PubMed: 17554118]

38. Vassilopoulou-Sellin R, Guinee VF, Klein MJ, et al. Impact of adjuvant mitotane on the clinical course of patients with adrenocortical cancer. Cancer. 1993; 71:3119–3123. [PubMed: 8490842]

39. Postlewait LM, Ethun CG, Tran TB, et al. Outcomes of adjuvant mitotane after resection of adrenocortical carcinoma: A 13-Institution study by the US Adrenocortical Carcinoma Group. J Am Coll Surg. 2016; 222:480–490. [PubMed: 26775162]

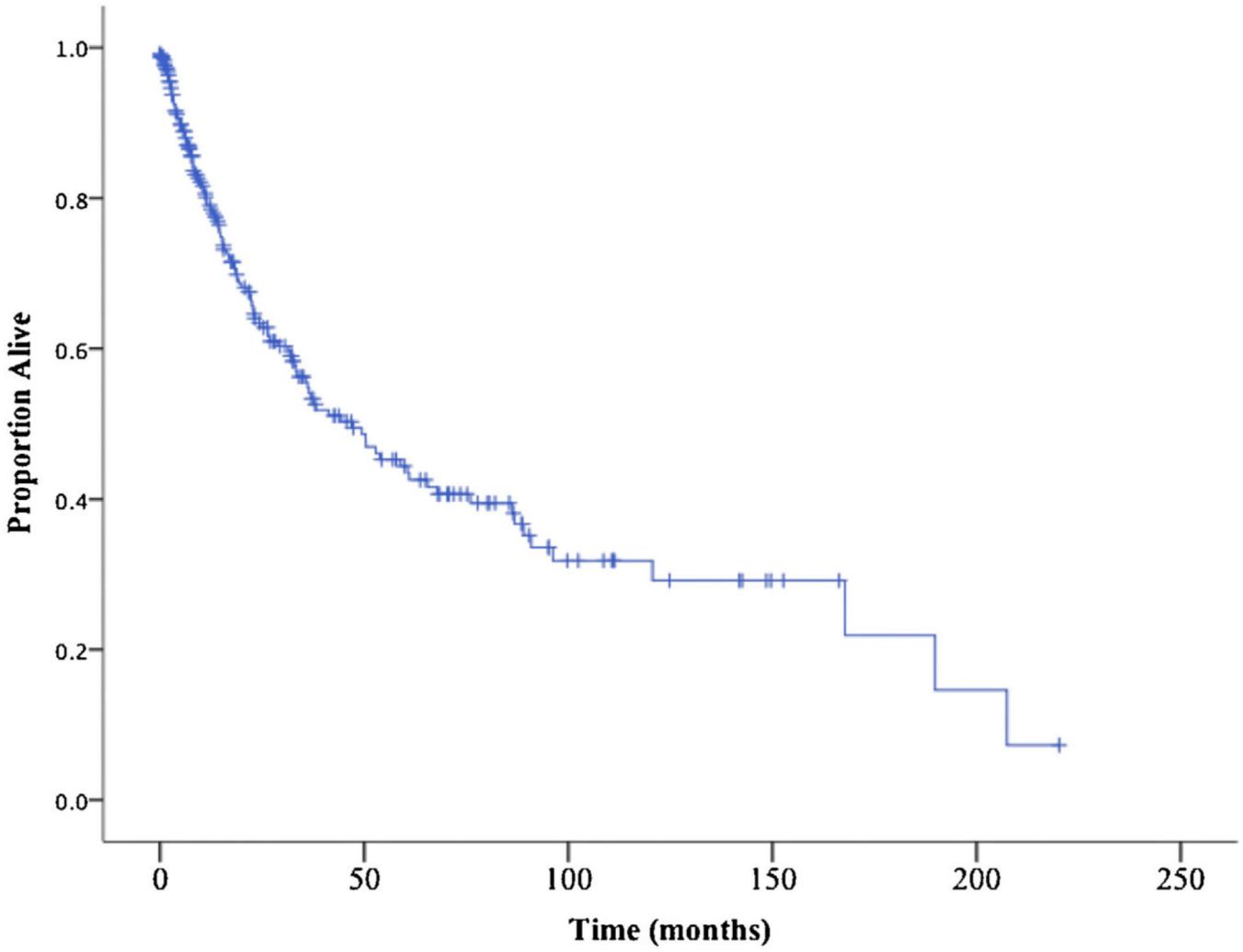

Fig. 1.

Kaplan–Meier curve demonstrating overall survival of 256 patients who underwent resection of ACC (median survival 47 months).

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TABLE I

Clinicopathologic Characteristics of 180 Patients with Adrenocortical Carcinoma Stratified by Their Survival Outcome

	Alive <2 yrs (n = 73)	**Alive 2–5 yrs (n = 57)**	**Alive 5–10 yrs (n = 37)**	**Alive >10 yrs (n = 12)**	***P*-value**
Preoperative					
Age (median, IQR)	54 (44–65)	56 (47–62)	52 (44–58)	49 (37–52)	0.180
Female	42 (57.5)	34 (58.6)	23 (62.2)	10 (83.3)	0.395
Non-White	16 (22.5)	9 (15.8)	7 (20.6)	1 (9.1)	0.639
CAD	7 (9.7)	7 (12.3)	3 (8.1)	1 (9.1)	0.939
CHF	4 (5.6)	1 (1.8)	0 (0)	1 (9.1)	0.197
COPD	6 (8.2)	4 (7)	0 (0)	2 (16.7)	0.120
CKD	5 (6.8)	3 (5.3)	0 (0)	0 (0)	0.444
DM	20 (27.4)	9 (15.8)	4 (10.8)	1 (8.3)	0.126
BMI (median, IQR)	29 (24–35)	27 (24–31)	26 (23–29)	25.5 (25–36)	0.326
Incidentaloma	27 (37.5)	19 (35.8)	17 (48.6)	4 (36.4)	0.651
Weight loss (n = 166)	12 (17.1)	8 (15.4)	6 (18.2)	0 (0)	0.581
Abdominal pain (n = 165)	32 (44.4)	30 (57.7)	11 (35.5)	3 (30)	0.155
Palpable Mass (n = 162)	7 (9.9)	12 (24.5)	4 (12.5)	2 (20)	0.147
Leg Edema (n = 159)	20 (29.4)	8 (16.3)	2 (6.3)	1 (10)	0.033
Hormonal hypersecretion					
Non-secreting	33 (46.5)	35 (66)	16 (48.5)	8 (72.7)	0.013
Cortisol-secreting	23 (32.4)	4 (7.5)	8 (24.2)	0 (0)	
Non-cortisol	11 (15.5)	11 (20.8)	6 (18.2)	3 (27.3)	
Pathology					
Tumor size (median, IQR)	13 (10–15.8)	12 (7–16.5)	11 (8.5–13.7)	11.7 (9–15)	0.506
Tumor weight (grams) (median, IQR)	487.5 (239.9–1365)	355.5 (133.1–1226)	370 (210–1030)	610 (360–1050)	0.647
T-stage (n = 159)					
T1	0 (0)	2 (4)	2 (6)	1 (11.1)	0.007
T2	18 (26.9)	27 (54)	16 (48.5)	4 (44.4)	
T3	31 (46.3)	17 (34)	12 (36.4)	3 (33.3)	
T4	18 (26.9)	4 (8)	3 (9.1)	1 (11.1)	
N stage					

	Alive <2 yrs (n = 73)	Alive 2–5 yrs (n = 57)	Alive 5–10 yrs (n = 37)	Alive >10 yrs (n = 12)	*P*-value
N0	15 (20.5)	14 (24.1)	9 (24.3)	2 (16.7)	0.060
N1	15 (20.5)	6 (10.3)	0 (0)	2 (16.7)	
Nx	43 (58.9)	38 (65.5)	28 (75.7)	8 (66.7)	
M1	31 (44.3)	6 (10.7)	1 (3)	1 (9.1)	<0.001
Margins					
R0	30 (45.5)	42 (84)	25 (78.1)	6 (85.7)	<0.001
R1	26 (39.4)	5 (10)	7 (21.9)	1 (14.3)	
R2	10 (15.2)	3 (6)	0 (0)	0 (0)	
Lymphatic invasion (n = 105)	30 (65.2)	18 (50)	3 (18.8)	3 (42.9)	0.012
MVI (n = 93)	32 (74.4)	18 (60)	7 (41.2)	1 (33.3)	0.056
High mitotic rate (n = 76)	21 (65.6)	16(61.5)	8 (57.1)	2 (50)	0.883
Necrosis (n = 139)	50 (86.2)	42 (91.3)	25 (96.2)	9 (100)	0.489
Capsular invasion (n = 119)	40 (78.4)	18 (50)	12 (48)	4 (57.1)	0.012
Atypical (vs. ACC) (n = 127)	4 (7.5)	2 (4.4)	3 (14.3)	1 (12.5)	0.391
Operative					
Other organs resected	46 (63.9)	20 (36.4)	13 (36.1)	4 (33.3)	0.004
OR time minutes (median, IQR)	251 (171–366)	181 (123–294)	179 (132–230)	173 (106–173)	0.152
EBL (per mL) (median, IQR)	1150 (300–2350)	450 (150–1175)	500 (200–900)	400 (200–400)	0.010
Open (vs. laparoscopic)	63 (88.7)	43 (78.1)	30 (81.1)	8 (80)	0.377
Intraoperative blood transfusion (n = 122)	31 (56.4)	12 (33.3)	5 (20)	1 (16.6)	0.006

Parenthesis represent percentages unless otherwise indicated. CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; BMI, body mass index; IQR, interquartile range; LVI, lymphovascular invasion; yrs, years; MVI, microvascular invasion

TABLE II

Postoperative Outcomes Following Adrenocortical Carcinoma Resection

	Alive <2 yrs (n = 73)	Alive 2–5 yrs (n = 57)	Alive 5–10 yrs (n = 37)	Alive >10 yrs (n = 12)	*P*-value
Any complication	27 (40.9)	17 (35.4)	3 (10.3)	3 (37.5)	0.019
Grade >3 complication (n = 127)	10 (18.2)	4 (9.8)	1 (4.2)	1 (14.3)	0.310
Reoperation (n = 149)	5 (7.7)	0 (0)	1 (3.2)	0 (0)	0.218
Intra-abdominal abscess (n = 149)	3 (4.6)	0 (0)	0 (0)	0 (0)	0.417
Respiratory failure (n = 148)	6 (9.4)	1 (2.2)	0 (0)	1 (12.5)	0.132
Renal failure requiring dialysis (n = 148)	4 (6.3)	0 (0)	0 (0)	0 (0)	0.239
Pulmonary embolism (n = 147)	3 (4.6)	2 (4.4)	0 (0)	0 (0)	0.781
Length of stay in days (median, IQR)	7 (5–10)	6 (4–8)	6 (4–7)	6 (4–10)	0.4352
Readmission within 90 days (n = 136)	17 (27.4)	4 (10.2)	3 (10.7)	2 (28.5)	0.082
Adjuvant Chemotherapy (n = 168)	16 (25.4)	11 (19)	4 (11.4)	1 (8.3)	0.334
Adjuvant Mitotane (n = 151)	30 (51.7)	25 (46.3)	7 (23.3)	0 (0)	0.002
Adjuvant Radiation (n = 147)	5 (8.8)	5 (9.6)	3 (10.7)	0 (0)	0.917

IQR, interquartile range; yrs, years.

TABLE III

Clinicopathologic Characteristics of 12 10-Year Survivors After Resection of ACC

Age (years)	Sex	Hormonal secretion	Size (cm)	TNM	Margins	Adjuvant therapy	Recurrence	DFI (months)	Treatment for Recurrence	Status	Survival (months)
46	F	Nonsecreting	15.0	T2NxM0	R0	None	No	NA	NA	NED	143
49	M	Nonsecreting	NR	NR	R0	None	No	NA	NA	NED	220
73	F	Nonsecreting	4.5	T1NxM0	R0	None	Lung (distant)	108.8	None	DOD	168
65	F	Virilizing/feminizing	13.0	T2NxM0	R0	None	No	NA	NA	DOD	207
49	F	Nonsecreting	9.8	T2NxM0	NR	None	No	NA	NA	NED	125
50	F	Nonsecreting	8	T2NxM0	R0	None	No	NA	NA	DOC	190
33	F	NR	20.0	T3NxM0	NR	None	Spine (distant)	36.1	Mitotane and radiation	DOD	121
2	F	Virilizing/feminizing	19.5	T3N1M0	R1	Cisplatin, VP-16	LN (local)	2.3	Surgery and chemotherapy	NED	166
32	F	Virilizing/feminizing	NR	NR	NR	None	Lung (distant)	4.3	Surgery only	AWD	142
49	F	Nonsecreting	13.0	T3N0M0	R0	None	Distal Pancreas (local)	39.1	Surgery only	AWD	149
42	F	Nonsecreting	9.0	T2NxM0	NR	None	Liver (local)	98.4	Surgery and mitotane	AWD	150
55	M	Nonsecreting	10.5	T4N1M1	NR	None	Liver (local)	48.5	Surgery, SBRT, chemotherapy	AWD	153

NR, not recorded; F, female; M, male; N/A, not applicable; NED, no evidence of disease; DOD, died of disease; DOC, died of other causes; AWD, alive with disease; DFI, disease free interval.