Published in final edited form as:

World J Surg. 2016 March ; 40(3): 706–714. doi:10.1007/s00268-015-3307-y.

Incidence of Perioperative Complications Following Resection of Adrenocortical Carcinoma and Its Association with Long-Term Survival

Georgios Antonios Margonis^{#1}, Neda Amini^{#1}, Yuhree Kim¹, Thuy B. Tran², Lauren M. Postlewait³, Shishir K. Maithel³, Tracy S. Wang⁴, Douglas B. Evans⁴, Ioannis Hatzaras⁵, Rivfka Shenoy⁵, John E. Phay⁶, Kara Keplinger⁶, Ryan C. Fields⁷, Lindsey E. Moses⁷, Sharon M. Weber⁸, Ahmed Salem⁸, Jason K. Sicklick⁹, Shady Gad⁹, Adam C. Yopp¹⁰, John C. Mansour¹⁰, Quan-Yang Duh¹¹, Natalie Seiser¹¹, Carmen C. Solorzano¹², Colleen M. Kiernan¹², Konstantinos I. Votanopoulos¹³, Edward A. Levine¹³, George A. Poultsides², and Timothy M. Pawlik¹

¹ Department of Surgery, Johns Hopkins Hospital, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Blalock 688, Baltimore, MD 21287, USA

² Department of Surgery, Stanford University School of Medicine, Stanford, CA, USA

³ Department of Surgery, Emory University, Atlanta, GA, USA

⁴ Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

⁵ Department of Surgery, New York University School of Medicine, New York, NY, USA

⁶ Department of Surgery, The Ohio State University, Columbus, OH, USA

⁷ Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

⁸ Department of General Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

⁹ Department of Surgery, University of California San Diego, San Diego, CA, USA

¹⁰ Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

¹¹ Department of Surgery, University of California San Francisco, San Francisco, CA, USA

¹² Department of Surgery, Vanderbilt University, Nashville, TN, USA

¹³ Department of Surgery, Wake Forest School of Medicine, Winston-Salem, NC, USA

[#] These authors contributed equally to this work.

Abstract

Background—The association of postoperative complications with long-term oncologic outcomes remains unclear. We sought to determine the incidence of complications among patients who underwent surgery for adrenocortical carcinoma (ACC) and define the relationship of morbidity with long-term survival.

Methods—Patients who underwent surgery for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the US ACC group study. The incidence and type of the postoperative complications, the factors associated with them as well their association with long-term survival were analyzed.

Results—A total of 265 patients with median age of 52 years (IQR 44–63) were identified; at surgery, the majority of patients underwent an open abdominal procedure (n = 169, 66.8 %). A postoperative complication occurred in 99 patients for a morbidity of 37.4 %; five patients (1.9 %) died in hospital. Factors associated with morbidity included a thoraco-abdominal operative approach (reference: open abdominal; OR 2.85, 95 % CI 1.00–8.18), and a hormonally functional tumor (OR 3.56, 95 % CI 1.65–7.69) (all $P < 0.05$). Presence of any complication was associated with a worse long-term outcome (median survival: no complication, 58.9 months vs. any complication, 25.1 months; $P = 0.009$). In multivariate analysis, after adjusting for patient- and disease-related factors postoperative infectious complications independently predicted shorter overall survival (hazard ratio (HR) 5.56, 95 % CI 2.24–13.80; $P < 0.001$).

Conclusion—Postoperative complications were independently associated with decreased long-term survival after resection for ACC. The prevention of complications may be important from an oncologic perspective.

Introduction

Adrenocortical cancer (ACC) is a rare, but aggressive endocrine malignancy [1]. Surgical resection, often in combination with postoperative chemotherapy and/or radiotherapy, offers the best hope for long-term survival with an estimated 5-year survival of 13–81 % [2]. Most studies reporting on prognosis following ACC resection have focused largely on operative and tumor specific factors. Among these factors, the most consistent prognostic factors include tumor stage, high mitotic index/Ki67, and surgical margin status [3–7]. Over the last decade, the occurrence of a perioperative postoperative complication has also emerged as a factor possibly associated with long-term outcomes following surgery for several malignancies. Specifically, several investigators have reported the negative impact of postoperative complications on long-term survival of patients with colorectal, hepatocellular carcinoma (HCC), head and neck, as well as esophageal cancer [8–12]. Our own group has noted that postoperative complications impacted negatively on long-term outcomes after hepatic resection for intrahepatic cholangiocarcinoma (ICC) and colorectal liver metastasis (CRLM) [13, 14]. Other investigators, however, have failed to find an association between perioperative morbidity and long-term survival [15–17]. Interestingly, organ-specific postoperative complications—particularly infectious ones—may have variable effects on survival among patients with different malignancies [18–22]. The effect of morbidity on long-term oncologic outcomes has been mechanistically attributed to an increased systemic inflammatory response that, in turn, may increase the risk of cancer progression and decrease survival [23–26].

An association between postoperative complications and long-term outcomes following oncologic surgery may be particularly important to elucidate, as the risk of perioperative morbidity can potentially be modified. To our knowledge, no study to date has explicitly examined the association of perioperative complications with long-term oncological

outcomes among patients undergoing adrenal resection for ACC. Furthermore, identifying risk factors associated with complications could lead to an increased awareness and facilitate earlier treatment. Given this, the aim of the current study was to identify risk factors associated with the occurrence of postoperative complications, as well evaluate the association of postoperative complications, and particularly of infectious complications, with the long-term outcomes including recurrence-free survival (RFS) and overall survival (OS), among patients undergoing adrenal resection for ACC.

Materials and methods

Study design

Patients who underwent surgery between January 1993 and December 2014 for ACC were identified from 13 major academic centers in the United States. The US Adrenocortical Carcinoma Group (US ACC Group) was established in 2014; data were collected in a retrospective manner. The multi-institutional collaboration was coordinated by Stanford University. The study was not funded. The data we used concern only primary surgery for ACC. The 13 institutions participating in the study included Johns Hopkins Hospital, Baltimore, MD; Emory University, Atlanta GA; Stanford University, Palo Alto, CA; 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. The Institutional Review Board of the participating institutions approved the study. Standard demographic, perioperative, and clinicopathologic data were collected and included the following: age, sex, race, comorbidities, presenting symptoms, T stage, tumor size, tumor laterality, hormonal functional status, capsular invasion, and lymph node status. Data on surgical approach, multi-organ resection and margin status (negative [R0], microscopically positive [R1], or macroscopically positive [R2]) were obtained. Hormone-functional status was determined in a standardized fashion for all participating institutions by using certain variables such as 24-h urinary cortisol values, cortisol values after low dose dexamethasone suppression, ACTH levels, aldosterone levels, DHEA-sulfate levels, and testosterone levels. Other recorded data included the receipt of perioperative chemotherapy/radiotherapy and adjuvant mitotane. Short-term outcomes included length of hospital stay, re-operation, and postoperative morbidity and mortality. Complications were categorized using the Clavien–Dindo classification: minor complications were classified as grade I and II, major complications as grade III and IV [27].

Among those patients who experienced multiple complications, the highest grade of complication was used for analytic purposes. Complications were dichotomized as infectious (wound infection, abdominal abscess, pneumonia, urinary tract infection, clostridium difficile infection, and sepsis) versus non-infectious (all other complications) for the purposes of analyses. The date of the last follow-up visit, and recurrence, and survival

information were collected. Recurrence was defined as a biopsy-proven ACC or a lesion deemed suspicious on cross-sectional imaging.

Statistical analysis

Demographic, clinicopathologic, and perioperative characteristics of the study cohort were stratified according to the occurrence of postoperative complications. Continuous variables were presented as medians with interquartile range (IQR) and categorical variables were described as frequencies and distributions. The differences between groups were assessed by the χ^2 or Mann–Whitney test, as appropriate. Logistic regression analysis was used to explore factors associated with postoperative complication; results were reported as odds ratio (OR) with 95 % confidence interval (95 % CI). The Kaplan–Meier survival method was utilized to estimate the median, 1-, 3-, and 5-year RFS and OS. Patients who died within 30 days of surgery were excluded from the survival analyses. Univariate and multivariate survival analyses were performed using the Cox proportional hazards model, with results presented as hazard ratio (HR) with 95 % CI. Factors that were included in the univariate/multivariate model were selected based on clinical interest and scientific knowledge derived from the scientific literature. The discrimination ability was assessed using the Harrell's concordance index (c-index) [28]. Analyses were performed using the Stata 12.0 statistical software package (Stata Corp, College Station, TX, USA), and a P value of <0.05 (two tailed) was considered statistically significant.

Results

Demographic and clinicopathologic characteristics

A total of 265 patients were included in the study. A summary of demographic and clinicopathologic characteristics is presented in Table 1. Median patient was 52 (IQR 44–63) years; the majority of patients were female ($n = 164$, 61.9 %) and Caucasian ($n = 207$, 81.5 %). ACC was diagnosed as an incidental finding on cross-sectional imaging in 110 patients (43.8 %), whereas 102 patients (41.6 %) had hormone-functional tumors. At the time of presentation, one fifth of patients ($n = 48$, 18.7 %) had metastatic disease. The most common tumor location was the left adrenal gland ($n = 146$, 56.4 %); the median size of the tumors was 11.5 cm (IQR 8–15). At the time of surgery, most patients underwent open abdominal adrenal resection ($n = 169$, 66.8 %), whereas 44 patients (17.4 %) underwent minimally invasive surgery; the remaining 40 (15.8 %) underwent thoraco-abdominal surgery. Multi-organ resection (adrenal gland plus at least one additional organ) was performed in 122 (48.4 %) patients. On final histology the surgical margin was microscopically negative (R0) in 155 (68.9 %), microscopically positive (R1) in 55 (24.4 %), and macroscopically positive (R2) in 15 patients (6.7 %). Capsular invasion was noted in 104 patients (59.4 %). Lymph nodes were harvested in only 83 patients and 29 of them were found to have lymph node metastases (34.9 %). Overall, 123 patients (46.4 %) received postoperative systemic chemotherapy, whereas only a small subset (5 patients, 2 %) received preoperative chemotherapy. Postoperative mitotane was administered to 85 patients (41.3 %) and postoperative radiotherapy was administered to 20 patients (9.6 %).

Postoperative morbidity

Postoperative morbidity is summarized in Table 2. Overall, 99 patients experienced a postoperative complication, for a morbidity of 37.4 %. In total, 73 (73.7 %) patients had a minor (grade I–II) whereas 26 (26.3 %) patients had a major (grade III–IV) complication. Complications were divided in an organ-specific manner: postoperative adrenal insufficiency ($n = 55$, 20.8 %), pulmonary ($n = 28$, 10.6 %), and cardiovascular ($n = 19$, 7.2 %) were most common. Overall, ten patients (4.5 %) underwent a re-operation within 30 days and five patients (1.9 %) died in hospital.

Several factors were associated with postoperative complication after resection of ACC. On univariate analysis, age, preoperative diabetes mellitus, hormone-secreting tumors, capsular invasion, operation type, tumor margin, and multi-organ resection were each associated with postoperative complications (Table 3). On multivariate analysis, complications were more likely to occur in patients with hormone-secreting tumors (OR 3.56, 95 % CI 1.65–7.69; $P = 0.001$) versus non-functional lesions. Patients undergoing thoraco-abdominal resection were also more likely to develop postoperative complications (reference open abdominal or posterior; OR 2.85 95 % CI 1.00–8.18; $P = 0.05$). In addition, patients who underwent an MIS approach tended to have a lower risk of developing postoperative complications (OR 0.48, 95 % CI 0.22–0.98; $P = 0.05$).

Long-term clinical outcomes

Median RFS for the entire cohort was 15.9 (95 % CI 11.0–22.1) months. The 1-, 3-, and 5-year RFS was 55.5, 31.9, and 20.9 %, respectively (Table 4). On univariate survival analysis, patients with any postoperative complication had a comparable RFS versus patients without complications (median survival: no complication, 18.8 months vs. 1 complication, 11.8 months; $P = 0.33$) (Table 4).

Median overall survival for the entire cohort was 49.4 (95 % CI 33.5–68.0) months. One-, three-, and five-year overall survival were 80.4, 56.4, and 45.1 %, respectively (Table 4). On univariate survival analysis, patients with any postoperative complication had a worse long-term survival compared with patients who did not experience a complication (median survival: no complication, 58.9 months vs. 1 complication, 25.1 months; $P = 0.009$) (Fig. 1). Of note, patients with adrenal insufficiency had a worse long-term survival compared with patients who did not experience a complication (HR 1.63, 95 % CI 1.01–2.63; $P = 0.04$); in contrast, patients with adrenal insufficiency had a comparable survival versus those patients who experienced a complication other than postoperative adrenal insufficiency (HR 0.96, 95 % CI 0.52–1.77; $P = 0.91$). On multivariate analysis, the occurrence of any postoperative complication was associated with an increased risk of death (HR 1.68, 95 % CI 1.07–2.63; $P = 0.02$) after controlling for patient- and disease-specific factors (Table 5). Of note, patients with infectious complications had worse survival than patients who did not experience a complication (reference no complication, HR 3.32, 95 % CI 1.41–7.82; $P = 0.006$) (Table 5). On multivariate analysis, after controlling for patient- and disease-specific factors, the presence of infectious complications remained associated with a worse overall survival (HR 5.56, 95 % CI 2.24–13.80; $P < 0.001$) (Table 5). In contrast, patients with non-infectious complications did not have higher risk of death versus patients who had no

complication (HR 1.50, 95 % CI 0.94–2.40; $P = 0.09$). When controlling for patient, disease as well as treatment-specific factors, the occurrence of infectious complications remained associated with an increased risk of death (HR 3.32, 95 % CI 1.24–8.83; $P = 0.02$) (Table 5).

Discussion

The very low incidence of ACC and the lack of centralized care for patients with ACC in high volume, tertiary centers have precluded large studies that can report on the incidence, grade, and organ-specific characteristics of postoperative complications occurring after ACC resection [29]. To the best of our knowledge, no previous study has explicitly examined the association of postoperative morbidity with long-term outcomes among patients undergoing an ACC resection. Almost every previous study has examined long-term outcomes exclusively in relation to well-known tumor-related factors, such as tumor stage, high mitotic index/Ki67, and surgical margin status [3–7]. Investigating the role of patient-related factors such as postoperative complications was first suggested by Laurent et al. who suggested a relation between postoperative complications and worse long-term outcomes in CRLM [8–14, 30]. In the present cohort, postoperative morbidity occurred in approximately one third of patients, and perhaps more importantly, complications were associated with worse long-term outcomes. In fact, patients who experienced a postoperative complication had a 68 % higher risk of death on long-term follow-up. In particular, infectious complications impacted a patient's risk of death—consistent with previous reports that have noted how activation of inflammatory mediators around the time of surgery can adversely impact long-term patient outcomes [31–33].

Of note, over 1 in 3 patients experienced some type of complication around the time of surgery for ACC. The incidence of postoperative morbidity in the current study may seem relatively high, especially given that patients were treated at specialized tertiary centers. Most patients, however, had advanced disease. For example, the median tumor size of ACC lesions among patients treated in the current study was 11 cm and roughly one-half of patients had a multi-organ resection that involved resection of the adrenal gland plus at least one additional organ. These data indicate that a relatively high morbidity may have been attributed to technical challenges associated with operating on large, more complex tumors. Of note, the incidence of postoperative morbidity was lower among patients undergoing a minimally invasive (25 %) versus open (41 %) ACC resection ($P = 0.04$)—undoubtedly related to patient selection. Eichhorn–Wharry et al. previously compared the morbidity of laparoscopic versus open adrenalectomy using the Clavien classification system [34]. In this study, the authors used the National Surgical Quality Improvement Program (NSQIP) database to compare the laparoscopic versus open approach for patients undergoing an adrenalectomy for any indication. The authors noted that the laparoscopic approach was feasible, safe, and associated with lower complications even after correcting for multiple comorbidities. In the current study, we similarly noted that an MIS approach could be performed with low morbidity in appropriately selected patients with ACC.

The current study is important because it specifically examined the association of postoperative morbidity with long-term outcomes among patients with ACC, which previously had been unknown. Of note, perioperative morbidity was strongly associated with

long-term outcomes (Fig. 1). These findings are consistent with previous studies the examined other solid malignancies, which reported worse prognosis among patients who developed postoperative complications [8–14]. In addition to complication occurrence, we also noted that the type of complication was associated with outcome. Specifically, infectious postoperative complications were an independent predictor of worse OS. Farid et al. reported on the independent prognostic role of infectious complications on long-term outcomes after CRLM resection [20]. Artinyan et al. similarly demonstrated that the negative effect of perioperative morbidity on long-term outcomes after CRC resection was largely mediated by infectious complications [19]. In a separate study, Scaife et al. queried the NSQIP database for solid malignancies and investigated the relationship of infectious complications with long-term outcomes [22]. The authors noted that infectious complications were associated with over a threefold increased risk of death in the long-term. A number of underlying mechanisms may be responsible for the negative impact of infectious complications on long-term outcomes. For example, infectious complications are associated with excessive levels of pro-inflammatory cytokines that include IL-1, IL-6, IL-8, and TNF- α [35–38]. In turn, this pro-inflammatory milieu may exert an immunosuppressive effect by decreasing the number, as well as impairing the function of cytotoxic T lymphocytes and NK cells [39–41]. In turn, this immunosuppression may augment the growth of occult micrometastases. Another interesting finding in the current study was how patients with hormone-secreting tumors were also at an increased risk of perioperative morbidity—including infectious complications. Hormone secretion, and especially cortisol secretion, is a well-known factor that predisposes to infection possibly by decreasing circulating CD4 cells and inhibiting the synthesis of most cytokines, probably by inducing the synthesis of I kappa B α , a protein that traps and thereby inactivates nuclear factor kappa B [42].

The current study had several limitations. As with all retrospective analysis, selection bias was a possibility. Another limitation involved sample size. Although the current study involved 13 major tertiary medical centers, the sample size remained relatively small ($n \approx 300$) and this impacted our ability to do certain subset analyses. In addition, data regarding preoperative medical treatment for tumor hormone secretion were lacking. Finally, although the multi-institutional nature of the cohort lends greatly to the generalizability of the present study, it did preclude standardized treatment protocols. This lack of treatment standardization should, however, have minimal impact on the main hypothesis being tested. Of note, all participating centers were tertiary centers in which ACC was treated by experienced teams in both the operative and perioperative setting. Therefore, the data may not be completely generalizable (e.g., incidence and management of postoperative complications) to the community hospital setting.

In conclusion, perioperative complications following surgery for ACC were relatively common. The occurrence of perioperative complications was associated with an increased risk of worse long-term outcome. In particular, infectious postoperative complications were an independent predictor of decreased long-term survival, even after adjusting for patient, disease, and treatment-specific factors. Postoperative complications, particularly infectious ones, are potentially preventable. As such, ongoing efforts need to be devoted to mitigate

perioperative morbidity in order to improve both quality of care, as well as long-term outcomes following surgery for ACC.

References

1. 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. doi:10.1007/s00268-010-005-0329-x. [PubMed: 16680602]
2. Fasnacht M, Johanssen S, Quinkler M, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a revised TNM classification. *Cancer.* 2009; 115:243–250. [PubMed: 19025987]
3. Ayala-Ramirez M, Jasim S, Feng L, et al. Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. *Eur J Endocrinol.* 2013; 169:891–899. [PubMed: 24086089]
4. Beuschlein F, Weigel J, Saeger W, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab.* 2015; 100:841–849. [PubMed: 25559399]
5. 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]
6. Else T, Williams AR, Sabolch A, et al. Adjuvant therapies and patient and tumor characteristics associated with survival of adult patients with adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2014; 99:455–461. [PubMed: 24302750]
7. Ip JC, Pang TC, Glover AR, et al. Improving outcomes in adrenocortical cancer: an Australian perspective. *Ann Surg Oncol.* 2015; 22:2309–2316. [PubMed: 25319576]
8. Chok KS, Ng KK, Poon RT, et al. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. *Br J Surg.* 2009; 96:81–87. [PubMed: 19065644]
9. de Melo GM, Ribeiro KC, Kowalski LP, et al. Risk factors for postoperative complications in oral cancer and their prognostic implications. *Arch Otolaryngol Head Neck Surg.* 2001; 127:828–833. [PubMed: 11448358]
10. Law WL, Choi HK, Lee YM, et al. The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer. *Ann Surg Oncol.* 2007; 14:2559–2566. [PubMed: 17522945]
11. Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. *Ann Surg.* 2009; 250:798–807. [PubMed: 19809297]
12. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. *Br J Surg.* 2005; 92:1150–1154. [PubMed: 16035134]
13. Mavros MN, de Jong M, Dogeas E, et al. Impact of complications on long-term survival after resection of colorectal liver metastases. *Br J Surg.* 2013; 100:711–718. [PubMed: 23364914]
14. Spolverato G, Yakoob MY, Kim Y, et al. Impact of complications on long-term survival after resection of intrahepatic cholangiocarcinoma. *Cancer.* 2015; 121:2730–2739. [PubMed: 25903409]
15. Ancona E, Cagol M, Epifani M, et al. Surgical complications do not affect longterm survival after esophagectomy for carcinoma of the thoracic esophagus and cardia. *J Am Coll Surg.* 2006; 203:661–669. [PubMed: 17084327]
16. D'Annunzio T, D'Journo XB, Trouse D, et al. Respiratory complications after oesophagectomy for cancer do not affect disease-free survival. *Eur J Cardiothorac Surg.* 2012; 41:e66–e73. discussion e73. [PubMed: 22408043]
17. Dubois-Rande JL, Herve C, Duval-Moulin AM, et al. Prehospital thrombolysis. Evaluation of preliminary experiences at Val-de-Marne. *Arch Mal Coeur Vaiss.* 1989; 82:1963–1966. [PubMed: 2515822]

18. Andarib A, Ramana-Kumar AV, Bartlett G, et al. Influence of postoperative infectious complications on long-term survival of lung cancer patients: a population-based cohort study. *J Thorac Oncol.* 2013; 8:554–561. [PubMed: 23459402]
19. Artinyan A, Orcutt ST, Anaya DA, et al. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. *Ann Surg.* 2015; 261:497–505. [PubMed: 25185465]
20. Farid SG, Aldouri A, Morris-Stiff G, et al. Correlation between postoperative infective complications and long-term outcomes after hepatic resection for colorectal liver metastasis. *Ann Surg.* 2010; 251:91–100. [PubMed: 19858702]
21. Ruan DY, Lin ZX, Li Y, et al. Poor oncologic outcomes of hepatocellular carcinoma patients with intra-abdominal infection after hepatectomy. *World J Gastroenterol.* 2015; 21:5598–5606. [PubMed: 25987785]
22. Scaife CL, Hartz A, Pappas L, et al. Association between postoperative complications and clinical cancer outcomes. *Ann Surg Oncol.* 2013; 20:4063–4066. [PubMed: 24052315]
23. Elaraj DM, Weinreich DM, Varghese S, et al. The role of interleukin 1 in growth and metastasis of human cancer xenografts. *Clin Cancer Res.* 2006; 12:1088–1096. [PubMed: 16489061]
24. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell.* 2010; 140:883–899. [PubMed: 20303878]
25. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg.* 2011; 253:890–899. [PubMed: 21394013]
26. Voronov E, Carmi Y, Apte RN. The role IL-1 in tumor-mediated angiogenesis. *Front Physiol.* 2014; 5:114. [PubMed: 24734023]
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004; 240:205–213. [PubMed: 15273542]
28. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996; 15:361–387. [PubMed: 8668867]
29. Mihai R. Diagnosis, treatment and outcome of adrenocortical cancer. *Br J Surg.* 2015; 102:291–306. [PubMed: 25689291]
30. Laurent C, Sa Cunha A, Couderc P, et al. Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. *Br J Surg.* 2003; 90:1131–1136. [PubMed: 12945082]
31. Horowitz M, Neeman E, Sharon E, et al. Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Rev Clin Oncol.* 2015; 12:213–226. [PubMed: 25601442]
32. Tsuchiya Y, Sawada S, Yoshioka I, et al. Increased surgical stress promotes tumor metastasis. *Surgery.* 2003; 133:547–555. [PubMed: 12773983]
33. van der Bij GJ, Oosterling SJ, Beelen RH, et al. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. *Ann Surg.* 2009; 249:727–734. [PubMed: 19387333]
34. Eichhorn-Wharry LI, Talpos GB, Rubinfeld I. Laparoscopic versus open adrenalectomy: another look at outcome using the Clavien classification system. *Surgery.* 2012; 152:1090–1095. [PubMed: 23158180]
35. Abramovitch R, Marikovsky M, Meir G, et al. Stimulation of tumour growth by wound-derived growth factors. *Br J Cancer.* 1999; 79:1392–1398. [PubMed: 10188881]
36. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001; 357:539–545. [PubMed: 11229684]
37. Nespoli A, Gianotti L, Bovo G, et al. Impact of postoperative infections on survival in colon cancer patients. *Surg Infect (Larchmt).* 2006; 7(Suppl 2):S41–S43. [PubMed: 16895503]
38. Wong MP, Cheung N, Yuen ST, et al. Vascular endothelial growth factor is up-regulated in the early pre-malignant stage of colorectal tumour progression. *Int J Cancer.* 1999; 81:845–850. [PubMed: 10362127]

39. Bogden AE, Moreau JP, Eden PA. Proliferative response of human and animal tumours to surgical wounding of normal tissues: onset, duration and inhibition. *Br J Cancer*. 1997; 75:1021–1027. [PubMed: 9083338]
40. Horn F, Henze C, Heidrich K. Interleukin-6 signal transduction and lymphocyte function. *Immunobiology*. 2000; 202:151–167. [PubMed: 10993289]
41. Menetrier-Caux C, Montmain G, Dieu MC, et al. Inhibition of the differentiation of dendritic cells from CD34(+) progenitors by tumor cells: role of interleukin-6 and macrophage colony-stimulating factor. *Blood*. 1998; 92:4778–4791. [PubMed: 9845545]
42. Scheinman RI, Cogswell PC, Lofquist AK, et al. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. *Science*. 1995; 270:283–286. [PubMed: 7569975]

Fig. 1.
Overall survival stratified by occurrence of postoperative complications

Table 1

Clinicopathologic characteristics of patients who underwent resection for adrenocortical carcinoma

	Total, (n = 265)	No complication (n = 166)	Complication (n = 99)	P value
Age, years, median	52 (44–63)	51 (42–61)	55 (48–65)	0.07
Female, n (%)	164 (61.9)	99 (59.6)	65 (65.7)	0.33
White race, (n = 254)	207 (81.5)	129 (81.6)	78 (81.3)	0.06
Comorbidities				
Cardiac comorbidities	29 (10.9)	14 (8.4)	15 (15.2)	0.09
Chronic obstructive pulmonary disease	19 (7.2)	14 (8.4)	5 (5.1)	0.30
Liver disease	9 (3.4)	5 (3.1)	4 (4.0)	0.66
Diabetes mellitus	44 (16.6)	19 (11.5)	25 (25.3)	0.003
Incidental finding, (n = 251)	110 (43.8)	70 (45.1)	40 (41.7)	0.59
Hormone-Functional status, (n = 245)				
Nonsecreting	143 (58.4)	105 (68.2)	38 (41.8)	0.001
Cortisol	54 (22.0)	21 (13.6)	33 (36.3)	
Mineralocorticoid	13 (5.3)	8 (5.2)	5 (5.5)	
Sex hormone	35 (14.3)	20 (13.0)	15 (16.5)	
Laterality (n = 259)				
Right	113 (43.6)	72 (44.4)	41 (42.3)	0.73
Left	146 (56.4)	90 (55.6)	56 (57.7)	
Capsular invasion, (n = 175)	104 (59.4)	53 (53.0)	51 (68.0)	0.05
T stage (n = 236)				
I	12 (5.1)	9 (6.5)	3 (3.1)	0.22
II	99 (42.0)	62 (44.6)	37 (38.1)	
III	90 (38.1)	52 (37.4)	38 (39.2)	
IV	35 (14.8)	16 (11.5)	19 (19.6)	
N stage (n = 265)				
N0	54 (20.4)	34 (20.5)	20 (20.2)	0.43
N1	29 (10.9)	15 (9.0)	14 (14.1)	
Nx	182 (68.7)	117 (70.5)	65 (65.7)	
Tumor size, cm, median	11.5 (8–15)	11 (7.5–15)	12 (9.5–15)	0.21
Operation type, (n = 253)				
Open abdominal or posterior	169 (66.8)	107 (68.6)	62 (63.9)	0.003
Minimally invasive surgery	44 (17.4)	33 (21.2)	11 (11.3)	
Thoraco-abdominal surgery	40 (15.8)	16 (10.3)	24 (24.7)	
Metastatic at time of presentation(n = 257)	48 (18.7)	25 (15.8)	23 (23.3)	0.14
Margin (n = 225)				
R0	155 (68.9)	103 (75.2)	52 (59.1)	0.03
R1	55 (24.4)	28 (20.4)	27 (30.7)	
R2	15 (6.7)	6 (4.4)	9 (10.2)	
Multi-organ resection	122 (48.4)	66 (42.9)	56 (57.1)	0.03
Neo-adjuvant chemotherapy (n = 246)	5 (2.0)	1 (0.7)	4 (4.2)	0.06

	Total, (<i>n</i> = 265)	No complication (<i>n</i> = 166)	Complication (<i>n</i> = 99)	<i>P</i> value
Adjuvant chemotherapy (<i>n</i> = 265)	123 (46.4)	71 (42.8)	52 (52.5)	0.12
Adjuvant Radiotherapy (<i>n</i> = 209)	20 (9.6)	12 (9.2)	8 (10.3)	0.79
Adjuvant mitotane (<i>n</i> = 206)	85 (41.3)	45 (34.9)	40 (52.0)	0.02

Table 2

Postoperative morbidity of patients who underwent resection for adrenocortical carcinoma

	No. (%) (n = 265)
Overall complication	99 (37.4)
Minor complication	73 (73.7)
Major complication	26 (26.3)
Complication grade (Dindo–Clavien classification)	
No Complication	166 (62.6)
I	11 (4.2)
II	62 (23.4)
III	15 (5.6)
IV	11 (4.2)
Types of postoperative complication	
Postoperative adrenal insufficiency	55 (20.8)
Infectious	17 (6.4)
Pulmonary	28 (10.6)
Gastrointestinal	12 (4.5)
Urogenital	14 (5.3)
Cardiovascular	19 (7.2)
Systemic	6 (2.3)
Number of complications	
No complication	166 (62.6)
1 organ	69 (26.0)
2 organs	18 (6.8)
3 organs	7 (2.6)
C4 organs	5 (1.9)
Postoperative blood transfusion	41 (15.5)
Perioperative blood loss (ml), median (IQR)	700 (200–1800)
Re-operation	10 (4.5)
In hospital mortality	5 (1.9)
Length of hospital stay, days, median (IQR)	6 (4–9)

Some patients experienced more than one complication. All types of complications were documented in this table; thus, the sum of specific type of complications may be greater than the number of overall complications

Table 3

Logistic regression analysis of factors associated with postoperative complication

	<u>Univariable analysis</u>		<u>Multivariable analysis</u>	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Age	1.02 (1.00–1.03)	0.05	1.03 (0.99–1.06)	0.06
Male sex	0.77 (0.46–1.30)	0.33	–	
Cardiac comorbidities	1.94 (0.89–4.21)	0.09	–	
Chronic obstructive pulmonary disease	0.58 (0.20–1.66)	0.31	–	
Liver disease	0.93 (0.66–1.30)	0.66	–	
Diabetes mellitus	2.61 (1.32–5.05)	0.004	1.85 (0.75–4.62)	0.18
Incidental finding	0.87 (0.52–1.45)	0.59	–	
Hormone secreting tumors	2.99 (1.74–5.11)	<0.001	3.56 (1.65–7.69)	0.001
Right adrenal tumor	0.92 (0.55–1.52)	0.73	–	
Capsular invasion	1.88 (1.01–3.52)	0.05	1.46 (0.66–3.21)	0.35
T stage				
I/II	Ref			
III/IV	1.49 (0.88–2.51)	0.14	–	
N stage				
N0	Ref			
N1	1.59 (0.64–3.96)	0.32	–	
Nx	0.94 (0.50–1.77)	0.86	–	
Tumor size	1.01 (0.97–1.06)	0.63	–	
Operation type				
Open abdominal or posterior	Ref		Ref	
Minimally invasive Surgery	0.57 (0.27–1.22)	0.15	0.47 (0.14–1.59)	0.23
Thoraco-abdominal Surgery	2.59 (1.28–5.24)	0.008	2.85 (1.00–8.18)	0.05
Metastatic at time of presentation	1.61 (0.85–3.03)	0.14	–	
Margin				
R0	Ref			
R1	1.91 (1.02–3.57)	0.04	1.17 (0.47–2.89)	0.73
R2	2.26 (0.78–6.58)	0.13	1.38 (0.37–5.15)	0.63
Multi-organ resection	1.78 (1.07–2.97)	0.03	1.84 (0.75–4.62)	0.18
Neo-adjuvant chemotherapy	6.48 (0.71–58.86)	0.10	–	

Table 4

Long-term clinical outcomes stratified by occurrence of complication

	All patients	No complication	Postoperative complication	<i>P</i> value
Recurrence-free survival				
Median (months)	15.9 (11.0–22.1)	18.8 (11.8–27.8)	11.8 (8.1–20.5)	0.33
1 year (%)	55.5	59.1	48.3	
3 year (%)	31.9	34.5	24.6	
5 year (%)	20.9	20.3	24.6	
Overall survival				
Median (months)	49.4 (33.5–68.0)	58.9 (37.0–89.1)	25.1 (15.6–167.8)	0.009
1 year (%)	80.4	87.8	67.5	
3 year (%)	56.4	62.5	46.5	
5 year (%)	45.1	48.9	40.1	
Length of hospital stay (days)	6 (4–9)	5 (4–7)	7 (5–11)	<0.001

Table 5

Multivariate cox regression analysis demonstrating association of type of complication with long-term survival

	Hazard Ratio (95 % CI) [*]	P value	C-index
Univariate analysis			
Overall complications	1.66 (0.13–2.45)	0.01	
Infectious complications	3.32 (1.41–7.82)	0.006	
Non-infectious complications	1.54 (1.03–2.31)	0.03	
Multivariate analysis ^a			
Overall complications	1.68 (1.07–2.63)	0.02	0.74
Infectious complications	5.56 (2.24–13.80)	<0.001	0.75
Non-infectious complications	1.50 (0.94–2.40)	0.09	
Multivariate analysis ^b			
Overall complications	1.03 (0.63–1.67)	0.91	0.76
Infectious complications	3.32 (1.24–8.83)	0.02	0.77
Non-infectious complications	0.90 (0.54–1.50)	0.68	

^{*} Reference group is no complications group

^a Adjusted for patient and disease-specific factors: age, gender, T stage, N stage, Metastasis

^b Adjusted for T stage, N stage, metastasis, adjuvant chemotherapy, resection margin, multi-organ resection, and type of resection