Aldosterone Producing Adrenocortical Carcinoma: A Case Report and Systematic Review of the Rare Disease

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Abstract

Introduction: Functional adrenocortical carcinoma is very uncommon. Aldosterone producing adrenocortical carcinoma (APAC) is rare malignancy with incidence of less than 10

Index terms—

1 M

Results: A total of 93 cases were included for analysis. The Apart form a single review on the disease published by Seccia (10) on 2005, there is not another conclusive analysis of APAC cases. Many cases have been reported and published since then. We herein present a case managed in our institute, and have searched and analyzed the online data base (1955-2020) of APAC cases to review demographic characteristics, clinical and histological features, and treatment outcomes of the APAC.

2 II.

3 Case Report

A 40 years gentleman with one year history of hypertension under medication presented with left sided lumbar pain and non projectile vomiting in April 2020. He gave history of weight loss of 21 kg in past 7 months and had polydipsia. There was no history of headache, muscle weakness, loss of consciousness, chest pain or shortness of breath. He was smoker and consumes mixed diet. On examination the blood pressure was 170/100 mmHg. Other general physical and systemic examination was unremarkable. The total blood count was within normal limit. Blood sugar was 120mg/dl. The presentation and the disease stage were the significant covariates of the disease survival.

The incidence of the adrenocortical carcinoma (ACC) is 1-2 per million population per year which is more common in age group 40-50 years. Approximately half to two third of the adrenocortical carcinoma is functional and fewer than 10% present with hyperaldosteronism (5,6) Aldosterone producing adrenocortical carcinoma (APAC) is responsible for about 20% of resistant hypertension in adult and is also called as mineralocorticoid hypertension. (7) The diagnosis of APAC is based on presence of hypokalemia, high serum aldosterone level, and suppressed plasma renin activity associated with adrenal computed tomography radiographic findings suggestive of malignancy (7)(8)(9) blood sodium and potassium level was 145 meq/L and 2.0 meq/L respectively. The ultrasound abdomen revealed left adrenal mass which was confirmed by contrast computed tomography of abdomen. Contrast enhanced Computed tomography (CECT) [figure **??** (a)] revealed heterogeneously enhancing left adrenal mass that was 5x6x5.7 cm in size with well defined margin abutting the spleen, pancreas and posterior abdominal wall. The mass had displaced the left kidney inferiorly.

With diagnosis of aldosterone secreting adrenal tumor patient underwent transperitoneal laparoscopic left adrenalectomy, figure **??** (b) and (c). The intraoperative and postoperative period was uneventful. The histopathological report revealed adrenocortical carcinoma stage II with low mitotic count. The serum aldosterone level and Plasma renin activity done one week post surgery was normal. The CECT scan done 9 months post surgery had normal findings and patient was normotensive and normokalemic during the follow up.

4 III.

5 Methods

The online literature search on aldosterone producing adrenocortical carcinoma was performed through Pub Med, Google scholar, and Scopus search engine. The study design of this review is depicted in figure **??**. The cited references were cross examined for APAC cases. Full article with confirmed diagnosis of adult aldosterone producing adrenocortical carcinoma were included in this review. The patient's information pertaining patient demography, clinical presentation, biochemical investigations, histopathological findings, and treatment outcomes, and follow up details were extracted. A database was then constructed for statistical analysis.

IV.

6 Results

We identified 100 cases from 71 academic articles on aldosterone producing adrenocortical carcinoma published in year between 1955 and 2020. Out of 100 only 93 were eligible for data base construction and analysis. More than half of the cases were from American region (after World Health Organization). The mean age of the study population was 45.7±15.0 (Range 17-79 years). Majority of the patients were between 17-60 years (77.4%) with male female ratio of 1:1. 4 Median disease free survival was 25 months (95% CI-16.5-33.5) and median overall survival was 36 (95% CI-18 -54). Female had higher median overall survival than male (27 vs 18 months). Patient age $>$ 60 years had significantly lower median disease free survival (14 months) than age group ? 60 years (30 months). The overall recurrence rate was 55%; Liver (35%), Lungs (22.5%), local recurrence (15%), Bones (12.5%) and abdominal lymph nodes (12.5%). In Cox regression analysis patient age at diagnosis, and the staging characteristics (size, lymph nodes involvement, invasion and distant spread) were the significant (p=0.05) covariates of the disease free and overall survival.

V.

7 Discussion

The first case of adrenocortical carcinoma presenting with hyperaldosteronism was published in There were no enlarged lymph nodes and metastatic lesion elsewhere in the body. The serum aldosterone concentration was 535 ng/dl (normal 2.52-39.2 ng/dl) and the plasma renin activity was 0.5 ng/ml/hr with aldosterone renin ratio (ARR) 1070 ng/dl/ng/ml-hr. The serum and urinary metanephrine and nor-metanephrine was normal. The serum cortisol level was 10.6 ng/ml (normal 6.4-21 ng/ml). The summary statistics; mean ± SD, median (and range) were calculated as appropriate after testing for normality. The difference in distribution of the categorical variables were evaluated using Chi Square test and P$<$0.05 was considered significant. The disease free survival time was defined as the time between initial treatment with curative intent and the first radiological evidences of adrenal tumor, local recurrence or metastasis. While overall survival interval was defined as the time between initial treatment (or initial diagnosis if initial treatment date is not available or if the treatment was not offered) to censoring at death or end of study. Kaplan Meier analysis was done to plot the disease free survival and overall survival. Cox regression proportional hazard analysis was performed to evaluate the correlation between disease variables and outcomes (disease free or overall survival) 1955 by Foye (10) and Jerome W. Conn further

The demographic and biological features of the APAC remained same when we moved from series of 58 cases published in 2005 (10) to 93 cases in this review. Hypertension and hypokalemia were the most consistent sign of Conn's syndrome (17) and the later was commonly associated (83%) with muscle weakness. Contrary to the ACC in general (15), APAC was predominantly found on right side. CECT characteristics are the mainstay of diagnosing malignant adrenal mass. At cutoff of 4 cm, sensitivity and specificity of diagnosing malignant adrenal incidentaloma was 93% and 76%. (18,19) sampling for hyperaldosteronism is indicated to confirm unilateral disease if the CT scan is not abnormal, shows bilateral disease, or unilateral disease in patient age $>$ 35 years. (25) It is not always easy to confirm benign and malignant adrenal tumors based on histopathological features. The differentiation of malignant form benign adrenal mass essentially depends on local invasion and distant metastasis. Tumor size larger than 5 cm and greater than 100 gm has malignant potential. Weiss criteria is the simple and reliable system to diagnose malignant adrenal tumor with threshold of total score ? 3. The five criteria used in the updated Weiss system include: $>$6 mitoses/50 high-power fields, ?25 percent clear tumor cells in cytoplasm, abnormal mitoses, necrosis, and capsular invasion. (26)(27)(28) In this review 80% (55/75) of the APAC were larger than 5 cm, 60% (24/35) were larger than 100 gm and 57 % (33/58) had mitotic count $>$ 20/high power field. Histopathological and molecular diagnosis of APAC often has limitations. A total of three cases of adrenal tumor diagnosed as carcinoma one and half year after primary surgery. (10,29,30) There are several marker(alpha-inhibin, Melanin A, SF-1) that can identify the origin of adrenal tumor as well as differentiate the benign from malignant elaborated the spectrum of clinical features of hyperaldosteronism in 1965. (11) The largest series were published by Mouat and Kendrick in 2019 and 2002 respectively. (12,13) Aldosterone hypersecretion is the least common (0-7%) among the functional adrenocortical carcinoma (ACC). Though surgery remain potentially curative in early stage ACC, the recurrence and metastasis post surgery were

common. The effect of functionality on tumor behavior and outcome is not quite predictable. (6,(14)(15)(16) The analysis and review was done to highlight and update the clinicpathological behavior of the APAC.

The characteristic CECT findings of the APAC were heterogeneous enhancement, calcification, capsular invasion, irregular margin, local infiltration, renal or inferior venacava thrombosis, and metastatic lesion. The published research showed that the unenhanced CT attenuation ?10 HU or a combination of tumor size ?4 cm and HU ?20 almost excludes adrenal malignancy. (20,21) There is increase probability of adrenal malignancy with the increase size of the tumor (55% for tumor >10 cm).(**??**2) However, 26.7% of the reported APAC size in this analysis were ? 5 cm and 20% (2/10) of the stage IV tumor were size ? 5 cm. Positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) is valuable tool for diagnosing malignant adrenal tumor. PET-CT (with an SUV cutoff value of 3.1) has sensitivity, specificity, positive predictive value, and negative predictive values for malignant adrenal tumor of almost 100%. (23) Radiological imaging has limitation in diagnosing tumor less than 1 cm, and bilateral tumors. A systematic review of 38 studies found inappropriate management of 37.8% of primary aldosteronism cases when diagnosis was determined by CT/MRI alone.(**??**4) Adrenal venous The primary hyperaldosteronism manifest with triad of hypertension, spontaneous hypokalemia, and metabolic alkalosis. Primary hyperaldosteronism is suspected when serum potassium < 3.5 meq/L, plasma renin activity less than 1 ng/ml/hr, and plasma aldosterone concentration ? 10ng/dl, and PAC/PRA >20 ng/dL per ng/mL/hour. (7,21) The combination of a PAC > 20 ng/dLand a PAC/PRA ratio > 30 ng/dL per ng/mL/hour have a sensitivity and specificity of 90 percent for the diagnosis aldosterone producing tumor (26), and was consistent findings in this study. Study says 9-37% of the primary hyperaldosteronism can present with normal serum potassium level. (27) In this review 7%-9% of APAC had normal laboratory findings (normokalemic, normal PAC and PRA level). In normokalemic but hypertensive cases the diagnosis of APAC is confirmed with additional testing (23); 24 hour urine aldosterone, sodium, and creatinine on high sodium diet, fludrocortisone suppression testing, and or saline suppression testing can confirm the diagnosis in suspicious cases.

Most of the adrenocortical carcinoma are sporadic and some are components of several hereditary cancer syndrome. (28) Less than 10% ACC present with virilization alone or feminization or hyperaldosteronism. (5,28) adrenal tumor (Ki67 proliferation index, overexpression of TP53, IGF-2, and cyclin E) however, they are not sufficiently discriminatory. (31,32). Surgery is the mainstay treatment for potentially resectable stage I to stage II adrenocortical carcinoma. (35,36) Routine lymphadenectomy had shown improved recurrence free survival and decreased disease specific death (hazard ratio [HR] 0.54, 95% CI 0.29-0.99). (37) Open surgery is recommended method of surgery for ACC. (38,39) European clinical practice guideline recommends laparoscopic surgery for adrenal tumor less 6 cm in absence of local invasion. (36) However studies had shown comparable outcome from open and adrenalectomy even for tumors upto 10 cm. (40,41) We found patient age at diagnosis and staging characteristics significant ($p<0.05$) predictors of disease free survival and overall survival. Metastasis at presentation; capsular, vascular, and adjacent organ invasion; tumor necrosis; mitotic activity were proven significant covariates of disease specific survival in adrenocortical carcinoma. Markers of proliferation like mitotic rate, and Ki67 expression has prognostic value as well. (42,43) Recurrence rate of APAC was 55% which is comparable with the recurrence rate of ACC (60-80%) in general. Liver and lungs were the two most common site of APAC recurrence. Adjuvant mitotane therapy has shown improved recurrence free survival and indicated for histologically high-grade disease, intraoperative tumor spillage or fracture, and some large tumors with vascular or capsular invasion. (44)(45)(46) However National Comprehensive Cancer Network (NCCN) guidelines suggest that mitotane be "considered" (category 3 recommendation) for all patients with resected low-or high-grade localized ACC regardless of stage or tumor size. (47) We found no uniform criteria of using adjuvant therapy in this study 14/93. Cytotoxic chemotherapy (etoposide, doxorubicin, and cisplatin) in combination with mitotane is suggested in rapidly progressive, high grade and metastatic disease. (48)(49)(50) Post operative radiation therapy is beneficial in local control of disease and suggested in incompletely resected ACC, stage III disease, those who have tumor spillage, and for all patient with high grade ACC. (36) VI.

8 Conclusion

APAC is a rare adrenal malignancy that requires meticulous evaluation before offering definitive surgery. Recurrence rate is high with dismal prognosis. Further research on tumor biology, natural history, and treatment outcome can add more to the understanding of this rare variant of adrenal malignancy. Declarations Funding Not applicable According to German ACC registry the fiver year disease specific survival of adrenocortical carcinoma for stages I, II, III, and IV were 82%, 61%, 50%, and 13% respectively. (33) We found that the aldosterone producing adrenocortical carcinoma had more dismal prognosis with mean and median disease free survival of 49 months and 25 months respectively. Incoherence in the stage specific median disease free survival (Stage I < Stage II) might be due to variable follow up duration of the heterogeneous and small number of cases in each stage (figure **??** and 4). Occult micro metastasis is presumably responsible for the early recurrence and disease progression. (34) In this series the recurrence rate among the size group of 0-5 cm; 6-10 cm; 11-15 cm; and > 15 cm were found to be 50%, 55%, 42%, and 100% respectively.

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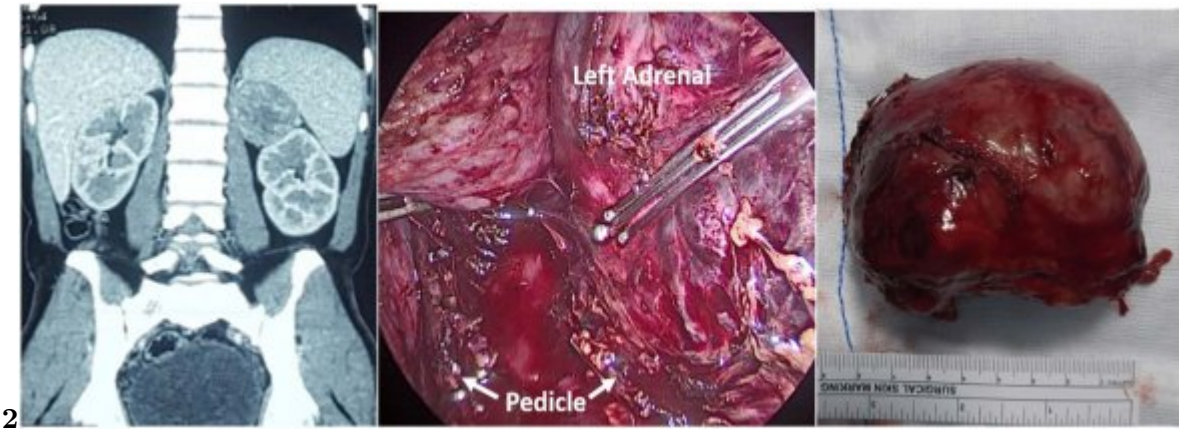

Figure 1: Figure 1 :Figure 2 :

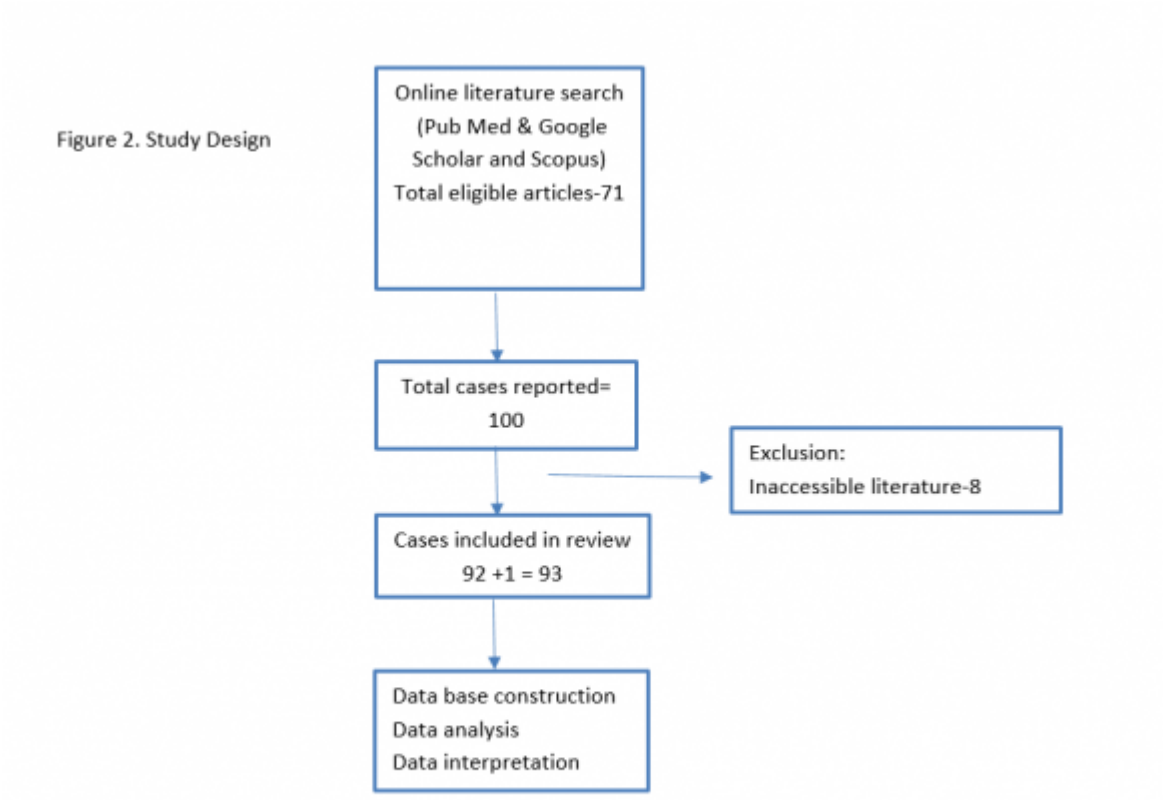

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Figure 2: Figure 3 :Figure 4 :

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Abstract-Introduction: Functional adrenocortical carcinoma is very uncommon. Aldosterone producing adrenocortical carcinoma (Conclusion: Aldosterone producing adrenocortical carcinoma is one of the rare types of functional adrenal malignancy. Any suspected case should undergo thorough clinical, radiological and biochemical evaluation. Surgery is the mainstay treatment and adjuvant therapy has no conclusive role in disease free survival. A large cases series and multicenter study could further add scientific evidence for management of the APAC.

[Note: Methods: A case history, clinical and treatment details of an APAC in 40 years gentleman is presented. Online search of the literature on APAC was done and details were extracted to construct database for statistical analysis. The summary measures were done in mean, median, or range after testing for normality. Kaplan Meier analysis and Cox regression proportional hazard analysis were done to evaluate the survival and the survival covariates respectively. mean age of the study population was 45.7±15 years. APAC is more common in female than male gender. Muscle weakness, headache, and hypertension were the common clinical features. Hypokalemia (mean-2.3±0.5 meq/l), high plasma aldosterone level (median 45 ng/dl), Low plasma renin activity (median-0.25 ng/ml/hr) were the biochemical abnormalities observed in the study cases. Majority of the disease were in stage II (38.7%) at presentation, followed by stage I (21.5%). The median disease free survival was 25 months and overall survival was 36 months. Age at]

Introduction

ost of the adrenal tumor are benign non-functional incidentaloma.(1) Cortisol hypersecretion (9.2%) followed by pheochromocytoma (4.2%) and aldosteronoma (1.6%) is the most common hormonal abnormality in functional adrenal incidentaloma. The prevalence of the primary and secondary adrenal malignancy was 1.9% and 0.7% among adrenal incidentaloma.(2-4)

Figure 3:

hypertensive medications even after surgery. According to American Joint Committee on Cancer (AJCC) 8 th edition the adrenocortical carcinomas of the study group were classified into Stage I-21.5%, Stage II-38.7%, Stage III-16.1%, and Stage IV-17.2%. The staging details were not available in about 6.5% (n=6) cases. 89% of the patient underwent surgery irrespective of the disease stage.

Figure 4:

70% of the reported APAC in

this study were pure aldosterenoma and 30% were mixed (hyperaldosteronism with hypercortisolism-20%, hyperaldosteronism with hypercortisolism and hyperandogeniemia-7%, and hyperaldosteronism with hyperandrogenemia-3%).
adenoma presented with metastatic adrenocortical

Figure 5:

1

Figure 6: Table 1 :

2

Figure 7: Table 2 :

.1 Conflicts of interest/Competing interests

We declare no conflict of interest or competing interests

.2 Ethics approval Not applicable

.3 Consent to participate

.4 Not applicable

.5 Consent for publication All authors consent to publication of this paper

.6 Availability of data and material

All data is available for review by contacting Dr. Bikash Thapa

.7 Code availability Not applicable

.8 Authors' contributions

BT and BB both has made substantial contributions to the conception or design of the work; the acquisition, analysis, interpretation of the data, and manuscript writing.

[Cleveland Clinic experience. J Clin Endocrinol (2005)] , *Cleveland Clinic experience. J Clin Endocrinol* Metab2005 Feb. 90 (2) p. .

[Schulick and Brennan (1999)] , R D Schulick , M F Brennan . *Adrenocortical carcinoma. World J* Urol1999 Feb. 17 (1) p. .

[Metser et al. (2006)] '18F-FDG PET/CT in the evaluation of adrenal masses'. U Metser , E Miller , H Lerman , G Lievshitz , S Avital , E Even-Sapir . *J Nucl* Med2006 Jan. 47 (1) p. .

[Porpiglia et al. (2011)] 'A debate on laparoscopic versus open adrenalectomy for adrenocortical carcinoma'. F Porpiglia , B S Miller , M Manfredi , C Fiori , G M Doherty . *Horm* Cancer2011 Dec. 2 (6) p. .

[Mantero et al. (2000)] 'A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Society of Endocrinology'. F Mantero , M Terzolo , G Arnaldi , G Osella , A M Masini , A Ali , M Giovagnetti , G Opocher , A Angeli . *J Clin Endocrinol* Metab2000 Feb. 85 (2) p. .

[Rossi et al. (2000)] *A thoracic mass with hypertension and hypokalaemia*, G P Rossi , R Vendraminelli , M Cesari , A C Pessina . Lancet2000 Nov 4. 356 p. 1570.

[Reznik et al. (2004)] 'Aberrant adrenal sensitivity to multiple ligands in unilateral incidentaloma with subclinical autonomous cortisol hypersecretion: a prospective clinical study'. Y Reznik , H Lefebvre , V Rohmer , B Charbonnel , A Tabarin , P Rodien , P Lecomte , S Bardet , C Coffin , J Mahoudeau . *Clin Endocrinol (Oxf)* 2004 Sep. 61 (3) p. .

[Lim et al. (2014)] 'Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism'. V Lim , Q Guo , C S Grant , G B Thompson , M L Richards , D R Farley , W F Young , Jr . *J Clin Endocrinol* Metab2014 Aug. 99 (8) p. .

[Calabrese et al. (2019)] 'Adjuvant mitotane therapy is beneficial in non-metastatic adrenocortical carcinoma at high risk of recurrence'. A Calabrese , V Basile , S Puglisi , P Perotti , Pia A Saba , L Berchialla , P Porpiglia , F Veltri , A Volante , M Reimondo , G Berruti , A Terzolo , M . *Eur J* Endocrinol2019 Jun 1. 180 (6) p. .

[Henley et al. (1983)] 'Adrenal cortical carcinoma–a continuing challenge'. D J Henley , J A Van Heerden , C S Grant , J A Carney , P C Carpenter . *Surgery* 1983 Dec. 94 (6) p. .

[Wooten and King (1993)] *Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature*, M D Wooten , D K King . Cancer1993 Dec 1. 72 p. .

[Angeli et al. ()] 'Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group'. A Angeli , G Osella , A Ali , M Terzolo . *Horm* Res1997. 47 (4-6) p. .

[Icard et al. (1992)] *Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery*, P Icard , Y Chapuis , B Andreassian , A Bernard , C Proye . Surgery1992 Dec. 112 p. .

[Stojadinovic et al. (2002)] 'Adrenocortical carcinoma: clinical, morphologic, and molecular characterization'. A Stojadinovic , R A Ghossein , A Hoos , A Nissan , D Marshall , M Dudas , C Cordon-Cardo , D P Jaques , M F Brennan . *J Clin* Oncol2002 Feb 15. 20 (4) p. .

[Ng and Libertino (2003)] 'Adrenocortical carcinoma: diagnosis, evaluation and treatment'. L Ng , J M Libertino . *J* Urol2003 Jan. 169 (1) p. .

[Boscaro et al. (1995)] 'Adrenocortical carcinoma: epidemiology and natural history'. M Boscaro , F Fallo , L Barzon , O Daniele , N Sonino . *Minerva* Endocrinol1995 Mar. 20 (1) p. .

[Szolar et al. (2005)] *Adrenocortical carcinomas and adrenal pheochromocytomas: mass and enhancement loss evaluation at delayed contrastenhanced CT*, D H Szolar , M Korobkin , P Reittner , A Berghold , T Bauernhofer , H Trummer , H Schoellnast , K W Preidler , H Samonigg . Radiology2005 Feb. 234 p. .

[Seccia et al. (2005)] 'Aldosterone-producing adrenocortical carcinoma: an unusual cause of Conn's syndrome with an ominous clinical course'. T M Seccia , A Fassina , G G Nussdorfer , A C Pessina , G P Rossi . *Endocr Relat* Cancer2005 Mar. 12 (1) p. .

[Kendrick et al. (2002)] *Aldosterone-secreting adrenocortical carcinomas are associated with unique operative risks and outcomes*, M L Kendrick , K Curlee , R Lloyd , D R Farley , C S Grant , G B Thompson , C Rowland , W F Young , Jr Van Heerden , JA . Surgery2002 Dec. 132 p. . (discussion 12)

[Pommier and Brennan] *An eleven-year experience with adrenocortical carcinoma*, R F Pommier , M F Brennan .

[Funder et al. ()] 'Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline'. J W Funder , R M Carey , C Fardella , C E Gomez-Sanchez , F Mantero , M Stowasser , W F Young , Jr Montori , VM . *J Clin Endocrinol* Metab2008.

[Conn et al. (1964)] 'Clinical Characteristics of Primary Aldosteronism from an Analysis of 145 Cases'. J W Conn , R F Knopf , R M Nesbit . *Am J* Surg1964 Jan. 107 p. .

[Tritos et al. (2000)] 'Clinical features and prognostic factors associated with adrenocortical carcinoma: Lahey Clinic Medical Center experience'. N A Tritos , G W Cushing , G Heatley , J A Libertino . *Am* Surg2000 Jan. 66 (1) p. .

[Fassnacht and Allolio (2009)] 'Clinical management of adrenocortical carcinoma'. M Fassnacht , B Allolio . *Best Pract Res Clin Endocrinol* Metab2009 Apr. 23 (2) p. .

[Allolio and Fassnacht (2006)] 'Clinical review: Adrenocortical carcinoma: clinical update'. B Allolio , M Fassnacht . *J Clin Endocrinol* Metab2006 Jun. 91 (6) p. .

[Hamrahian et al.] *Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas*, A H Hamrahian , A G Ioachimescu , E M Remer , G Motta-Ramirez , H Bogabathina , H S Levin , S Reddy , I S Gill , A Siperstein , E L Bravo .

[Delivanis et al. (2018)] 'Diagnostic performance of unenhanced computed tomography and (18) Ffluorodeoxyglucose positron emission tomography in indeterminate adrenal tumours'. D A Delivanis , I Bancos , T D Atwell , G D Schmit , P W Eiken , N Natt , D Erickson , S Maraka , W F Young , M A Nathan . *Clin Endocrinol (Oxf)* 2018 Jan. 88 (1) p. .

[Fassnacht et al. (2018)] 'European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors'. M Fassnacht , O M Dekkers , T Else , E Baudin , A Berruti , R De Krijger , H R Haak , R Mihai , G Assie , M Terzolo . *Eur J* Endocrinol2018 Oct 1. 179 (4) p. .

[Reibetanz et al. (2012)] 'Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma'. J Reibetanz , C Jurowich , I Erdogan , C Nies , N Rayes , H Dralle , M Behrend , B Allolio , M Fassnacht . *Ann* Surg2012 Feb. 255 (2) p. .

[Brix et al. (2010)] 'Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients'. D Brix , B Allolio , W Fenske , A Agha , H Dralle , C Jurowich , P Langer , T Mussack , C Nies , H Riedmiller , M Spahn , D Weismann , S Hahner , M Fassnacht . *Eur* Urol2010 Oct. 58 (4) p. .

[Sgourakis et al. (2015)] 'Laparoscopic versus Open Adrenalectomy for Stage I/II Adrenocortical Carcinoma: Meta-Analysis of Outcomes'. G Sgourakis , S Lanitis , A Kouloura , P Zaphiriadou , K Karkoulias , D Raptis , A Anagnostara , C Caraliotas . *J Invest* Surg2015 Jun. 28 (3) p. .

[Fassnacht et al. (2009)] *Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification*, M Fassnacht , S Johanssen , M Quinkler , P Bucsky , H S Willenberg , F Beuschlein , M Terzolo , H H Mueller , S Hahner , B Allolio . Cancer2009 Jan 15. 115 p. .

[Fassnacht et al. (2016)] 'Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors'. M Fassnacht , W Arlt , I Bancos , H Dralle , J Newell-Price , A Sahdev , A Tabarin , M Terzolo , S Tsagarakis , O M Dekkers . *Eur J* Endocrinol2016 Aug. 175 (2) p. .

[Allolio et al. (2004)] 'Management of adrenocortical carcinoma'. B Allolio , S Hahner , D Weismann , M Fassnacht . *Clin Endocrinol (Oxf)* 2004 Mar. 60 (3) p. .

[Schteingart et al. (2005)] 'Management of patients with adrenal cancer: recommendations of an international consensus conference'. D E Schteingart , G M Doherty , P G Gauger , T J Giordano , G D Hammer , M Korobkin , F P Worden . *Endocr Relat* Cancer2005 Sep. 12 (3) p. .

[Stewart (1999)] *Mineralocorticoid hypertension*, P M Stewart . Lancet1999 Apr 17. 353 p. .

[NCCN clinical practice guidelines in oncology (2021)] *NCCN clinical practice guidelines in oncology*, https://www.nccn.org/professionals/physician_gls Jan 14, 2021. National Comprehensive Cancer Network (NCCN

[Deckers et al. ()] 'Peritoneal carcinomatosis following laparoscopic resection of an adrenocortical tumor causing primary hyperaldosteronism'. S Deckers , L Derdelinckx , V Col , J Hamels , D Maiter . *Horm* Res1999. 52 (2) p. .

[Williamson et al. (2000)] *Phase II evaluation of cisplatin and etoposide followed by mitotane at disease progression in patients with locally advanced or metastatic adrenocortical carcinoma: a Southwest Oncology Group Study*, S K Williamson , D Lew , G J Miller , S P Balcerzak , L H Baker , E D Crawford . Cancer2000 Mar 1. 88 p. .

[Mattsson and Young (2006)] 'Primary aldosteronism: diagnostic and treatment strategies'. C Mattsson , W F Young , Jr . *Nat Clin Pract* Nephrol2006 Apr. 2 (4) p. 30.

[Hough et al. (1979)] 'Prognostic factors in adrenal cortical tumors. A mathematical analysis of clinical and morphologic data'. A J Hough , J W Hollifield , D L Page , W H Hartmann . *Am J Clin* Pathol1979 Sep. 72 (3) p. .

[Miller et al. (2010)] 'Proposal for modification of the ENSAT staging system for adrenocortical carcinoma using tumor grade'. B S Miller , P G Gauger , G D Hammer , T J Giordano , G M Doherty . *Langenbecks Arch* Surg2010 Sep. 395 (7) p. .

[Cawood et al. (2009)] 'Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink?'. T J Cawood , P J Hunt , O' Shea , D Cole , D Soule , S . *Eur J* Endocrinol2009 Oct. 161 (4) p. .

[Sturgeon et al. (2006)] 'Risk assessment in 457 adrenal cortical carcinomas: how much does tumor size predict the likelihood of malignancy?'. C Sturgeon , W T Shen , O H Clark , Q Y Duh , E Kebebew . *J Am Coll* Surg2006 Mar. 202 (3) p. .

[Umakoshi et al. (2020)] 'Role of Aldosterone and Potassium Levels in Sparing Confirmatory Tests in Primary Aldosteronism'. H Umakoshi , R Sakamoto , Y Matsuda , M Yokomoto-Umakoshi , H Nagata , T Fukumoto , M Ogata , Y Ogawa . *J Clin Endocrinol* Metab2020 Apr 1. 105 (4) .

[Mouat et al. (2019)] 'Somatic mutations in adrenocortical carcinoma with primary aldosteronism or hyperreninemic hyperaldosteronism'. I C Mouat , K Omata , A S Mcdaniel , N G Hattangady , D Talapatra , A K Cani , D H Hovelson , S A Tomlins , W E Rainey , G D Hammer , T J Giordano , T Else . *Endocr Relat* Cancer2019 Feb. 26 (2) p. .

[Kempers et al. (2009)] 'Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism'. M J Kempers , J W Lenders , L Van Outheusden , G J Van Der Wilt , Schultze Kool , L J Hermus , A R Deinum , J . *Ann Intern* Med2009 Sep 1. 151 (5) p. .

[Lau and Weiss (2009)] 'The Weiss system for evaluating adrenocortical neoplasms: 25 years later'. S K Lau , L M Weiss . *Hum* Pathol2009 Jun. 40 (6) p. .

[Khan et al. ()] 'Vincristine, cisplatin, teniposide, and cyclophosphamide combination in the treatment of recurrent or metastatic adrenocortical cancer'. T S Khan , A Sundin , C Juhlin , E Wilander , K Oberg , B Eriksson . *Med* Oncol2004. 21 (2) p. .

[Aubert et al. (2002)] 'Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors'. S Aubert , A Wacrenier , X Leroy , P Devos , B Carnaille , C Proye , J L Wemeau , M Lecomte-Houcke , E Leteurtre . *Am J Surg* Pathol2002 Dec. 26 (12) p. .

[Fassnacht and Allolio (2010)] 'What is the best approach to an apparently nonmetastatic adrenocortical carcinoma?'. M Fassnacht , B Allolio . *Clin Endocrinol (Oxf)* 2010 Nov. 73 (5) p. .