The impact of patient-, disease-, and treatment-related factors on survival in patients with adrenocortical carcinoma

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Abstract

Introduction: Adrenal cortical carcinoma (ACC) is a rare and aggressive endocrine tumour. Most present with advanced disease and have poor prognosis. Optimal treatment includes complete surgical resection. There is limited evidence for the efficacy of chemotherapy and radiation at different stages in this disease. There remain many inconsistencies with respect to diagnosis and workup. There is a lack of uniform guideline recommendations and consensus data.
Methods: We performed a retrospective chart review of all patients at London Health Sciences Centre between 1990 and 2015 using ICD coding. All paper and electronic charts were reviewed and data was collected. Statistical analysis and survival curves were performed.
Results: A total of 29 patients were included in our study. Median age was 55 years (interquartile range [IQR] 45-–63); 14 (48%) were male and 15 (52%) were female. Approximately half (14 or 48%) of our patients presented symptomatically. Almost half (41%) of tumours were metabolically active, producing hormones. Most (88%) underwent surgical intervention. Surgical margin status was available in about half of patients, and lymphadenectomy was performed in a third (n=8) of open adrenalectomy patients. A third received mitotane treatment (8 [73%] adjuvant and 3 [27%] palliative) and a third of patients received radiation. Two- and five-year median overall survival was 53% and 27%, respectively.
Conclusions: ACC is a rare and aggressive tumour. This is the largest Canadian series reported to the best of our knowledge. Limited data for guidelines exists and treatment

and workup patterns are inconsistent. Collaborative randomized and prospective studies on a global basis are needed.

Introduction

Adrenal cortical carcinoma (ACC) is a rare tumour with a worldwide incidence of 2 per million people, and is responsible for 0.2% of all cancer deaths. It is one of the most aggressive endocrine tumours.[1] Due to the rare and aggressive nature of the disease, limited studies are available with respect to optimal management and cancer specific outcomes.[2] Additionally patients with ACC generally have poor outcomes with 30-70% presenting with advanced disease.[3] Currently, there are limited treatment guidelines yet most experts would recommend *en bloc* complete resection of involved structures and regional lymphadenectomy for localized disease.[4]

Various prognostic factors have been assessed including advanced stage, factors related to surgical resection, grade, age, hormonal secretion, and sex.[1] The gold standard for treatment continues to remain surgical resection as alternative treatments such as chemotherapy and radiation have limited efficacy.[5] The most commonly used chemotherapeutic, and the only Federal Drug Agency (FDA) and Health Canada approved agent is mitotane, with response rates ranging from approximately 10-30% in both single and multi-chemotherapy regimens.[3] Diagnosis remains challenging as many are only diagnosed after hormonal or metabolic disturbances are demonstrated as approximately 50% of tumours are functional. The remainder present incidentally with non-specific symptoms or no symptoms at all with diagnosis only after cross-sectional imaging.[6]

The goal of our study was to examine these patients retrospectively at our institution over a long time period to further characterize treatment and patient factors related to the disease. We present a case series with descriptive analysis.

Methods

All patients between 1990 and 2015 diagnosed with a primary carcinoma of the adrenal cortex were identified using ICD codes C74 and 194 and histology code 83703 treated at the London Regional Cancer Program in London, Ontario, Canada. All patients were included if they were at least 18 years of age, and complete data was available.

Patient electronic records and paper charts were retrospectively reviewed and data recorded into an electronic database. Collected data include demographics, clinical presentation, pre-operative imaging, surgical parameters, histological and pathological data, the use of chemotherapy or radiation treatment and assessment of functionality of the tumours. Staging was characterized using the European Network for the Study of Adrenal tumours (ENSAT) which is slightly different from the American Joint

Committee Cancer (AJCC) and differs by stage grouping.[7] Resection status was also reported when available.[8]

Descriptive statistics were used to analyze the data. Kaplan-Meier survival analysis was completed using statistical software, Stata 14.1. This study was approved by the Western University Research Ethics Board.

Results

We identified 29 patients between 1990 and 2015 with diagnosis of primary adrenal cortical carcinoma.

Demographic and baseline characteristics of the included patients are shown in Table 1. The median age was 55 years (IQR 45-63). Fourteen (48%) were male and fifteen (52%) were female. As seen in Table 1, half of the patients (48%) were symptomatic. Of those with symptoms, the three most common were anemia, weakness and weight gain (21%, 17% and 14% respectively).

Further clinical details are seen in Table 2. Of the 29 patients, only 24 underwent surgical intervention, with 20 (88%) undergoing open adrenalectomy and 4 (16%) undergoing laparoscopic approach. Surgery was completed by six different surgeons, four urologists and two general surgeons. Median tumour size was 12.8 cm. There was a relatively equal amount of left-sided (17, 59%) and right-sided (12, 41%) tumours. Margin status was reported in only of 11 (46%) surgically managed patients, of which 7 (29%) were R0 and 4 (17%) considered R1. The remaining 13 (54%) had unknown resection status. Lymphadenectomy was performed in 8 (33%) surgical patients, with an average lymph node count of 2, all with an open procedure, and 4 (17%) had positive disease. With respect to functionality, 8 (28%) secreted glucocorticoids, 5 (17%) secreted sex hormones, 2 (7%) secreted mineralocorticoids and only 2 (7%) secreted more than one type. For metabolic work-up, there was inconsistency in the types of tests that were ordered for each patient. The most common tests obtained were urinary cortisol and catecholamines. More than half (16, 55%) had recurrence of disease. Of these 11 (69%) were distant, with 6 of these symptomatic, and the remaining 5 (31%) having both local and distant disease but were asymptomatic. Only 1 patient (3%) was treated with adjuvant radiation, 9 (31%) received palliative radiation, and 11 (38%) received mitotane, of which 8 (73%) were adjuvant and 3 (27%) were palliative. Two and five-year median overall survivals were 53% and 27%, respectively as seen in Figure 1. Figure 2 further illustrates survival by ENSAT stage.

Discussion

Adrenal cortical carcinoma is an extremely rare malignancy, and therefore there remains a lack of clear management and treatment guidelines.[1] In an attempt to further understand

the disease, we examined retrospectively the patients at our tertiary care center. This is to our knowledge, the largest Canadian series that has been examined to date.

In our series, approximately 50% of patients presented asymptomatically and had incidental findings, but symptom presentation from selected series can be highly variable ranging from Cushingoid features to simply constitutional symptoms.[9] Similar to other series 17 (59%) of patients had non-hormonally active tumours.[6] Of those that are metabolically active, the majority seem to harbour glucocorticoid secretion.[10] Our study attempted to look at the exact metabolic work-up for these lesions, but the data was so variable it could not be analyzed. This illustrates the inconsistent work-up for these patients. It could be speculated that diagnostic tests may depend on whether patients are being treated in an academic or community setting, whether the patients are being seen by a general surgeon, a urologist or endocrinologist or simply due to lack of understanding of the disease.[1] From our study we see that the most commonly ordered tests are urinary cortisol and urinary catecholamines. Despite inconsistencies, many studies suggest that a metabolic work-up may be critical as it can help risk stratify tumours, as it has been suggested that androgen secreting tumours tend to be associated with poor outcomes.[5] Furthermore metabolic work-up is required to clarify the need for antagonizing therapy secondary to increased hormone secretion and subsequent planning for post-operative metabolic disturbances.[5] Finally it is also crucial to ensure appropriate identification of a pheochromocytoma.[5] The European Network for the Study of Adrenal tumours (ENSAT) suggests a workup which includes basal cortisol, ACTH, dehydroepiandrostenedione sulfate (DHEAS), 17-hydroxyprogesterone, testosterone, androstenedione, and estradiol. Also recommended is a dexamethasone suppression test and urinary free cortisol.[8] These urine studies can be important as some previously deemed non-active tumours may actually secrete urine metabolites.[8]

Most ACC tumours are initially identified on imaging using computerized tomography, with features including size >4cm, lack of well-defined margins, heterogeneity and increased vascularity, local invasion, rapid growth, central low attenuation, unenhanced CT attenuation >10 Hounsfield units, signs of metastases, calcification and high contrast washout (less than 50% at 10 minutes).[5] Other proven imaging modalities include 18F-fluorodeoxyglucose positron emission tomography to help differentiate malignant from benign adrenal malignancies.[8] While most are identified initially based on imaging, confirmation occurs via histopathology and categorized according to Weiss criteria or the Helsinki score.[5,11] This includes examining nuclear grade, mitoses, atypical mitoses, clear cell involvement, diffuse architecture, confluent necrosis, venous invasion, sinusoidal invasion and capsular infiltration.[3,12] Generally the presence of at least (three) of these criteria is used as a cut-off, but its reproducibility has been challenging.[8] We attempted to examine this in our patient cohort

but the results were scattered, incomplete and inconsistent to warrant reporting. This could stem from a lack of clear consensus among pathologists due to its reproducibility and illustrates a potential area for refinement.[5] Margin status was poorly reported in our series with less than half of patients having this addressed in final pathologic reports. As margin status is the single most important predictive factor for long term survival, this illustrates a deficiency and demonstrates the importance of standardized reporting, of which standardized templates are now available.[8] In addition to limitations regarding pathologic reporting, our study did attempt to examine histological data including use of the Weiss criteria. Unfortunately, it was similarly poorly reported, with some patients having zero criteria mentioned with not one study examining all eight criteria. On average patients had 3.6 (IQR 2.75-4.25) of the Weiss criteria, ranging from either 0 to 7 out of 8. Atypical mitosis and necrosis were the most commonly reported metrics, with commentary on architecture and clear cell quantity were least reported.

Treatment strategies at our institution do align with many studies which recommend surgical resection as the mainstay of treatment.[9] It is the only proven curative treatment for the disease yet recurrence rates are high.[5] Some studies have recommended these surgeries only be performed at high volume centers and that an open approach with lymph node dissection should be performed. Lymphadenectomy has been shown beneficial for overall survival in R0 patients.[13] Minimally invasive surgery is usually reserved for lower stage I-II disease.[5,8] The low number of minimally invasive cases in our series does illustrate an inadequacy and may suggest variable surgeon skills/training, low volume of these cases as the disease is so rare or may be a reflection of the large time period for which the data was accumulated.

For those with disseminated, incompletely resected disease or poor surgical candidates, other treatment options are limited. These include radiation therapy or chemotherapy with mitotane, an adrenolytic drug, which has previously been shown as the most effective chemotherapy despite significant toxicity and low response.[1] A retrospective European study of over 120 patients illustrates the importance of the plasma concentration of the mitotane itself, illustrating that >14 mg/L is associated with prolonged recurrence free survival.[14]

In our study, fewer than half of patients received mitotane, 8 of which received it in the adjuvant setting and 3 in the palliative setting. Similarly large database studies have shown that less than half of patients received mitotane treatment with either disseminated or incompletely resected disease.[1] Despite studies showing that mitotane use can be beneficial for recurrence free survival and tumour regression both in the adjuvant and metastatic setting, there is no clear data for a benefit for overall survival and its role continues to remain controversial in the adjuvant, metastatic or salvage setting.[2,15] Inconsistent use may be due to the large toxicity profiles (gastrointestinal, neurologic

metabolic and endocrine effects), as well as challenges in ensuring optimal blood concentration levels for appropriate periods of time due to its narrow therapeutic window.[5,16] It is important to consider that mitotane is often required to be given in combination with other chemotherapeutic agents such as etoposide, doxorubicin or cisplatin and raises concern regarding impact on the contralateral adrenal gland and the related functional consequences.[5] There has yet to be any case of rapid and complete remission of ACC with mitotane monotherapy.[17] Furthermore, only two prospective multicenter randomized trials exist. The FIRM-ACT study showed that mitotane with etoposide, doxorubicin and cisplatin (EPDM) is superior to streptozocin-mitotane (SM).[18] In this study, patients with advanced ACC were randomized to EPDM or SM with a primary endpoint of survival.[19] Although no significant difference in overall survival was seen, with the EPDM group there were higher response rates and improved median progression free survival seen.[19] The other prospective study includes the ADIUVIO trial, a phase 3 multicenter randomized trial which is attempting to look at low to intermediate recurrence risk patients treated with mitotane versus observation in the adjuvant setting which is currently still in accrual.[18]

Only one patient received adjuvant radiation in our series, while the other received palliative radiation mainly for pain control. Its role is controversial and the limited value of radiation has been demonstrated.[20] Studies have shown poor outcomes, but radiation has been suggested in situations of residual microscopic disease, patients unsuitable for surgery or chemotherapy, and for palliation.[5] The least controversial remains its role in the palliative setting for symptomatic local disease control.[18]

Survival data in our study was very poor with a two- and five-year overall survival of 53% and 27% respectively. Survival stratified by ENSAT stage appears to correlate outcomes by stage. When survival is stratified by positive lymph node status (n=4), two-year survival for those with positive lymph nodes was 0%, and two- and five-year survival for those with negative nodes (n=4) was 75% and 25%, respectively. When survival was stratified by mitotane status, two- and five-year overall survival for those who received mitotane as 36% and 18%, respectively, and similarly for those who did not receive mitotane, two- and five-year overall survival was 50% and 22%, respectively. Reported survival data in the literature is variable, inconsistent and thus numerous predictive factors are being explored. In our series this may be reflective of inadequate surgical technique as stage and surgical resectability seem to be the most predictive thus far.[18,21] Interestingly, a large database review showed no significant survival improvement between 1985-2005 owing to the lack of large and randomized studies evaluating effective treatment therapies.[1]

Recently, significant focus has been made on further understanding this disease. From a histopathologic perspective, focus has been placed on Ki67, a marker of proliferation, which has been reproducible to be predictive of recurrence and survival.[8] Other studies have further suggested the role of lymphadenectomy in optimizing disease response.[13] With the lack of effective systemic agents, studies have looked at metformin. It has shown promising anti-neoplastic effects in other malignancies, as well as preliminary in-vitro studies examining the role of mTOR, WNT signaling and angiogenesis pathways.[5,13,22,23]

The main limitations of our study include the small sample size, retrospective nature, lack of complete data, and single-centre experience. The long time period is also a limitation, although we were able to chronicle inherent changes in technology, surgeon training and treatment patterns for this rare disease Due to the small sample size statistical analyses were limited.

Conclusion

Our series demonstrates that adrenal cortical carcinoma is a rare malignancy with associated poor outcomes and prognosis. This is the largest reported Canadian series to the best of our knowledge. More importantly, we highlight the continued inconsistency and lack of consensus regarding treatment options and management strategies. This demonstrates the significant need for large collaborative studies in addition to prospective randomized studies to to optimize treatment of this rare, but aggressive cancer.

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Figures and Tables

Fig. 1. Kaplan-Meier curve for overall survival.

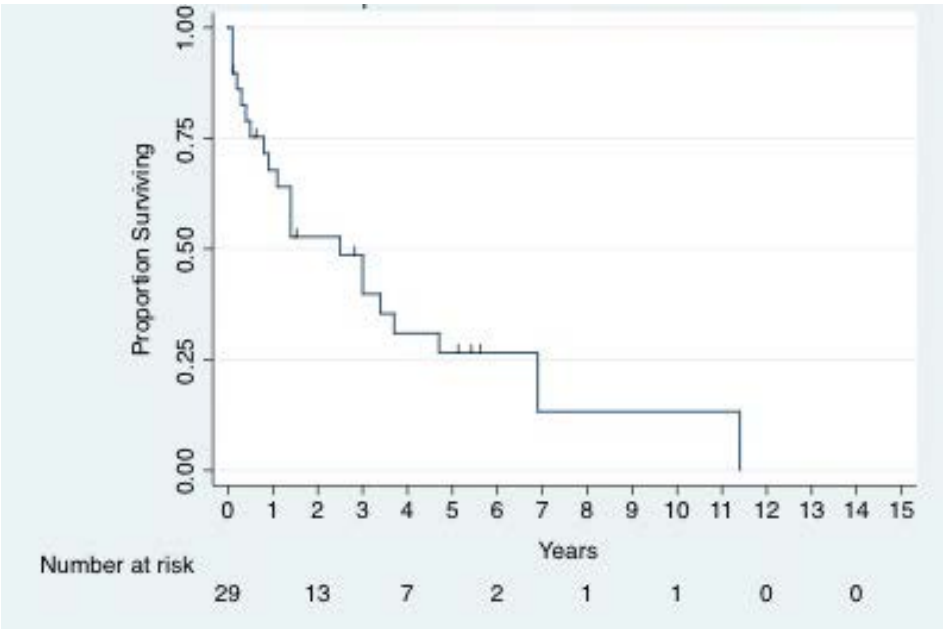

Fig. 2. Kaplan-Meier curve for overall survival (by European Network for the Study of Adrenal Tumours [ENSAT] stage).

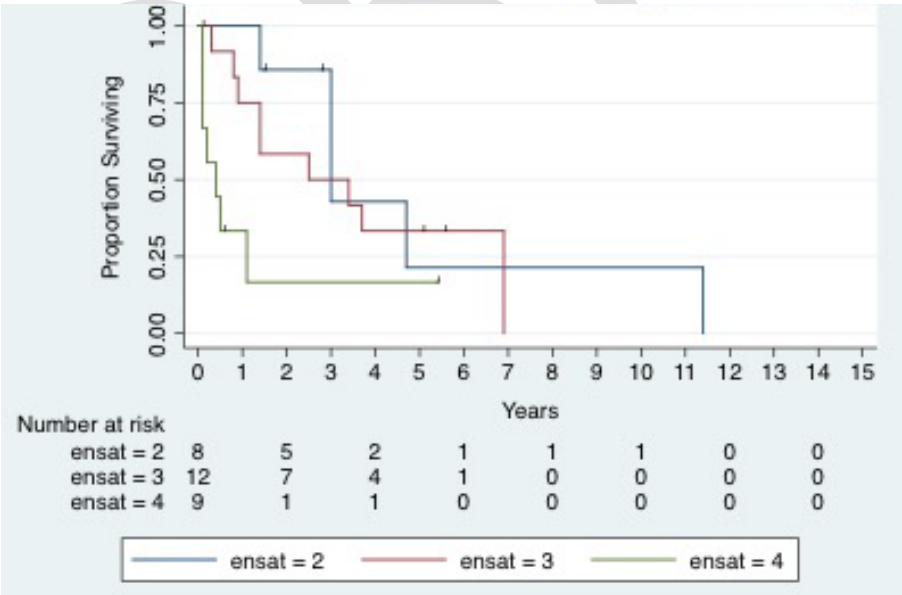

Table 1. Patient demographics	
Characteristic	**Patients, n (%)**
Median age (IQR)	55 (45–63)
Median BMI (range)	25.3 (20.2–38.7)
Gender	
Male	14 (48)
Female	15 (52)
Race	
Caucasian	27 (93)
Other	2 (7)
Presentation	
Weight gain	4 (14)
Weakness	5 (17)
Anemia	6 (21)
Hirsutism	2 (7)
Bruising	3 (10)
Diabetes	0 (0)
Weight loss	3 (10)
Fever	1 (3)
Anorexia	2 (7)
Asymptomatic	15 (52)

BMI: body mass index; IQR: interquartile range.

Table 2. Clinical characteristics		
	n	%
Metabolically active (at least one)	12	41
Glucocorticoid secretion	8	28
Sex hormone secretion	5	17
Mineralocorticoid secretion	2	7
Surgery	24	83
Open adrenalectomy	20	69
Lymphadenectomy	8	40
Positive	4	50
Negative	4	50
Average # of nodes	2	
Median # of nodes	1.5	
Laparoscopic adrenalectomy	4	14
Lymphadenectomy	0	0
Margin status		
Not reported	13	54
Open	12	
Lap	1	
Reported	11	46
Positive	4	36
Open	3	
Lap	1	
Negative	7	64
Open	5	
Lap	2	
Resection status		
R0	4	
R1	7	
R2	0	
Rx	13	
Average tumour size, cm (IQR)	12.8	9.1–16.6
Recurrence		
Yes	16	55
Local	0	
Asymptomatic	0	

Symptomatic	0	
Distant	11	
Asymptomatic	5	
Symptomatic	6	
Both	5	
Asymptomatic	5	
Symptomatic	0	
No	13	45
Mitotane		
Yes	11	38
Adjuvant	8	28
Palliative	3	10
No	18	62
Radiation		
Yes	10	34
Adjuvant	1	
Palliative	9	
tumour bed	3	
Bone	3	
Brain	1	
Lung	1	
Soft tissue mass	1	
No	19	66
ENSAT stage		
1	0	0
2	8	28
3	12	41
4	9	31

ENSAT: European Network for the Study of Adrenal Tumours; IQR: interquartile range.