Surgery 166 (2019) 524–533

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Oncocytic subtypes of adrenal cortical carcinoma: Aggressive in appearance yet more indolent in behavior?

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ARTICLE INFO

Article history:
Accepted 19 May 2019
Available online 28 August 2019

ABSTRACT

Background: Adrenal cortical carcinoma is an aggressive malignancy and typically heralds a poor prognosis. The oncocytic subtype of this neoplasm is rare but may be associated with more favorable outcomes.
Methods: The Provincial Cancer Registry was searched for cases of adrenal cortical carcinoma between 1992 and 2017. Comprehensive chart reviews were performed and data gathered related to presentation, treatment, and outcomes.
Results: In the study, 82 patients with adrenal cortical carcinoma were identified. Complete data were available for 67 patients (82%). In the 41 patients who underwent resection, 9 (22%) had oncocytic subtypes. When compared with the total group of adrenal cortical carcinomas, the oncocytic subtypes were larger at presentation (19.8 cm vs 11.0 cm), more commonly symptomatic and hormonally active, and despite larger tumor size, were often early stage I and II. Recurrent disease was observed in 3 out of 9 oncocytic subtype (vs 23 out of 32 adrenal cortical carcinoma), with greater median time to recurrence (17.5 vs 8 months). Univariate analysis suggested that age, T-stage, M-stage, and overall stage were associated with survival. There was a trend toward improved overall survival for patients with oncocytic subtype on Kaplan-Meier and multivariate analysis.
Conclusion: Despite our small numbers of patients with oncocytic subtype, our data suggest that oncocytic subtype are typically larger at presentation but more often early stage and recur less frequently than adrenocortical carcinomas. Modifications to treatment and surveillance strategies may be appropriate in this subtype.

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive neoplasm of the endocrine system with a reported incidence of between 0.5 to 2 per million. These malignancies have a poor prognosis due at least in part to their tendency to present with advanced disease. Even after resection for cure, recurrence is common and 5-year survival is only 30% to 50%.[1,2] With metastatic disease, the median survival is <1 year.[3] Resection is the mainstay of treatment with curative intent. Postoperative systemic treatment may provide some benefit in patients at greater risk for recurrence, although robust, prospective data are lacking to support this assertion. Clinical factors that predict survival include early stage, absence of hormone production, young age, and negative operative margins.[1,2]

Oncocytic neoplasms (ONs) are rare epithelial neoplasms. They can occur in a number of tissues, including the thyroid, parathyroids, kidney, pituitary gland, salivary glands, and adrenal cortex.[4] Pathologically, these neoplasms are comprised largely of oncocytes. This term of oncocytic neoplasms was coined initially in the 1930s to refer to large, polygonal cells with prominent granular eosinophilic cytoplasm owing to abundant cytoplasmic mitochondria.[4,5] Oncocytic adrenocortical carcinoma (OAC) is a rare subset of these neoplasms. To date, approximately 36 have been reported in the literature.[6–11] Adrenocortical oncocytic neoplasms can be either benign or malignant and frequently contain high-grade nuclear features and a solid growth pattern.[12] This possibility limits the application of the original Weiss criteria, which are used for the histopathologic classification of conventional adrenal cortical neoplams in the assessment of oncocytic tumors.[13] In the absence

Presented at the Central Surgical Association Annual Meeting, March 7–9, 2019, in Palm Harbor, FL.

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https://doi.org/10.1016/j.surg.2019.05.049
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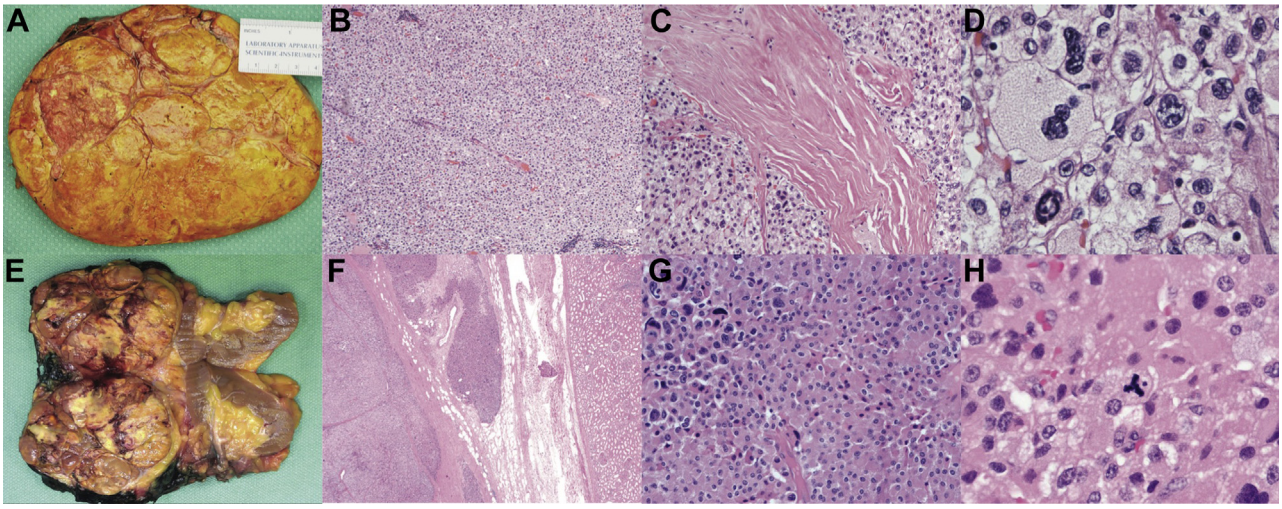

Fig 1. Histologic Images comparing ACCs and the OAC of type ACCs. (*A*) Gross image of the cut surface of a conventional ACC. The tumor is multinodular, soft, yellow, and contains fibrous bands (arrows). (*B*) Photomicrograph of a conventional ACC with diffuse architecture (hematoxylin and eosin stain [H&E] stain 100×). (*C*) A conventional ACC with thick fibrous bands (H&E stain 200×). (*D*) A conventional ACC: the neoplastic cells have vacuolated cytoplasm and high-grade nuclear features (H&E stain 400×). (*E*) Gross image of the cut surface of an OAC with an attached portion of kidney. The tumor is soft, friable and has tan-brown color. Extensive necrosis is present (yellow areas). (*F*) Photomicrograph of an OAC invading perinephric fat but not the kidney (right; H&E stain 20×). (*G*) Photomicrograph of an OAC with diffuse growth pattern. The neoplastic cells have abundant granular eosinophilic cytoplasm and high-grade nuclear features (H&E stain 200×). (*H*) An atypical tripolar mitotic figure in an OAC (H&E stain 600×).

of clear indicators of malignancy, such as local invasion and metastatic disease, the modified Lin-Weiss-Bisceglia (LWB) criteria may aid in defining these tumors as either benign, malignant, or of unknown malignant potential.[5] The pathologic diagnosis of malignancy is made if at least one major criterion is present (mitotic rate >5 mitoses per 50 high power fields, any atypical mitotic figures, or venous invasion). The presence of one or more minor criteria (size >10 cm or weight >200 g, microscopic necrosis, or capsular or sinusoidal invasion) indicates borderline malignant potential. The absence of these criteria indicates that the tumor is benign. OANs predominantly are composed of large epithelial cells with granular eosinophilic cytoplasm (Fig 1).[5,12]

Local experience and available literature suggest oncocytic ACCs (OACs) may behave in a more indolent manner compared to conventional ACCs.[8] If these tumors demonstrate a different clinical course from the more conventional ACC, this knowledge may inform prognostic conversations with patients and guide treatment and follow-up decisions. The objective of this study was to compare the clinical presentation, treatment, and outcomes of patients with OACs compared with those patients with conventional ACCs treated in Alberta, Canada.

Methods

Study design

Patients with ACCs of both the oncocytic and conventional subtypes were identified using the Alberta Cancer Registry. The search terms adrenal cortical carcinoma, adrenal adenocarcinoma, adrenal, and malignant tumor were used to identify patients between January 1992 and December 2017. Patients were included if they received treatment and follow-up in the province of Alberta.

Once identified, the records for each patient were reviewed to ensure appropriate diagnostic coding for inclusion into the study. Data collected included demographics (age, sex), disease at presentation (clinical presentation, biochemical functional status, preoperative imaging), treatment (operative date, details of operation, use of adjuvant therapies), histopathology, and outcomes (recurrence, survival, and cause of death). Vital status was noted in the Alberta Cancer Registry and cause of death was sought from the clinical record.

The subset of patients who underwent operative resection were identified. In our series, the patients with oncocytic neoplasms were classified according to the modified LWB criteria. Those with at least one major criterion were considered malignant; all other neoplasms were excluded. Pathology reports were reviewed in conjunction with an experienced endocrine pathologist, and when the tumor type was unclear in the report, the original pathology slides were reviewed. Unresected tumors could not be classified.

The primary aim of this study was to compare the overall survival of patients with conventional ACC versus patients with OAC. Additional comparisons between groups included presentation, extent of resection, recurrence, and development of metastases. The prognostic significance of sex, age, functional status (hormone production), stage, and adjuvant therapy (mitotane, chemotherapy) were also examined. Tumor staging was determined by the TNM classification for ACCs according to the American Joint Committee on Cancer, eighth edition. This study was approved by the Health Research Ethics Board of Alberta Cancer Committee (study ID: HREBA.CC-17-0529).

Statistical analysis

Because of the small number of OACs, statistical analyses were primarily descriptive. Categorical variables are provided as totals and frequencies. Continuous variables were reported as median with interquartile range (IQR). Comparisons between patient groups were assessed by Wilcoxon rank-sum (continuous variables), χ^2 test, and Fisher exact test (categorical variables). Kaplan-Meier curves were used to compare differences between groups for recurrence free survival and overall survival (OS) using the log-rank test. Univariate survival analyses were performed using the Cox proportional hazards model. A multivariate survival analysis was performed for the entire ACC group, but no subgroup multivariate analysis could be performed for the subgroups (conventional ACC or OAC), because the n values were too small. Comparisons between OAC and conventional ACCs should be interpreted with caution because of the small number of OACs ($n = 9$). Analyses were

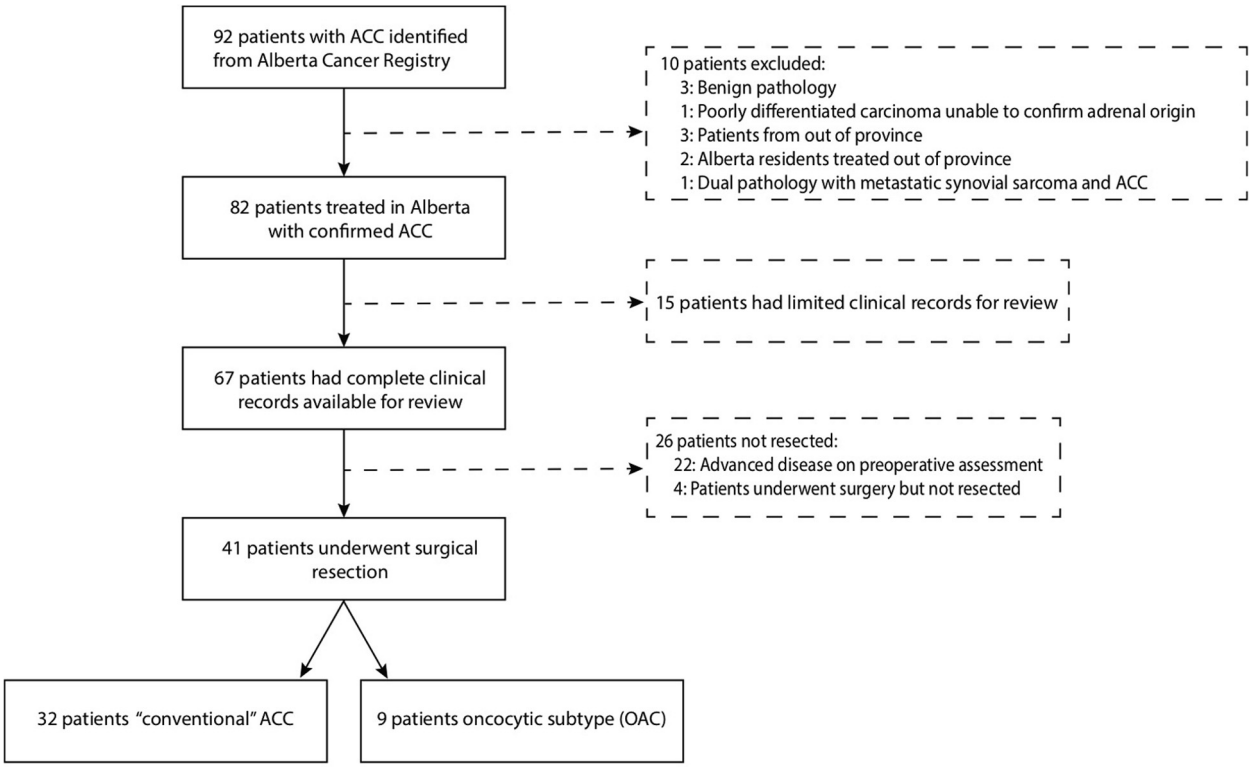

Fig 2. Flow chart demonstrating patients included in study. ACR, Alberta Cancer Registry.

performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 92 patients diagnosed with ACC in Alberta between January 1992 and December 2017 were identified from the Alberta Cancer Registry (Fig 2). Of these patients, 10 were excluded (3 benign pathology, 1 unclassified tumor, 5 out of province, and 1 had concurrent pathology of both metastatic synovial sarcoma and ACC). Of the remaining 82 patients, 15 had limited available clinical data (diagnosis and vital statistics) leaving 67 with complete data. Of these 67 patients, 41 underwent resection with curative intent, and 4 were deemed unresectable intraoperatively. Of those patients who underwent resection, 9 were found to have OACs and 32 were conventional ACCs.

Patient demographics for the entire cohort ($n = 82$), including those patients not resected, are presented in Table I. The median age of the cohort was 57.0 years (IQR 42.8–66.0), and 58% were female. Of the 67 patients with full clinical data, the majority (46; 69%) presented with symptoms, most commonly pain (63%). Tumors were identified as an incidental finding on imaging for other purposes in 20 out of 67 (30%), including 4 for investigation of new onset hypertension. One OAC was detected on ultrasonography for investigation of a benign Leydig tumor of the testis. Hormonally functional neoplams were noted in 4 out of 9 of the OAC group, 21 out of 32 (66%) of the conventional ACC group, and 12 out of 26 (46%) of the unresectable group. The most common hormones secreted were cortisol and sex steroids.

Details of treatment and pathology are listed in Tables II and III. Operative details were available for 45 patients. Disease was found to be more extensive than suspected on preoperative imaging in 4 patients; these patients were deemed unresectable intraoperatively and are not included in these tables. In the OAC group, 8 out of 9 patients underwent an open operation and 1 had a laparoscopic, transperitoneal approach. In the conventional ACC group ($n = 32$), 28 (88%) had a planned open operation with 1 posterior approach. Four patients had a laparoscopic resection, in which 2 were converted to open; one was a planned conversion to assist mobilization, and the other was due to a 5.9 cm diameter tumor with unexpected invasion to adjacent structures. Operative approach was unable to be ascertained for one patient. Multiorgan resection was performed in 7 out of 9 (78%) OACS and 18 out of 32 (56%) ACCs; the most common adjacent organ resected was the kidney.

The median tumor size was 19.8 cm (4.2–28.5 cm) in the OACs and 11.0 cm (2.5–19.5 cm) in the conventional ACCs ($P = .034$). Although invasion of adipose tissue was seen in 2 out of 9 OACs, no pathologic evidence of adjacent organ invasion was noted (Table III). Despite greater rates of locally advanced disease in the ACC group, rates of R0/R1 resection were similar. Stage I/II disease was found in 7 out of 9 patients with an OAC compared with 39% of conventional ACCs ($P = .060$). No patients in the OAC group had metastases at presentation compared with 7 out of 32 (23%) in the conventional ACC group. Of these latter 7 patients with conventional ACCS, resection was undertaken owing to uncertainty of diagnosis ($n = 2$), concurrent resection of liver metastases ($n = 3$), Ongoing pulmonary emboli from tumor thrombus ($n = 1$), and unclear rationale ($n = 1$). In the OAC group, 2 out of 9 patients received postoperative adjuvant mitotane, 1 received cytotoxic chemotherapy, and none received radiation. In the conventional ACC group, 18 out of 32 (56%) patients received mitotane, 12 (38%) received cytotoxic chemotherapy, and 5 (16%) received radiation therapy (most due to bony and lung metastases for palliation of hemoptysis; none to the adrenal bed).

Patterns of recurrence are shown in Table IV. Recurrent disease was identified in 3 out of 9 OACs and 23 out of 32 (72%) of conventional ACCs ($P = .053$). Locoregional and metastatic recurrences

Table I
Baseline characteristics of patients diagnosed with adrenocortical carcinoma (ACC)

Characteristic	Total ACC ($n = 82$)		Tumors resected				Not resected ($n = 26$)		*P* value
			Oncocytic subtype ($n = 9$)		Other ACC ($n = 32$)				
Sex									.067
Female	47	58%	2	22%	19	59%	15	58%	
Male	34	42%	7	78%	13	41%	11	42%	
Age, y									.670
Median (IQR)	57	(43–66)	57	(46–59)	52	(42–62)	65.5	(58–73)	
Laterality									.254
Left	41	50%	7	78%	16	50%	9	35%	
Right	41	50%	2	22%	16	50%	17	65%	
Symptomatic	46/67	69%	8/9	89%	21/32	66%	17/26	65%	.240
Pain/discomfort	29/46	63%	5/8	63%	12/21	57%	12/17	71%	
Loss of weight	16/46	35%	5/8	63%	3/21	14%	8/17	47%	
Weakness	12/46	26%	1/8	13%	6/21	29%	5/17	29%	
Incidental finding	20/67	30%	1/9	11%	12/32	38%	7/26	27%	.228
Hormone secreting tumor	37/67	55%	4/9	44%	21/32	66%	12/26	46%	.276
Cortisol	28/37	76%	3/4	75%	16/21	76%	9/12	75%	
Mineralocorticoid	2/37	5%	0/4	0%	2/21	10%	0/12	0%	
Sex hormone	22/37	59%	3/4	75%	11/21	52%	8/12	67%	
Multiple hormones	14/37	38%	2/4	50%	7/21	33%	5/12	42%	

A total of 82 patients diagnosed with ACC identified from the Alberta Cancer Registry. Complete clinical data set was available for 67 patients and limited clinical data was available for 15 patients. Histologic subtype was only available from those patients who underwent resection. *P* values shown reflect comparison of oncocytic subtype to Other ACC.

were observed. Many patients had recurrence at more than one site. Time to recurrence was 17.5 months in the OAC group and 8.0 months in the conventional ACC group. Of the patients with OACs, 1 recurred at both locoregional and distant sites, and 2 recurred as isolated pulmonary metastases. In the conventional ACC group, 4 had locoregional recurrence, 10 had distant metastatic recurrence, and 9 had combined distant and locoregional recurrence.

The median OS for ACC was 36 months (Table IV). Seven of the 9 patients with OAC remain alive without evidence of disease (78%) vs 19% of the patients with conventional ACCs ($P = .009$). A Kaplan-Meier analysis with the long-rank test (Fig 3) suggested a trend toward improved survival for patients in the OAC group ($P = .0623$). With only 1 event, the median survival in the OAC group has not yet been reached. Among all 67 patients, on univariate analysis (Table V), age, stage, operative resection, and metastases were significant predictors of survival ($P < .05$). Tumor subtype (OAC vs ACC) trended toward statistical significance ($P = .097$). When all ACC neoplams were controlled for stage and hormonal status on multivariate analysis, sex ($P = .078$), age ($P = .058$), and oncocytic subtype ($P = .081$) trend toward statistical significance for survival (Table V). When patients presented with metastatic disease or were deemed unresectable, median OS was 3 months (IQR: 1–7 months). No multivariate analysis could be done for the OAC or conventional ACC subgroups because of the small numbers ($n = 9$).

Table II
Treatments received according to tumor subtype

Treatment performed	Tumors resected				*P* value
	oncocytic subtype (n = 9)		Other ACC (n = 32)		
Surgery performed	9	100%	32	100%	
Surgical technique					
Open anterior	8	89%	27	84%	
Open posterior	0	0%	1	3%	
Laparoscopic transperitoneal	1	11%	2	6%	
Laparoscopic converted to open	0	0%	2	6%	
Multiorgan resection	7	78%	18	56%	.441
Organs resected					
Kidney	7		13		
Liver	0		5		
Spleen	3		3		
Pancreas	3		3		
Bowel	2		0		
Inferior vena cava/tumor thrombectomy	0		7		
Lymphadenectomy performed	7	78%	17	53%	.262
Adjuvant therapy					
Mitotane	2	22%	18	56%	.130
Adjuvant intent	2	100%	8	44%	
Palliative intent	0	0%	10	56%	
Chemotherapy	1	11%	12	38%	.228
Adjuvant intent	0	0%	3	25%	
Palliative intent	1	100%	9	75%	
Radiation therapy	0	0%	5	16%	.568
Tumor bed			0	0%	
Other sites			5	100%	

Table III
Pathologic features of ACC

Characteristic	Tumors resected				*P* value
	oncocytic subtype ($n = 9$)		Other ACC ($n = 32$)		
Tumor size, cm					.034
Median (range)	19.8	(4.2–28.5)	11.0	(2.5–19.5)	
Other organs invaded	2	22%	15	45%	.262
Extra-adrenal adipose	2		15		
Kidney	0		3		
Liver	0		3		
Diaphragm	0		1		
Inferior vena cava	0		4		
T stage					.302
T1	1	11%	1	3%	
T2	6	67%	13	41%	
T3	2	22%	12	38%	
T4	0	0%	5	16%	
N stage					.738
N0	5	56%	13	41%	
N1	0	0%	3	9%	
Nx	4	44%	16	50%	
M stage					.175
M0	9	100%	24	77%	
M1	0	0%	7	23%	
Stage					.060
I/II	7	78%	12	39%	
III/IV	2	22%	19	61%	
Resection margins					1.000
R0	7	78%	23	74%	
R1	2	22%	8	26%	

Note that TNM staging was only available for 32 patients as one patient original pathology was unavailable for review and diagnosis was on evidence of recurrent disease. Where the operative description did not explicitly outline lymphadenectomy was performed or tumor was resected en bloc with adjacent organs Nx was documented for N stage.

Discussion

OACs are a rare subtype of ACC. Because OACs may represent a more indolent variant of what is typically an aggressive and often fatal disease, OACs deserve further study. Our results support the impression of our local experience and the limited literature that OACs seem to follow a more indolent course with delayed recurrence and improved survival.[8] Although the results suggesting a trend toward significance in survival were detected, the *n* value of only 9 patients with OAC make this analysis of uncertain value; nevertheless, we suspect that survival is greater and recurrence is less in this subgroup of OACs. Wong and colleagues collated cases of OACs from their own series of 13 patients and the literature. They found 84 cases (of which 20 were OACs) with sufficient follow-up to

Table IV
Recurrent and progressive disease patterns in patients with resected ACC

	Tumors resected				*P* value
	oncocytic subtype ($n = 9$)		Other ACC ($n = 32$)		
Recurrent/progressive disease detected	3	33%	23	72%	.053
Locoregional	0	0%	4	17%	
Metastatic	2	67%	10	43%	
Both locoregional and metastatic	1	33%	9	39%	
Time to recurrence, mo					.732
Median (IQR)	17.5	(8.3–26.8)	8.0	(2.0–20.0)	
Site of recurrence					
Adrenal bed	1		9		
Retroperitoneal/aortocaval nodes	1		6		
Liver	1		16		
Lung	3		12		
Bone	0		5		
Other	0		2		
Overall survival, mo					
Median (95% CI)			36	(15–136)	
Vital status					.009
Alive without evidence disease	7	78%	6	19%	
Alive with evidence disease	1	11%	6	19%	
Died of disease	1	11%	17	53%	
Died of other disease	0	0%	3	9%	

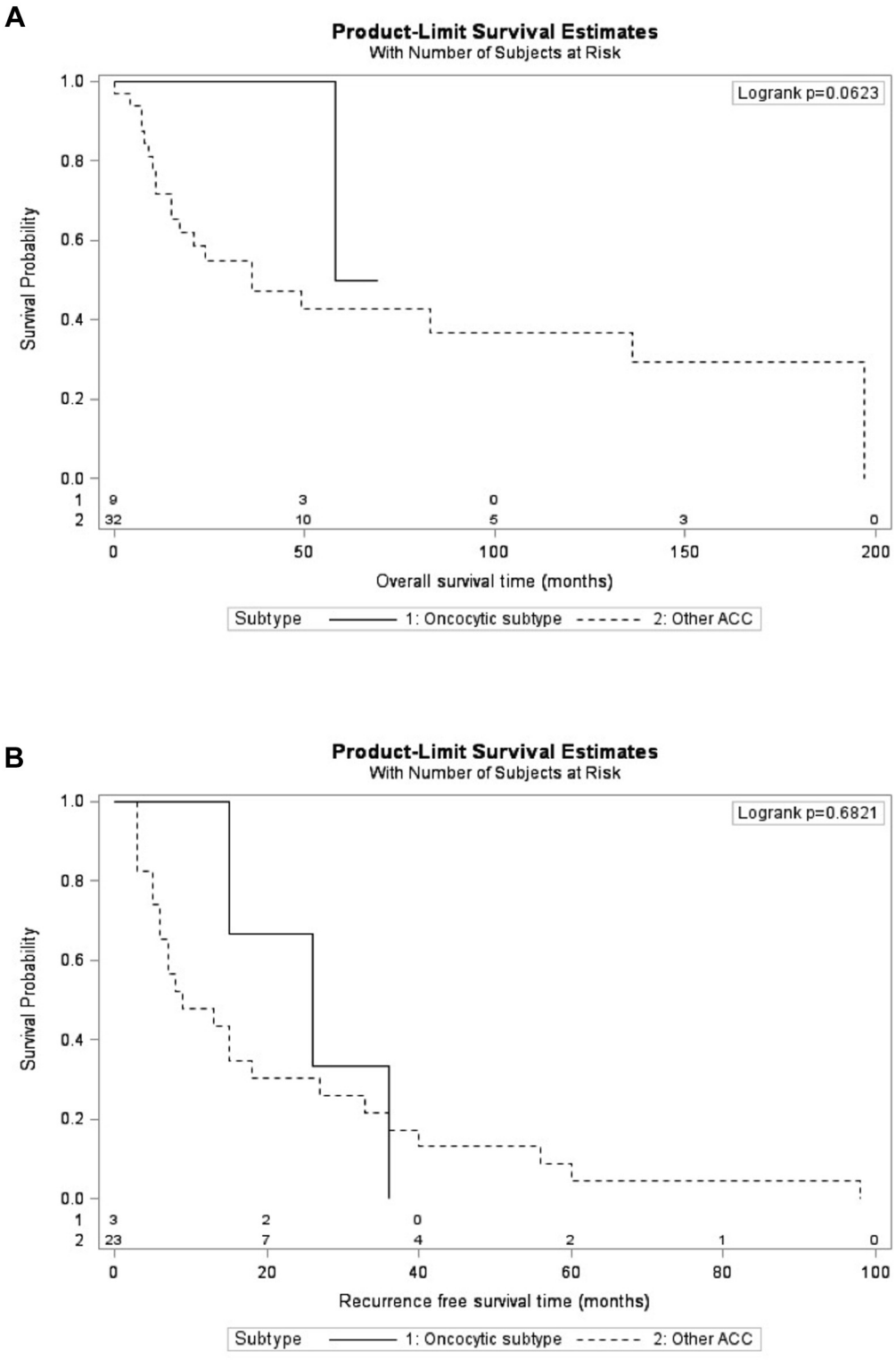

Fig 3. Kaplan Meier curves demonstrating (*A*) overall survival and (*B*) recurrence free survival stratified by oncocytic versus non-oncocytic (other ACC) subtype. Only patients with resected tumors were included in this analysis.

calculate median survival. They reported a median survival for OACs of 58 months (95% CI, 27.5–88.5 months).[8] The authors compared this to estimates from the literature showing a 14 to 32 month survival for patients with conventional ACC. Although our data support the concept that OACs have a more indolent clinical course, they also suggest these malignant neoplasm may present with a larger tumor and appear deceptively more aggressive on preoperative imaging or at operative exploration (for an example on imaging see Fig 4). Indeed, 8 out of 9 were approached with a planned open procedure, and 7 out of 9 underwent multiorgan

Table V
Univariate and multivariate analysis of factors associated with overall survival among all 67 patients with complete data

	Univariate			Multivariable		
	hazard ratio	95% CI	P value	hazard ratio	95% CI	P value
Sex						
Male	Reference			Reference		
Female	1.003	0.573–1.755	.992	0.576	0.312–1.065	.078
Age	1.028	1.009–1.047	.003	1.017	0.999–1.035	.058
Symptomatic						
No	Reference					
Yes	1.103	0.635–1.918	.727			
Incidental finding						
No	Reference					
Yes	0.816	0.418–1.591	.550			
Hormone secreting tumor						
No	Reference			Reference		
Yes	1.387	0.805–2.39	.238	1.205	0.622–2.333	.580
Metastatic ACC at presentation						
No	Reference					
Yes	2.597	1.472–4.582	.001			
Surgery						
No	Reference					
Yes	0.225	0.125–0.407	<.001			
Multiorgan resection						
No	Reference					
Yes	0.415	0.213–0.809	.010			
Lymphadenectomy performed						
No	Reference					
Yes	0.314	0.153–0.647	.002			
Histologic subtype						
ACC	Reference			Reference		
OAC	0.181	0.024–1.364	.097	0.16	0.020–1.253	.081
T stage						
T1/2	Reference					
T3/4	2.900	1.467–5.731	.002			
N stage						
N0	Reference					
N1/x	2.004	1.026–3.916	.042			
M stage						
M0	Reference					
M1/x	2.006	1.144–3.519	.015			
Stage						
I/II	Reference			Reference		
III/IV	3.910	1.711–8.935	.001	1.589	0.586–4.304	.363
Resection margins						
R0	Reference					
R1/2	2.050	0.874–4.810	.099			
Mitotane						
No	Reference					
Yes	0.671	0.368–1.224	.193			
Chemotherapy						
No	Reference					
Yes	1.157	0.624–2.143	.643			
Radiation						
No	Reference					
Yes	0.886	0.352–2.230	.797			
Other organs involved						
No	Reference					
Yes	0.866	0.444–1.690	.674			

Note that no subgroup analysis for conventional ACC or OACs was possible.

resection. Despite this, pathologic analysis revealed these neoplasms to be of an early stage with occasional extension into the surrounding adipose tissue but with no pathologic evidence of direct organ invasion. Paradoxically, the surgeon may be led to pursue a course of operative treatment that may be more aggressive than is warranted, but because a biopsy of ACCs before resection is not recommended in resectable lesions, limited information is available to help make the distinction between OACs and conventional ACCs preoperatively.

Primary dependence has been placed on preoperative imaging to predict the malignant potential of adrenocortical lesions. Traditional features on computed tomography (CT) that inform decisions regarding risk of malignancy include size, attenuation on unenhanced imaging, and IV contrast washout.[14] On magnetic resonance imaging, concerning features include the presence of an isointense to hypointense signal on T1 imaging, a hyperintense signal on T2 images, and a heterogeneous signal drop on chemical shift.[15] Given that both OACs and ACCs are lipid-poor tumors, CT and magnetic resonance imaging are unable to distinguish benign from malignant lesions regardless of size, attenuation, or handling of the contrast agent.[16] Although OACs tend to be large and give the appearance of a locally advanced cancer as indicated by the use of multiorgan resection in many of these patients, we demonstrated they are unlikely to invade adjacent organs. Limited data extending

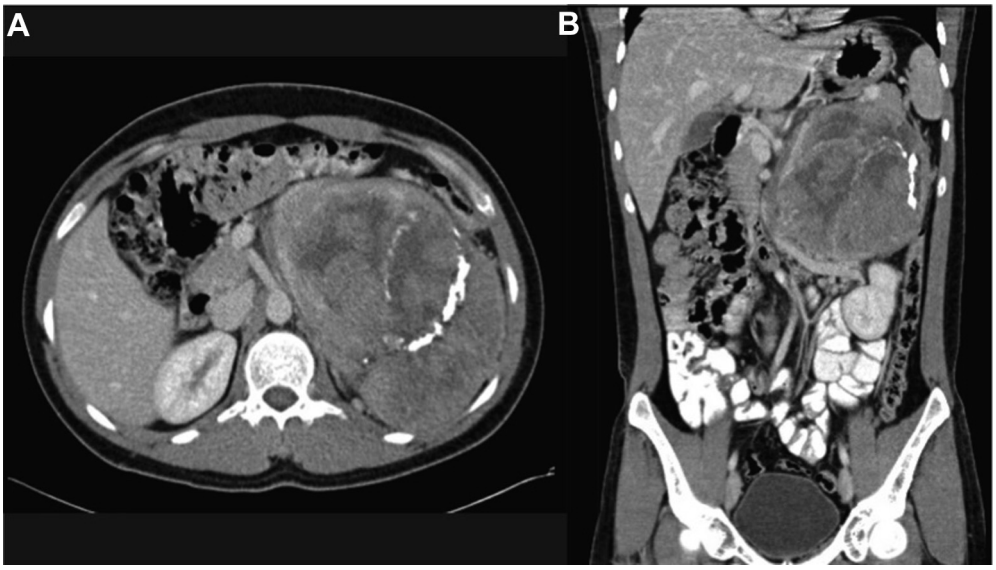

Fig 4. CT images of a patient with a large OAC of the left adrenal gland. (*A*) Axial and (*B*) coronal views demonstrating a large adrenal mass occupying left upper quadrant with heterogeneous enhancement, central necrosis, and areas of calcification. The mass seems to be intimately related with but not invading adjacent organs.

from case reports exists in the literature regarding ^{18}F-FDG PET activity in these tumors. Both benign and malignant OACs may be PET-avid.[17,18]

In the absence of clear markers of malignancy (invasion and metastases) the distinction between benign and malignant ACs presents challenges for the pathologist.[13,19] The Weiss criteria are used commonly to assess the malignant potential of cortical neoplasms.[13,20] Both benign and OACs have diffuse architecture and high-grade nuclear features, which are markers of malignancy in the Weiss criteria. Given the more indolent nature of OACs, this interpretation could lead to overtreatment. In 2004, Bisceglia et al acknowledged the inaccuracy of the traditional Weiss criteria when applied to OACs and proposed a modified set of criteria, the LWB criteria, for the classification of these neoplams.[5] In our series, the OACs were classified according to LWB criteria. Benign tumors or tumors of uncertain malignant potential were excluded.

The LWB criteria have been shown by Wong and colleagues to predict malignant potential accurately.[8] These authors were the first to provide evidence that the prognosis of OACs may be more favorable than conventional ACCs. Our study provides additional evidence to support the perceived more indolent biologic behavior of these malignant neoplasms. OACs were originally reported to have low rates of hormone secretion; however, our series and others have shown these tumors frequently produce hormones.[8,9,12]

Currently, there is considerable interest in the genomics of ACC as predictors of clinical outcome. Two recent, large genomic studies have confirmed and identified common driver mutations and demonstrated subtypes of ACC based on genomic expression with distinct clinical outcomes.[16,21] A common deletion in mitochondrial DNA (mtDNA 4977 bp) has been described in other oncocytic neoplasms and is present in approximately 50% of oncocytic adrenal neoplasmss.[22] Additional studies explain the molecular basis of different biologic behavior observed in these neoplasms compared with conventional ACCs. Ultimately, this distinction may lead to potential applications in diagnosis and treatment decisions.

Recommendations concerning adjuvant treatment with mitotane, cytotoxic chemotherapy, and radiation therapy are based on limited, largely retrospective data, even for conventional ACCs.[23] Guidelines for adjuvant therapy of OACs generally follows the recommendations for conventional ACCs; however, given that oncocytic variants may have a more favorable biologic behavior, this observation may impact the expected therapeutic benefits of these treatments. At our institution, patients are imaged at 3 to 6 month intervals using CT with or without PET until metastases are detected or if there is no evidence of disease after 24 months. Although our sample size is small ($n = 9$), patients with OACs have demonstrated improved survival compared to conventional ACCs, and hence, less intense surveillance may be warranted in this population.

We acknowledge the inherent limitations of this retrospective cohort study. Also, with such a small number of patients with OACs ($n = 9$), a formal robust statistical analysis of our patient cohorts and comparison of conventional ACCs and OACs is not possible. OACs are rare neoplasms, and thus the sample size renders it difficult to draw definitive conclusions. Nevertheless, our data in conjunction with previous publications supports the assertion these Malignant neoplasms appear to behave more favorably than conventional ACCs. By using data provided by the Alberta Cancer Registry, we think this is an accurate representation of ACC in this population and allows us to compare the influence of histologic subtype within a population with similar environmental exposures, pathologic reporting, and treatment strategies. Our experience represents a large cohort of ACCs in Canada and confirms similar outcomes published recently by Punjani et al.[24]

In conclusion, OACs are a rare subtype of ACCs. Our findings suggest they may produce hormones more frequently than reported previously in the literature. Despite their frequent large and aggressive morphologic appearance on preoperative imaging, OACs tend to be of lower stage, rarely invade adjacent organs, and seem to have improved survival with fewer recurrences compared to conventional ACCs. Awareness of this OAC subtype of ACCs may help guide decisions about future treatment and surveillance and result in more accurate predictions for patient prognosis.

Funding/Support

The authors have indicated that they have no funding regarding the content of this article.

Conflict of interest/Disclosure

The authors have no conflicts of interest to declare.

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Discussion

Dr Tina W.F. Yen (Milwaukee, WI): Congratulations on a very nicely presented study using the Alberta Cancer Registry on a very rare tumor, and a very rare tumor subtype. Among the 41 cases of adrenocortical carcinoma who underwent surgical resection, you demonstrate that almost a fifth to a quarter had the oncocytic subtype, and these patients tended to have larger tumors but less frequent and limited local invasion, be earlier stage with a trend towards potentially lower rates of recurrence and a trend towards improved survival.

I have 4 questions.

First, regarding operative approach, a total of 5 patients under a laparoscopic resection, and 2 were converted to an open approach. Do you have additional information on these 5 cases? When were their surgeries performed? Were these cases radiographically concerning for adrenocortical carcinoma? What were the tumor sizes? As you know, there is data to support an increased risk for local recurrence and peritoneal spread of adrenocortical carcinoma when removed laparoscopically. In your practice, what surgical approach, open versus laparoscopic, do you perform if there is a high radiographic suspicion for adrenocortical carcinoma?

Second, I'm not sure if you showed this in your presentation, but among the 32 in the conventional ACC group who underwent resection, at least in your manuscript, you showed that 7, almost a quarter, had M1 disease at presentation. Where were the sites of distant metastases? Were these sites known preoperatively? Did any undergo resection of their distant metastases?

Third, for the overall survival analysis, you show a trend towards improved survival in the oncocytic subtype group. Beyond controlling for stage, did you control for any other factors? What other variables were included in your model? Was this analysis confined to just the 41 who underwent surgical resection? Given the small sample size, you report huge confidence intervals in your manuscript. Should a multivariate analysis be performed with such a small cohort of patients?

Lastly, given the findings that demonstrate a more indolent and potentially more favorable prognosis of the oncocytic subtype, which are in line with other study results, will you consider modifying your treatment and surveillance strategies for patients with this rare subtype?

Dr Adrian Harvey: In regards to your first question, there were 5 patients that underwent a laparoscopic with 2 conversions. These patients typically had indeterminate appearing adrenal lesions on the smaller end of the spectrum. In the 3 that underwent completed laparoscopic resection, there was no intraoperative concerns noted for invasion.

In the 2 that were converted to an open procedure, one of those patients had evidence of invasion, as well as a noted tumor thrombus extending into the inferior vena cava and thus was converted very early.

The second patient with a conversion to open had a reasonable assessment of risk of adrenocortical carcinoma, but a difficult body habitus, and we felt that the liver mobilization would be technically easier laparoscopically. So we proceeded with an initial laparoscopic procedure with a high likelihood/planned conversion to open in that patient.

You are quite right, I didn't mention it here, but in the manuscript, there were 7 patients with metastatic disease at presentation in the conventional ACC group. Again, due to the retrospective nature, it's sometimes hard to be delineate what the thinking of the clinicians were at the time of diagnosis. Most of these patients fall

into a couple of categories. Number one, they had equivocal findings at the time of their surgery that subsequently turned out to prove to be metastases over the next 6 months. So given that these findings were there on initial imaging, we categorized them as having metastatic disease at their initial presentation.

The second main category would be an unclear diagnosis. An example would be there was a patient with a large pelvic mass and an adrenal mass and the patient was originally thought to have a sarcoma with metastasis to the adrenal. Upon resection, and final pathology that this is in fact was adrenal cancer with a large peritoneal met, and this was completely resected.

Regarding resection of the metastases, an additional 2 patients, other the one I just mentioned, had liver procedures, either resection or combined resection and RFA with the goal of an R0 end state after the initial surgery.

With regards to your third question, you are quite right and that we were a bit optimistic to do a multivariate analysis on the small number of patients. What we wanted to see was because the stage was different between the oncocytic and conventional groups, if we control for stage, would there still be the suggestion of a difference, which there was. We limited ourselves to 5 variables, and the analysis was done on the 67 patients including unresectable, and they included the stage oncocytic type, hormonal status, age, and gender.

For your final question whether or not this can modify treatment, I think it can certainly modify the discussions related to prognosis. It's difficult to discuss modifying treatment, particularly surgical treatment, because the diagnosis of an oncocytic variant invariably occurs postoperatively. If in the future we can find some way to imaging or other tests to recognize this preoperatively, it may influence the surgeon's likelihood of multi visceral resection or conversion to open, but at this point in time in our practice we don't alter our treatment based on that.

Dr Christopher R. McHenry (Cleveland, OH): Dr. Harvey, your presentation was excellent. I want to address the issue of postoperative treatment. As you have indicated there is a high incidence of recurrence with adrenocortical carcinoma, and in particular local recurrence.

In light of that, patients with locally advanced disease are treated with Mitotane and may also receive radiation therapy.

What was remarkable to me is that none of the patients with the oncocytic variant of ACC developed local recurrence. So, my question is does the diagnosis affect your recommendations for Mitotane therapy and radiation therapy, postoperatively?

Again, I enjoyed your presentation.

Dr Adrian Harvey: There was actually 1 patient in the oncocytic group that had a combined distant metastatic and local recurrence.

In terms of Mitotane therapy, 2 of our 9 patients got Mitotane postoperatively. So there was only about 20% of our oncocytic variant group got Mitotane postoperatively, and it was around 60 to 70% in our conventional group.

So we seem to already be doing that and I don't know if that was a conscious decision based on the pattern of recurrence. But that seems to be one of the strongest differences, and the recurrence occurs less often, and is later in the oncocytic group. It remains to be seen whether or not that can be modified through the use of Mitotane. But given that number of patients have difficulty tolerating Mitotane, particularly at the levels we would like to provide it to have an effect, it may be prudent to withhold that in oncocytic carcinoma in the future.

Dr Samuel Snyder (Harlingen, TX): I thank you for bringing this important aspect of adrenal cancer to our attention. It helps us to continue to be aggressive as we approach these tumors.

Knowing that the oncocytic tumors had a more favorable prognosis, looking back at the tumors that were declared unresectable, did you examine them to see if possibly some of them actually could have been resected or approached more aggressively?

My second question dovetails into that. The oncocytic tumors were treated more aggressively with multi-organ resection. Could that be partially responsible for the more favorable outcomes?

Dr Adrian Harvey: In the unresectable group, it's hard to tell which are oncocytic and which are not. But given the retrospective review, it's hard to delineate the reasoning of the surgeon as to why these were deemed unresectable and why different ones were considered resectable. Many of them were because of presence of metastatic disease. Due to these limitations we were not able to do that first analysis.

With respect to your second question, I would be more inclined to believe that if there was evidence of pathological invasion on the final pathology report. With only 2 patients having invasion into the surrounding adipose tissue, it's hard to imagine that multi visceral resection contributed to the improved recurrence rates and survival rates or apparent improved rates in those patients, although with that small number of patients, I certainly couldn't say that definitively.