

Clinical Case

Virilizing Adrenocortical Carcinoma with Liver Metastases: A Case Report

Carcinoma Adrenocortical Virilizante com Metástases Hepáticas: Relato de Caso

 Catarina Gomes¹,  Pedro Azevedo¹,  Rita Roque¹,  José António Pereira¹,  Rita Garrido¹

1. Serviço de Cirurgia, Hospital Beatriz Ângelo, Loures, Portugal

Corresponding Author/Autor Correspondente:

Catarina Gomes [catarinagomes96@gmail.com]

Serviço de Cirurgia, Hospital Beatriz Ângelo, Av. Carlos Teixeira 3, 2674-514 Loures, Portugal

<https://doi.org/10.34635/rpc.1184>

ABSTRACT

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with an incidence of approximately 1–2 cases per million population per year. Clinical presentation varies widely and may result from hormone hypersecretion or mass effect. Virilization in women is highly suggestive of ACC. Prognosis is strongly related to tumor stage, as metastatic disease is associated with poor outcomes.

We report the case of a 41-year-old woman who presented with a 10-month history of abdominal and lumbar pain, amenorrhea, hirsutism, and progressive virilization. Physical examination revealed male-pattern hair distribution and a palpable abdominal mass. Laboratory tests showed markedly elevated androgen levels, including total testosterone and dehydroepiandrosterone sulfate. Computed tomography revealed a large right adrenal mass measuring 10 × 16 cm with compression of adjacent structures. Positron emission tomography demonstrated intense metabolic activity and suggested hepatic invasion. After multidisciplinary discussion, the patient underwent *en bloc* resection including right adrenalectomy, right hepatectomy, and cholecystectomy. Histopathological examination confirmed a high-grade adrenocortical carcinoma with a Ki-67 proliferation index of approximately 40% and hepatic metastases (ENSAT stage IV). Early postoperative imaging revealed further hepatic disease progression. The patient subsequently received systemic therapy with mitotane and chemotherapy but developed treatment-related toxicity and progressive metastatic disease. She was referred to palliative care and died six months after surgery.

ACC remains a rare but highly aggressive malignancy. Although complete surgical resection is the cornerstone of treatment, patients with stage IV disease have a poor prognosis despite multimodal therapy. This case highlights the aggressive natural history of metastatic ACC and the challenges associated with its management.

Keywords: Adrenocortical Carcinoma; Liver Neoplasms/secondary; Mitotane; Neoplasm Metastasis; Virilism

Received/Recebido: 31/03/2026 **Accepted/Aceite:** 25/05/2026 **Published online/Publicado online:** 00/00/000 **Published/Publicado:** 30/09/2026

© Portuguese Society of Surgery 2026. Re-use permitted under CC BY-NC. No commercial re-use.

© Sociedade Portuguesa de Cirurgia 2026. Reutilização permitida de acordo com CC BY-NC. Nenhuma reutilização comercial.

RESUMO

O carcinoma adrenocortical (CAC) é uma neoplasia maligna rara e agressiva, com uma incidência de aproximadamente 1–2 casos por milhão de habitantes por ano. A apresentação clínica é muito variável e pode resultar de hipersecreção hormonal ou do efeito de massa tumoral. A virilização nas mulheres é altamente sugestiva de ACC. O prognóstico está fortemente relacionado com o estágio tumoral, sendo que a doença metastática está associada a resultados clínicos desfavoráveis.

Relatamos o caso de uma mulher de 41 anos, que se apresentou com uma história de 10 meses de dor abdominal e lombar, amenorreia, hirsutismo e virilização progressiva. Ao exame objetivo, apresentava distribuição pilosa de padrão masculino e uma massa abdominal palpável. Os exames laboratoriais revelaram níveis marcadamente elevados de androgênios, incluindo testosterona total e sulfato de dehidroepiandrosterona (DHEA-S). A tomografia computadorizada revelou uma volumosa massa adrenal direita, com 10 × 16 cm, condicionando compressão das estruturas adjacentes. A tomografia por emissão de positrões (PET) demonstrou intensa atividade metabólica e sugeriu invasão hepática.

Após discussão multidisciplinar, a doente foi submetida a ressecção em bloco, incluindo adrenalectomia direita, hepatectomia direita e colecistectomia. O exame histopatológico confirmou um carcinoma adrenocortical de alto grau, com um índice proliferativo Ki-67 de aproximadamente 40% e metástases hepáticas, correspondendo a estágio IV da classificação ENSAT. A avaliação imagiológica realizada precocemente no pós-operatório revelou progressão adicional da doença hepática. Posteriormente, a doente iniciou terapêutica sistêmica com mitotano e quimioterapia, tendo, contudo, desenvolvido toxicidade relacionada com o tratamento e progressão da doença metastática. Foi referenciada para cuidados paliativos e faleceu seis meses após a cirurgia.

O CAC permanece uma neoplasia rara, mas altamente agressiva. Embora a ressecção cirúrgica completa constitua a pedra angular do tratamento, os doentes com doença em estágio IV apresentam um prognóstico reservado, apesar da abordagem multimodal. Este caso evidencia a história natural agressiva do ACC metastático e os desafios associados ao seu tratamento.

Palavras-chave: Carcinoma Adrenocortical; Metástases Neoplásicas; Mitotano; Neoplasias do Fígado/secundária; Virilismo

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with an estimated incidence of approximately 1–2 cases per million population per year.¹

Hormone-secreting ACC occurs more frequently in women than in men and most commonly presents with hypercortisolism (Cushing syndrome), virilization, or a mixed Cushing–virilizing syndrome. The presence of virilization strongly suggests ACC. Cortisol excess is the most common laboratory abnormality and is frequently associated with autonomous androgen secretion.² Presentation with an abdominal mass is a classic clinical manifestation, occurring in approximately 30%–36% of patients at diagnosis. This presentation is typically associated with advanced disease, large tumor size, and a more aggressive clinical course, posing significant challenges for optimal treatment.¹

Liver metastasis indicates stage IV disease and represents one of the most common sites of distant spread, occurring in approximately 66% of patients with metastatic ACC. Stage IV ACC carries a poor prognosis, with a 5-year survival rate of less than 15% and a median overall survival of approximately 5–8 months without treatment.³

CASE REPORT

A 41-year-old woman presented with a 10-month history of abdominal and lumbar pain, virilization, amenorrhea, hirsutism, asthenia, anorexia, and early satiety. Physical examination revealed increased hair growth on the face and abdomen with a male-pattern distribution, clitoromegaly, as well as a palpable abdominal mass in the upper quadrants extending to the umbilical region.

Laboratory evaluation showed markedly elevated androgen levels, including dehydroepiandrosterone sulfate (DHEA-S) of 5.37 µg/mL (normal range 0.25–2.2 µg/mL), total testosterone of 2160 ng/dL (normal range 15–70 ng/dL), and free testosterone of 79 pg/mL (normal range 0.8–2.5 pg/mL). The 24-hour urinary free cortisol level was 41 µg/24 hours (normal range 28.5–213.7 µg/24 hours), and metanephrines were within normal limits.

The abdominal magnetic resonance imaging (MRI) (Fig. 1) revealed a 16x10x12 cm right adrenal mass with lobulated contours, predominantly solid, with internal hypodense areas. The lesion caused extrinsic compression of the right hepatic lobe, inferior vena cava, right kidney, and right colon. Small lumbo-aortic lymph nodes were present without pathological features.

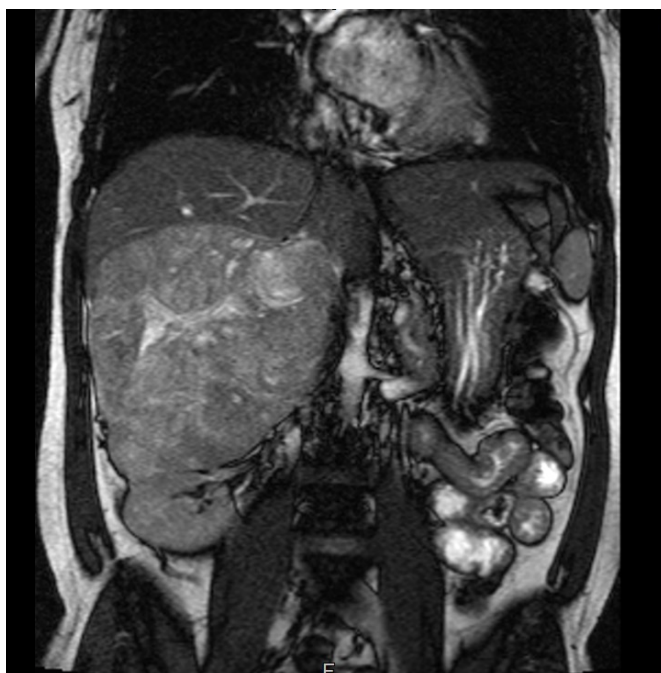


Figure 1 – Coronal section of T2-weighted abdominal MRI showing a 16×10×12 cm heterogeneous right adrenal mass with lobulated contours, compressing the right hepatic lobe.

Distant staging with positron emission tomography (PET) demonstrated intense hypermetabolic uptake of the lesion (SUVmax 14), suggestive of malignancy, with possible hepatic invasion by contiguity. Early hepatic metastasis in segments IV/V could not be excluded.

Following multidisciplinary discussion, the patient was proposed for upfront surgery with curative intent. She underwent exploratory laparotomy, which revealed a large mass involving the right adrenal gland and the right hepatic lobe, as well as a suspicious lesion in segment IVb. An *en bloc* resection was performed, including right adrenalectomy, right hepatectomy, and cholecystectomy, without intraoperative complications.

The surgical specimen (Fig. 2) consisted of an *en bloc* resection including the right hepatic lobe, right adrenal gland, and gallbladder. The tumor weighed 650 g and measured 210 mm at its largest dimension. The margins appeared expansile, with no macroscopic evidence of direct invasion into the hepatic parenchyma. Two nodules were identified in the liver measuring 40 and 45 mm, with similar morphology to the adrenal tumor, suggestive of metastases.

Histological examination demonstrated a high-grade malignant neoplasm of the right adrenal gland with a solid and nested growth pattern. The tumor was composed predominantly of

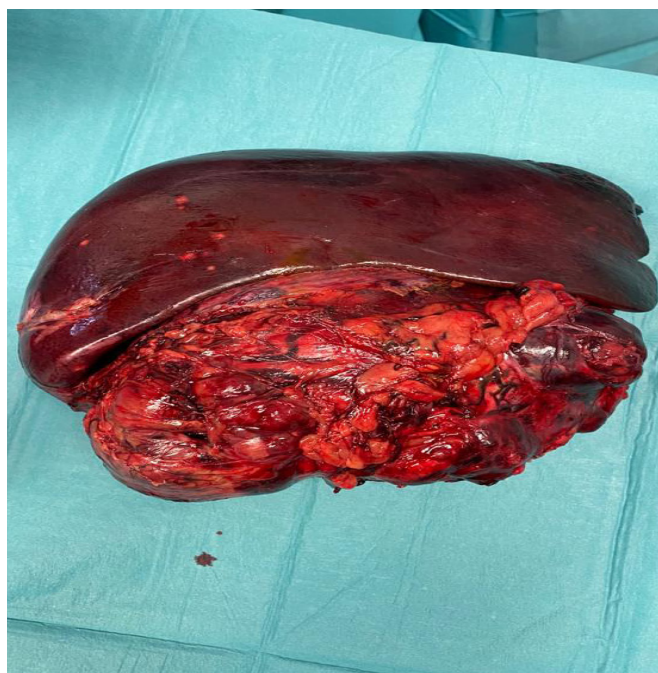


Figure 2 – Surgical specimen.

cells with eosinophilic cytoplasm (oncocytic type), with areas of granular or clear cytoplasm and nuclei with prominent nucleoli. Numerous mitoses (>20 per 50 high-power fields) and extensive necrosis were observed. The tumor breached the adrenal capsule with invasion of adjacent soft tissues, and multiple lymphovascular invasions were identified.

Immunohistochemical staining was positive for synaptophysin (strong and diffuse), inhibin, and focally for Melan-A, and negative for AE1/AE3, CAM5.2, TTF-1, S-100, and chromogranin. The Ki-67 proliferation index was approximately 40%. Two hepatic metastases were confirmed and completely excised. The tumor focally involved the resection margin near the adrenal gland (5 mm). The final pathological staging was pT3 Nx M1 R1.

On postoperative day 8, due to increased inflammatory parameters, a computed tomography (CT) scan was performed, revealing a new hypervascular nodule in segment II of the liver, suggestive of disease progression. The remainder of the postoperative course was uneventful, and the patient was discharged on postoperative day 11. After discharge, chemotherapy with mitotane was initiated.

At the 1-month postoperative follow-up, the patient showed a decrease in serum androgen levels, with total testosterone of

69 ng/dL (normal range 15–70 ng/dL) and androstenedione of 3.9 µg/mL (normal range 0.4–4.1 µg/mL). Partial regression of virilization symptoms was also observed.

After multidisciplinary discussion, thermoablation was proposed for the hepatic nodule identified on CT scan. However, a follow-up MRI performed three months after surgery revealed multiple hepatic metastases (Fig. 3), and the procedure was therefore not performed.

The patient was referred to a specialized center for further treatment and started adjuvant therapy with mitotane combined with chemotherapy. Mitotane was discontinued after one month due to hepatic toxicity. Disease progression occurred during chemotherapy, and the patient was subsequently referred to palliative care. She died six months after surgery.

DISCUSSION

Adrenocortical carcinoma is a rare and aggressive malignancy. Despite advances in diagnostic imaging and oncologic management, ACC remains a major clinical challenge due to its aggressive biological behavior, frequent hormonal activity, and poor overall prognosis.⁴

Clinical presentation varies depending on tumor size and hormone secretion. Approximately 60% of patients present with endocrine syndromes related to excess steroid production. Cortisol hypersecretion is the most common hormonal abnormality and is often associated with autonomous androgen secretion. In women, androgen

excess may manifest as hirsutism, amenorrhea, clitoromegaly, a presentation that strongly suggests malignant adrenal disease.¹ Our patient presented with progressive virilization and markedly elevated androgen levels, findings consistent with hormonally active ACC.

Imaging plays a crucial role in diagnosis and staging. ACC typically appears as a large, heterogeneous adrenal mass with necrosis or hemorrhage, often exceeding 10 cm, in diameter, at diagnosis. CT and MRI are essential for evaluating local invasion, while FDG-PET may help identify malignant lesions and detect metastatic disease.⁵ The most common sites of metastasis include the liver, lungs, lymph nodes, and bone. According to the European Network for the Study of Adrenal Tumours (ENSAT) classification, stage IV disease is defined by the presence of distant metastases and is associated with the worst prognosis.

Complete surgical resection with negative margins (R0 resection) remains the cornerstone of treatment and represents the only potentially curative option for ACC. For localized disease (ENSAT stages I–III), surgery is recommended as first-line treatment and should be performed in experienced centers due to the technical complexity and the importance of avoiding tumor rupture.^{6,7}

The role of surgery in stage IV disease remains controversial. In selected patients with limited metastatic burden, aggressive surgical resection of the primary tumor and metastases may provide survival benefit and symptom control. However, many patients present with disseminated disease and the

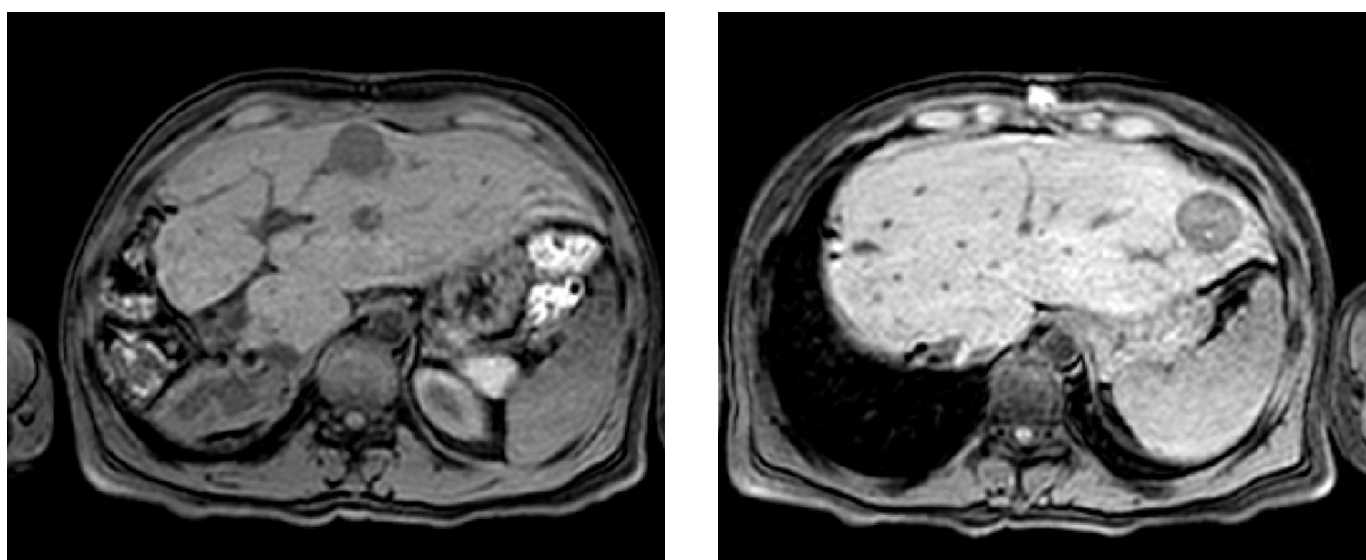


Figure 3 – Axial section of abdominal MRI depicting multiple new hepatic lesions suggesting liver metastasis.

benefit of extensive surgery is uncertain.⁸ In the present case, extensive surgery was performed due to the potentially resectable disease, but histopathology confirmed metastatic disease and aggressive tumor biology.⁹

Systemic therapy is the main treatment modality for advanced ACC.⁷ Mitotane, an adrenolytic drug that selectively destroys adrenal cortical cells, remains the foundation of medical therapy. It may be administered alone or in combination with cytotoxic chemotherapy. The most widely recommended first-line regimen for advanced ACC is the combination of etoposide, doxorubicin, and cisplatin (EDP) with mitotane. However, treatment responses are often limited and associated with significant toxicity.¹⁰

Local therapies such as radiofrequency ablation, embolization, or radiotherapy may be considered in selected patients with metastatic disease, mainly for palliative purposes or control of limited lesions. Nevertheless, evidence supporting these strategies remains limited.¹¹

Prognosis in ACC is largely determined by tumor stage, completeness of surgical resection, and tumor proliferation rate. The ENSAT staging system has strong prognostic value, with five-year survival rates of approximately 65%–82% for stage I, 58%–68% for stage II, 41%–55% for stage III, and only 10%–20% for stage IV disease. High Ki-67 proliferation index, as observed in this case, is associated with aggressive tumor behavior and poorer survival.¹²

The clinical course of our patient illustrates the aggressive natural history of metastatic ACC. Despite extensive surgery and systemic therapy, rapid disease progression occurred with the development of multiple hepatic metastases. The patient ultimately required palliative care and died six months after

surgery. This outcome highlights the limited effectiveness of current therapeutic strategies for advanced ACC.

CONCLUSION

Adrenocortical carcinoma is a rare but highly aggressive malignancy with poor prognosis, particularly in metastatic disease. Complete surgical resection remains the only potentially curative treatment; however, many patients present with advanced disease requiring systemic therapy with limited effectiveness. Early diagnosis, multidisciplinary management, and treatment in specialized centers remain essential to optimize outcomes.

LEARNING POINTS

- Adrenocortical carcinoma is a rare endocrine malignancy with an incidence of approximately 1–2 cases per million per year.
- Virilization in women with an adrenal mass strongly suggests malignant adrenal disease.
- Imaging with CT, MRI, and PET plays a crucial role in diagnosis, staging, and detection of metastatic disease.
- Complete surgical resection (R0) is the only potentially curative treatment and should be performed in specialized centers.
- Stage IV ACC has a very poor prognosis despite multimodal therapy.
- Mitotane-based therapy combined with chemotherapy represents the main systemic treatment for advanced disease.
- Multidisciplinary management and early integration of palliative care are essential in progressive metastatic disease.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

CONTRIBUTORSHIP STATEMENT

CG: Bibliographical search, data collection, analysis and interpretation of results, drafting of the article.

PA, RR, JAP and RG: Critical review of the content of the article.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

DECLARAÇÃO DE CONTRIBUIÇÃO

CG: Pesquisa bibliográfica, recolha de dados, análise e interpretação dos resultados, redação do artigo.

PA, RR, JAP e RG: Revisão crítica do conteúdo do artigo.

Todos os autores aprovaram a versão final do manuscrito para publicação e assumem responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

REFERENCES

1. Fassnacht M, Puglisi S, Kimpel O, Terzolo M. Adrenocortical carcinoma: a practical guide for clinicians. *Lancet Diabetes Endocrinol.* 2025;13:438–52. doi:10.1016/S2213-8587(24)00378-4
2. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101:1889–916. doi:10.1210/jc.2015-4061
3. Kuhlman JJ, Rao S, Sacchi de Camargo Correia G, Wolf E, Tawfiq R, Li S, et al. Assessment of survival and role of chemotherapy in patients with adrenocortical carcinoma: Insights from SEER Database (2000–2021). *J Clin Oncol.* 2025;43:16_suppl. doi:10.1200/JCO.2025.43.16_suppl.e16610
4. Nastos C, Papaconstantinou D, Paspala A, Pararas N, Vryonidou A, Pikouli A, et al. The impact of adrenocortical carcinoma hormone secreting status as a predictor of poor survival: a systematic review and meta-analysis. *Langenbecks Arch Surg.* 2024;409:316. doi:10.1007/s00423-024-03507-5
5. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. *J Urol.* 2003;169:5–11. doi:10.1016/S0022-5347(05)64023-2
6. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger RR, et al. 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. *Eur J Endocrinol.* 2018;179:G1–46. doi:10.1530/EJE-18-0608
7. Jasim S, Habra MA. Management of Adrenocortical Carcinoma. *Curr Oncol Rep.* 2019;21:20. doi:10.1007/s11912-019-0773-7
8. Dy BM, Strajina V, Cayo AK, Richards ML, Farley DR, Grant CS, et al. Surgical Resection of Synchronously Metastatic Adrenocortical Cancer. *Ann Surg Oncol.* 2015;22:146–51. doi:10.1245/s10434-014-3944-7
9. Wängberg B, Khorram-Manesh A, Jansson S, Nilsson B, Nilsson O, Jakobsson CE, et al. The long-term survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane. *Endocr Relat Cancer.* 2010;17:265–72. doi:10.1677/ERC-09-0190
10. Berruti A, Terzolo M, Sperone P, Pia A, Della Casa S, Gross DJ, et al. Etoposide, doxorubicin and cisplatin plus mitotane in the treatment of advanced adrenocortical carcinoma: a large prospective phase II trial. *Endocr Relat Cancer.* 2005;12:657–66. doi:10.1677/erc.1.01025
11. Veltri A, Basile D, Calandri M, Bertaggia C, Volante M, Porpiglia F, et al. Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation. *Eur Radiol.* 2020;30:6958–64. doi:10.1007/s00330-020-07019-w
12. Miller BS, Gauger PG, Hammer GD, Giordano TJ, Doherty GM. Proposal for modification of the ENSAT staging system for adrenocortical carcinoma using tumor grade. *Langenbecks Arch Surg.* 2010;395:955–61. doi:10.1007/s00423-010-0698-y

