

Surgery of the adrenal metastases

Cirugía de las metástasis suprarrenales

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Abstract

Background: Adrenal metastases are the most common malignant lesions of the adrenal glands and the second most common tumor after adenomas. The location of the primary tumor is described: lung (39%), breast (35%), gastrointestinal tract, among other. Several studies show that surgery improves survival in selected cases. **Method:** Retrospective and single-center observational study of patients operated for adrenal metastasis over a period of 11 years. The characteristics of the disease and surgical results were described. **Results:** 14 suprarenalectomies were performed. The average age was 65.85 years. The primary tumors described: non-small cell lung carcinoma (42.8%) and clear cell renal carcinoma (14.20%). In 92.8% the injury was unilateral. In 64.2% it was metachronous. An initial laparoscopic approach was performed in 85.71%. The morbidity of our series was 14.28%. The median overall survival was 30 months. Survival was 75% per year, 55.5% at 3 years and 40% at 5 years. **Conclusions:** Age, primary location, degree of differentiation, histological type, size greater, laterality, disease-free interval, chemotherapy and surgical technique are not associated with changes in survival. In the presence of a single adrenal mass, surgical evaluation is mandatory and surgery could play a role in patients with metastases in other locations with control of the primary disease.

Keywords: Adrenal metastasis. Associated factors. Adrenalectomy. Survival.

Resumen

Antecedentes: Las metástasis suprarrenales son las lesiones malignas más frecuentes de las glándulas suprarrenales. Como localización del tumor primario se encuentran el pulmón (39%), la mama (35%), el riñón y el tracto gastrointestinal, entre otros. La cirugía mejora la supervivencia en casos seleccionados. **Método:** Estudio observacional, retrospectivo y unicéntrico de pacientes intervenidos de suprarrenalectomía por metástasis suprarrenal en un periodo de 11 años. Se describen las características de la enfermedad y los resultados quirúrgicos. **Resultados:** Se realizaron 14 suprarrenalectomías. La media de edad de los pacientes fue de 65.85 años. Los tumores primarios fueron carcinoma no microcítico pulmonar (42.8%) y carcinoma renal de células claras (14.20%). En el 92.8% de los casos fue unilateral y en el 64.2% metacrónica. Se realizó laparoscopia inicial en el 85.71%. La morbilidad fue del 14.28%. La mediana de supervivencia global fue de 30 meses. La supervivencia fue del 75% al año, el 55.5% a los 3 años y el 40% a los 5 años. **Conclusiones:** La edad, la localización primaria, el grado de diferenciación, el tipo histológico, el tamaño, la lateralidad, el intervalo libre de enfermedad, la quimioterapia y la técnica quirúrgica no se asocian a cambios en la supervivencia. Ante una masa suprarrenal única, la valoración quirúrgica es mandatoria y la cirugía podría ocupar un papel en pacientes con metástasis en otras localizaciones con control de la enfermedad primaria.

Palabras clave: Metástasis suprarrenal. Factores asociados. Suprarrenalectomía. Supervivencia.

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Introduction

Adrenal metastases are the most common malignant lesions of the adrenal glands and the second most common tumor after adenomas. Currently, with the use of imaging tests for the diagnosis, staging, and follow-up of malignant tumors, they are increasingly diagnosed incidentally.

The adrenal glands are the fourth most common site of metastases, and about 30% to 70% of incidentally discovered masses in patients with a history of cancer or newly diagnosed extrarenal adrenal neoplasm are metastases^{1,2}.

The location of the primary tumor is described as the lung (39%), the breast (35%), melanoma, the gastrointestinal tract, the pancreas and the kidney, among other places³.

Adrenal metastatic dissemination occurs via the hematogenous route, and can be bilateral due to its important blood supply⁴. They are described in isolation in less than 1% of cases⁵.

Most patients with adrenal metastases are asymptomatic, although they may have localized symptoms, such as back or abdominal pain due to the tumor mass effect and possible involvement of the splanchnic nerves. They are not "functioning" tumors and do not usually cause adrenal insufficiency; bilateral adrenal involvement less than 90%.

The median time from cancer diagnosis to identification of adrenal metastases is approximately 2.5 years, although up to 22 years after initial treatment of primary tumors have been described. Isolated adrenal metastases rarely occur prior to identification of the primary malignancy⁶.

Surgery plays an important role in the treatment of adrenal lesions suspected of metastasis, as several studies describe an improvement in survival after resection.

Method

A retrospective, single-center observational study was conducted that included all patients older than 18 years who with a diagnosis of adrenal metastases underwent adrenalectomy in the endocrine surgery unit of a tertiary hospital, with a favorable report from the center's endocrine tumors committee, over a period of 11 years (2009-2019). Data were obtained from the hospital's electronic medical record.

Metastases were considered synchronous if they were detected within a period of less than 6 months

from the diagnosis of the primary tumor, and metachronous if the interval was longer. It was decided to use this definition in accordance with the reviewed literature, in which some cases have also been published under the name of antechronic metastasectomy⁷.

Demographic characteristics, comorbidity, medical-surgical history, clinical presentation, characteristics of surgery, surgical results, pathology, mortality, and survival were described.

In the clinical presentation of the disease, the presence of symptoms or adrenal insufficiency was described.

The surgeries were performed by specialists from the endocrine surgery unit. The type of surgery, approach and surgical time were described.

Perioperative mortality was defined as that which occurred during admission or within 30 postoperative days.

Statistical analysis was performed with the *Statistical Package for the Social Sciences* (SPSS v. 15). Quantitative variables with normal distribution according to the Kolmogorov-Smirnov test were compared using the Student's t test, while the Mann-Whitney test was used for evidence of non-normality. Categorical variables were compared using the test of χ^2 (Fisher's exact test). A p value < 0.05 was considered significant.

Results

In our center, 113 adrenalectomies were performed in the study period (2009-2019), of which 14 (12.4%) were due to adrenal metastases. 71.40% (10 cases) were men and 28.57% (4 cases) were women, with a mean age of 65.85 years.

The most frequent primary tumors were non-small cell lung carcinoma (42.8%) and clear cell renal carcinoma (14.20%), also finding metastasis of spindle cell sarcoma, infiltrating lobular carcinoma of the breast, hepatocellular carcinoma, colorectal adenocarcinoma, and esophageal adenocarcinoma (Table 1).

In 92.8% (13 cases) the lesion was unilateral. In the case of bilateral involvement, the primary tumor was located in the lung. The most affected adrenal gland was the one on the right side (57.1%), and in the cases of clear cell renal tumor, 50% of the metastasis was ipsilateral.

In 64.2% (9 cases), adrenal metastasis was metachronous, with a mean onset time from primary diagnosis of 48 months (8-132 months). 28.57% (4 cases) were synchronous metastases and there was one case of antechronic metastasis.

Table 1. Primary lesions causing metastasis in our series

Primary tumor	Cases	Percentage
Lung non-small cell carcinoma	6	42.8%
Renal clear cell carcinoma	2	14.20%
Lung neuroendocrine carcinoma	1	7.14%
Spindle cell sarcoma	1	7.14%
Infiltrating lobular carcinoma of the breast	1	7.14%
Hepatocellular carcinoma	1	7.14%
Colorectal adenocarcinoma	1	7.14%
Esophageal adenocarcinoma	1	7.14%

In 13 patients, the metastatic lesion was diagnosed and confirmed with computed tomography (CT) and positron emission tomography (PET); PET/CT was not performed in only one case, and fine needle aspiration was performed in one case of non-small cell lung carcinoma.

The diagnosis of adrenal metastases in all cases was a finding. Likewise, at diagnosis, six patients (48.8%) had metastatic lesions in another location and seven patients received neoadjuvant therapy. In 85.7% (12 cases) surgery of the primary tumor was performed before adrenalectomy. In one case, the primary tumor was diagnosed after adrenal surgery, and in the other, primary surgery was ruled out because it was stage IV squamous cell carcinoma of the esophagus.

Regarding the surgical characteristics of our series, an initial laparoscopic approach was performed in 85.71% (12 cases), converting only one case to open surgery due to abundant bleeding. In the rest of the patients, initial open surgery was decided because they were tumors with a size > 14 cm. In two cases resection of other organs was associated, in one of them subtotal gastrectomy and in another hepatic segmentectomy of the V segment. Average surgery time was 241 minutes. 28.5% (4 cases) required blood transfusion.

The mean tumor size was 5.33 cm (1.3-15 cm), and the histological grade was G1 in 7.1%, G2 in 42.85%, and G3 in 35.7%. Complete resection was performed in 85.71% (12 cases).

Morbidity in our series was 14.28%: two cases classified as Clavien-Dindo IIIa and V, respectively. One patient presented postoperative biliary fistula (the case of associated hepatic segmentectomy) that required percutaneous drainage and another suffered hemorrhagic *shock* resulting in death. Postoperative

mortality was 7.10% (1 case). The average hospital stay was 6.29 days (2-15 days).

50% (7 cases) received adjuvant therapy. 71.4% (10 cases) presented a relapse of the systemic disease and only one patient had a local relapse. Mean disease-free time was 20.6 months (3-58 months). Median overall survival was 30 months (4-111 months). Survival was 75% at one year, 55.5% at 3 years, and 40% at 5 years.

Discussion

Surgery for adrenal metastases has evolved completely, going from being a sign of disseminated disease and a contraindication to surgery to becoming an emerging, safe therapeutic option with positive prognostic implications in certain tumors and selected cases.

According to what has been published in numerous series, the tumor that most frequently metastasizes to the adrenal gland is lung adenocarcinoma, reaching up to 87.5%⁷ of cases, compared to 42.8% in our series. Four patients had metachronous metastases, one synchronous and one antechronous, the latter being very infrequent and without reference to any sequential treatment in this regard⁸.

De la Quintana et al.⁹ describe non-small cell lung carcinoma as the most frequent, with 51.4% of cases, coinciding with our series, in which no case of small cell carcinoma was found, traditionally considered a disease widespread and manageable with palliative chemotherapy⁴. At the time of diagnosis, three patients had metastases in another location: brain, lung, and bone, respectively, with a good response to neoadjuvant therapy. The neoadjuvant indications considered in our series were metastases in another location, antechronous and synchronous. Jalón-Monzón et al.⁷ do not consider neoadjuvant chemotherapy as long as the primary tumor is controlled and there is no disease elsewhere.

The incidence of adrenal metastases from renal cell carcinoma is described in 2-10% of cases, and in autopsy series in 6-29%³. Adrenal involvement is rare¹⁰ and affects the ipsilateral gland more frequently¹¹⁻¹³. In our series, one case had ipsilateral involvement and two metachronous cases. Ipsilateral adrenal involvement may occur from hematogenous dissemination of isolated cells or from tumor thrombosis via the renal vein or adrenal vein, and direct extension through the renal capsule may occur in large or upper pole tumors. Metachronous metastases have been reported up to

23 years after nephrectomy¹⁴. Lau et al.¹⁵, in a series of 56 cases, observed 24 synchronous and 32 metachronous lesions with a maximum time to the appearance of adrenal metastases after nephrectomy of 23 years.

Laparoscopic approach is currently considered the initial approach in the surgical treatment of adrenal involvement¹⁶. In our series, the approach used was transabdominal laparoscopic and open surgery was decided in two cases because they were tumors larger than 14 cm.

In patients with single metastases in which complete surgical removal is possible, 5-year survival rates of 23-35% have been reported^{13,17,18}, being the most favorable prognosis in those patients with a longer time interval since nephrectomy¹⁹. In our series, the median survival was 30 months, coinciding with that published by De la Quintana et al.⁹, which shows a median of 37.3 months, and less than that of the series by Hatano et al.⁶, with an average of 63 months. It is worth mentioning that, in our series, 50% of the patients had metastases in other locations at the time of diagnosis.

In our series, overall mortality was 7.10% (1 case) due to metastasis of 15 cm of hepatocarcinoma in a previously undiagnosed cirrhotic patient.

Overall survival at one year was 75% in our series, lower than that of Hatano et al.⁶, which was 92%. At 5 years it is 40%, coinciding with De la Quintana et al.⁹, who reported 42.86%, and with Hatano et al.⁶, who reported 56%. Jalón-Monzón et al.⁷ found some prognostic factors associated with survival: age, primary location, degree of differentiation, histological type, and treatment of the primary, but without finding a significant correlation. On the other hand, De la Quintana et al.⁹ include size > 4 cm, laterality, disease-free interval, chemotherapy and surgical technique as prognostic factors, but without finding any factor that influences survival, except for tumor size. Hatano et al.⁶ describe that metachronicity, size <4 cm, and the histological type of renal cell carcinoma have better survival. In our series we did not observe a significant association with any of the factors mentioned.

References to surgery for adrenal metastases of colorectal origin, hepatocellular carcinoma, and breast carcinoma are, as in our series, anecdotal, with two cases of colorectal origin, one case of hepatocellular carcinoma, and one case of breast carcinoma.

In all our cases, the surgical indication was justified for therapeutic purposes, after discussion in the endocrine tumors committee.

In patients with non-small cell lung cancer and single metastatic adrenal lesions, surgery improves survival in selected cases: controlled primary disease, tumor <4 cm, disease-free interval > 6 months, and metastasis located only in the adrenal gland^{8,19}. However, there are few data on patients with small cell carcinoma.

Conclusions

Tumors other than non-small cell lung cancer have not been shown to improve overall survival or disease-free interval. Even so, in the presence of a single adrenal mass, surgical evaluation is mandatory. On the other hand, in our series, 50% of the patients had metastases located in other organs and, even so, survival is similar to that of patients with a single metastasis, indicating that surgery could also play an important role in this type of patients, clearly with control of the primary disease.

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Conflicts of interest

The authors declare not to have any conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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