Surgery for recurrent adrenocortical carcinoma: A multicenter retrospective study

Guénolé Simon, MD,[a] François Pattou, MD, PhD,[b] Eric Mirallié, MD,[a] Jean Christophe Lifante, MD, PhD,[c] Claire Nominé, MD,[d] Vincent Arnault, MD,[e] Loïc de Calan, MD,[e] Cécile Caillard, MD,[a] Bruno Carnaille, MD,[b] Laurent Brunaud, MD, PhD,[d] Nathalie Laplace, MD,[c] Robert Caiazzo, MD, PhD,[b] *and* **Claire Blanchard, MD,[a]** *Nantes, Lille, Lyon, Nancy, and Tours, France*

Background. *Adrenocortical carcinoma is a rare neoplasm with a high rate of recurrence. We studied the impact of surgery on the survival in recurrent adrenocortical carcinoma patients.*
Methods. *We performed a retrospective review of patients with recurrent adrenocortical carcinoma, managed in 5 French University Hospitals between 1980 and 2014. We compared surgery and medical management for ACC recurrence.*
Results. *Fifty-nine patients were included, 46 of whom had an initial R0 resection. Twenty-nine patients underwent reoperation for recurrence, while 30 had nonoperative treatments. Operated patients had a greater median overall survival after recurrence than nonoperated patients (91 vs 15 months;* $P < .001$*). Patients operated on for local or distant recurrence had similar overall survival (110 vs 91 months;* $P = .81$*). In nonoperated patients, types of medical managements did not impact survival. Surgery for recurrence (*$P = .037$*) and a disease-free interval between initial resection and recurrence >12 months (*$P = .059$*) were both prognostic factors for improved survival, whereas age, stage, and tumor size (*$P \geq .2$ *each) were not. A Ki67 <25% tended to be associated with better overall survival (*$P = .051$*).*
Conclusion. *Both surgery for recurrence and disease-free interval between the initial resection of an adrenocortical carcinoma and recurrence >12 months are associated with better overall survival. (Surgery 2017;161:249-56.)*

From the Clinique de Chirurgie Digestive et Endocrinienne (CCDE),[a] Institut des Maladies de l'Appareil Digestif (IMAD), Centre Hospitalier Universitaire (CHU) Nantes-Hôtel Dieu, Nantes, France; the Chirurgie Générale et Endocrinienne,[b] CHU Lille, Lille, France; the Service de Chirurgie Endocrinienne et Générale,[c] CHU Lyon, Lyon, France; the Service de Chirurgie Digestive, Hépatobiliaire, Pancréatique, Endocrinienne et Cancérologique,[d] CHU Nancy, Nancy, France; and the Service de Chirurgie Digestive Endocrinienne et Bariatrique, et Transplantation hépatique,[e] CHU Tours, Tours, France

Adrenocortical carcinoma (ACC) is a rare neoplasm with a poor prognosis. Estimated annual incidence is 1–2 per million inhabitants.[1,2] Women are affected more often; indeed, a recent analysis of the literature showed a median female to male ratio of 1.6 (range 0.9–2.6).[3] Most tumors are diagnosed at an advanced stage with invasion of adjacent organs or metastatic disease. Patients may either be asymptomatic or have symptoms due to hormonal release by the neoplasm due to a mass effect.

Complete resection is the only curative treatment for ACC.[4] Patients with European Network for the Study of Adrenal Tumors (ENSAT) stages I–II (intra-adrenal tumors) with a complete resection have a 5-year survival of 40%.[5] Despite complete initial resection, recurrences occur in up to 74% of patients.[6] There are 2 types of recurrences: local recurrences and distant metastases. Local recurrences are more frequent and are often symptomatic because of the mass effect of the tumor and/or hormonal secretion. Patients with metastatic ACC have an overall 5-year survival of <20%.[7] Recurrences are a turning point in ACC, because they are often disseminated, and the treatment is mainly medical. Some selected patients, however, may benefit from reoperation in an attempt to resect completely the recurrence.[8]

The authors declare no conflicts of interest.

Accepted for publication August 16, 2016.

Reprint requests: Claire Blanchard, MD, Clinique de Chirurgie Digestive et Endocrinienne, CHU Tours, Tours, France. E-mail: claire.blanchard@chu-nantes.fr.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2016.08.058

For unresectable tumors, therapeutic options are limited. Mitotane is the first drug used for nonoperable patients and used often as adjuvant therapy in selected patients with controversial outcomes.[3,9] Different systemic chemotherapies have been tried, but the effects are often temporary. In a randomized study, patients treated with a combination of etoposide, doxorubicin, and cisplatin had an overall survival of 14.8 months.[10] Some studies showed a benefit of postoperative external radiotherapy on the site of the adrenalectomy in advanced tumors; however a retrospective cohort showed discordant results.[11]

Patients with ACC have not benefited from the global improvement in oncologic treatments compared to other tumors.[12] Currently, the management of ACC recurrence is not standardized and remains limited to a few chemotherapy options but with poor efficacy. If possible, complete resection of the recurrence seems to be the only option to increase survival.[13,14] Currently, a few studies have shown a benefit on survival in patients undergoing reoperation for recurrent ACC but with a median survival after recurrence of >60 months.[13,14]

The first objective of this study was to define the role of operative intervention in the management of local or distant ACC recurrences. The second objective was to find predictive factors for improved survival with operative resection. Therefore, we evaluated outcomes of patients with recurrent ACC after initial resection in 5 French University Hospitals.

METHODS

We performed a retrospective study of patients with recurrence after initial resection for an ACC between 1980 and 2014 in five French University Hospitals: Lille, Lyon, Nancy, Nantes, and Tours. Data on initial diagnosis, operative intervention, histopathologic findings, and treatment procedures were collected retrospectively. All patients were followed in regular interval with clinical, biologic, and radiologic examinations according to local recommendations.

Patients with histologically confirmed ACC who had a local or distant recurrent disease after initial complete resection (R0 or R1) were eligible for evaluation. We excluded patients with an R2 resection at the initial operation. Stage classification was based on the ENSAT classification.[15] Tumors located in the adrenal bed were considered as local recurrences, whereas other locations were considered as distant metastases. Nonoperative treatments were mitotane, cytotoxic chemotherapy combination of etoposide and platinum in first-line, radiotherapy, and others (cryoablation and radiofrequency ablation).

Table I. Site of recurrent adrenocortical carcinomas

Site	n *(%)*
Isolated recurrences	42 (71)
Adrenalectomy site	24 (41)
Liver	8 (14)
Lung	8 (14)
Brain	1
Bones	1
Multiple recurrences	17 (29)
Adrenalectomy site + metastases	10 (17)
Adrenalectomy site + liver	1
Adrenalectomy site + lung	3 (5)
Adrenalectomy site + liver + lung	2
Adrenalectomy site + liver + bones	1
Adrenalectomy site + liver + lung + bones	3 (5)
Multiple metastases	7 (12)
Liver + lung	5 (9)
Liver + lung + bones	2

Disease-free interval (DFI) was calculated as the time between the initial resection and the date of the diagnosis of recurrent disease. Overall survival (OS) after recurrence was defined as the time between the date of the recurrence and the death or last follow-up. Survival curves were made using the Kaplan-Meier method, and the log-rank test was used to compare continuous, nonparametric variables between subgroups. Univariate and multivariate analyses were conducted to find relevant prognostic variables using a Cox proportional hazards model. The association between each variable and the OS was expressed as a 95% confidence interval (CI) for the hazard ratio (HR). Statistical calculations were performed with SPSS statistics software (version 23.0; IBM Corp, Armonk, NY).

RESULTS

Sixty-one patients, followed for recurrence after initial operative resection, were identified in 5 French University Hospitals. Two patients were excluded because of an initial R2 resection. Of the 59 patients, 46 (78%) had an R0 resection, and 13 (22%) had an R1 resection. Patients were classified by ENSAT stage as follow: 5 (9%) patients were stage I, 23 (39%) were stage II, 22 (37%) were stage III, 3 (5%) were stage IV, 6 (10%) had an unknown stage.