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Percutaneous Bilateral Adrenal Radiofrequency Ablation in Severe Adrenocorticotropic Hormone-dependent Cushing Syndrome

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ABSTRACT

Objectives: The objectives of the study were to evaluate adrenal radiofrequency ablation (RFA) as a method of treatment in patients with severe adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome, among whom bilateral adrenalectomy is not a suitable option.

Material and Methods: Five patients with ACTH-dependent Cushing syndrome underwent RFA of both adrenal glands. Four of them presented with Cushing disease unsuccessfully treated with pituitary surgery and medical therapy, while one patient had ACTH-dependent Cushing syndrome due to pancreatic endocrine tumor with liver metastases. All patients were disqualified from adrenalectomy due to morbid obesity or lack of consent.

Results: A technical success was obtained in all cases, with only one re-intervention necessitated by a cooling effect of the inferior vena cava. Despite pre-procedural adrenergic blockade, severe hypertension was noted during the procedure in three cases, this being treated immediately using direct-acting vasodilators. No complications occurred otherwise. In all cases, significant improvement of clinical symptoms was observed, as well as marked decreases in levels of serum cortisol, free urine cortisol, and dehydroepiandrosterone sulfate.

Conclusion: Bilateral RFA under CT-guidance is technically feasible and clinical improvement can be achieved using the method. In patients disqualified from adrenal surgery, RFA might be considered as an alternative method of ACTH-dependent Cushing syndrome treatment.

Keywords: Cushing syndrome, Cushing disease, Adrenal ablation, Adrenalectomy, Radiofrequency ablation

INTRODUCTION

Cushing syndrome is a disorder characterized by prolonged glucocorticoid excess. It can be caused by exogenous steroid use, adrenocorticotropic hormone (ATCH) producing pituitary adenoma (Cushing disease), ectopic production of ACTH, or adrenal tumors.

The main signs and symptoms of Cushing syndrome include obesity, edema, cardiovascular events, diabetes, infections, muscle weakness, and depression. Some of these symptoms, especially cardiovascular events and infections, can prove life-threatening.

Typical treatment of ACTH-dependent Cushing syndrome involves surgical removal of a pituitary adenoma or ectopic ACTH-secreting tumor. While medical therapy is a typical treatment for patients with persistent hypercortisolism following pituitary surgery, it fails frequently.[1]

Should these therapies fail, bilateral adrenalectomy can be used as the next treatment; though some patients are not good candidates for this procedure on account of their marked obesity. Moreover, while peptide receptor radionuclide radiotherapy (PRRT) can also be effective in these patients, this is associated with significant risk of hypopituitarism.[2]

Case reports have been published on microwave adrenal ablation in ectopic Cushing syndrome,[3,4] but no radiofrequency ablation (RFA) cases have so far been reported. Furthermore, lacking is published data on adrenal ablation in patients with Cushing disease. Under those circumstances, the work detailed here has sought to evaluate the efficacy and safety of adrenal RFA in five patients with Cushing syndrome (including four with Cushing disease).

MATERIAL AND METHODS

The study was approved by the Warsaw Medical University Bioethical Committee. Five patients (three women and two men; mean age 44; range 25–70) who had undergone CT-guided RFA of both adrenal glands were included in this study and four of them presented with Cushing disease. All had been treated by means of pituitary surgery (one of them 3 times), while two had also received peptide receptor radionuclide therapy. The fifth patient suffered from ACTH-dependent Cushing syndrome due to unresectable pancreatic neuroendocrine tumor (NET) with liver metastases. He was treated surgically (with primary tumor resection), followed by PRRT. The inclusion criteria were morbid obesity or lack of consent that disqualified the patient from adrenalectomy.

Lack of follow-up was the exclusion criterion, and two patients with ectopic Cushing syndrome treated with RFA were excluded from the study for that reason.

The most common symptoms the patients presented with were obesity, diabetes, hypertension, osteopenia, and depression [Table 1].

The procedures were conducted in an interventional CT suite, under general anesthesia with intra-arterial blood-pressure monitoring. Doxazosin mesylate was administered for 2 weeks before the procedure, to limit hypertensive crisis during the ablation. In all cases, the posterior approach was chosen in ipsilateral decubitus to prone position. The procedures were performed under CT guidance (Aquilion One, Toshiba/Canon). During ablations StarBurst Talon Semi-Flex electrodes were used with 9 min ablation time and with end point temperature of 105°C. The "heat sink" effect generated by IVC proved a significant limiter of right-adrenal ablation, and the procedure had to be repeated in the first patient. In the following four patients, the "heat sink" effect was reduced by displacing IVC with hydrodissection (5% Glucose, 100–300 ml). In two patients, hydrodissection was used to displace splenic vessels and the pancreas [Figure 1].

Ablation required multiple applications of heat to achieve overlapping ablation zones covering long, hyperplastic adrenal glands. The mean number of applications per procedure was 4.6.[3-6]

Figure 1: A 43-year-old woman with Cushing syndrome presented with diabetes and hypertension. Non-enhanced CT showing an electrode (white arrow) targeting the left adrenal and Chiba needle (black arrow) for hydrodissection (arrowhead), to displace the splenic artery and pancreas (asterisk).

Table 1: Clinical data of the patients before ablation.

Patient	Sex/age	Cause of hypercortisolemia	Effects of hypercortisolemia	Previous treatment
1	M/25	Cushing disease	Obesity, hypertension, osteopenia	Pituitary surgery (×3)
2	F/48	Cushing disease	Obesity, diabetes, hypertension, osteopenia	Pituitary surgery Cyber Knife
3	F/43	Cushing disease	Overweight, diabetes, hypertension, osteopenia	Pituitary surgery (×2) Gamma Knife
4	F/35	Cushing disease	Overweight, prediabetes, osteopenia, depression	Pituitary surgery
5	M/70	Ectopic ACTH secretion, NET of pancreas, liver metastases	Diabetes, hypertension, hypokalemia	Liver surgery and PRRT

PRRT: Peptide receptor radionuclide therapy

Serum cortisol, free urine cortisol, dehydroepiandrosterone sulfate (DHEA-S), and ACTH levels were all measured ahead of the procedure and at follow-up times ranging from 18 to 24 months.

In all patients with osteopenia, bone mineral density was measured using densitometry.

Post-procedural contrast-enhanced CT was carried out immediately after the procedure, to exclude potential complications and allow for the assessment of the volume of the adrenal ablation zone [Figures 2 and 3].

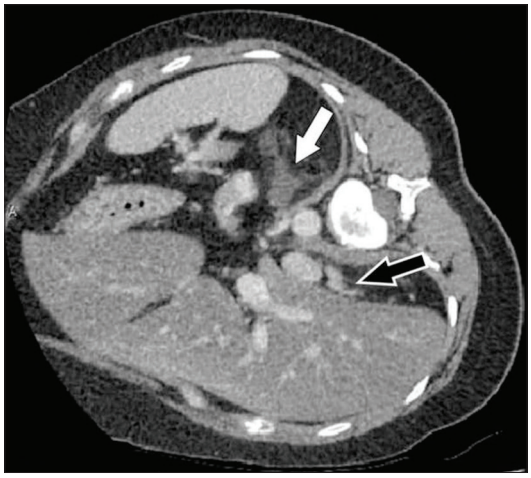

Figure 2: A 43-year-old woman with Cushing syndrome presented with diabetes and hypertension underwent ablation of the left adrenal. Contrast-enhanced CT showing prominent enhancement of right adrenal (black arrow) before ablation, and hypoattenuating left adrenal (white arrow) corresponding with complete ablation.

Figure 3: A 43-year-old woman with Cushing syndrome presented with diabetes and hypertension underwent ablation of both adrenals. Contrast-enhanced CT (arterial phase) showing complete ablation of both adrenals (white and black arrows), in a patient with hyper-vascular hepatic metastases of a neuroendocrine tumor (black asterisks).

Due to the high probability of hypertensive crisis arising, the patients were screened pre-procedurally for intracranial aneurysms, using MR angiography without contrast administration (time of flight sequence).

RESULTS

The complete ablation zone was defined as a lack of contrast enhancement (coagulated tissue) on contrast-enhanced CT in the venous phase. Due to prominent enhancement of hyperplastic adrenal glands before the procedure, assessment of the ablation zone proved relatively easy.

A technical success was taken to have been achieved where ablation of at least 80% of adrenal gland volume had taken place.

On this basis a technical success rate of 100% was obtained, with only one re-intervention necessary, due to a cooling effect of the internal vena cava.

Despite pre-procedural preparation through adrenergic blockade, severe hypertension was noted in three patients. Radiofrequency current was terminated and direct-acting vasodilators (nitroprusside) administered immediately. Maximal systolic pressure ranged from 180 to 300 mmHg. RFA was continued with following blood pressure normalization. None of the patients presented with Nelson syndrome and no other complications occurred. No patient required antibiotic therapy.

Clinical improvement was observed in all cases [Tables 2 and 3]. Effects in all patients included reduction in body weight, blood pressure normalization, and improved carbohydrate metabolism. In two out of four patients, densitometry confirmed improvements as regards bone mineral density.

Follow-up also revealed significant improvement in terms of laboratory results. While before the procedure the mean morning serum cortisol level was 39.8 (28.8–61.6) μg/dl, by follow-up this had declined to 8.66 (4.7–16) μg/dl. Likewise, the mean free urine cortisol level pre-procedure was 402 (188.9–820.2); as opposed to 38.2 (20.5–57.2) at follow-up. Mean morning DHEA-S before the procedure was in turn 285.5 (195–450), as compared with 22.8 (10–41) at follow-up. Morning serum ACTH went up in four of the patients with Cushing disease, while decreasing slightly (from 350 to 310 pg/ml) in the patient with NET.

At follow-up, two patients were found to require hydrocortisol supplementation.

DISCUSSION

Cushing syndrome is a debilitating, potentially life-threatening disease. There is, furthermore, a small group of patients in whom all treatment methods (pituitary surgery,

Table 2: Clinical and laboratory effects of ablation.

Patient	Serum cortisol 8 AM (5–22 µg/dl)		Free urine cortisol (1–111 µg/24 h)		DHEA-S (8 AM) F (58–227 µg/dl) M (41–405 µg/dl)		ACTH (8 AM) (5–46 pg/ml)		Clinical effects
	Before	After	Before	After	Before	After	Before	After	
1	39.4	5.1 (sup)	310.5	20.5	450	36	56	79	Body weight reduction, blood pressure normalization, bone mineral density improvement
2	36.3	9.7	285.2	57.2	195	41	59	120	Body weight reduction, blood pressure normalization, improvement of carbohydrate metabolism
3	28.8	7.5	188.9	44.8	228	15	54	75	Body weight reduction, blood pressure normalization, bone mineral density improvement, improvement of carbohydrate metabolism
4	31.9	4.7 (sup)	405.3	25.0	243	10	94	341	Body weight reduction, no depression, normal carbohydrate metabolism, hydrocortisol supplementation
5	62.6	16	820.2	43.3	310	12	350	310	No carbohydrate metabolism disorders, normal blood pressure, normal potassium levels

sup: Hydrocortisol supplementation needed at follow up. after: 18–24 months after ablation. Normal values in parentheses

Table 3: Clinical effects of ablation.

Patient	Body weight (kg)		Blood pressure (mmHg)		Glucose levels (mg/dl)	
	Before	After	Before	After	Before	After
1	95	82	150/100	125/85	105	92
2	93	85	160/110	130/80	120	89
3	88	76	150/110	130/80	180	98
4	78	69	130/88	125/80	110	90
5	79	77	170/110	120/80	159	91

adrenalectomy, radiotherapy, or medical therapy) have either failed or have not proved feasible. In that light, this report has sought to document the efficacy of bilateral adrenal ablation as an alternative treatment in such patients. Specifically, four patients with Cushing disease and one with ectopic Cushing syndrome presented, in the light of a failure of the typical modes of treatment referred to. Notably, adrenalectomy in these patients was ruled out by their morbid obesity or lacks of consent, with the result that bilateral adrenal RFA was performed instead.

In all of the patients reported on here, adrenal ablation had the effect of reducing levels of serum cortisol, free urine cortisol, and DHEA-S significantly. Furthermore, the decreases in question were found to be present 18 or even 24 months after ablation. ACTH levels increased in all of the patients other than the ectopic Cushing syndrome patient. There was also considerable improvement regarding such clinical symptoms as body weight, diabetes, hypertension, and mineral bone density [Tables 2 and 3].

RFA of adrenal glands in tumor treatment has been reported on widely,[5-10] and multiple publications describe ablation of functioning adrenal tumors.[11-15] In turn, the few published reports on microwave adrenal ablation in ectopic Cushing syndrome[3,4,16] note a significant decrease in serum cortisol levels, although with follow-up periods only between a week and 5 months in length. Sarma *et al*.[4] reported how adrenal ablation in two patients with ectopic Cushing syndrome resulted in normalization of serum cortisol. However, the follow-up period was again a relatively short one (at 2–3 months). A second report[3] presented a patient

with ectopic Cushing syndrome treated by way of right adrenal microwave ablation. Before this, the patient had had pancreatic tumor resection, as well as a splenectomy, left adrenalectomy, and left nephrectomy. Following ablation, his serum-cortisol level decreased from 1976 to 74 nmol/L (71.6–2.6 μg/dl).

The results of our study have proved to be consistent with such past research, sustaining a theory that, where other methods have failed, adrenal ablation can be an effective method of treating Cushing syndrome. The fact that it can also be effective in patients with Cushing disease is something that has not been published on previously.

Incidences of hypertensive crisis are a well-known complication in patients undergoing percutaneous adrenal ablation procedures.[17,18] This complication was also present in our group of patients. The most severe hypertension was noted in our first patient, in whom the procedure commenced with adrenal-limb ablation. Our view is that it is worth first ablating the adrenal body, with the probable result of thrombosis of adrenal veins and prevention of extensive catecholamine release in the course of the procedure. Even though pre-procedural adrenergic blockade does not eliminate the risk hypertensive crisis, it can be effectively managed with nitroprusside sodium.

This is the first report on adrenal ablation as a method of treating Cushing disease. It furthermore details by far the largest group of patients with Cushing syndrome to be treated in this manner, and also extends to the longest-ever follow-up. In addition, this is the first report on RFA in patients with Cushing syndrome (as opposed to the microwave ablation detailed in the previous reports).

The small number of patients is nevertheless the main limitation of this study.

CONCLUSION

Radiofrequency ablation is shown to be effective in patients with severe, drug-resistant, ACTH-dependent Cushing syndrome, among whom adrenal surgery is precluded. Further studies on larger numbers of patients will nevertheless be necessary if the role of ablation in such cases is to be determined fully.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Resmini E. Persistent comorbidities in cushing's syndrome after endocrine cure. Adv Endocrinol 2014;2014:231432.
2. Pivonello R, de Leo M, Cozzolino A, Colao A. The treatment of cushing's disease. Endocr Rev 2015;36:385-486.
3. Zener R, Zaleski A, van Uum SH, Gray DK, Mujoomdar A. Successful percutaneous CT-guided microwave ablation of adrenal gland for ectopic cushing syndrome. Clin Imaging 2017;42:93-5.
4. Sarma A, Shyn PB, Vivian MA, Ng JM, Tuncali K, Lorch JH, *et al*. Single-session CT-guided percutaneous microwave ablation of bilateral adrenal gland hyperplasia due to ectopic ACTH syndrome. Cardiovasc Intervent Radiol 2015;38:1335-8.
5. Wolf FJ, Dupuy DE, MacHan JT, Mayo-Smith WW. Adrenal neoplasms: Effectiveness and safety of CT-guided ablation of 23 tumors in 22 patients. Eur J Radiol 2012;81:1717-23.
6. Wood BJ, Abraham J, Hvizda J, Alexander HR, Fojo T. Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. NIH Public Access 2008;148:825-32.
7. Mayo-Smith WW, Dupuy DE. Adrenal neoplasms: CT-guided radiofrequency ablation-preliminary results. Radiology 2004;231:225-30.
8. Hasegawa T, Yamakado K, Nakatsuka A, Uraki J, Yamanaka T, Fujimori M, *et al*. Unresectable adrenal metastases: Clinical outcomes of radiofrequency ablation. Radiology 2015;277:142029.
9. Carrafiello G, Laganà D, Recaldini C, Giorgianni A, Ianniello A, Lumia D, *et al*. Imaging-guided percutaneous radiofrequency ablation of adrenal metastases: Preliminary results at a single institution with a single device. Cardiovasc Intervent Radiol 2008;31:762-7.
10. Gunjur A, Duong C, Ball D, Siva S. Surgical and ablative therapies for the management of adrenal "oligometastases"-a systematic review. Cancer Treat Rev 2014;40:838-46.
11. Arima K, Yamakado K, Suzuki R, Matsuura H, Nakatsuka A, Takeda K, *et al*. Image-Guided radiofrequency ablation for adrenocortical adenoma with cushing syndrome: Outcomes after mean follow-up of 33 months. Urology 2007;70:407-11.
12. Johnson SP, Bagrosky BM, Mitchell EL, McIntyre RC, Grant NG. CT-guided radiofrequency ablation of an aldosterone-secreting primary adrenal tumor in a surgically unfit patient. J Vasc Interv Radiol 2008;19:1115-7.
13. Liu SY, Ng EK, Lee PS, Wong SK, Chiu PW, Mui WL, *et al*. Radiofrequency ablation for benign aldosterone-producing adenoma. Ann Surg 2010;252:1058-64.
14. Mendiratta-Lala M, Brennan DD, Brook OR, Mowschenson PM, Sheiman RG, Goldberg SN. Efficacy of radiofrequency ablation in the treatment of small functional adrenal neoplasms. Radiology 2011;258:308-16.
15. Nishi N, Tanaka J, Minagawa A. Cushing syndrome treated by radiofrequency ablation of adrenal gland adenoma. Jpn J Radiol 2012;30:274-6.
16. Chan C, Roberts JM. Ectopic ACTH syndrome complicated

by multiple opportunistic infections treated with percutaneous ablation of the adrenal glands. BMJ Case Rep 2017;2017:bcr2017221580.
17. Chini EN, Brown MJ, Farrell MA, Charboneau JW. Hypertensive crisis in a patient undergoing percutaneous radiofrequency ablation of an adrenal mass under general anesthesia. Anesth Analg 2004;99:1867-9.
18. Atwell TD, Wass CT, Charboneau JW, Callstrom MR, Farrell MA, Sengupta S. Malignant hypertension during cryoablation of an adrenal gland tumor. J Vasc Interv Radiol 2006;17:573-5.

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