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# **Surgical and Oncological Results of Treatment of Metastases of Renal Cell Carcinoma to the Contralateral Adrenal Gland**

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## **1. Introduction**

Urooncological diseases account about 40% of all oncological pathologies in men and more than 10% in women. Renal cell carcinoma (RCC) accounts for about 4% of all adult malignancies and is the most lethal urological cancer. 60 920 new cases of RCC have been diagnosed in the US in 2011 and 13 120 died of cancer [1]. The patient death rate from RCC has decreased in the last 15 years due to the improvements in early diagnosis and surgical treatment of the disease [1]. However, it is estimated that 1/3 of the patients with localized cancer will develop distant metastasis after radical treatment [2]. Therefore, early identification of metastatic disease, timely and proper treatment is the main goal in the management of RCC.

The most common sites of metastases of RCC are: lymph nodes, lungs, liver, bones and brain [3]. It is known that the disease can metastasize to almost every organ. Adrenal metastasis of RCC is relatively rare. It can be: synchronous or metachronous; ipsilateral, contralateral or bilateral; solitary or part of a massive metastatic spread. Malignant involvement of the ipsilateral adrenal gland has been detected in up to 10% of the radical nephrectomy specimens [4-8]. Contralateral adrenal metastasis however, is uncommon. In the autopsy study of more than 400 patients who had undergone nephrectomy for RCC, the solitary contralateral adrenal metastasis has been detected in only 2.5% of cases [9].

The predisposing factors for the disease spread and the optimal treatment of this rare complication are not fully understood. It is well-known that some patients with isolated metastasis may benefit from surgical treatment. However, the optimal diagnosis and treatment of the contralateral adrenal metastasis from RCC is not yet well defined. The available infor-

mation on the outcomes of various treatment options of this complication is limited and mainly based on a sporadic case reports.

In this chapter we analyze all 65 cases of the contralateral adrenal metastases of RCC reported in the literature [10-32]. Our single center experience of treatment of four patients with this complication is also presented. The chapter describes the current view on the pathogenesis, diagnosis and management as well as the surgical, pathological and oncological results of treatment of this rare complication.

The natural course of the RCC is unpredictable. The disease can metastasize to any organ, any time even many years after the operation [33, 10]. Metastasis from the RCC has been discovered as late as 23 and 31 years after radical nephrectomy [33, 34]. The contralateral adrenal metastasis from RCC is extremely rare. Only 69 cases (including our series) can be found in the literature.

The exact reasons of late development of the adrenal metastasis are not completely clear. One of the possible explanations could be that some metastases, especially those of low grade, can grow very slowly. Besides, improper patient follow-up i.e. not using a routine imaging studies for a long time might explain the late detection of some metastasis.

Adrenal metastasis from renal tumors is more common to the ipsilateral adrenal gland. The pathological mechanisms for secondary involvement of the contralateral adrenal gland are unknown. It is thought that the disease spreads via hematogenous route as in case of other organ metastases. However, the autopsy studies illustrate that contralateral adrenal metastases occur far more often than should be expected on the basis of organ size [18]. Explanation of this fact can be a rich blood supply of the adrenal gland and its high blood volume-to-unit weight ratio [35]. It has been speculated that as far as the contralateral adrenal metastasis has occurred the adrenal gland will have a higher affinity to the RCC cells than other organ tissues [4]. In another words, if the tumor cell reaches the adrenal gland the later acts as a fertile soil and stimulates raise of these cells [18]. In consistent with this theory some studies are showing that the adrenal metastases from the contralateral primary RCC grew to a considerable size without metastasing to other organs. Utsumi T, et al. describe a huge (85X90mm) contralateral adrenal metastasis that had invaded the kidney, renal vein, and inferior vena cava but without any involvement of other organs [32].

The risk-factors for development of the adrenal metastasis have been analyzed by some of the studies. Importance of the several clinicopathological features of the primary RCC has been reported. These are: tumor size, left sided tumor, advanced T-stage, and upper-pole tumor location [4, 36].

Adrenal metastases are usually anatomically and functionally silent and patients rarely have symptoms or signs of adrenal insufficiency. Therefore, abdominal imaging is not routinely used for follow-up and the isolated contralateral adrenal metastasis from RCC is rarely diagnosed during a lifetime. This should contribute to the late disease diagnosis, treatment and the worse prognosis.

Due to rare occurrence, the optimal diagnostic approach to a solitary contralateral adrenal metastasis in the patients with a history of RCC is controversial. It can be different from the

adrenal incidentalomas. Imaging studies usually cannot verify with certainty the adrenal masses detected in the patients previously operated due to the RCC. It is always difficult to determine whether the mass is: primary adrenal tumor (carcinoma), benign tumor (i.e. an adrenal cortical adenoma) or metastasis. Preoperative diagnosis of synchronous adrenal metastases is relatively easy and is mainly based on radiological findings from abdominal CT and/or MRI. The finding of solitary adrenal mass without elevated serum adrenocortical hormones is strongly suggestive of a metastatic lesion. Metastatic adrenal tumors are usually well-vascularized as compared with the adrenal cortical adenoma or primary adrenal carcinoma. The later ones are more hypovascular [30].

CT is a highly specific in diagnosing adrenal metastases. In 82% of cases reported in the literature, contralateral adrenal metastases have been diagnosed by abdominal CT. Antonelli et al. reviewed clinical records of 1179 surgically treated RCC patients and found that 15 had suspicious findings in the contralateral adrenal glands on CT. Only one of the 15 surgically removed adrenals was found to be free of tumor. The authors reported positive and negative predictive value of CT as 73% and 96% in detecting the adrenal metastases. Remarkably, the positive predictive value of CT in diagnosing the contralateral adrenal metastases was higher [32]. It should be noted that accuracy of CT for distinguishing between benign and malignant contralateral adrenal nodules has improved recently using CT protocols to evaluate the wash-out of contrast media [37].

We've analyzed the records of six hundred twenty nine patients who underwent radical nephrectomy for RCC in our center between 1991 and 2005. The mean patient age was  $55.7 \pm 11.3$  years (range: 12-85 years). 422 (67.2%) were man and 207 (32.8%) were women. The mean follow-up is  $60.5 \pm 1.7$  months (range: 1-187 months). The pathological stage distribution of the tumor was the following: T1 -132 (21%); T2 - 229 (36.4%); T3 - 256 (40.7%); T4 - 12 (1.9%) patients. 123 (19.4%) cancers were G1, 277 (44.1%) - G2 and 229 (36.5 %) - G3. Morphological evaluation revealed clear cell RCC in 475 patients (75.6%). 38 (6.1%) patients had lymph node and 28 (4.5%) patient had distant metastases at the time of surgery. 170 (27%) tumors were discovered incidentally, 332 (52.8%) were locally symptomatic and 127 patients (20.2%) had a systemic disease symptoms.

Four cases (0.6%) of isolated contralateral adrenal metastasis have been diagnosed with the mean follow-up of 83.3 months (range: 23-196 months). In accordance with the existing data from the literature all four metastases have been detected by CT. The metastases have been diagnosed synchronously in one (0.1%) and metachronously in three (0.5%) cases. Mean age of the patients was 56 years (range: 47-68 years). All the patients underwent adrenalectomy through flank incision above the 11th rib. No patient received any form of adjuvant systemic therapy.

All four patients had undergone contralateral radical nephrectomy due to the conventional RCC. All removed kidneys and adrenal were sent to the department of pathology of the same institution (National Centre of Urology). The same team of personnel according to the single protocol has technically processed all the tissue specimens. The surgical margins of the primary nephrectomy specimens were recorded as positive or negative based on the gross and microscopic examination of the specimen. The adrenal gland was

examined macroscopically, sliced in 2- to 3-mm cross sections and processed for further microscopical evaluation.

Morphological parameters assessed for both the primary and metastatic tumors included: stage, histological subtype, nuclear grade and presence of tumor necrosis. The stained slides from all tumor and metastases specimens were reviewed by urological pathologist, as described previously [38]. Shortly, the resected kidneys and adrenals were evaluated macroscopically. The maximal tumor size was measured and 1.5 x 2cm tissue samples were taken for further assessment. Specimens were fixed, stained and evaluated by the same pathologist according to conventional technique. The tumors were staged according to the AJCC classification system and graded according to Fuhrman's grading system.

The mean (range) diameter of the primary renal tumor was 76±27.9 mm (12-200 mm) and the mean diameter of the adrenal metastases was 6.4 cm (range: 3–9 cm). The clinical and pathological features of the primary tumors for the 4 patients with contralateral adrenal metastasis are summarized in Table 1. The pathological stage of the adrenal metastasis was pT<sub>2</sub>N0 and pT3aN0 in two patients each. Grade 2 tumor was detected in one and grade 3 in three cases.

N	Age	Sex	Time from surgery to metastasis (months)	Side of metastasis	Stage	Grade	Follow-up	Patient status
1	47	M	18	Right	T3a	3	31	Dead
2	58	M	64	Right	T2	3	78	Dead
3	57	F	24	Right	T3a	3	165	Alive
4	73	F	156	Left	T2	2	180	Alive

**Table 1.** The characteristics of four patients with contralateral adrenal metastasis.

One patient had synchronous contralateral adrenal metastasis. The mean time from the primary nephrectomy to contralateral adrenal metastasis for the remaining three patients was 65.5 months (range: 18–156 months).

Adrenal biopsy can be advocated in some cases. The biopsies of RCC has been lately abandoned due to the following reasons: a) the predictive value of the imaging findings usually is so high that a negative biopsy result would not alter the management strategy; b) 10-20% of biopsies are reported to be non-conclusive; c) high risk of complications associated with the biopsy [39].

Early diagnosis and treatment of metachronous adrenal metastases is more challenging as it can occur many years after the operation. This depends on the mode of follow-up, diagnostic techniques used and early referral of the patient to the specialized clinic. In our study the adrenal metastases have been detected at the mean 65.5 months after radical nephrectomy. A wide variability of latency in diagnosis of the metastases has been reported by others as

well. These data indicate on the necessity of prolonged surveillance, especially in the high risk patients i.e. with advanced disease stage [31, 40].

The survival of patients with RCC mainly depends on the disease spread. Widely metastatic RCC usually have a poor prognosis with a mean survival of 11 months. On the contrary, in the patients with solitary or limited metastases resection of the metastases can be associated with prolonged survival (30% survival at 5 years) [39]. Reports of successful outcomes and subsequent long-term survival after treatment of solitary metastases of the RCC justify an aggressive surgical approach [10]. In light of the existing data, complete resection of the primary renal and metastatic adrenal tumors should be the main clinical strategy in these patients. Thus, in case of adrenal metastases whether it is synchronous or metachronous, ipsilateral or contralateral, complete removal of adrenal gland is a treatment of choice providing the best results [30].

Adrenalectomy can be performed either laparoscopically, retroperitoneoscopically or by robotic surgery, decreasing the surgery-associated morbidity and hospital stay [20]. We've performed open adrenalectomy in all our patients. The operation was uneventful in all of them. The mean operation time was 136 minutes (range: 110-160 minutes). All metastases were clear cell RCC tumors. The mean blood loss was 175 ml (range: 50-350 ml). The mean hospital stay was 6 days (range: 4-10 days). No patient had positive surgical margins from the adrenalectomy. There are no data on the efficacy of any form of systemic therapy in the treatment of solitary adrenal metastasis.

The available data on the outcome of the surgical treatment of the contralateral adrenal metastases form RCC are limited and biased. Table 2 summarizes the data of 65 patients with contralateral adrenal metastasis reported in the literature [10-32]. Characteristics of the patients (age, sex), interval between the primary surgery and diagnosis of the adrenal metastasis, and clinical outcome of the patients are described.

These are mainly the case reports of 1-2 cases. The biggest series of 11 cases has been reported by Lau WK, et al. from the Mayo clinic in 2003. In this report 82% of the metastases were metachronous, diagnosed at the mean 4.2 years (0-9.2 years) after the nephrectomy. Other relatively big series of 7 and 8 patients have been reported by Plawner J. and Antonelli A. in 1991 and 2006, respectively.

57% of all metastases reported up to now have been detected synchronously and 43% were discovered metachronously at the mean 2.8 years (0-23 years) after the radical nephrectomy. 58% of the patients were male and 42% were female. The majority (62%) of metastases developed on the left side. Abdominal CT was the preferred method of diagnosis in the vast majority of cases (82%) followed-up by arteriography (6%) and IVP (2%).

At the mean follow-up of 6.8 years (0.3-14.3 years) 29 patients (55%) were alive without evidence of disease and 18 patients (34%) were dead of disease. Surgical removal of the adrenal gland was the only treatment used in these patients. None of the patients received any form of adjuvant systemic therapy.

Reference	N of cases	Chronicity	Age (years)	Sex	Time from nephrectomy (years)	Side	Method of diagnosis	Follow-up (years)	Patient status
10	1	s	NS	NS	0	NS	NS	0.6	NED
12	2	s, s	58, 80	M, M	0, 0	L, R	NS, IVP	1.5, 1.8	DOD, NED
13	2	s, s	54, 57	M, F	0, 0	R, L	Art, Art	3, NS	NED, NS
14	2	s, s	54, 55	F, F	0, 0	L, R	CT, Art	1.7, 2	NED, NED
15	2	m, m	57, 46	M, F	0.5, 1	R, L	CT, CT	2.2, 1.8	NED, NED
16	2	s, m	67, 68	M, M	0, 15	R, L	CT, CT	0.4, 1	NED, NED
17	2	m, m	46, 69	M, M	2, 4	L, R	CT, CT	2.5, 4	DOD, NED
18	1	s	60	F	0	R	CT	0.8	NED
19	7	s, s, m, s, m, m, s	63, 55, 55, 48, 70, 57, 71	All M	0, 0, 3.6, 0, 7, 6.8, 0	L, R/L, R, R, L, L, L	NS	14.3, 4.8, 0.8, 0.6, 5, 2.7, 6.7	DOD, DOD, DOD, DOD, NED, NED, DOD
20	2	m, m	49, 82	M, M	5, 5	R, R	CT, CT	0.3, 1.3	NED, NED
21	5	All m	47, 59, 69, 57, 72	F, F, F, M, M	1.5, 1.5, 5.3, 2, 17.8	NS	All CT	2, 0.7, 3.7, 5.3, 3.5	DOD, DOD, NED, NED, NED
22	2	s, m	63, 64	M, F	0, 4	L, L	CT, CT	1, 5	NED, NED
23	1	s	52	M	0	R	CT	7	NED
24	1	m	52	M	0.8	R	CT	7.3	NED
25	1	m	NS	M	23	NS	NS	1	NED
26	1	s	NS	NS	0	NS	CT	NS	NS
27	4	s, s, s, m	All NS	All NS	0, 0, 0, NS	NS	NS	9, 5.4, NS, NS	DOD, AWD, NS, NS
28	1	m	63	M	22	L	CT	5.6	NED
29	1	m	50	F	7.5	R	CT	2.5	NED
30	11	m, m, m, m, s, m, m, s, m, m	69, 43, 49, 64, 54, 54, 67, 53, 68, 70, 79	M, M, M, M, M, M, F, M, M, F, M	6.1, 7.3, 9.2, 9.1, 0, 1, 6.7, 5.8, 0, 0.8, 1	L, L, R, R, R, L, L, L, R, R, L	All CT	1.7, 0.9, 1.9, 0.5, 6.6, 9.9, 3.4, 3.7, 9.2, 4.4, 1.2	DU, DOD, DOD, NED, DOD, DOD, DOC, DOD, NED, DOD, DOD
31	8	s-6, m-2	NS	NS	NS	NS	All CT	NS	NS
32	1	s	64	M	0	R	CT	0.5	NED

Art, arteriography; AWD, alive with disease; DOC, dead of other causes; DOD, dead of disease; DU, dead of unknown cause; F, female; IVP, intravenous pyelogram; L, left; m, metachronous; M, male; NED, no evidence of disease; NS, not stated; R, right; s, synchronous.

**Table 2.** Characteristics of the patients treated for the contralateral adrenal metastasis published in the literature.

From our series of four patients, two are alive 141 and 24 months after adrenalectomy without signs of disease recurrence. Two patients died from multiple metastases 13 and 14 months after adrenalectomy, including the patient with synchronous contralateral adrenal metastasis.

For the entire group of patients, the 5 and 10 years disease-specific survival rates were 61.5 % and 25.6%, respectively. The 5-year overall survival for metastatic (N+ and M+) disease was significantly worse as compared with the non-metastatic disease (6.25% and 72.8%, respectively) ( $p=0.0001$ ).

There was no statistically significant difference when the survival of patients with solitary adrenal lesions was compared to that of the patients with organ-confined primary RCC. Furthermore, no differences in survival have been detected between the patients with synchronous or metachronous adrenal metastasis ( $p=0.346$  for overall survival;  $p=0.256$  for disease-specific survival). With multivariate statistical analysis the presence of solitary adrenal metastases was not predictive of the clinical prognosis of the patients following adrenalectomy.

The biggest number of the patients with contralateral adrenal metastasis from RCC reported in the literature is 11 [30]. This number is small for making the strong conclusions. Majority of the available studies indicate that the surgical treatment of the complication is worthwhile in selected patients [22, 23]. One study demonstrated that patients in whom RCC metastases (both synchronous and metachronous) were clinically confined to the adrenal gland had statistically better survival rates than those with diffuse metastasis [31]. In about one-third of the RCC patients with isolated adrenal metastasis, surgical resection of the metastasis led to an apparently curative outcome [32]. The longest disease-free survival after removing a contralateral adrenal metastases from RCC is 12.1 years [41], and the longest overall survival is 14.3 years [20]. In accordance with the literature, we didn't find statistically significant survival difference between the patients with localized RCC and solitary contralateral adrenal metastasis. Furthermore, with multivariate statistical analysis the presence of solitary adrenal metastases was not predictive of the clinical prognosis of the patients following adrenalectomy.

The exact reason why do these patients survive longer remains unclear. The several possible explanations exist. It has been speculated that this is a localized disease and that complete removal of the tumor improves prognosis. Another explanation is that the patient's immune system can probably inhibit microscopic disease after tumor debulking. Finally, it has been postulated that this may be a naturally selected group of patients with slow-growing cancer which is not very aggressive and does not metastasize readily [19].

## 2. Conclusion

In conclusion, the solitary contralateral adrenal metastasis from RCC is an extremely rare clinical complication that can occur very late after the radical nephrectomy. The increased

use of radiological diagnostic tests like: ultrasound, CT and/or MRI has led to more efficient detection of these lesions. Aggressive surgery remains the treatment of choice in these cases improving prognosis in some of the patients. There is no doubt that the existing data are limited and we need more studies to define the optimal management strategy in the patients with contralateral adrenal metastasis from RCC.

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