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Review

Metastatic Carcinomas of the Adrenal Glands: From Diagnosis to Treatment

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Abstract. *Background/Aim: Adrenal glands are one of the most common sites of cancer metastasis. The treatment options include either surgery or chemotherapy and/or radiotherapy while certain diagnosis is made via percutaneous biopsy or fine needle aspiration (FNA), guided by CT scan. This review aimed to present the current practice regarding the diagnosis and treatment of adrenal cancer metastasis. Materials and Methods: A PRISMA-compliant systematic search of the PubMed, Cochrane, EMBASE, AMED, CINAHL, WoS, BIOSIS, LILACS, ASSIA, SCEH, SCIRUS databases, and JIT medical feed sources was performed through November 5th, 2018. Results: A total of 87 original studies including 660 patients with adrenal metastasis were analyzed. Most preferred treatment was excision of the gland in 76.58% of the cases, while most of adrenal metastases were found at autopsy (43.88%) followed by computed tomography guided biopsy (33.09%). Conclusion: Adrenalectomy following metastatic disease to the adrenals should be performed when the lesion is isolated in the gland and the site of primary cancer has or can be resected.*

The adrenal glands are commonly infiltrated with metastases in patients with a variety of neoplastic diseases; taking into account their weight, adrenal glands are considered the most common site of metastasis (1). Large autopsy studies have shown that the percentage of cancers which give metastases to the adrenal glands is about 42% for lung (2), 58% for breast (2), 16% for gastric (3), 10.3% for esophageal (3), 14% for colorectal cancer (4) and 50% for malignant melanomas (2). Metastases to the adrenals have also been reported for renal cell carcinoma (5-15), hepatocellular carcinoma (16, 17), carcinoma of the bladder (18), lymphoma (19-21), seminoma of the testis (19) and osteogenic sarcoma (22). In patients who have an adrenal mass and an extra-adrenal malignancy, the frequency of this mass being metastatic ranges from 32% to 73% (23).

Metastatic carcinomas are in most cases asymptomatic because metastatic lesions fail to destroy enough tissue to produce clinical signs or symptoms of insufficiency (24). In only a few reported cases they caused Addison's disease, (2, 9, 18-21, 25) or hypoaldosteronism (16). They are discovered incidentally during an imaging procedure (incidentalomas), in patients with proven malignant disease (26), and their prevalence ranges from 0.3% to 5% in patients having abdominal CT scans (27).

Materials and methods. An exhaustive literature search between 1976 and November 5th of 2018 was performed using PubMed (Medline), Cochrane Library/Cochrane Register of Controlled Trials, EMBASE, AMED (Allied and Complimentary Medicine Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), ISI Web of Science (WoS), BIOSIS, LILACS (Latin American and Caribbean Health Sciences Literature), ASSIA (Applied Social Sciences Index and Abstracts), SCEH (NHS Evidence Specialist Collection for Ethnicity and Health) and SCIRUS databases. The authors also searched just-in-time (JIT) medical feed sources as returned from Terkko (provided by the National Library of Health Sciences - Terkko at the

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University of Helsinki). The following MESH terms were used in combination with Boolean operators (AND, OR, NOT): "adrenal", "metastasis", "metastatic", "cancer", "carcinoma". Two independent authors (ES, AI) screened all articles retrieved by the initial search as well as the reference lists of the relevant studies. A total of 87 original studies including 660 patients with adrenal metastasis were included.

Diagnosis: Imaging techniques. The most widely preferred and accepted imaging technique for the detection of metastatic adrenal carcinomas is computed tomography (CT). Allard and colleagues have calculated sensitivity and specificity of CT for the detection of metastatic adrenal lesions; a low sensitivity (20.1-41.1%) and high specificity (99.4%) were documented (28).

Antonelli *et al*. have analyzed 1,179 patients treated for renal cancer; of the 914 ipsilateral adrenal glands removed during renal surgery, 854 (93.5%) were normal on pathological examination, 28 (3%) had a benign pathology, six (0.8%) were directly infiltrated by the tumour and 26 (2.7%) were metastatic. CT had sensitivity, specificity and positive/ negative predictive values of 47%, 99%, 73% and 96%, respectively (29).

Porte *et al*. studied the sensitivity and specificity of CT, MRI and CT plus MRI by examining 443 patients with operable non-small cell lung cancer (NSCLC), 32 of whom had an adrenal mass. The combination of CT and MRI had 80% specificity and 100% sensitivity. The imaging features of adrenal metastases were non-specific and size alone was not sufficient for discriminating between metastatic lesions and non-functioning adenomas (30).

In a previous study of ours, the size of an adrenaloma as reported on a CT scan was usually less than the size reported on the histology report. In an analysis of 76 operated patients, we found that the mean estimated diameter of the adrenal tumor was 4.64 cm on the CT scan and 5.96 cm. in the pathology report (27). It seems that the shape of the adrenal mass found on CT, as well as the homogeneity or heterogeneity of the mass, are poor indicators of metastatic disease (31, 32). However, some investigators suggest that the size is the most helpful CT criterion in distinguishing between metastasis and benign masses. Thus, isolated adrenal masses greater than 3 cm in diameter in patients with known primary cancer, should be viewed with suspicion (31).

Burt *et al*. have studied the ability of Magnetic Resonance Imaging (MRI) to predict whether an adrenal mass in patients with operable NSCLC is benign or malignant. Twenty-seven patients with a unilateral adrenal mass were entered in the study and the results of MRI diagnosis were compared with those of CT-guided percutaneous needle aspiration. With sensitivity of 100%, specificity of 24%, false-positive rate of 67% and false-negative rate of 0%, the researchers concluded that even the best currently available MRI scanning techniques cannot replace biopsy in the evaluation of adrenal masses in patients with lung cancer (33). Goerg and colleagues have used ultrasound for the detection of adrenal masses in patients with bronchogenic carcinoma. An abdominal ultrasound was obtained from 410 patients with lung cancer as part of initial staging and in 44 of them (11%) an adrenal mass was discovered. Furthermore, ultrasound guided fine-needle biopsy of the adrenal tumors was performed together with sonographic follow-up examinations and 42 adrenal masses (95%) proved to represent metastases confirmed by progression or regression during sonographic follow-up examinations. The diagnosis of metastatic disease can be given by the change in the size of the adrenal masses under sonographic follow-up examination. It has been suggested that ultrasound guided fine-needle biopsy should only be performed in cases in which prompt diagnosis affects management decision (34). The sonographic characteristics of bilateral adrenal metastases were the subject of the study of Zornoza and Bernardino, who reviewed more than 50 patients with adrenal masses (35). Among them, ten patients were found to have bilateral metastases to the suprarenal glands, which in the transverse plane appeared like the "head light" of a car. This characteristic prompted the investigators to describe the "head light" sign as an accurate sonographic method for diagnosing bilateral adrenal metastases (35).

In addition, Loccoco and colleagues found that a PET-CT scan in the preoperative diagnostic work-up was an independent positive prognostic factor, suggesting the relevance of a proper staging process in oligometastatic NSCLC patients (36).

Quraishi and colleagues have studied 25 patients with lung cancer with iodocholesterol adrenal scans and portrayed iodocholesterol adrenal scanning as a promising technique for the detection of adrenal metastases, but more studies are needed to confirm these results (37). Leitha and associates have reported 100% sensitivity, 100% accuracy and 100% specificity when using ^{123}I-Tyr-3-Octreotide for the detection of adrenal metastases in patients with small-cell lung cancer (38).

In recent years, positron emission tomography (PET) has been employed in the diagnosis of metastatic adrenal carcinomas. Studies have confirmed the ability of PET to distinguish malignant from benign tissues (39-41).

Diagnosis: Fine needle aspiration (FNA). Obtaining adrenal tissue has become easier with the advent of CT and ultrasonography, which facilitate accurate needle placement (15). Luciani and colleagues have suggested that the combination of CT, ultrasound and aspiration cytology is useful in the differential diagnosis of secondary (metastatic) from primary adrenal carcinomas (15). Berkman *et al*. have achieved diagnostic accuracy of 100% in 15 out of 16 patients with adrenal mass following CT-guided percutaneous

Table I. *Reported studies on the use of computed tomography (CT) and fine needle aspiration (FNA) in the detection of adrenal metastases.*

First author	Primary cancer	No. of patients examined	No. of patients with adrenal mass found (%)	Masses detection technique	No. of patients with adrenal metastases (%)	Technique to prove metastases
Allard (28)	Lung cancer	91 (181 glands)	Depended on the reader	CT	32 (53 glands) (35%)	Histopathologic examination at autopsy
Berkman (42)*		16	16 (100%)	CT	4 (25%)	CT-guided biopsy
Chapman (46)	Non-small cell lung cancer	38	5 (13%)	CT	5 (13%)	CT-directed fine needle aspiration
Ettinghausen (44)	Non-small cell lung cancer	246	10 (4.1%)	CT	4 (1.6%)	Needle aspiration
Harper (47)	Small cell bronchogenic cancer	50	7 (14%)	Axial CT	7 (14%)	Postmortem examination
Nielsen (48)	Non-small cell lung cancer	84	15 (18%)	CT	4 (4.7%)	CT-guided percutaneous needle aspiration
Oliver (32)	Non-small cell lung cancer	330	32 (9.7%)	CT	8 (2.4%)	CT-guided biopsy, Follow-up
Pagani (43)	Non-small cell lung cancer	172	20 (12%)	CT	19 (11%)	Percutaneous needle biopsy
Paivansalo (49)†		75 (86 glands)	75 (86 glands)	CT	38 glands	Histologically, angiography and follow-up, U/S or CT follow-up, course of disease
Porte (30)	Non-small cell lung cancer	443	32 (7.2%)	CT, MRI	18 (4%)	CT-guided biopsy
Sandler (31)	Lung cancer	110	11 (10%)	CT	11 (10%)	CT-guided biopsy, follow-up
Seidenwurm (2)	Various cancers‡	21	21 (100%)	CT	21	Gross pathologic postmortem examination
Whittlesey (50)	Lung cancer	185	5 (2.7%)	CT	6 (3%)§	5-percutaneous biopsy 1-postmortem examination

*The authors selected 16 patients with adrenal masses; †The adrenal tumours examined were either primary or metastatic; ‡All patients selected had adrenal metastases indicated by gross pathologic postmortem examination; §Adrenal metastases were found in one patient at postmortem examination and not by CT.

aspiration. The authors suggested that CT-guided adrenal biopsy should replace open surgical biopsy for the detection of adrenal metastases because of it is safe and accurate (42).

Pagani has also recommended percutaneous needle biopsy of adrenal masses. Nevertheless, such biopsy should not be preceded, in the case of cancer patients, with normal CT images of the adrenals, because there are complications associated with this technique (43). Porte and associates have claimed that CT-guided biopsy is almost always required for the characterization of an adrenal mass as metastasis, before potentially curative therapy, since it showed 100% sensitivity and specificity in 443 patients with operable NSCLC, 32 of whom had adrenal an adrenal mass (29). Besides, in the study carried out by Ettinghausen and Burt the cytologic diagnosis of malignancy had also 100% accuracy (44).

Aspiration cytology under CT or ultrasound guidance can be regarded as the procedure of choice in the diagnostic evaluation of adrenals in patients with malignant neoplasms, as long as the cytologic findings are correlated with the clinical and laboratory data (45). For instance, concerning secondary adrenal carcinomas from small and non-small cell carcinoma of the bronchus, CT guided preoperative evaluation is of paramount importance (46-50). The results of all relevant studies are shown in Table I.

Treatment: Non-surgical treatment. Seven studies (1, 19, 51-54) with 122 cases of medically treated secondary adrenal carcinomas are reviewed in Table II. Regarding the site of the primary tumor, the above cases consist of 81 hepatocellular carcinoma (HCC), 25 lung cancers, 14 melanomas, one lymphoma and one unknown.

Yuan and associates have studied 81 cases of HCC and suggested that radiotherapy offers a noninvasive approach with promising local control and acceptable tolerability (54). The median survival period was 15 months. The survival rate at 1, 2, 5 year was 59.9, 35.0, and 12.9%, respectively (54). Branum and colleagues have studied 24 patients with metastatic melanoma, fourteen of whom were treated with chemotherapy for unresectable adrenal tumors at the time of diagnosis. Among these 14 patients, at the time of publication, 11 patients had died with a median survival of 6 months, whereas three remained alive at 8, 37 and 132 months, respectively (1).

Table II. *Review of adrenal metastases non-surgically treated.*

First Author	n	Age/ Gender	Primary site (histologic type)	Treatment	Median survival
Branum (1)	14	49*	Melanoma	Chemotherapy (Dacarbazine, Lomustin, Bleomycin, Vincristine)	3 alive: ≥8,37,132 mo 11 dead: 6±1 mo
Carey (19)	1	57/M	Malignant lymphoma (Large cell)	Chemotherapy (Vincristine, Doxorubicin, Cyclophosphamide, Prednizone)	6 mo
Higashiyama (51)	4	54-65/M	Lung (3 Adenocarcinoma, 1 Squamous cell)	3 Chemotherapy (Tegafur, Cisplatin, Vindesine Sulfate), 1 Radiation	3.5 mo (2-6 mo)
Luketich (52)	6	42-75/5M, 1F	Lung (3 Adenocarcinoma, 2 Squamous cell, 1 Large cell)	Chemotherapy (Mitomycin, Cis-platinum, Vinblastine)	8.5 mo
Soffen (53)	16	47-85†	15 Lung (7 Adenocarcinoma, 3 Squamous cell, 3 Large cell, 2 Small cell), 1 Unknown	Radiotherapy	3.8 mo (0.5-11 mo)
Yuan (54)	81	34-82/77M, 4F	Hepatocellular	18 patients helical tomotherapy and 63 conventional radiotherapy	15 mo (1, 2, 5 year 59.9, 35.0, and 12.9% respectively)

*Average age. Gender not specified; †Gender not specified. mo: Months.

Soffen and colleagues have studied 16 patients with symptomatic adrenal metastases who received palliative radiotherapy. Fifteen patients had lung cancer as primary malignancy, whereas one had squamous cell carcinoma of unknown primary origin. All patients were treated with radiation for symptomatic disease; median survival was 3.8 months (range=0.5-11 months). Based on this outcome, the authors concluded that prognosis for patients receiving palliative radiotherapy for symptomatic adrenal metastases is poor despite high probability of achieving effective palliation (53). In the remaining three studies (19, 51, 52) low survival has also been reported, suggesting that non-surgical treatment of adrenal metastases is combined with poor results. The same conclusion can be drawn by three studies (1, 51, 52) comparing surgical with medical treatment of adrenal metastases.

Treatment: Surgical treatment. A total of 67 cases of secondary adrenal carcinomas surgically treated were identified (Table III). Most cases pertained to lung and renal cancer (55-78).

Surgical treatment – Lung cancer as primary site. In the case of metastasis of lung cancer to the adrenals, surgical intervention is usually avoided, even if the primary cancer is well controlled (*i.e.* stage T1-2 N0) (79), as distant metastases from lung carcinoma are thought to indicate incurability (75). Nevertheless, a few cases of adrenalectomy for metastatic carcinoma of the lung with good results have been reported (50, 51, 64, 65, 67, 69, 73, 80-85). Aggressive approach may prove beneficial for some carefully selected patients, from other primary sites apart from lung und bronchus (86-108).

There have also been reported cases for patients with synchronous and metachronous solitary brain metastases from NSCLC that were treated by surgical removal (109).

Prolonged survival after adrenalectomy was first reported in 1982 by Twomey and colleagues regarding two patients with large cell lung cancer with solitary metastases to the right adrenal gland. The patients remained alive after the resection of the adrenals for fourteen and five years, respectively. This outcome made the authors believe that adrenalectomy should be performed in cases with special features such as good functional status of the patient, aggressive treatment of the primary neoplasm, care to rule out functioning adrenal tumors and the use of CT scans and angiography in order to define the extent of the tumor involvement (55).

Among the 83 cases with isolated adrenal metastases from lung cancer, which were reported in 21 articles (49, 50, 55, 64, 65, 67, 69, 71, 73-75, 78-87), fifty-one cases had sufficiently detailed reports to allow safe conclusions (49, 55, 64, 65, 67, 69, 70, 78-80, 82-85). The remaining 32 cases have been reported in three large-scale studies conducted by two institutions (51, 73, 78) and in two other smaller case reports (71, 74). Among the above 51 patients, synchronous adrenal metastases occurred in 22 patients and metachronous adrenal metastases in 29 patients; 23 were alive at the time of the report with a mean survival of 49 months (range=3-168 months), with 5 patients being 5-year survivors. The remaining 28 patients were dead at the time of the report with a mean survival of 15 months (range=4-36 months). Finally, all the operations conducted were open adrenalectomies apart from four performed by Bendinelli and associates (78), one performed by our team (79), two

performed by Heniford and colleagues (82), one performed by Tsuji and associates (83), five performed by Valeri and colleagues (85), one performed by Chen and associates (86), and six performed by Kabebew and colleagues (87), which were all laparoscopic.

Taira and colleagues have described a case of surgical treatment by bilateral adrenalectomy of metachronous bilateral adrenal metastases of NSCLC. Three years and six months later, the patient was doing well, with no evidence of recurrence suggesting that selected patients with solitary adrenal metastases of NSCLC can benefit from an aggressive treatment approach, even if such metastases are bilateral (110).

Suzuki and colleagues have reported an attempt of laparoscopic adrenalectomy of an adrenal metastasis from a poorly differentiated adenocarcinoma of the lung, but the procedure had to change to open surgery because of severe adhesions between the adrenal neoplasm and the kidney (71). Yokosuka and colleagues have presented pulmonary adenocarcinoma metastasizing to the adrenal glands, which caused adrenal insufficiency leading to impaired consciousness. After one year under chemotherapy treatment the patient died of disseminated intravascular coagulation due to the tumor (111).

Laparoscopic adrenalectomy has become the gold standard for the treatment of the majority of benign adrenal masses; regarding secondary adrenal carcinomas, this procedure seems also to ensure a beneficial therapeutic approach for the treatment of isolated adrenal metastases (78, 79, 82, 83, 85-87). In certain patients, who present no contraindications, laparoscopic adrenalectomy could be preformed safely with a complete absence of local recurrences (78, 79, 82, 83, 85-87). Laparoscopic adrenalectomy may prove very useful in special cases of isolated adrenal metastases, but larger studies are needed.

Kim *et al*. from the Memorial Sloan-Kettering Cancer Center of New York have reviewed 17 cases of lung cancer metastasized to the adrenal glands. There were nine and eight synchronous and metachronous adrenal metastases; the median survival after the adrenalectomy was 14 months (81). In another large-scale study performed at Mayo Clinic fifty-two patients with metastatic adrenal carcinomas were reviewed, of which eleven had lung cancer as primary malignancy. Forty per cent of all patients had a 2-year survival rate, and there was no significant difference in survival rates between patients with primary tumors in different locations (73).

Two studies (50, 51) have compared surgical with non-surgical treatment of adrenal metastases in patients with lung cancer. Luketich and Burt have studied fourteen patients with NSCLC and a solitary adrenal metastasis. Eight of these patients underwent resection of both the lung cancer and the adrenal metastasis, whereas the remaining six patients received only chemotherapy. All patients treated medically were dead by 21 months, with a median survival of 8.5 months. In the surgical group the median survival was 31 months with three patients being alive at the time of publication at 3, 21 and 61 months after operation, respectively. This outcome suggests that adrenalectomy in cases of complete control of the primary malignancy (51).

Higashiyama *et al*. have studied nine patients with adrenal carcinomas secondary to lung cancer, five of which underwent surgical resection of the adrenals, whereas the rest four received palliative therapy without adrenalectomy. Four and one of the adrenalectomized patients received chemotherapy and radiation, respectively, as an adjuvant therapy after the operation. Three and one of the patients treated with palliative therapy received chemotherapy and radiation, respectively. The results suggested that adrenalectomy could be effective for metastatic adrenal lesions from lung cancer in patients who have well controlled primary malignancy and long period between pulmonary resection and detection of adrenal metastases (not less than 7 months), adrenal metastasis is the initial metastasis, and no co-metastatic lesions are detected in other organs. Besides, in most cases adjuvant therapy in addition to adrenalectomy may be necessary, given the high incidence of metastases to other tissues (50).

Surgical treatment - Renal cancer as primary site. Regarding adrenal metastases from renal cancer, there have been 99 cases recorded (54, 55, 58-60, 61, 64, 68, 70, 72, 73, 76, 77, 81, 82, 85, 87), and among them seventy-three cases have been reported in detail (54, 55, 58-60, 61, 64, 68, 70, 72, 73, 76, 77, 81, 82, 85, 87). The remaining 26 cases were from two institutions and only summarized data have been presented (73, 81). Among the previously referred 73 patients, synchronous adrenal metastases occurred in 58 patients and the remaining 15 patients had metachronous metastases with time to detection ranging from 6 months to 19 years (median disease-free: 62 months). Among the 73 patients, thirty-two were alive at the time of the report with a mean survival of 36.6 months (range=7-122 months), with only four patients being 5-year survivors. Among the remaining 40 patients, 38 were dead at the time of the report with a mean survival of 27.7 months (range=1-172 months) and survival after adrenalectomy was not specified for two patients. Finally, 62 of the patients had an open adrenalectomy and only ten had laparoscopic one (77, 81, 85, 87).

Kim and associates have reviewed 11 metastatic adrenal carcinomas from malignancies of the kidneys, among which were 9 adenocarcinomas (renal cell carcinoma), one transitional cell carcinoma and one carcinoma of the collecting duct. There were six and five synchronous and metachronous adrenal metastases, respectively, and the median survival after adrenalectomy was 55 months (81). In a study conducted at Mayo Clinic, among the 52 patients reviewed, there were 15 cases of kidney malignancy

Table III. *Review of adrenal metastases treated surgically.*

First Author	Year	n	Primary site	Treatment of metastases	Survival after ADR
O'Dea (55)	1978	1	Kidney	ADR	Alive: ≥7 mo
Foucar (56)	1979	2	Kidney	ADR	1 Alive: ≥22 mo 1 Dead: 14 mo
Twomey (57)	1982	2	Lung	ADR & 1Rd	Alive: ≥5, 14 yr
Previte (6)	1982	2	Kidney	ADR	Alive: ≥20, 24 mo
Neal (7)	1982	2	Kidney	ADR	1 Alive: ≥3 yr, 1 not specified
Campbe (118)	1983	2	Kidney	ADR	1 Dead: 20 mo, 1 not specified
Goldenberg (9)	1983	1	Kidney	ADR	Dead: 6 mo
Fox (58)	1986	1	Kidney	ADR	Alive: ≥18 mo
Selli (10)	1987	3	Kidney	ADR	Dead: 20 days, 6, 9 mo
Duggan (59)	1987	1	Kidney	ADR	Dead: 6 mo
Tasca (60)	1987	1	Kidney	ADR & Ch	Dead: 1 mo
Hasegawa (11)	1988	2	Kidney	ADR	Alive: ≥22, 26 mo
Carey (61)	1988	1	Melanoma	ADR & Ch	Alive: ≥12 mo
Fujita (62)	1988	1	Rectum	ADR	Alive: ≥2 yr
Lemmers (63)	1989	2	Kidney	ADR	1 Alive: ≥12 mo 1 Dead: 14 mo
Raviv (64)	1990	3	Lung	ADR & 1Ch+Rd	Dead: 24, 25, 35 mo
Reyes (65)	1990	4	Lung	ADR & 2Ch, 1Rd, 1Ch+Rd	2 Alive: ≥5, 24 mo 2 Dead: 10, 13 mo
Winter (66)	1990	8	Kidney	ADR	3 Alive: ≥39, 52, 58 mo 5 Dead: 18, 20, 28, 31, 35 mo
Plawner (12)	1991	7	Kidney	ADR	2 Alive: ≥32, 60 mo 5 Dead: 7, 9, 58, 80, 172 mo
Huisman (13)	1991	2	Kidney	ADR	1 Alive: ≥48 mo 1 Dead: 29 mo
Branum (1)	1991	10	Melanoma	ADR & 2 Ch	6 Alive: ≥8, 10, 12, 70, 83, 105 mo 4 Dead: 3, 8, 9, 112 mo
Yu (24)	1992	1	Kidney	ADR	Dead: 7 mo
Potepan (22)	1992	1	Osteogenic Osteosarcoma	ADR	not specified
Dobnig (21)	1992	1	Non-Hodgkin Lymphoma	ADR & Ch, Rd	Alive: ≥16 mo
Kirsch (67)	1993	1	Lung	ADR & Ch	Alive: ≥2 yr
Higashiyama (51)	1994	5	Lung	ADR & 4Ch, 1Rd	2 Alive: ≥24, 40 mo 3 Dead: 9, 17, 20 mo
Sagalowsky (68)	1994	21	Kidney	ADR	4 Alive: ≥9,32,114,122 mo 17 Dead: 2,3,6,7,7,12,12,13,28, 28,33,35,40,45,48,55,86 mo
Ayabe (69)	1995	3	Lung	ADR & 2Ch	2 Alive: ≥75, 109 mo 1 Dead: 20 mo
Barnes (70)	1995	1	Kindey	ADR	Alive: ≥7 y
Halachmi (71)	1996	3	Lung	ADR	not specified
Dieckmann (72)	1996	1	Kidney	ADR	Alive: ≥9 mo
Lo (73)	1996	52	15 Kidney, 11 Lung, 7 Colon, 3 Malignant melanoma, 3 Stomach, 2 Urinary bladder, 2 Uterus, 1 Breast, 1 Prostate, 1 Gallbladder, 1 MFH, 5 Unknown	ADR & 6Ch, 4Rd	22 Alive: 1 mo – 8.9 yr* 30 Dead: 1 mo – 8.6 yr†
Suzuki (74)	1997	1	Lung	ADR	Dead: 8 mo
Urschel (75)	1997	1	Lung	ADR & Ch	Alive: ≥9 yr
Sapienza (76)	1997	1	Kindey	ADR	Alive: ≥15 mo
Elashry (77)	1997	2	Kidney	ADR (Laparoscopic)	Alive: ≥11, 16 mo
Bendinelli (78)	1998	4	Lung	ADR (Laparoscopic) & Ch	1 Alive: ≥8 mo 3 Dead: 9, 10, 18 mo
Linos (79)	1998	1	Lung	ADR (Laparoscopic)	Alive: ≥1 yr
Porte (80)	1998	11	Lung	ADR	3 Alive: ≥6, 10, 66 mo 8 Dead: 4, 4, 6, 6, 8, 13, 14, 24 mo

Table III. *Continued*

Table III. *Continued*

First Author	Year	n	Primary site	Treatment of metastases	Survival after ADR
Kim (81)	1998	37	17 Lung, 11 Kidney, 5 Colon & Rectum, 1 Esophagus, 1 Mediastinum, 1 Melanoma, 1 Unknown	ADR & 5Ch, 5Rd	median: 21 mo
Heniford (82)	1999	10	4 Kidney, 2 Lung, 2 Colon, 1 Adrenal, 1 Melanoma	ADR (9 Laparoscopic)	9 Alive: ≥0.5 – 19 mo (mean: 8.3 mo) 1 Dead: 4.5 mo
Tsuji (83)	1999	1	Lung	ADR (Laparoscopic)	Alive: ≥18 mo
De Perrot (84)	1999	1	Lung	ADR & Rd	Alive: ≥60 mo
Valeri (85)	2001	6	5 Lung, 1 Kidney	ADR (Laparoscopic)	3 Alive: ≥3, 5, 16 mo 3 Dead: 18, 36, 36 mo
Chen (86)	2002	1	Lung	ADR (Laparoscopic)	Dead: 10 mo
Kabebew (87)	2002	13	6 Lung, 3 Kidney, 2 Lymphoma, 1 Melanoma, 1 Colon	ADR (Laparoscopic)	Mean: 3.3 yr (1-7 yr)
Einat (88)	2002	1	Ovary	ADR (Laparoscopic)	Alive: ≥24 mo
Lam (89)	2002	21	1 Rectum, the rest not specified	ADR	1 Alive: ≥72 mo The rest not specified
Patlas (90)	2004	1	Ovarian	Decline treatment	
Gerber (91)	2004	14	Lung	ADR (Laparoscopic)	Alive: ≥24 mo
Marcier (92)	2005	23	Lung	ADR	Alive: ≥6 mo
Tsalis (93)	2005	1	Hepatocellular	ADR	Alive: ≥6 mo
Miyoshi (94)	2005	1	Lung	ADR	Alive: ≥18 mo
Shoji (95)	2006	1	Colorectal	ADR	Alive: ≥12 mo
Utsumi (96)	2008	1	Renal	ADR	Alive: ≥12 mo
Fumagali (97)	2010	1	Esophagogastric junction	ADR	Alive: ≥6 mo
Liu (98)	2010	1	Breast	ADR	Alive: ≥36 mo
Raz (99)	2011	21	Lung	ADR	Alive: ≥12 mo
Thrumurthy (100)	2011	1	Colorectal	ADR & 2Ch	Alive: ≥24 mo
Washino (101)	2012	1	Bladder	ADR & 3Ch	Alive: ≥36 mo
Zakaria (102)	2013	1	Bladder	ADR	Alive: ≥36 mo
Solaini (103)	2013	1	Seminoma	ADR	Alive: ≥18 mo
Mouka (104)	2016	1	Endometrial	ADR & Ch	Alive: ≥18 mo
Yuan (105)	2017	34	Lung	ADR (Laparoscopic) & ADR	Median ≥45 mo
Eddaoualline (106)	2018	1	Ewing Sarcoma	ADR & 12Ch	Alive: ≥36 mo
Hanato (107)	2018	25	Lung, Kidney, Ovary, Soft Tissue, six Others	ADR (Laparoscopic) & ADR	Median ≥14 mo
Nugroho (108)	2018	1	Hepatocellular carcinoma-cholangiocarcinoma	ADR	Alive: ≥12 mo
Total		399	99 Kidney, 176 Lung, 17 Melanoma, 17 Colon & Rectum, 3 Stomach, 3 Urinary bladder, 3 Malignant Lymphoma, 2 Uterus, 1 Esophagus, 1 Mediastinum, 1 Ovary, 1 Kidney, 1 Soft Tissue, 2 Breast, 1 Prostate, 1 Gallbladder, 1 MFH, 1 Osteogenic Osteosarcoma, 1 Hepatocellular, 1 Esophago-gastric junction, 1 cholangio-carcinoma, 1 Cervix, 2 Ovary, 1 Adrenal, 1 Ewing Sarcoma, 1 Hepatocellular, 1 Seminoma 2 Bladder, 3 Colorectal, 26 not specified, 6 Unknown		

*Median: 24 mo; †Median: 13 mo. ADR: Adrenalectomy; Ch: chemotherapy; Rd: radiation; mo: months; yr: years; MFH: malignant fibrous histiocytoma.

metastasized to the adrenals and 40% of all patients had a 2-year survival (73).

Surgical treatment - Other primary sites

Apart from malignancies of the lung and kidney among other primary sites (88-108), eleven studies with 79 cases of other primary cancers metastatic to the adrenal glands which were treated with adrenalectomy were identified (Table III). Two of these studies that have been conducted at the Memorial Sloan-Kettering Cancer Center of New York (81) and Mayo Clinic (73), respectively, summarized the data. The remaining nine studies (1, 21, 22, 61, 62, 82, 85-89) contained sufficient data but number of cases was small or had insufficient data. The larger of these two studies, conducted by Branum and associates, have compared surgical with non-surgical treatment of 24 patients with melanoma metastatic to the adrenals. Fourteen patients were treated with chemotherapy (Table II), whereas the remaining ten patients underwent adrenalectomy. All 10 patients had unilateral metastasis to the adrenal gland. At the time of publication, six of the operated patients remained alive for 8, 10, 12, 70, 83 and 105 months, respectively, and four were dead 3, 8, 9 and 112 months after the adrenalectomy, respectively. Among the 14 patients who received chemotherapy, 3 were alive and 11 dead, as described above. Survival analysis revealed a significant survival advantage in the surgically treated group ($p=0.0095$), supporting that patients with isolated adrenal metastases may benefit from an aggressive treatment of the adrenal disease (1).

Conclusion

As a general principle, resection of a single site metastatic disease should be attempted, considering that the operation is feasible and without major morbidity and if the primary malignancy can be (or was) also surgically treated in a curative intent (112, 113). In the case of metastatic adrenal carcinomas, the main problem is to establish preoperatively that the metastasis is truly isolated (114). Once this has been achieved, adrenalectomy seems to be the procedure of choice, as it has the potential to offer prolonged survival.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

ES and ID performed the literature search and wrote the paper; AI and DC screened the retrieved articles and performed data extraction; DIA and MS created the tables; DA critically revised the final manuscript.

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