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Laparoscopic Adrenalectomy for Metastatic Disease

Maurice Matter[1]*, Tobias Zingg[1] and Luis Schiappacasse[2]

[1]Department of Visceral Surgery, Lausanne University Hospital and University of Lausanne, Switzerland

[2]Department of Oncology, Radio-oncology Unit, Switzerland

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Corresponding author:
Maurice Matter
Head Surgeon, Department of Visceral Surgery, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland,
Email: maurice.matter@chuv.ch

ABSTRACT

Adrenal surgery for metastatic disease is unfrequently performed. Pooled analyses showed a survival benefit and adrenal surgery in this setting is a validated procedure in the endocrine and oncology guidelines. Respecting the rules for open surgery (safety and R0 surgery), laparoscopic adrenalectomy also combines the advantage of minimal invasive procedure in patients with decreased performance status. We reviewed 24 patients with 28 adrenalectomies (21 laparoscopically) for metastatic lung cancer (16), renal cancer (4), melanoma (3), and Merkel cell carcinoma (1). R0 was achieved in 24 patients and we observed a median overall survival after adrenal surgery of 39 months. Some patients had a stereotactic radiotherapy. In patients with a controlled limited metastatic disease (oligometastatic state), stereotactic radiotherapy has emerged as an efficient alternative despite no histologic proof of its efficacy. The advantage of an abscopal effect still await definitive proof and recognition. While awaiting comparative or randomized studies, there is no consensus and adrenal surgery remains the main treatment when possible.

INTRODUCTION

Metastatic disease to the adrenal cortex can be explained by flowing tumor cells in a richly vascularized tissue [1], lymphatic drainage or organotropism [2]. Malignancies well known to metastasize to the adrenal glands include breast cancer, melanoma, Non-Small-Cell Lung Cancer (NSCLC), gastric cancer, colorectal cancer, esophageal cancer, renal cell carcinoma, hepatocellular carcinoma, bladder carcinoma, lymphoma and others, based on autopsy series or during the course of the disease [3,4]. The differential diagnosis of an adrenal mass is large and requires a full endocrine workup [5]. Standard imaging in this setting is an unenhanced CT [6], or an 18FDG PET-CT [6,7]. A fine-needle aspiration biopsy has a 91% adequacy rate, 1% indeterminate rate [8] and a 2.5% complication rate [9]. Adrenal metastasis can be synchronous or metachronous, with a worse prognosis for the former in NSCLC for example [10], unilateral or bilateral, with a potential risk of adrenal insufficiency [11].

Open and minimal invasive adrenal surgery (laparoscopic and retroperitoneoscopic) are safe procedures in dedicated expert centers [12]. Laparoscopic adrenalectomy for metastatic disease follows the same guidelines and limitations as for minimal invasive surgery (size, adhesion, risk of conversion, intention to treat with R0 resection) [13,14] in selected patients [15,16]. At the time of check-point inhibitors, adrenalectomy is performed for synchronous and metachronous metastases, but also in

oligometastatic disease (metastases limited to localized sites with potentially curative treatment) [10,17,18], allowing for synchronous adrenalectomy and lung surgery for example [19]. Surgery is limited by the extent of local disease and the patient's performance status. As an interesting alternative, stereotactic radiotherapy has emerged as an efficient alternative [20,21] with a potentially synergetic effect by combining stereotactic radiotherapy and immunotherapy [22]. There is however no consensus and there are no comparative studies for these two main treatments for adrenal metastases. Our aim was to review our single-institution experience in laparoscopic adrenal surgery for metastatic disease with a focus on combinations with the emergence of stereotaxic radiotherapy.

MATERIAL & METHODS

Since 2006 (dedicated and then ESES certified endocrine surgeon (MM)) we performed 208 adrenalectomies (mean of 14 per year), Including 174 for benign disease (Conn: 65, pheochromocytoma: 45, Cushing: 25, incidentaloma-adenoma: 22, others: 17) or malignant (adrenocortical cancer: 8, leiomyosarcoma: 1) and 28 for metastases in 24 patients, who are reviewed. Laparoscopic adrenalectomy is performed in contralateral decubitus position (3 trocars on the left side and four on the right side), while open adrenalectomy was performed in supine position with a sub-costal (preferred) or midline laparotomy. A compartmental resection of the adipose tissue including the adrenal gland was the rule. Post-operative survival was the time interval since adrenal surgery or the second adrenal surgery.

For radiotherapy technique: patients receiving adrenal Stereotactic Body Radio Terapy (SBRT) were treated using a CyberKnife M6 robotic system (Accuray Inc., Sunnyvale, CA) or a Volumetric Modulated Arc Therapy (VMAT) using an Elekta Synergy HD Linac (Elekta Limited, Crawley, UK). Delivered doses ranged from 36 Gy in 6 fractions to 40 Gy in 5 fractions (prescribed to the 80% isodose), depending on the anatomical configuration of the lesion.

Statistical analysis: chi-square test for univariate analysis and Kaplan Meier survival curves (Stataâ software Statacorp LLC). The protocol was accepted par the local Ethics Committee (2021-01035).

RESULTS

There were 14 men and 10 women. Median age at adrenalectomy was 59 years (36-78). ASA scores were 2 in 16 patients and 2 in 12 patients. Primaries (Table 1) included 16 lung malignancies (11 adenocarcinomas, 2 large cell carcinomas, 2 lung NECs and 1 sarcoma of the pulmonary artery), 4 renal carcinomas, 3 melanomas and 1 Merkel cell carcinoma. There were 9 right and 19 left adrenalectomies. Malignancies in paired organs showed a concordant relationship between the side of the organ and the side of the adrenal metastasis in 9 out of 22.

Table 1: Indications and sequences of therapy for 28 adrenalectomies.

Surgical adrenalectomy for metastasis (N = 28)		synchronous (9)	1st metachronous (15)	2nd controlateral (4)*
Histology :				
Lungs :				
NSCLC adenocarcinoma	11	5	6	
Large cell	2	2		
Neuroendocriene (NEC)	2	1	1	1
Sarcoma pulm. artery	1	0	1	1
Renal carcinoma	4	1	3	1
Melanoma	3	0	3	1
Merkel carcinoma	1	0	1	

*There were additional stereotactic radiotherapy in 3 lung adenocarcinoma patients to the 4 controlateral surgical adrenalectomy.

Table 2: Surgery for 24 patients (28 adrenalectomies).

Mean duration of surgery :		
Laparoscopy min. (sd)	21	130 (+/- 37)
Laparotomy min. (sd)	7	143 (+/- 28) (NS)
Conversion to laparotomy		2/21 (9.5%)
Complications (Clavien's score)	no	20
	2	7
	3	1
Hospital stay (median, range)		5 (1-10)
Surgical margins		
	R0	24
	R1	4
Largest size of (cm. mean, range)		
adrenal compartment		8.3 (3.0 - 15.9)
adrenal metastasis		4.8 (1.3 - 11.0)

Synchronous adrenal metastasis was observed in 9 patients (8 lung malignancies) and metachronous in 15 (> 6 months), with a median delay of 25 months (6-444) since surgery for the primary tumor. Twenty-eight adrenalectomies were performed in 24 patients, laparoscopically in 21, including 2 conversions (large hematoma post biopsy and infiltration to the adjacent kidney) and in 7 as a planned open adrenalectomy (malignant infiltration or planned combined surgery). When compared to

the other (non-malignant non-metastatic) adrenalectomies, laparoscopic surgery was less frequently performed: in 89.5% versus 75% respectively (p<0,05). Mean duration of surgery was not significantly different between laparoscopy and laparotomy: 129.6 min. (SD: 36.6) and 142.6 min. (SD: 28.2) respectively. Adrenal surgery always removed the adrenal compartment: the mean largest diameter of the surgical specimen was 8.3 cm. (3-15.9) while the metastasis itself had a mean largest diameter of 4.8 cm. (1.3-11). R0 surgery was possible in 24 adrenalectomies, and R1 in four cases (3 NSCLC and 1 Merkel carcinoma), caused by either diffuse invasion of the surrounding fat or metastasis adjacent to the adrenal gland, and the median size of the metastases did not differ between these two groups. Despite a neoadjuvant treatment (radiotherapy, chemotherapy or check-point inhibitor therapy) in 11 patients, viable cells formed 25% to 100% of the metastatic neoplasm on histopathology examination (Figure 1).

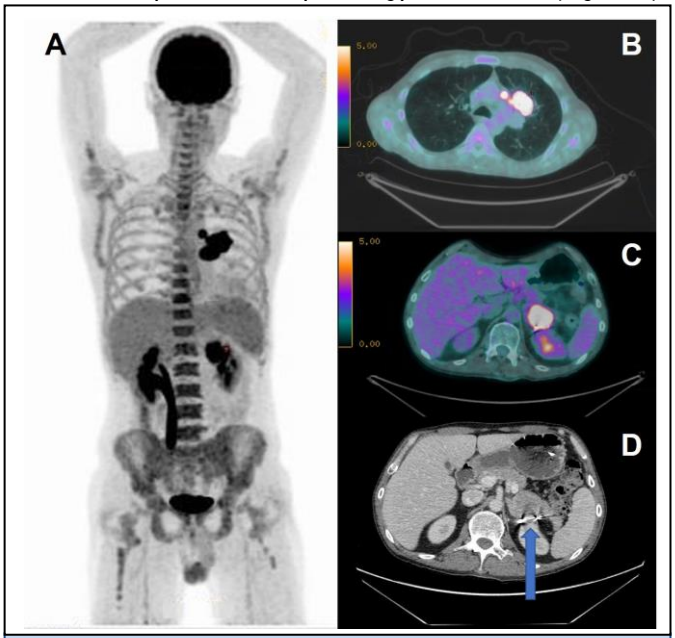

Figure 1: Man 44 years old with a large cell lung cancer T4 N2 M1 (adrenal gland). Initial treatments included neoadjuvant chemotherapy (Platin-Navelbin and Carboplatine) combined with lung- mediastinal radiotherapy (66 Gy) followed by stereotactic adrenal radiotherapy (40 Gy) and then superior left lobectomy and mediastinal dissection. As PET-CT showed no satisfying adrenal response, an adrenalectomy was performed 2 months later. Resection was R0 with 85% living tumor cells in a 6 x 4.5 x 4 cm metastasis. The patient survived 28 more months. A: pretreatments PET-CT. B and C: lung and adrenal disease. D: adrenal CT with adrenal coils (arrow) for targeting stereotaxic radiotherapy.

No patients underwent simultaneous bilateral adrenalectomy. The American Society of Anesthesiologists (ASA) physical status classification system at the time of surgery showed 16 ASA 2 status and 12 ASA 3 status. Median hospital stay was 5 days (1-10). Grade 2 surgical morbidity according to Clavien's classification was observed in 7 patients (urinary sepsis, difficult pain control) and grade 3 in one patient (laryngospasm). No mortality was observed.

During the follow-up, 4 patients had a contralateral adrenalectomy (time interval of 3,7,27 and 103 months from the first adrenalectomy) and a controlateral stereotactic radiotherapy in 3 patients (time interval of 7, 9 and 15 months). Overall survival of theses 7 patients was not different when compared with the patients having only one metastatic adrenal gland. No patient had stereotactic radiotherapy as a first-line therapy. Thirteen patients died with a median survival of 22 months (3-74), 11 are alive: 2 in remission (12 & 140 months), 4 with stable disease (4, 40, 46 & 153 months) and 3 with progressive disease (15,42,85 months). Overall, there was a median survival of 39 months (3-153) (Figure 2).

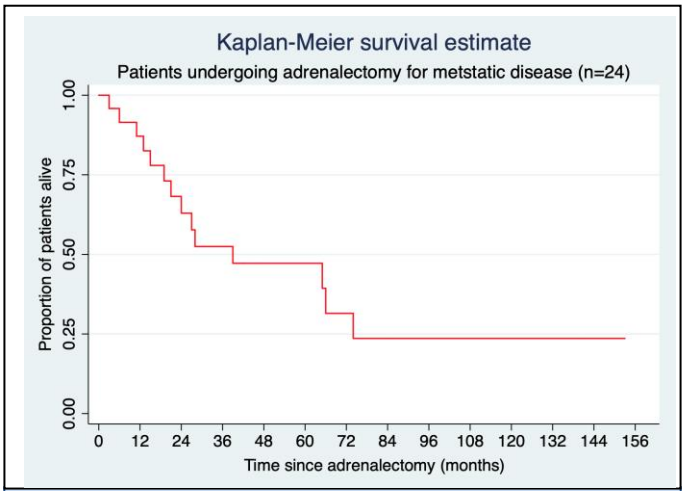

Figure 2: Overall survival in 24 patients (with 28 adrenalectomies).

DISCUSSION

Adrenal surgery for metastatic disease is un-frequently performed and pooled analyses are regularly published for obtaining larger numbers. Gao et al. combined 13 retrospective studies with a total of 98 NSCLC patients covering a 25-year period with heterogeneous management but showing a median overall survival of 18 months with a significant survival advantage for metachronous versus synchronous metastases [19]. Goto et al retrospectively reviewed the activity of 11 centers over 15 years including 67 patients with a median survival of 46 months [16]. In the recent

large study of Russo et al [18], 174 patients over a period of more than 20 years had a median survival of 36 months with isolated adrenal metastases and 39.6 months with concomitant extra-adrenal metastases. A complete review of all adrenal surgery for metastatic disease is beyond the scope of this is study, however it is a now recognized and validated treatment for improving survival in selected patients [23,24,25]. Higher complication rates in adrenal surgery are significantly associated with malignancy, bilateral adrenalectomy and low-volume surgeons [26]. Laparoscopic adrenalectomy is recognized as a safe technique and it's use increases accordingly [27]. It was the surgical approach used in 41% [18], 46% [24], 56,7% [28], 69% [19], 75% (present study), 91% [29] and 95% [30] of the respective studies. Laparoscopic adrenalectomy has been shown to be safe while oncologically appropriate for adrenal metastases.

Laparoscopic adrenalectomy for malignancy must follow the same guidelines as open surgery regarding the intention for R0 resection. In doubt an open procedure must be performed in case adjacent organs (kidney, abdominal wall) are involved. Size only (cutoff) is not a limiting factor, surgical skills and experience are however mandatory [12,23,31]. Performance indicators for laparoscopic adrenalectomy for malignancy are rates of R0 resection and conversion to open surgery. In the present study, a conversion rate of 9.5% (2/21) was observed. One case was due to adhesion to the adjacent kidney and the other due to adhesion to the inferior vena cava following preoperative radiotherapy. This conversion rate is like recently published series: 3.2%-15.5% [16,30-33], where the main reasons for conversion were bleeding and adhesions (previous surgery or oncological uncertainty). In the present series, R0 resection was achieved in 85.7% (24/28), like the 73.3%-86.5% described in other studies [16,31-33]. R1 is regarded as a significant adverse survival risk factor [16,33]. The two R1 (fully laparoscopic) resections were observed despite realizing a full compartmental adrenal resection. While our mean largest metastatic diameter was 4.8 cm, the mean largest diameter of the complete specimen was 8.3 cm, with a relatively constant adrenal size of about 7 cm. NSCLC adrenal metastasis represented the major indication in this study and more than half in a synchronous manner. A separate survival analysis is not possible due to the small case numbers. Synchronous NSCLC treatment is a validated option. De Wolf et al analyzed 59 NSCLCs, of which 26 with synchronous adrenal metastasis: the median survival of 77 months was neither influenced by synchronous nor metachronous presentation; only by mediastinal N status [34]. Likely due to the heterogenous series, there are discordant results regarding the influence of synchronous versus metachronous presentation [24,28,30,31,35]. On the other side, there is an agreement regarding the influence of origin of the primary: survival is better with renal cancer metastases compared to NSCLC, melanoma, or other primaries [24,29,30,33].

Surgical access and techniques in adrenalectomy for malignant disease are limited by the size of the tumor and by respecting safe oncological margins. Retroperitoneoscopic adrenalectomy for malignancy is limited by size (< 4 cm) and infiltration according to Walz [36]. Our mean size for the metastasis was 4.8 cm (1.3 - 11.0) and mean size for the adrenal compartment (providing safety margins) was 8.3 cm (3.0 - 15.9). Surgeons must also be confident in their techniques. In the large EUROCRINE database, adrenalectomy for malignancy was performed mainly by open laparotomy and in only 6% by retroperitoneoscopy [37]. In their systematic review and meta- analysis of retroperitoneoscopic versus laparoscopic adrenalectomy, Constantinides et al concluded that, overall, there were no differences in duration of surgery, blood loss, time to ambulation or complication rates between the two techniques [38].

The origin of the metastatic process in adrenal glands is still a matter of debate, between seed and soil (circulating cells), lymphatic network or organotropism. For paired organs as origin of the primary, we observed an ipsilateral localization in 9 patients and a contralateral localization in 13. De Wolf observed a non-significant median survival difference in ipsilateral involvement (48.3 months, 2.9-120.6) versus for contralateral (77.1 months, 0.6-122.6, P= 0.358) [34]. Majority of published series involved patients with NSCLC, renal carcinoma, or melanoma. In these patients the oligometastatic concept seems to apply at best at the time of check-point inhibitors therapies, compared with breast, gastric or colorectal cancer having their own therapies for metastatic states but where adrenal metastasis goes possibly with a multimetastatic state or a late stage of the natural oncological

history. Oligometastatic state can be a solitary adrenal metastasis or adrenal metastasis with other metastatic sites under control [10,17,18]. In 3 NSCLC patients Stereotactic Body Radiation Therapy (SBRT) was applied due to progression of the metastatic disease in the contralateral adrenal gland while on check-point inhibitors. A meta-analysis including 39 studies reporting the outcome of 1006 patients with adrenal metastases treated with SBRT between 2009 and 2019 showed a 1- and 2-years local control rate of 82% and 63% [20]. They found a strong positive association between SBRT dose and local control, and even an association with 2-year overall survival when a higher median biological equivalent dose (BED10) of 80 Gy or 100 Gy was used (compared to a BED10 of 60 Gy). The overall rate of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher toxicity was 1.8% in these series. Indirect response included pain control and imaging with PET [39].

Adrenalectomy following SBRT is difficult to find in the literature. One NSCLC patient with a metachronous (36 months) metastasis had SBRT. Due to progression of the disease, a laparoscopic adrenalectomy was performed and concerted due to extensive fibrosis and local adhesions to the vena cava (R1 resection with fully viable cells). As another patient with suspicious adrenal metastasis from breast cancer was ultimately found to have a simple adenoma at resection (false positive PET-CT) [6,7], we must emphasize the necessity for pre-treatment FNA and a direct way to prove SBRT efficacy. The place for SBRT, when compared with adrenalectomy should motivate a prospective study. On one side there is the possibility for a proven R0 resection. Adrenalectomy morbidity is limited as witnesses by a EUROCRINE study [37] with a 9.6% overall morbidity (Dindo-Clavien grade I-II: 5.8%, grade III-IV: 3.3% and grade V: 0.5%) but performance status is an issue for general anesthesia. On the other side, SBRT is feasible in any condition but limited by its dose-related toxicity [20]. One of the last published series of adrenal metastases treated by SBRT, including 37 oligometastatic lung cancer patients with 38 adrenal lesions found a dose-response relationship between a BED10 > 72 Gy and better local control (1- and 2-year local control of 100% versus 54.1 and 45% when lower doses were delivered), without observing a significant toxicity [40,41].

The possible synergetic effect obtained by combining stereotactic radiotherapy and immunotherapy [22] is a promising phenomenon. Radiotherapy can release immunogenic cell death able to trigger the immune system, leading to a kind of adaptative immune response. It is based on a speculative mechanism and interesting hypothesis, and while awaiting definitive proof, surgical adrenalectomy remains the only way to realize a confirmed R0 adrenal resection.

Severe limitations of the study include the retrospective analysis of highly selective but heterogeneous patients with different pathologies and a limited follow-up. All patients were discussed in multidisciplinary tumor boards: lung neoplasms, endocrine malignancies, or melanoma. On the other hand, the endocrine surgeons' team was stable over time with a corresponding high expertise (mean of 14 adrenalectomies, range: 3-24) in conformity with current requirements according to ENETS (> 6 per year). Moreover the same team performed laparoscopic living donor nephrectomy increasing technical performance and anatomical facilities (300 procedures during the same time laps).

CONCLUSION

At the present time, laparoscopic adrenalectomy should be the preferred treatment for patients with oligometastatic disease involving the adrenal gland. When surgery is not feasible or when metastatic state is progressing, SBRT is a promising alternative. Prospective studies must assess the precise role of these two options. The other non-surgical options (ethanol injection, ultrasound-guided percutaneous microwave ablation, CT-guided laser-induced interstitial thermotherapy, cryoablation, or combinations thereof) may also participate to an abscopal effect to be further evaluated.

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