Adrenocortical Carcinoma, Adrenal Lymphoma and Metastases to Adrenal Gland

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Contents

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Case Presentation

The patient is a 50-year-old female who was presented with left flank pain for 3 months associated with nausea, significant weight loss and reduced appetite. She also had an episode of haematuria. Past medical history was significant for anxiety and depression, with the former increasing over recent months as well. There is no significant comorbidity. Medication includes quetiapine, sertraline and propranolol. On physical examination, her vital signs are within normal range, and her abdomen is soft with some mild tenderness in the left upper quadrant with a palpable fullness over this area.

A CT of the abdomen and pelvis with contrast was performed, showing a large heterogeneous high-attenuation mass originating from the left adrenal gland. The mass measured approximately 14 cm in the greatest dimension. The mass was pushing the left kidney inferiorly and the small and large bowel loops anteriorly. The left renal vein appeared to be thrombosed. Minor clot burden was also noted at the confluence of the left renal vein and the inferior vena cava (IVC).

A subsequent whole-body PET/CT scan showed the large necrotic left adrenal mass to be markedly FDG-avid (SUVmax = 16.5). The tumour was invading the left renal vein with tumour thrombus extending into the IVC. There was a concern for invasion into the upper pole of the left kidney. There was no evidence of distant disease.

Urine metanephrines were all within normal ranges: 3-methoxytyramine = 50 nmol/mmol (normal, 0–220 nmol/mmol), metadrenaline = 60 nmol/mmol (normal, 0–150 nmol/mmol) and normetadrenalin = 360 nmol/mmol (normal, 0–450 nmol/mmol). In addition, her laboratory data show increased levels of androstenedione = 25.9 nmol/L (normal, 3–8 nmol/L), dehydroepiandrosterone sulphate = 62.1 umol/L (normal, 0.0–10.4) and testosterone = 7.2 nmol/L (normal, 0.5–2.6 nmol/L). Her urine steroid profile showed high concentrations of dehydroepiandrosterone = 115,210 μg/L (normal $\mu = 327 \pm 244$) and androstenedione = 44,955 μg/L (normal $\mu = 770 \pm 420$).

Questions

1. A 36-year-old patient presents at the emergency room with severe hypertension (210/110 mmHg) and right upper quadrant pain. He is very anxious and sweaty. His routine bloods are normal. A CT scan identifies a 10 cm right adrenal mass. The next step should be:
   1. Measure plasma metanephrines' level.
   2. Cancel the previously planned biopsy of this mass.
   3. Measure the blood response to a 40 mg propranolol dose.
   4. Check full blood count and blood film for possible lymphoma.

   (a) Only (1) and (2) and (3) are correct.
   (b) Only (1) and (2) and (4) are correct.
   (c) Only (3) is correct.
   (d) Only (1) and (2) are correct.
   (e) All are correct.
2. A 56-year-old patient presents with abdominal pain and microscopic blood in urine. A computed tomography of kidneys, ureters and bladder is performed to look for renal stones. An 8 cm left suprarenal mass is seen consistent with adrenal origin. The next steps should be:

1. Arrange PET/CT (depending on the biochemical work-up).
2. Check urine/plasma metanephrines.
3. Refer to appropriate MDT.
4. Arrange biopsy of mass.
   (a) Only (1) and (2) and (3) are correct.
   (b) Only (1) and (2) and (4) are correct.
   (c) Only (3) is correct.
   (d) Only (1) and (2) are correct.
   (e) All are correct.

3. An 88-year-old male with heart failure and dementia is referred from nursing home with abdominal pains. CT scan reveals a 12 cm right adrenal mass with suspicion of invasion into the IVC and liver. The next appropriate steps would be:
   1. Refer to MDT.
   2. Palliative care.
   3. PET/CT.
   4. Check urine steroid profile.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.
4. A 45-year-old female attends with suspected gallstones and has an MRCP. This reveals gallstones and an incidental 10 cm right adrenal mass with tumour extension into the IVC. The next steps should be:
   1. PET/CT.
   2. Urine metanephrines and steroid profile.
   3. Refer to MDT with plan for mitotane chemotherapy.
   4. Refer to MDT with plan for surgical excision.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.
5. An 80-year-old fit and healthy patient with a previous history of surgically excised sigmoid cancer 6 years ago is referred with an enlarging PET-avid right adrenal mass measuring 22 mm. It is suspected to be a metastasis. This is the sole site of recurrence. The next steps should include:
   1. Refer to MDT.
   2. Biopsy of the lesion.
   3. Check renin/angiotensin levels.
   4. Check urine steroid profile.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.

6. The correct treatment for a 22 mm isolated left adrenal metastasis could include:
   1. Laparoscopic resection
   2. Retroperitoneoscopic resection
   3. Open surgery
   4. Radiotherapy
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.
7. A 70-year-old male presents with marked weight loss, nausea, anorexia, orthostatic dizziness and joint pain. On clinical suspicion, a paired morning cortisol and ACTH are taken, revealing a decreased cortisol with a raised ACTH. A contrast-enhanced CT revealed bilateral adrenal masses. It is suspected to be bilateral lymphoma with adrenal insufficiency. The next steps should include:
   1. Refer to MDT.
   2. Biopsy of the lesion.
   3. Check urine metanephrines.
   4. Check urine steroid profile.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.
8. An 85-year-old patient presenting with intentional weight loss undergoes a CT scan which reveals bilateral adrenal masses, measuring 3.4 × 3.2 cm lesion on the right side and a 3.1 × 2.2 cm lesion on the left side. A subsequent biopsy shows diffuse large B-cell lymphoma.

The next steps should include:
   1. Refer to MDT.
   2. Check urine metanephrines and urine steroid profile.
   3. Check paired morning cortisol and ACTH.
   4. Laparoscopic removal of the largest tumour.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (4) is correct.
      (d) Only (1) and (3) are correct.
      (e) All are correct.

22.1 Introduction

The adrenal glands are frequently affected by a wide variety of growths that either cause symptoms or are found incidentally on cross-sectional imaging performed for not related issues. Their overall incidence is about 3–10% for the whole popula-

tion and is increasing with the age [1]. The majority of these tumours are small, benign and non-functioning adenomas. This chapter will focus on three rare entities: adrenocortical carcinoma (ACC), primary adrenal lymphoma (PAL) and metastases to adrenal gland from other primary tumour sites.

22.2 Adrenocortical Carcinoma

22.2.1 Clinical Presentation

Adrenocortical carcinoma (ACC) is a rare tumour with an incidence of one to two/million population/year. It often presents at an advanced stage, and the median age at the time of diagnosis is in the fifth or sixth decade of life [2].

About two-thirds of patients present with signs of increased hormone secretion (i.e. Cushing's syndrome, virilization in females, feminization in males) [3]. Although cortisol overproduction is the most common (~40%), in the majority of patients, the tumour produces a range of hormones including both glucocorticoids and sex hormones [3, 4]. The overproduction of aldosterone is very rare [4].

Another one-third of patients present with symptoms related to the size and mass effect of their (large) tumour (i.e. pain, abdominal distension, early satiety, nausea/vomiting, weight loss, leg oedema) [3, 5]. The average diameter of palpable ACCs is about 12–15 cm, with a weight of >500 g [6].

More recently, an increasing number of ACCs are discovered as incidentalomas on cross-sectional imaging done for other indications [6, 7].

A minority of patients can be identified during screening of families with genetic mutations known to be associated with increased risk of ACC (e.g. Li-Fraumeni, multiple endocrine neoplasia type 1, Lynch syndrome, familial adenomatous polyposis, Gardner syndrome and Beckwith-Wiedemann syndrome) [5, 8].

22.2.2 Natural History

ACC has a dismal prognosis with an overall 5-year survival of <30%. This is partly due to the nature of the tumour and partly due to the often late presentation. In an analysis including 320 patients with stage III and IV disease [9], the outcomes for patients who did not undergo surgery were very poor, with a 1-year survival of ~15%.

Sites of metastatic disease include regional lymph nodes (25–46%), lungs (45–97%), the liver (48–96%) and bones (11–33%) [10].

22.2.3 Diagnosis

(i) *Clinical suspicion*

Both the presentation with symptoms of newly onset and rapid progression of hypersecretion of adrenal hormones and a palpable abdominal tumour are highly suspicious for a malignancy.

(ii) *Biochemical assessment*

As for all adrenal tumours, initial biochemical assessment should include:

- Plasma-free levels of metanephrines (to exclude phaeochromocytoma).
- Measurements of urinary free cortisol levels and overnight 1 mg dexamethasone suppression test (formal assessment of glucocorticoid axis).
- Measurements of DHEAS (dehydroepiandrosterone sulphate) and androstenedione for assessment of androgen secretion.
- Determination of plasma renin activity and aldosterone concentration is reserved for those individuals with hypertension (though aldosterone is seldom secreted by ACC).
- A urine steroid profiling can be undertaken [11]. This is a highly sensitive and specific biomarker tool for malignant adrenal lesions, as a pattern of predominantly immature, early-stage steroidogenesis can be seen in the urine of patients with ACC [11–13].
- Measurement of serum electrolytes should be done in all patients, as adrenal steroids can induce severe hypokalaemia needing preoperative correction.

(iii) *Cross-sectional imaging*

Most ACCs are large at presentation, with a diameter of >6 cm in over 90% of cases [14, 15], and there is an increasing risk of malignancy for larger tumours.

While the risk of malignancy is thought to be already considerably high at ~20% for tumours >6 cm, this increases to ~50% for those larger than 8 cm [16]. The risk of a tumour smaller than 4 cm being malignant was found to be considerably lower, hence the recommendation of adrenalectomy for non-functional incidentalomas measuring larger than 4 cm.

Other characteristics of ACC on computed tomography (CT) scan, besides a relatively large tumour size, include a well-defined margin with a thin enhancing rim, a central area of low attenuation and a tendency for extension into the inferior vena cava [15]. Relatively high unenhanced CT scan attenuation values (>10 Hounsfield units (HU)) on non-contrast CT scan have

a high sensitivity for diagnosing ACC but a rather low specificity [14, 15, 17].

On magnetic resonance imaging (MRI scan), ACC appears iso- or hypo-intense compared to the liver on T1-weighted images, while their appearance is hyper-intense on T2-weighted images [14, 18]. The chemical shifting that is usually seen in benign lipid-rich adenomas is virtually absent in the contrast-enhanced MR images of patients with ACC.

(iv) *Functional molecular imaging*

The majority of ACCs are avid on positron emission tomography/computed tomography (PET/CT) labelled with fluorine-18 fluorodeoxyglucose (FDG). The sensitivity and specificity for the diagnosis of ACC on FDG-PET/CT are high, at around 95% for both [19–21]. However, as metastatic lesions in the adrenal gland give a similar appearance, the FDG-PET/CT should not be used as a standalone diagnostic modality.

Imaging with ^{123}I-iodometomidate (i.e. radioactive iodine-labelled metomidate) is another promising imaging modality. Metomidate has a high affinity for 11β-hydroxylase, which is an enzyme located in the cortex of the adrenal gland that is essential in the synthesis of the hormones aldosterone and cortisol [21, 22]. In a study of 430 lesions, metomidate PET had 100% specificity, but a many lesions failed to show uptake leading to a low sensitivity of 38% [22].

(v) *Biopsy is not indicated*

Biopsy is not indicated in the work-up of possible ACC in order to avoid rupture of the capsule and spilling of tumour cells [6]. In general, adrenal biopsy should only be considered when primary adrenal lymphoma (PAL) is suspected or when trying to demonstrate adrenal metastases, as discussed later in this chapter.

(vi) *Histological assessment*

The difference between ACC and a benign adrenal tumour can be challenging. Some of the histological features associated with malignancy (capsular invasion or vascular invasion) can also be encountered in benign adrenal adenomas.

The *Weiss scoring system* remains the standard for the diagnosis of ACC. This score is based on the assessment of nine morphological parameters at light microscopy: nuclear grade, mitotic rate >5 per 50 HPFs, atypical mitotic figures, diffuse architecture, necrosis, venous invasion, and invasion of tumour capsule. A score <3 defines benign adenomas, a score >6 is associated with ACC, and a score of 3–6 raises suspicion of malignancy.

The proliferation marker Ki67 is considered an important prognostic marker for recurrence-free survival and overall sur-

vival. For example, in a study of over 300 patients, the clinical outcome differed significantly between patients with Ki67 <10%, 10–19% and >20% (median overall survival, 180 versus 113 versus 42 months) [23].

22.2.4 Treatment

Surgery is considered the only curative treatment. Patients with locally advanced disease treated without surgery have poor survival [9]. This will later be discussed in more details.

Adrenolytic chemotherapy with mitotane can be given either as adjuvant or palliative therapy. Mitotane is an isomer of dichlorodiphenyltrichloroethane (DDT) that is directly cytotoxic to adrenal tissue [24]. In the palliative setting, the aim of mitotane treatment is both the control of tumour growth progression and the reduction of hormone secretion. It has severe side effects (e.g. anorexia, nausea and vomiting but also adrenal insufficiency and crisis in some patients); moreover, the target therapeutic level and toxic range are narrowly together (14–20 ng/dL). While mitotane is frequently used as a monotherapy, for more aggressive tumours, it can be combined with chemotherapy treatment [25]. Based on the results of an international randomized trial (FIRM-ACT trial), mitotane plus etoposide, doxorubicin and cisplatin is now the established first-line cytotoxic therapy owing to a higher response rate and longer median progression-free survival than achieved with streptozocin-mitotane.

Retrospective studies on the use of adjuvant mitotane in ACC have shown mixed results [24]. A prospective randomized trial (ADIUVO) is currently recruiting patients, and possibly its results will impact on future protocols for ACC.

Although there are no guidelines that currently advise neoadjuvant medical treatment for ACC, clinicians at MD Anderson [26] described preoperative systemic treatment for patients with *borderline resectable tumours*, in order to achieve reduction of tumour burden. They reported a prolonged disease-free survival for those who underwent surgery after downstaging neoadjuvant systemic therapy.

Radiotherapy for ACC is limited because of technical difficulties to limit the irradiation field of the adrenal bed without affecting surrounding viscera. In a study of 78 patients treated at the University of Michigan, USA, the 3-year overall survival estimate for patients improved from 48.6% for patients without RT to 77.7% with RT (HR, 3.59) [27]. In addition, a systematic review of 362 citations showed that adjuvant RT dramatically reduces the local recurrence of ACC after surgery and that the treatment has a low acute and late toxicity, resulting in a high therapeutic index [28].

22.2.4.1 Indications for Surgery and Surgical Details

Complete surgical resection of the ACC is the backbone of treatment for localized disease.

For tumours not invading surrounding organs, guidelines advise to remove the adrenal gland and the surrounding fat and lymph node tissue. There is little data supporting a benefit of a more extensive lymph node dissection [6, 29]. Although lymph node dissection obviously does aid in the correct tumour staging, its influence on overall and disease-free survival remains controversial [30].

A topic of debate is the type of surgical approach that should be employed for these patients, i.e. an open resection or a minimally invasive approach. In general, the main objective is to obtain a complete R0 excision without tumour spill, including at least a nodal dissection of the renal pedicle. While open resection in the hands of an experienced adrenal surgeon currently is the gold standard for operative management of this disease [7], there are some studies supporting the performance of a laparoscopic resection, at least for a selected set of patients with small tumours.

Available data show that, as for other diseases, a laparoscopic approach is associated with a shorter length of stay, at least for tumours measuring ≤10 cm [31]. Moreover, a recent review of non-randomized controlled trials [32] reported that for patients with localized/locally advanced primary ACC, a laparoscopic approach seems to be comparable to a laparotomy not only in terms of obtaining negative surgical margins but also when addressing overall recurrence, disease-free survival and overall survival.

In order to achieve R0 resection margins, wide en bloc resection is necessary for many large tumours. As the cranial border of the perirenal space is not covered by Gerota's fascia, invasion of the liver and/or diaphragm (right-sided tumour) or spleen, pancreas and/or diaphragm (left-sided tumour) might occur and can sometimes only be appreciated during the surgical procedure [6, 10]. For these patients, an en bloc resection that includes not only the tumour but also the kidney, the adjacent invaded organs and the entire continuity of peri-adrenal and perirenal fat might be indicated in order to achieve negative margins [6]. Although only limited data exists to provide precise guidance, it is generally considered that the threshold for en bloc resection of adjacent organs should be low, mainly if there is macroscopic suspicion of invasion [8]. For such cases, an open adrenalectomy is the preferred approach.

An important subgroup of patients is those in whom the inferior vena cava is involved by tumour. In general, this involvement consists more often of a caval tumour thrombus

than of actual direct tumour extension into the venous wall [6, 33, 34]. For these patients, a formal thrombectomy should be undertaken. When there is frank invasion of the wall of the vena cava, this is usually only over a limited tract and is therefore amenable for partial caval resection with direct closure or by a patch. It has been shown that large vessel extension of the ACC is associated with poorer overall and recurrence-free survival [35].

Data on surgical debulking for ACC are scarce, but in general, several studies have shown that progression-free survival is similar in patients who undergo debulking (i.e. R2 resections) and for those treated non-surgically [36, 37]. Therefore, current guidelines state that only in selected cases (e.g. patients with severe hormone excess or serious symptoms from the tumour's mass effect such as vena cava compression), debulking surgery might be an option. It is generally advised that surgery should be considered if >80% of the tumour burden can be removed [38].

There is an ongoing effort to identify methods to centralize surgery for ACC, as the current service provision is unsatisfactory. The European Society of Endocrine Surgeons reviewed the evidence for a volume-outcome correlation in adrenal surgery and made the recommendations that adrenal surgery should continue only in centres performing at least 6 cases per year and that surgery for adrenocortical cancer should be restricted to centres performing at least 12 adrenal operations per year. Moreover, an integrated multidisciplinary team should be established in all such centres [39]. How this should be achieved will vary in each country. It is, however, the duty of every clinician to provide patients with the correct advice before reaching an informed decision about referral to a regional centre where appropriate expertise exists for the care of patients with such an aggressive malignancy.

22.2.5 Outcomes or Prognosis

ACC remains a disease with a dismal prognosis, with a reported overall 5-year survival rate between 16% and 47% [25, 40]. For the very few patients with stage I disease (i.e. tumours <5 cm with no signs of lymph node or distant metastases), median survival could be in excess of 10 years, but those with stage IV disease (distant metastases) are unlikely to survive more than 1 year after initial diagnosis [41]. Overall, ACC is a diverse cancer, and outcomes may therefore vary even among patients within the same tumour stage, due to the largely still unknown impact of different clinical, pathological and molecular factors [42].

22.3 Metastases to the Adrenal Gland

22.3.1 Clinical Presentation

The adrenal glands can be infiltrated with metastases from a variety of oncological diseases [43]. Moreover, metastatic tumours are the most common lesions of the adrenal gland at post-mortem examinations [44]. Adrenal metastases most commonly occur in patients with lung cancer, breast cancer, melanoma, renal cancer and gastrointestinal carcinomas [45, 46].

The typical route of spread is generally understood to be haematogenous, with the tumour cells nesting in the adrenal gland while travelling through its sinusoid-like blood vessel network. However, for lung cancer, there might be lymphatic spread instead [47].

Clinical presentation is usually silent, as metastatic lesions fail to destruct enough adrenal tissue to produce clinical signs or symptoms of insufficiency, although there are case reports of Addison's crisis due to bilateral adrenal metastases [48–55]. Consequently, most adrenal metastases are picked up on follow-up imaging.

As the cancer-related mortality for most malignancies has decreased over the past decades and patients therefore have a longer survival, the incidence of adrenal metastases diagnosed during oncological follow-up has gone up. Moreover, with the concomitant increased use of more protocolized follow-up regimens, these metastases are detected at an earlier stage.

22.3.2 Natural History

As adrenal metastases are always a sign of spreading of the primary malignant disease, not treating these lesions will result in a shorter survival. In a review of seven studies discussing the non-surgical treatment of adrenal metastases from different primary tumours, there were large variances per primary tumour site, and the median overall survival was poor (3–15 months) [43].

22.3.3 Diagnosis

As stated earlier, most metastatic adrenal lesions are silent in their presentation, and the diagnosis is therefore usually made on imaging scans which are part of the work-up for patients' initial disease.

Specific characteristics of adrenal metastases on computed tomography (CT) scan include their irregular shape and inhomogeneous nature, their tendency to be bilateral, their high unenhanced CT scan attenuation values (>20 Hounsfield units

(HU)) and their enhancement with intravenous contrast on CT scan [56]. Moreover, there is a distinct delay in contrast medium washout (an absolute contrast medium washout of less than 50% at 10 minutes post administration of contrast). This latter is mainly due to the increased microvascular density, which causes a slower flow of contrast fluid exiting the tumour, and to a high endothelial permeability resulting in accumulation of contrast fluid within the tumour [57]. Furthermore, some authors suggest that every isolated adrenal mass 'incidentaloma' measuring more than 3 cm in diameter in patients with a known history of cancer should be interpreted as suspicious for metastasis [58].

On magnetic resonance imaging (MRI scan), metastatic adrenal lesions generally are isointense or slightly less intense than the liver on T1-weighted images and have a high to intermediate signal intensity on T2-weighted MRI [59].

Due to their increased glucose metabolism, most adrenal metastases are avid on positron emission tomography/computed tomography (PET/CT) labelled with fluorine-18 fluorodeoxyglucose (FDG) [60, 61]. Several authors have reported a sensitivity of over 90% with a specificity close to 100% for FDG-PET/CT to differentiate benign from malignant adrenal lesions [62, 63].

The role of biopsy for adrenal lesions has been somewhat controversial. While open biopsy of the adrenal gland has now been abandoned in the work-up, most authors agree that CT- or US-guided fine-needle aspiration (FNA) cytology can be considered the procedure of choice in the diagnostic evaluation of adrenal nodules in patients with known malignant neoplasms [64–66]. Other techniques to obtain tissue for biopsy can be via *endoscopic ultrasound* (*EUS*)-guided *FNA* [67, 68]. While performing an image-guided FNA may be indicated in patients with known malignant disease and a newly discovered adrenal mass with suspicious characteristics on imaging, it is important to exclude increased metanephrine production (i.e. phaeochromocytoma) before proceeding with such a biopsy. Moreover, adrenal biopsy might not be indicated in patients with already known widespread metastatic disease. Risks of FNA biopsy of the adrenal gland include haematoma of the adrenal gland or liver, pancreatitis, pneumothorax, formation of an adrenal abscess and tumour seeding along the needle track; however, overall this is considered a safe procedure with complication rates reported as low as 2.8% [69, 70].

A rare scenario involves patients presenting with an adrenal incidentaloma but no previous history of malignancy. If the incidentaloma is enlarging on serial scans or if the initial tumour dimeter is over 4 cm, such patients are offered laparoscopic adrenalectomy for the potential risk of malignancy (i.e. ACC), and occasionally the final histological diagnosis could be of a metastatic lesion from a clinically silent primary tumour.

22.3.4 Treatment

To establish a tailor-made treatment, all patients with adrenal metastases require multidisciplinary evaluation to determine the appropriateness of surgical intervention [71]. Such decisions are likely to be different based on the primary site of malignancy and the suspicion/evidence for any additional metastatic disease.

Overall, the only curative option for patients with metastatic disease to their adrenal gland is complete (R0) resection of all known disease. Several studies have underlined the more favourable outcomes for patient after resection of disease compared with non-operative management [43, 71–73]. Therefore, as a general principle, resection of a single-site adrenal metastatic disease should be attempted, considering that the operation is feasible with minimal morbidity.

For synchronous metastases, the treatment for the adrenal metastasis should be offered after completion of curative treatment for the primary tumour (e.g. lung resection followed by laparoscopic adrenalectomy).

For metachronous metastases, the decision to operate for the adrenal metastasis would be influenced by the time to recurrence (better outcomes when metastasis was diagnosed some 6–12 months after the initial treatment for primary malignancy).

For patients with metastases in multiple sites or extensive tumour burden, treatment with systemic chemotherapy or palliative-supportive care should be undertaken [71]. Alternatively, recent reports on stereotactic body radiation therapy (SBRT) for adrenal metastasis show that this treatment has the possibility to provide good short-term local control with an excellent safety profile [74, 75].

For non-surgical candidates, percutaneous image-guided ablation therapy, such as chemical ablation, radiofrequency ablation, cryoablation and microwave ablation, has been shown of clinical value [76–80]. Overall, adrenal ablation is well-tolerated by patients and has the advantage that it can be performed under sedation or general anaesthesia. Although several studies have shown this technique to be feasible and that there does seem to be some survival benefit from this therapy, clear data on oncological outcomes is not yet available.

22.3.4.1 Indications for Surgery and Surgical Details

Before surgery is contemplated, assessment of plasma-free levels of metanephrines is mandatory to rule out phaeochromocytoma. In general, a complete endocrine assessment should also include measurements of urinary free cortisol levels and overnight 1 mg dexamethasone suppression test.

Adrenal metastasis is often confined within the gland itself, providing a good opportunity for achieving en bloc removal. The main features of a successful adrenalectomy are a wide resection with negative margins (i.e. a R0 surgical resection) and the absence of tumour spill during the procedure.

As for most adrenal tumours, traditionally, open surgery was the preferred operation for patients with adrenal metastasis. The first report of laparoscopic adrenalectomy for malignancy was published in 1999 [81]. Although it has taken nearly two decades to do so, laparoscopic adrenalectomy is currently the standard treatment for metastatic disease to the adrenal glands. The non-oncological benefits of minimally invasive surgery have long been established also for other indications, i.e. shorter postoperative hospitalization, less intra- and postoperative complications as well a greater patient compliance [82, 83]. Furthermore, several large studies showed that the survival for patients undergoing a laparoscopic adrenalectomy for metastasis is similar to the open approach [83, 84].

More recently, posterior retroperitoneoscopic adrenalectomy has been utilized in the resection of adrenal metastasis [85]. Similar as for the anterior laparoscopic approach, several studies have shown this to be a safe and feasible technique [85–87]. An added benefit of the retroperitoneoscopic approach is that it avoids the need for mobilization of adjacent intra-abdominal organs and that there is no impact of adhesions from possible previous abdominal surgeries. The main limitation is that the technique is more difficult to be mastered in centres with low-volume practice and that the small operative space creates additional challenges for an oncological resection (i.e. no tumour breaching/fragmentation during the dissection).

For cases in which wide surgical margins with en bloc excision of peri-adrenal fat cannot be achieved through a laparoscopic or retroperitoneoscopic approach, open adrenalectomy remains the gold standard technique. For those patients in whom local invasion is suspected on preoperative imaging, whose tumour is large, when there is significant lymphadenopathy or tumour thrombus in the vena cava, open adrenalectomy also remains the technique of choice. Several authors also suggested relative contraindications for a laparoscopic approach, such as morbid obesity, cardiovascular comorbidity or adhesions due to multiple prior abdominal surgeries [43, 71, 88].

A specific subgroup of patients who should be considered candidates for adrenalectomy are those in whom one or more other sites of metastatic disease are responding to systemic therapy, but there is a non-response deposit in one of the adrenal glands. This situation has been described as *sanctuary metastases*, and cases involving primary tumours as melanoma

and the uterus have been published [89, 90]. Overall advice from available literature is to perform early adrenal surgery in these patients.

22.3.5 Outcomes or Prognosis

Overall oncological outcomes for adrenalectomy for metastases are not easily assessed, as it comprises a heterogeneous group of patients with various primary tumour sites. Although there have not been any randomized studies performed to assess this and while there is a presumed bias in the patient selection for surgery, most studies report favourable outcomes after adrenalectomy for metastases. In a large multicentre European study of a total of 317 patients with histologically confirmed adrenal metastatic disease who underwent laparoscopic (n = 146) or open (n = 171) adrenalectomy, the median overall survival was 24 months for open adrenalectomy and 45 for laparoscopic adrenalectomy. Survival rates at 1 and 5 years were 68% and 29% for open surgery versus 88% and 46% for laparoscopy, respectively. Patients who underwent laparoscopic adrenalectomy showed a longer survival than open adrenalectomy individuals, although minimally invasive approach was attempted more commonly in less advanced disease which led to higher number of R0 resections [82].

22.4 Adrenal Lymphoma

22.4.1 Clinical Presentation

While series on autopsies have reported adrenal gland involvement in up to 25% of lymphoma patients (mainly non-Hodgkin's lymphoma) [91], actual primary adrenal lymphoma (PAL) is a very rare clinical entity. The majority of PAL (~70%) are diffuse large B-cell lymphoma subtype [92].

In a review of about 100 cases of PAL available in literature [92], a large portion of patients presented with symptoms common in lymphoma, including abdominal or lumbar back pain, fever of unknown origin, anorexia, weight loss and malaise. However, interestingly, as more than two-thirds of all patients had bilateral enlargement of the adrenal glands, these authors reported that a significant percentage of patients presented with signs of adrenal insufficiency. Moreover, PAL can also rarely manifest as frank Addison's disease [93]. Furthermore, the majority of cases on PAL available in literature included older males, with a mean age at presentation of 65 years and a male-to-female ratio of 2:1 [91, 92, 94].

22.4.2 Natural History

Overall, this disease has a very poor prognosis – even when treatment is provided. Available data shows that patients given only palliative treatment succumbed at a rapid rate [92]. However, due to the paucity of available data, how PAL compares with other types of lymphoma with similar histology is not known; therefore, no reliable statements regarding its natural history can be made [95].

22.4.3 Diagnosis

As PAL is a very rare disease, limited reports on the preferred diagnostic pathway are available [96]. Most diagnoses are made after performance of cross-sectional imaging scans. On imaging, PAL can easily be confused with an adrenal metastatic lesion.

On computed tomography (CT) scan, necrosis, haemorrhage and calcifications within the adrenal lesion are frequently seen [97, 98].

On magnetic resonance imaging (MRI scan), PAL tends to be hypo-intense on T1-weighted images, while it tends to be hyper-intense on T2-weighted images [94].

Positron emission tomography/computed tomography (PET/CT) labelled with fluorine-18 fluorodeoxyglucose (FDG) seems to be useful in demonstrating extra-adrenal locations of PAL, with one study reporting incidence of extra-adrenal locations in 70% of patients [94].

For the definite histological diagnosis, a biopsy is required. This can be obtained by a CT-guided needle biopsy or as a surgical biopsy [97, 98].

22.4.4 Treatment

Currently, no empirical protocols specifically for the treatment of PAL are available. Most authors describe local regimens consisting of multimodality treatment including chemotherapy or radiotherapy, while data supporting the preferred treatment options are not existing.

Chemotherapy is the most commonly used regimen. In a SEER-based analysis, receipt of chemotherapy was an independent factor for prolonged overall survival [95].

Traditionally, CHOP regimens were most frequently administered. This combination therapy consists of cyclophosphamide and hydroxydaunorubicin with oncovin and prednisone. Unfortunately, the outcomes were generally poor with overall reported survival rates from 20 to 50% [96]. More recently, reg-

imens containing rituximab combined with CNS prophylaxis have been proposed as alternate and, possibly, more promising treatment options for the treatment of PAL [99]. A complete remission rate of 55% and an overall response rate of 87% were reported in 31 patients who received R-CHOP (i.e. with rituximab) regimens [100].

The role of surgery in this disease has been controversial. While case reports on patients who underwent unilateral or even bilateral adrenalectomy for PAL are available [92, 101], the largest cohorts on surgical treatment for this disease reported no survival benefit for those who underwent surgery compared to those who were treated with medical treatment only [94, 100].

22.4.5 Indications for Surgery and Surgical Details

Although most data on the indications for adrenalectomy for patients with PAL are anecdotal, there are some case reports addressing this subject. It is therefore questionable if reliable statements regarding the benefit or indications of surgical treatment for this disease can be made [92].

The largest series addressing the surgical treatment for PAL included 28 patients of whom 4 underwent surgery, and it was found that adrenalectomy brought no survival benefit [94].

Similarly, there was no survival benefit for surgery in a group of 31 patients treated with an R-CHOP regimen, of whom 7 underwent adrenalectomy [100].

22.4.6 Outcomes or Prognosis

As mentioned before, the outcomes for patients presenting with PAL are poor. Less than 50% of patients who were treated with curative intent achieve a complete remission, while many of these develop relapse of their disease during the first months of follow-up as about a third of patients survived disease-free for at least 6 months [92]. Similarly, a report of 136 patients identified on the Surveillance, Epidemiology, and End Results (SEER) program (1983–2015) showed that the majority of patients presented with advanced-stage disease and reported an overall survival at 5 and 10 years of 19% and 3%, respectively. Independent prognostic factors correlated with adverse overall survival were age over 70 years and bilateral lesions [95].

Answers to the Questions

1. (d); 2. (a); 3. (d); 4. (b); 5. (d); 6. (a); 7. (a); 8. (a)

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