

Adrenal metastases

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The adrenal glands are one of the most prevalent sites for metastases from various malignancies and metastases are indeed the most frequent malignant tumors of the adrenals. The identification of incidental adrenal lesions, of which a high proportion are metastases, have increased since surveillance protocols in cancer treated patients were widely introduced. More sensitive and reliable methods of diagnostic imaging leads to earlier detection of adrenal metastases. If there are no signs and symptoms of disseminated malignant disease, it is essential to differentiate adrenal lesions. CT imaging diagnostics and MRI play the main role in differential diagnosis. Adrenal biopsy is not recommended and is of limited diagnostic value. Appropriate selection of patients with adrenal metastases for curative treatment is a great challenge. Hormonal evaluation should be performed prior to treatment. Adrenalectomy seems to be a reasonable treatment for isolated adrenal metastasis in suitable patients. Minimally invasive laparoscopic adrenalectomy is as effective as the open approach with proven reduction in postoperative pain, morbidity and length of stay. Non-surgical treatment such as stereotactic body radiation therapy (SBRT), radiotherapy with CyberKnife, percutaneous radiofrequency ablation, percutaneous microwave ablation, radiofrequency plus chemoembolization combined, have been reported with curative and palliative intent and have shown varied results.

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Introduction

The adrenal glands is one of the most prevalent sites for metastases from various malignancies. The most common types of adrenal tumors are benign cortical adenomas [1], however metastases are the most frequent malignant tumors of the adrenal gland. The existence of adrenal metastases in patients with a history of cancer varies in different series between 10 and 27% [2, 3]. Probably the reason for this frequently observed metastatic localization of various cancers is the rich sinusoidal blood supply of adrenal glands which favor this location for metastases [3]. Although most adrenal metastases are undoubtedly of hematogenous origin, it seems that they may develop via lymphatic spread from the lung [4]. Lymphatic drainage between the lung and

the retroperitoneum is well described and some ipsilateral adrenal metastases may come by a lymphatic pathway, therefore they may be considered more as locally advanced than distant metastases [5].

Surveillance protocols in cancer treated patients have increased the identification of incidental adrenal lesions, a high proportion of which are metastases. More sensitive and reliable methods of diagnostic imaging lead to earlier detection of adrenal metastases. In most cases it is part of disseminated disease; however, if isolated adrenal metastases are detected and removed surgically, this can provide an opportunity to improve the prognosis in selected patients [6, 7].

Selection of patients with adrenal metastases for curative treatment is a great challenge. The presence of an adrenal

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mass is reported in 1–4% patients undergoing imaging studies for various reasons [8]. The prevalence of such findings increases with age [9, 10]. The majority of these tumors are benign nonfunctional lesions. On the other hand, the frequency of adrenal metastases is high. However, usually they are an element of generalized disease, therefore such patients are rather candidates for systemic chemotherapy or palliative supportive care. In opposition to these data, number of adrenalectomies performed to treat metastases is very low from less than one performed in a surgical center per year [11], up to less than six a year [12, 13]. This is one of the reasons that makes it difficult to establish criteria to define which patients will benefit from adrenalectomy in terms of cure or increased survival. Data available in literature are heterogeneous and differ in the frequency of tumors that metastasize to the adrenals. These differences in the prevalence of different cancers to the adrenals depend on the author and the geographic origin. There is only scarce prospective data and a lack of randomized evidence to confirm that local therapy on the adrenal metastases alters the natural course of disease. Treatment of patients with adrenal metastases varies among institutions and is highly dependent on clinical discretion.

The benefits of adrenalectomy for metastases are still unclear but several retrospective studies have identified highly selected groups of patients with lung cancer, renal cell cancer and melanoma whose survival seems to be prolonged with surgery [11, 14, 15].

Diagnosis

Incidentally detected adrenal masses in patients with no known malignancy occur in 5% of all abdominal computed tomography (CT) examinations [16]. This incidence increases in patients with a known underlying malignancy to 9% [17]. With the adrenal mass of size larger than 4 cm which grows on follow up imaging within 1 year, the likelihood of a metastatic character is up to 71% [18]. Characteristics of suspicious mass include: large size (especially bigger than 4 cm) irregular contour, heterogeneous appearance and a temporal increase in size.

Essential diagnostic imaging of adrenals is CT, performed before and after i.v. contrast injection. It can detect adrenal masses larger than 5mm in diameter. Approximately 70% of adenomas can be identified using CT with no contrast enhancement. The remaining 30% of adenomas are lipid poor and are difficult to differentiate with this technique [19].

On unenhanced CT, lipid poor adenomas have a native density not greater than 10 Hounsfield units (HU), and in clinical practice 10 HU is the most widely used threshold attenuation value for the diagnosis of lipid-rich adrenal adenoma with a sensitivity and specificity of 89% and 100% respectively [20]. Malignant lesions and pheochromocytomas

are usually lipid poor, although clear cell renal carcinoma metastasis, adrenal carcinoma and some pheochromocytomas may be lipid rich [21]. Characterization of adrenal masses using contrast enhanced CT takes the advantage of the specific perfusion pattern of adenomas, they enhance rapidly after contrast administration and demonstrate a rapid loss of contrast medium. This phenomenon is called "contrast enhancement washout". Malignant lesions including metastases enhance rapidly but demonstrate a slower washout of contrast medium [22]. The contrast enhanced CT value is the attenuation value of the mass, measured in HU 60 s after intravenous contrast administration. The delayed attenuation is measured 10 or 15 min after contrast administration. Calculation of the absolute washout requires a Hounsfield value from unenhanced CT; relative contrast washout is calculated using 60 s and delayed values. An absolute contrast washout of > 60% and a relative contrast washout of > 40% characterize an adenoma with a sensitivity and specificity of 98 and 92% respectively [23].

Magnetic resonance imaging (MRI) of the adrenals should include T1 and T2 weighted images and chemical shift imaging (CSI). A normal adrenal gland has T1 and T2 signal intensity equal to or slightly lower than that of the normal liver [24]. Malignant tumors of the adrenal glands, including metastases in general, have a higher fluid content than adenomas and therefore are of higher signal intensity on T2-weighted images than the surrounding normal adrenal gland. After gadolinium enhancement, 90% of adenomas demonstrate homogenous or ring enhancement, while 60% of malignant masses have heterogeneous enhancement [25].

Chemical shift imaging is based on the fact that within a magnetic field, protons in water molecules oscillate at a different frequency than the protons in lipid molecules. Lipid rich adenomas lose signal intensity on out-of-phase images, compared with in-phase images, whereas malignant lesions that lack intracellular lipid remain unchanged. The combination of spin-echo signal characteristics, gadolinium enhancement and CSI has up to 90% accuracy in distinguishing between adenomas and non-adenomas [26].

Whole body positron emission tomography (PET) with [¹⁸F] fluorodeoxyglucose ([¹⁸F]FDG) demonstrates high sensitivity in detecting adrenal malignant lesions, with specificity ranging between 87 and 97%. A small number of adenomas and other benign lesions may mimic malignant lesions in PET [27]. Standardized uptake values (SUVs) of 2.68–3.0, differentiate malignant from benign adrenal masses. The ratio of SUV of the adrenal mass and that of the liver of 1.45, helps to distinguish malignant adrenal lesions from adenomas with a sensitivity of 100% and a specificity of 88%. Combined FDG-PET and CT data, including contrast washout characteristics, have a sensitivity and specificity of 100% and 98% respectively.

False positive results for malignancy in PET/CT occur in 3–13% of adrenal lesions and include adenomas, pheochromocytomas, inflammatory and infectious lesions. False negatives for malignancy have been reported in adrenal metastases with hemorrhage or necrosis, small (5–10 mm) and metastases from pulmonary bronchioloalveolar carcinoma or carcinoid tumors [28].

The biggest advantage of PET CT is the ability to distinguish localized or oligometastatic disease potentially curable by surgery from patients with disseminated cancer to be treated by systemic chemotherapy or supportive care. It is important to remember that PET is not reliable for identifying brain metastases and another brain imaging study, CT or preferentially MRI, should be performed, especially in cases of adrenal metastases from lung cancer.

Collision tumors

The term collision tumor refers to independently co-existing neoplasms with different behavioral, genetic, and histological features that are sharply demarcated and lack significant tissue mixture. In contrast to composite tumors which arise from a common neoplastic source, collision tumors arise from different neoplastic sources [29]. Many adrenal collision tumors remain undetected due to their small size. All of them are a diagnostic challenge, and tumors should always be evaluated separately as they may represent different types. Collision tumor should be suspected in a patient with a history of malignancy with the imaging revealing a heterogeneous adrenal mass. The most common adrenal collision tumors are adenomas with metastases like renal cell carcinoma or breast cancer [30, 31].

Adrenal biopsy

In general, adrenal biopsy is not recommended [32]. The only exception to this rule is suspicion of adrenal metastases if the expected findings are likely to alter the treatment of the individual patient. Data obtained from the literature are inconsistent. It is an invasive, expensive procedure with a potential for non-diagnostic results and complications. There have been a number of cases when biopsy did not alter clinical treatment of any of the patients who had undergone biopsy [33].

On the other hand, there are data from a relatively large number of patients proving that when used in the appropriate clinical setting, adrenal biopsy is a powerful tool in the diagnostic algorithm of the evaluation of adrenal masses with features suspicious for malignancy [34].

The present meta-analysis of adrenal biopsies diagnostic performance collected data from 32 studies [35]. Information from 2190 adrenal biopsies were analyzed. Pathology was reported only in 74% of cases, of which 51% (828) were classified as malignant. Of the malignant lesions, the majority were metastases — 83%. The most common primary

tumors were: lung (67.3%), kidney (7.6%), melanoma (3%), liver, breast and colon (2.3%), esophagus (2.1%), bladder (1.2%) and pancreas (1%).

The pooled non-diagnostic rate was 8.7% and pooled overall complication rate was 2.5%. Major complications included adrenal hematoma, pancreatitis, pneumothorax, hemothorax, perirenal hematoma, duodenal hematoma and hypertensive crisis. In one case, needle track metastases seeding occurred. Worth noting is that the rate of adverse events may be as high as 13.6% [36, 37]. It is very important to remember that inadvertent biopsy of pheochromocytomas can provoke ejection of catecholamines that may lead to severe life threatening adverse events. Endocrine evaluation, or at least screening with metanephrines, should be standard of care before the adrenal biopsy.

The sensitivity and specificity for diagnosis of metastases was 87% and 96% respectively.

Surgical treatment

The first report of adrenalectomy for adrenal metastases was published in 1982, describing the cases of two patients with long-term survival after resection of adrenal metastases from non-small cell lung cancer [38]. Further investigations demonstrated that resection of adrenal metastases from non-small cell cancer provided essentially longer survival compared to a conservative treatment [39].

So far, all the available data are from retrospective studies and there is high bias in the selection of candidates for adrenalectomy when comparing operated and non-operated patients. It should be remembered that adrenalectomy for metastasis is an infrequently performed procedure, even in specialized centers, and may not exceed 1 adrenalectomy per center per year [11]. The majority of the studies data are pooled from patients undergoing resection of adrenal metastases of all origins, whereas some studies focus on metastases from a single origin.

On pooling patient data, the three most common primary histologies were lung cancer (small and non-small), renal cell carcinoma and melanoma, representing 32%, 22% and 15% of patients respectively [40]. In another large series, the most frequent primary tumors were lung (46.6%), colorectal (13.5%), renal cell carcinoma (11.7%), breast (3.5%) and melanoma (3.5%) [6]. The relative prevalence of each primary malignant tumor varies according to the source of data and the geographic origin. Data from Asia reported a high prevalence of stomach (14%), esophagus (12%) and the liver/bile ducts cancers (10%) with a paucity of breast cancer and melanoma [41].

Patients considered for surgical treatment should fulfil such criteria as achieved control of extra adrenal disease, metastasis confined to the adrenal gland, performed biochemical evaluation of the tumor, diagnostic imaging that is highly suggestive of metastasis and appears resectable,

patient performance status warranting a surgical approach [42].

Most reports indicate that surgical treatment of adrenal metastases may have an important therapeutic value in selected patients, but no predictive factors have been clearly identified yet, and conclusions sometimes are contradictory.

The median survival of patients with surgically removed adrenal metastases was significantly better than the survival rates of patients without surgery, achieving 34 months versus 6 months respectively [43].

30 months median overall survival in patients with surgically removed adrenal metastases was reported in another paper with 1-, 3- and 5-year survival of 79%, 45% and 31% respectively. Patients with a lung primary had significantly shorter survival, with median survival of 17 months and 5-year survival of 27%, compared to patients with other primary cancers who had a median survival of 47 months and 5-year survival of 38%. Patients with synchronous metastasis had significantly shorter survival than those who presented metachronous lesions, with median survival of 14 vs 41 months, and 5-year survival of 21% vs 34%. Patients who had DFI < 12 months had worse outcomes compared to those with DFI > 12 months, with median survival of 13 vs 41 months and 5-year survival of 0% vs 39% [44].

In a multicenter study which assessed the results of adrenalectomy for solid cancer metastases in 317 patients, median overall survival for the whole cohort was 29 months. Survival at 1, 2 and 5 years was 80%, 60% and 35.4% respectively. Significant differences in the median survival time according to the type of the primary tumor were observed. Patients with renal cancer showed a better survival (median 84 months) compared with non-small lung cancer (median 26 months), those with colorectal cancer (median 29 months) and those with other tumor types (median 24 months). Patients with metachronous adrenal metastatic disease showed a median survival of 30 months compared with 23 months in patients with synchronous adrenal metastases [11].

Primary renal cancer seems to have the best prognosis in comparison to other primary cancers. In 41 patients, overall median survival was 14 months and 5 years survival were observed in 21%, for patients with primary renal, 5 years survival rate was 50% [45]. Significant differences in survival with regard to tumor type were seen in another report, with longer survival for patients with colorectal carcinoma or renal cell carcinoma and shorter for those with non-small lung cancer or melanoma [46]. Not only renal primary but also a tumor size smaller than 5 cm in multivariate analysis were independently associated with longer survival in series of 65 consecutive patients submitted to adrenalectomy for metastatic disease [47].

The findings of other studies are ambiguous regarding factors which determinate survival after adrenalectomy for

metastases. In a group of 90 patients with dominant primary melanoma and lung cancer and actual 5-year survival of 26.2%, there was no statistically significant difference in overall survival for those who underwent adrenalectomy for metastases from lung cancer compared with those with melanoma or another tumor [48].

The disease free interval (DFI), defined as the time when the patient is tumor-free prior to recognition of adrenal metastasis, is a prognostic factor related to more favorable outcomes in patients with adrenal metastases. A DFI > 6 months for lung cancer and > 12 months for melanoma is identified as an advantageous prognostic factor [49, 50].

Decreased overall survival was observed in patients with adrenal capsule disruption during surgery [51].

The reported effect of the primary tumor size in prognosing the outcome is controversial but appears to have some influence on survival [12, 52].

Previous metastasis surgery is a significant independent risk factor for worse prognosis with a hazard ratio of 5.8 in multivariate analysis [46].

Laparoscopy

Since first reported laparoscopic adrenalectomy in 1992 [53], this minimally invasive method has become the procedure of choice for resection of benign tumors of the adrenal glands [54]. The first report of laparoscopic adrenalectomy for malignancy was published in 1999 [55]. Like in other cancer surgeries, the critical issue is whether laparoscopic adrenalectomy can be considered equivalent to open surgery in terms of recurrence rates and survival time. Comparing results of open and laparoscopic adrenalectomy is difficult because usually the compared groups are small and analyzed retrospectively. Laparoscopic procedure is usually reserved for tumors not larger than 6 cm but it can be successfully performed even in tumors larger than 8 cm [56, 57].

The advantages of laparoscopic adrenalectomy are significantly less blood loss, a lower complication rate, and shorter length of hospitalization with no difference in survival between laparoscopy and open adrenalectomy [58].

Regarding long term oncological outcomes, analysis of 31 laparoscopic adrenalectomies and 63 open procedures showed similar results. Comparable rates of positive margins (22% vs 29%), local recurrence (11% vs 21%), and overall survival (median 31 months vs 30 months), were at a mean follow up of 42 months. The laparoscopic group experienced shorter operative time, lower estimated blood loss, shorter length of stay and fewer complications [59].

Tumor size, like in open surgery, has no influence on patient survival except for patients with metastases of colorectal cancer. Survival for the patients with small (< 6 cm) size tumors was significantly better than for those with large tumors [12].

Conversion rates vary from 2.7% [58] to 15.6% [13], and complication rates from 8.3% [57] to 18.1% [12].

Most of the described laparoscopic procedures were carried out by the lateral transperitoneal approach, but the posterior retroperitoneal approach may be also performed successfully [60], but there are data that show that retroperitoneal approach may be connected with a higher risk of unfavorable surgical outcomes [13].

Despite promising results, open surgery is still indicated for large tumors (larger than 6–8 cm), when preoperative imaging shows local invasion or discontinuous disease [61].

At present, the size of adrenal metastasis, the absence of extra adrenal invasion on imaging, the biology of the disease, and the performance status of the patient are the key factors that should indicate surgical removal by a laparoscopic approach which seems to be currently the first surgical option [57].

Nonsurgical treatment

Stereotactic body radiation therapy (SBRT) refers to the administration of large doses of highly conformal radiation with step dose gradients towards the surrounding normal tissue over a limited number of fractions. Over the past several years, there has been increasing interest in the use of SBRT for the treatment of adrenal gland metastases. Review of ten studies including 188 patients reveals that 1-year local control ranged from 44 to 100%, and 1-year overall survival ranged from 39.7 to 90% [62]. Overall survival was mainly influenced by the development of widespread distant metastases. Patients with metachronous metastasis (with a disease-free interval > 6 months), when compared to the whole study population, showed an unimproved 2-year overall survival of 55.6%, and median survival of 44.3 months. The toxicity of such treatment is limited to grade 2, with nausea and fatigue most commonly reported in up to 30–50% of patients.

In a more recent study, results of SBRT in ten patients with adrenal metastases were presented. Dose and fraction were determined on the basis of tumor size; patients received a total dose of 30 to 48 Gy in 3 to 5 doses. All of the patients received chemotherapy before or after SBRT. Median overall survival was 9.9 months. 90% of patients achieved control of treated adrenal gland metastasis with one patient experiencing progression of the adrenal gland metastasis 18.2 months after completion of treatment [63].

Radiotherapy with CyberNife robotic radiosurgery treatment is also used to treat metastases to the adrenals. Data from 23 patients were analyzed retrospectively. 19 of 23 patients achieved single-fraction radiosurgery with a median dose of 22 Gy and four were treated in three fractions with a median dose of 13.5 Gy. During follow-up (median time 23.6 months), local relapse was observed in 17% of patients with a mean time of 19 months to tumor progression [64].

Other methods of local control such as percutaneous radiofrequency ablation [65], percutaneous microwave ablation [66], radiofrequency plus chemoembolization combined [67], have been incidentally reported with small number of patients and limited value.

Miscellaneous

The adrenal glands may be occasionally the site of involvement in patients presenting with unknown primary cancer (5.8%). Isolated adrenal involvement is extremely rare (0.2%). Patients with unknown primary cancer and adrenal involvement had a poor overall prognosis, with a median survival of only 7 months [68].

Adrenal insufficiency in patients with bilateral adrenal metastases or unilateral adrenal metastases in patients with contralateral adrenalectomy is infrequent. It develops only in patients with large bilateral metastases with destruction of more than 90% of the adrenal cortex [69]. In a large retrospective study including 464 patients with adrenal metastases from various tumors, only five (1.1%) developed adrenal insufficiency [41]. In oncological patients, adrenal insufficiency may go unrecognized because the symptoms such as nausea, vomiting, weakness, orthostatic hypotension and laboratory anomalies such as hyponatremia and hyperkalemia may be linked to the underlying disease or to the cancer therapy.

Summary

There is no strong randomized evidence supporting the use of any adrenal metastasis therapy for improvement of survival in patients with limited disease. Treatment of such patients should be individualized under the care of a multidisciplinary team. Surgical treatment may be safe and effective in patients with metastasis isolated to the adrenal glands. When extra adrenal disease control is achieved, diagnostic imaging is highly suggestive of metastasis and actual patients performance status warrants a surgical procedure, complete hormonal evaluation, or at least pheochromocytoma exclusion, should be performed. Laparoscopy may be considered as a feasible and oncologically safe approach in selected patients.

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