REVIEW

Neoplastic metastases to the endocrine glands

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Abstract

Endocrine organs are metastatic targets for several primary cancers, either through direct extension from nearby tumour cells or dissemination via the venous, arterial and lymphatic routes. Although any endocrine tissue can be affected, most clinically relevant metastases involve the pituitary and adrenal glands with the commonest manifestations being diabetes insipidus and adrenal insufficiency respectively. The most common primary tumours metastasising to the adrenals include melanomas, breast and lung carcinomas, which may lead to adrenal insufficiency in the presence of bilateral adrenal involvement. Breast and lung cancers are the most common primaries metastasising to the pituitary, leading to pituitary dysfunction in approximately 30% of cases. The thyroid gland can be affected by renal, colorectal, lung and breast carcinomas, and melanomas, but has rarely been associated with thyroid dysfunction. Pancreatic metastasis can lead to exo-/endocrine insufficiency with renal carcinoma being the most common primary. Most parathyroid metastases originate from breast and lung carcinomas and melanoma. Breast and colorectal cancers are the most frequent ovarian metastases; prostate cancer commonly affects the testes. In the presence of endocrine deficiencies, glucocorticoid replacement for adrenal and pituitary involvement can be life saving. As most metastases to endocrine organs develop in the context of disseminated disease, surgical resection or other local therapies should only be considered to ameliorate symptoms and reduce tumour volume. Although few consensus statements can be made regarding the management of metastases to endocrine tissues because of the heterogeneity of the variable therapies, it is important that clinicians are aware of their presence in diagnosis.

Key Words

- ▶ glands
- ▶ cancer
- ▶ metastases
- ▶ pituitary
- ▶ adrenal
- ▶ thyroid
- ▶ ovaries

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Introduction

Cancer is a major public health issue in developed countries, with the presence of metastases being the most critical factor related to mortality (Uemura *et al.* 2016). In this context, endocrine organ metastases usually occur in the presence of extensive and/or progressive malignant disease.

Virtually any endocrine tissue can be affected as a distinctive feature of all endocrine organs is their abundant blood supply facilitating metastatic dissemination, with the pituitary and adrenal glands being the most clinically relevant organs involved (Shumarova 2016).

However, there are important differences regarding the frequency of metastases from other organs, the specific glands involved, and their overall prognosis. This is evident in patients with thyroid metastases (Wood *et al.* 2004, Calzolari *et al.* 2008); these are relatively rare compared to commonly encountered adrenal metastases, although the thyroid is the second mostly arterialised organ in the body after the adrenals (Oshiro *et al.* 2011 Shumarova 2016).

Until recently, metastases to endocrine organs were considered relatively rare; however, they are currently increasingly diagnosed following the improvement of diagnostic tools and intensive follow-up of patients with cancer (Kumar *et al.* 2004). Early detection is crucial, especially in the presence of isolated metastases, as their prompt therapy may have an impact on overall prognosis and survival depending on the nature of the primary tumour (Muth *et al.* 2010).

To date, no systematic documentation of the distribution and prevalence, along with clinicopathological and/or imaging characteristics of metastatic involvement of endocrine tissues from non-endocrine malignancies, has been performed. In the present review, we have therefore aimed to summarise the epidemiology and distinctive features of endocrine organ metastases from non-endocrine primary tumours, along with their treatment and their impact on the overall prognosis of such patients.

Methods

The PubMed and Cochrane databases were retrieved on May 17, 2019, to identify relevant articles applying the following keywords: 'adrenal', 'thyroid', 'parathyroid' and 'pituitary' glands, 'ovaries', 'testes', 'metastases', 'tumours', 'molecular markers', 'imaging', 'endocrine organ'. The above keywords were also combined with the Boolean operators AND/OR. Only English-written articles published the last 20 years (1999–2019) were included. We also excluded *in vitro* and *in vivo* studies. Additional relevant publications were identified from references of the retrieved articles (Fig. 1). Based on the abstracts and the full text of the selected studies, the incidence of the most common primary tumours with metastases in endocrine organs according to the larger studies was determined (Table 1). Studies in which it was not clearly documented that the lesion(s) in the endocrine organ was a secondary from another primary tumour were excluded.

Results

Adrenals

Epidemiology

The adrenals are the fourth most common metastatic site for all cancers after the lung, liver, and bone (Oshiro *et al.* 2011, Shumarova 2016). The frequencies of adrenal metastases at autopsy, adrenalectomy and fine-needle aspiration (FNA) biopsies were 3.1, 7.5 and 33%, respectively (Lam & Lo 2002) (Table 1). Although synchronous bilateral metastases are rare (<0.5%) (Ozturk 2015, Shumarova 2016), occurring mostly with melanoma, thyroid, sarcomatoid, hepatocellular, bladder and in 4% of patients with non-small-cell lung cancer (NSCLC) (Tanvetyanon *et al.* 2008), the prevalence of bilateral adrenal metastases in lymphomas reaches 71% (Peters *et al.* 2013, Bourdeau *et al.* 2018). Approximately 50% of melanomas, 30–40% of breast and lung, and 10–20% of renal and gastrointestinal cancers, metastasise to the adrenals in surgical series (Lam & Lo 2002, Wansaicheong & Goh 2016). Adrenal metastases from colorectal and bladder carcinoma occur in between 1.9 and 17.4% (Murakami *et al.* 2003) and 14% (Wallmeroth *et al.* 1999) of cases respectively. Additionally, in autopsy series of patients with prostate and hepatocellular cancer, adrenal metastases are found in 17–20% and 8.8–16.9% of cases respectively (Kawahara *et al.* 2009, Jung *et al.* 2016). A recent meta-analysis showed that the incidence of adrenal metastases in patients with an adrenal incidentaloma (AI) without any known history of malignancy ranged from 0.7 to 2.3% (Cawood *et al.* 2009). On the contrary, approximately 30–70% of AI in patients with a history of cancer were found to be metastases (Cingam & Karanchi 2019).

Pathogenesis

The abundant sinusoidal blood supply of the adrenals and the possible communication between the pulmonary and retroperitoneal lymphatic pathways facilitate the metastatic process (Shumarova 2016). Adrenal metastases may also occur by tumour spread via the vessel in Gerota's fascia, lymphatic vessels, arteries or retrograde venous embolism (Alt *et al.* 2011). In some cases, lung metastases are seen after adrenal metastases, raising the possibility of latent and silent lung metastases having already occurred at the time of adrenal metastasis detection (Murakami *et al.* 2003). In renal cancer, the development of adrenal metastasis has been linked to the size and the location of the tumour, with left-sided, upper pole and multifocal tumours more often being metastatic (Alt *et al.* 2011).

Figure 1

Flow diagram of the research tools used from PubMed and Cochrane databases.

Clinical manifestations

In a study of 464 patients with metastatic adrenal lesions, only 4% were symptomatic (Short *et al.* 1996). The spectrum of clinical presentation included lower chest,

back or abdominal pain, a palpable abdominal mass or symptoms and signs related to adrenal insufficiency, or rarely following adrenal haemorrhage (Hiroi *et al.* 2006, Sahasrabudhe & Byers 2009). Sparing 10% of the adrenal gland is sufficient for maintaining adequate adrenal function; thus, even bilateral metastatic spread to both adrenals rarely causes (<1%) adrenal insufficiency (Ozturk *et al.* 2015). Although higher rates (up to 25%) have been described in the literature, this is not a common clinical scenario (Lam & Lo 2002).

Nevertheless, evaluation of adrenal function in patients with metastases is always warranted to exclude adrenal insufficiency, necessitating appropriate hormonal substitution (Puccini *et al.* 2017). This is particularly relevant as the clinical presentation may be non-specific and symptoms may be attributed to the underlying disease.

Imaging

Ultrasonography (US) and computerised tomography (CT) are the most commonly utilised modalities because of their availability and non-invasive nature (Fig. 2A and B). Metastasis causing an AI in patients with no known malignancy occurs in 5% and this increases to 9–13% in patients with a known underlying malignancy (Sahdev *et al.* 2010).

The radiological distinction of adrenal metastases from an adenoma on CT imaging is based on tumour size and heterogeneity, these features exhibiting high specificity but low sensitivity. CT attenuation value (Tu *et al.* 2018), rim enhancement and the presence of irregular margins were not found to differentiate significantly between adenomas and malignant lesions (Tu *et al.* 2018). However, adenomas exhibit less than 10 Hounsfield Units (HU) on the unenhanced CT or show significant contrast washout (>60% absolute washout or >40% relative washout) (Park *et al.* 2012, Wale *et al.* 2017, Tu *et al.* 2018). On MRI, adenomas exhibit high intracellular lipid content with a chemical-shift index greater than 15% (McCarthy *et al.* 2016) (Fig. 2C). Furthermore, adrenal metastases are more likely if there is a greater than 20% increase in the size of the lesion on serial follow-up imaging at 6–12 months or in the presence of a new lesion greater than 5 mm at the same interval (Fassnacht *et al.* 2016).

Radionuclide imaging has also been utilised to define the nature of adrenal lesions in patients with underlying malignancies. ¹⁸Fluoro-deoxyglucose-positron emission tomography (¹⁸FDG-PET-CT) exhibits high sensitivity, specificity and accuracy, ranging from 93 to 100%,

Table 1 Epidemiological data of the primary tumours and associated metastases in endocrine organs based on clinical surgical and autopsy series.

Endocrine organ metastases	Frequencies (%) of metastases in autopsy series	Localisation and frequencies (%) of the primary tumours in clinical or surgical series
Adrenal	3.1% out of 468 autopsies in adrenal tissues (Lam & Lo 2002)	Melanomas (50%), breast and lung cancers (30–40%), renal and gastrointestinal malignancies (10–20%) (Lam & Lo 2002, Wansaicheong & Goh 2016)
Thyroid	1.9–24% (most common primary cancer: lung cancer, breast cancer, and melanoma) (Chung <i>et al.</i> 2012, Saito <i>et al.</i> 2014, Nixon <i>et al.</i> 2017, Straccia <i>et al.</i> 2017)	Renal cell cancer (48.1%), colorectal (10.4%), lung (8.3%) and breast cancer (7.8%), sarcoma (4.0%) and melanoma (4.0%) (Chung <i>et al.</i> 2012, Saito <i>et al.</i> 2014, Nixon <i>et al.</i> 2017, Straccia <i>et al.</i> 2017)
Parathyroid	5.3–11.9% (most common primary cancer: breast carcinoma) (Bauer <i>et al.</i> 2018)	Breast cancer (66.9%), melanoma (11.8%) and lung cancer (5.5%) (Chrisoulidou <i>et al.</i> 2012, Lee <i>et al.</i> 2013, Shifrin <i>et al.</i> 2015, Bauer <i>et al.</i> 2018)
Pituitary	0.14–28.1% of all brain metastases (Ravnik <i>et al.</i> 2016, Di Nunno <i>et al.</i> 2018)	Breast cancer (37.2%), lung cancer (24.2%), prostate (5%) and kidney (5%) (Ogilvie <i>et al.</i> 2005)
Pancreas	2% of all pancreatic neoplasms (Reddy & Wolfgang 2009, Apodaca-Rueda <i>et al.</i> 2019)	Renal cell cancer is the most common (at least 2% of all pancreatic malignancies), primary breast neoplasm (less than 3% of all cases) (Reddy & Wolfgang 2009, Apodaca-Rueda <i>et al.</i> 2019)
Ovary	nd ^a	Colorectal (33%), breast (10%), gastric (4.5–30%), and appendix tumours (de Waal <i>et al.</i> 2009)
Testes	0.02–2.5% (Kamble & Agrawal 2017)	Lymphoma and leukaemia (the most common), prostate (35%), lung (19%) and colon tumours (9%), melanoma (9%), and kidney tumours (7%) (Dogra <i>et al.</i> 2003)

nd, no data.

^aNot rare, 7% of all ovarian masses presenting as primary ovarian tumours are found to be metastatic in origin.

although false-positive findings can still occur in up to 9% of cases (Chong *et al.* 2006, Kim *et al.* 2018). Furthermore, ¹⁸FDG-PET findings are considered positive if the standardised uptake value (SUV) in the adrenal tumour is greater than or equal to the liver, with the optimal tumour/liver SUVmax threshold ratio being >1.5 (Guerin *et al.* 2017). Interestingly, in a recent study, it was also shown that the lower SUVmax values were found in non-functional adrenal masses (SUVmax of 3.2) when compared to functional adrenal masses, with cortisol-secreting masses presenting the highest SUVmax values.

However, setting a specific SUVmax value in the differentiation of malignant from benign adrenal lesions may be risky (Akkus *et al.* 2019). Table 2 shows the main characteristics of a benign adrenal tumour versus an adrenal metastasis on CT, MRI and ¹⁸FDG-PET-CT.

In addition, the combination of high-resolution CT and ¹⁸FDG-PET imaging has proved to be very accurate in distinguishing benign from malignant adrenal masses (Gross *et al.* 2009). However, only 13% of ‘suspected’ adrenal lesions were subsequently histologically confirmed to be cancerous (Lane *et al.* 2009). In the case of

Figure 2

(A) Adrenal US showing a left adrenal metastasis with a heterogeneous mass of 7.8 cm maximum diameter (white arrow) in a 77-year-old female patient with a poorly differentiated small-cell carcinoma of the lung. (B) Abdominal CT showing bilateral large heterogeneous adrenal lesions (white arrows) in a 40-year-old male patient with a primary lung adenocarcinoma. (C) MR1 T₁-weighted image showing a large non-homogeneously enhancing left adrenal (maximum diameter 8 cm) mass of low intensity (white arrow) in a 38-year-old patient with a well-differentiated G3 NET of unknown primary. US, ultrasound; CT, computerised tomography; MRI, magnetic resonance imaging.

Table 2 Distinctive characteristics of CT, MRI and ¹⁸FDG-PET in distinguishing benign adrenal tumours and adrenal metastasis from other primary tumours.

Imaging characteristics	CT (adenoma vs metastasis ^a)	MRI ^b	¹⁸ FDG-PET (adenoma vs metastasis ^b)	Statistical significance, <i>P</i>
Size	Smaller vs larger	nd	–	0.012
Entropy	Lower vs higher	nd	–	0.013
Tumour margin	No difference	nd	–	ns
Rim enhancement	No difference	Adrenal adenomas exhibit prompt mild enhancement, whereas malignant lesions exhibit intense enhancement		ns
Central vein sign	No difference	nd		ns
Heterogeneity	Less vs more heterogeneous	nd		0.001
Hounsfield measurement	<ul style="list-style-type: none"> • <10 UH vs >10 UH (sensitivity: 71%, specificity: 98%) • Absolute wash out >60%, relative wash-out >40% (sensitivity: 100%, specificity: 98%) 	–		
SUV	–	–	Malignant tumour SUVmax/Liver SUVmax threshold >1.5 (sensitivity: 86.7, specificity: 86.1%)	–

¹⁸FDG-PET, ¹⁸fluoro-deoxyglucose-positron emission tomography; CT, computerised tomography; MRI, magnetic resonance imaging; nd, no data; ns, not significant; SUV, standardised uptake value; UH, units of Hounsfield.

neuroendocrine tumours, the majority of which are well differentiated and slow growing, nuclear imaging with radioisotopes combined with tracers exhibiting affinity to somatostatin receptors expressed by these tumours, such as ⁶⁸Gallium-DOTATATE PET scanning, may identify previously unsuspected adrenal involvement (Kanakakis *et al.* 2013, Hofman *et al.* 2015).

Adrenal biopsy is rarely needed (Bancos *et al.* 2016) and should only be performed in suspicious cases after a pheochromocytoma or an adrenocortical carcinoma have been excluded, and only if the expected findings are likely to alter patient management (Bancos *et al.* 2016, Fassnacht *et al.* 2016).

Pathology

Adrenal cortical neoplasms express markers specific for steroid-producing cells such as steroidogenic factor 1 (SF1) and inhibin (Sbiera *et al.* 2010, Lin & Liu 2014). A panel of markers including melan-A and inhibin- α is currently used for this purpose, although of limited diagnostic accuracy (Lin & Liu 2014). On the contrary, SF-1 is considered a highly valuable immunohistochemical marker to determine the adrenocortical origin of an adrenal mass with high sensitivity and specificity (Sbiera *et al.* 2010) (Fig. 3). Table 3 summarises the most useful immunohistochemical markers in the diagnosis of metastases in endocrine organs.

Treatment and prognosis

The management of adrenal metastases includes surgical resection, therapy directed against the primary tumour (mostly systemic chemotherapy), locally ablative procedures, and/or radiotherapy (Lo *et al.* 1996).

Adrenalectomy is currently the most frequent approach for patients with isolated uni- or bilateral adrenal metastases (Uberoi & Munver 2009). Laparoscopic adrenalectomy has been associated with improved survival in some (Marangos *et al.* 2009), but not all, studies (Zheng *et al.* 2012). In a meta-analysis of 114 patients with NSCLC undergoing resection of isolated adrenal metastases, the five-year overall survival (OS) was 25% (Tanvetyanon *et al.* 2008). In another study of 52 patients undergoing resection of adrenal metastases, the OS at 2 years was 40%, with a median survival of 13 months; however, the number of long-term survivors was not reported (Lo *et al.* 1996). The mean post-adrenalectomy disease-free period was 19 months (range 0–97 months) and was considered the most predictive variable for survival (Muth *et al.* 2010, Puccini *et al.* 2017).

Non-surgical approaches including systemic chemotherapy, radiofrequency ablation (Wood *et al.* 2003) or trans-arterial (chemo)-embolisation (TA(C)E) (Duh 2003, Hsieh *et al.* 2005) of adrenal metastases showed a median survival of 11.1–13.6 months at 1 year compared

to 21.4 months after surgical resection (Park *et al.* 2012). Recently, stereotactic radiation therapy showed response rates ranging from 27 to 100% with grade I–II tumours (Chawla *et al.* 2009, Alongi *et al.* 2012, Desai *et al.* 2015). Tumour type, growth rate, and performance status of the patient are prognostic factors associated with oncological outcomes, postoperative recovery, and potential survival benefits.

Thus, according to existing data, the best evidence suggests that surgery is the preferred treatment strategy compared to non-invasive strategies for uni- or bilateral adrenal metastases when either isolated (Tanvetyanon *et al.* 2008, Zheng *et al.* 2012) or in oligometastatic disease in selected patients resulting in a survival benefit (Uemura *et al.* 2016). However, due to the absence of prospective studies, robust recommendations cannot be made.

Pituitary

Epidemiology

Pituitary metastases are found in 1% of resected hypophyseal lesions and in 0.14–28.1% of all brain metastases in autopsy series, occurring mostly in patients with extensive disease (Larkin *et al.* 2017, Di Nunno *et al.* 2018) (Table 1). Breast (37.2%) and lung (24.2%) cancers are the most common primary malignancies associated with pituitary metastases followed by the prostate (5%), kidney (5%) and lymphoma (Ogilvie *et al.* 2005, Javanbakht *et al.* 2018). Other primary cancers include gastrointestinal malignancies, melanoma, pancreas, larynx, renal, liver, and the ovary (Aung *et al.* 2002, Karamouzis *et al.* 2003, Komninos *et al.* 2004, Hirsch *et al.* 2005, Moreno-Perez *et al.* 2007). Occult pituitary metastases are reported in about 5% of patients with a known history of malignancy (Moreno-Perez *et al.* 2007).

Pathogenesis

Tumours can metastasise to the pituitary either through its rich blood supply from the portal pituitary vessels or through direct extension from juxtaseal and skull base foci, and from the suprasellar cistern through the meningeal system (Komninos *et al.* 2004, Di Nunno *et al.* 2018). The high incidence of pituitary metastases from breast cancer may be explained by the presence of the prolactin-rich environment of the pituitary that enhances the proliferation of breast tumour cells (Morita *et al.* 1998, Komninos *et al.* 2004). The posterior pituitary is most frequently affected, due to its vascularisation by the inferior hypophyseal artery, accounting for 85% of cases alone or in combination with the anterior lobe supplied from the hypophyseal portal system (Komninos *et al.* 2004, Di Nunno *et al.* 2018). Because the posterior pituitary is smaller than the anterior, the same volume of metastatic tissue in the posterior region will produce earlier symptoms compared to the anterior one (Javanbakht *et al.* 2018).

Clinical symptoms and diagnosis

Pituitary metastases are most often asymptomatic, as generally found in autopsy specimens, but 2.5–18.2% of patients may demonstrate symptoms (Komninos *et al.* 2004, He *et al.* 2015). In recent series of pituitary metastases confirmed by biopsy or surgery, the most common clinical presentations were panhypopituitarism (27.7%) and diabetes insipidus (DI) (27.7–70%) (Di Nunno *et al.* 2018, Javanbakht *et al.* 2018). The presence of DI is extremely rare in pituitary adenomas and should always direct towards another pathology (Javanbakht *et al.* 2018). Anterior hypopituitarism (20–37.7%), visual disturbance (30–48.8%) and headaches (35%) are also encountered, although their frequency may vary between series (He *et al.* 2015, Di Nunno *et al.* 2018, Javanbakht *et al.* 2018).

Figure 3

Metastasis of clear cell renal cell carcinoma (CCRCC) in the adrenal gland (×400). (A) Staining with haematoxyline & eosin (H&E). (B) Positive immunohistochemical (IHC) staining (intense nuclear expression) of SF1 in the adrenocortical cells. No IHC expression of SF1 in the neoplastic cells is noted. (C) Positive IHC staining of the CCRCC (intense membranous and nuclear expression of RCC antibody) in the neoplastic cells. SF1, steroidogenic factor 1.

Table 3 The most useful immunohistochemical markers in the diagnosis of metastases in endocrine organs.

Primary tumour/metastases in endocrine organs	Adrenal	Thyroid	Pituitary	Parathyroid	Ovary	Testes
Breast cancer	GATA3+, GCDFFP-15+, Mammaglobin+, MelanA-, SF-1 -, Synaptophysin -	GATA3+, GCDFFP-15+, Mammaglobin+, TTF-1 -, Pax-8-, Thyreoglobulin-, Calcitonin-	GATA3+, GCDFFP- 15+, Mammaglobin+, PIT-1 -, TPIT -, Pituitary hormones	GATA3+, GCDFFP- 15+, Mammaglobin+, PTH-	GATA3+, GCDFFP-15+, Mammaglobin+, Pax-8 -, SF-1 -, WT-1 -	GATA3+, GCDFFP-15+, Mammaglobin+, SALL-4-, Oct3/4-, LIN28a-, CD30-, Glypican-3
Lung cancer	TTF-1+, Napsin+, p40+, CK5/6+, MelanA-, SF-1 -, Synaptophysin -	Napsin+, p40+, CK5/6+, Pax-8-, Thyreoglobulin-	TTF-1+, Napsin+, p40+, CK5/6+, PTH-	TTF-1+, Napsin+, p40+, CK5/6+, PTH-	TTF-1+, Napsin+, p40+, CK5/6+, Pax-8-, SF-1 -, WT-1 -	TTF-1+, Napsin+, p40+, CK5/6+, SALL-4-, Oct3/4-, LIN28a-, CD30-, Glypican-3
Melanoma	SOX-10+, S100+, SF-1 -, Calretinin -	Sox-10+, S-100+, MelanA+, HMB-45+, TTF-1 -, Pax-8-, Thyreoglobulin-	Sox-10+, S-100+, MelanA+, HMB- 45+, PTH-	Sox-10+, S-100+, MelanA+, HMB-45+, Pax-8 -, SF-1 -, WT-1 -	Sox-10+, S-100+, MelanA+, HMB-45+, Pax-8 -, SF-1 -, WT-1 -	Sox-10+, S-100+, MelanA+, HMB-45+, SALL-4-, Oct3/4-, LIN28a-, CD30-, Glypican-3
Renal cell cancer	Pax-8+, RCC+, SF-1 -, Synaptophysin -, Calretinin -	RCC+, TTF-1 -, Thyreoglobulin-, Calcitonin -	Pax-8+, RCC+, SF-1 -, PIT-1 -, TPIT -, Pituitary hormones	Pax-8+, RCC+, PTH-	RCC+, Vimentin+, SF-1 -, WT-1 -	Pax-8+, RCC+, SALL-4-, Oct3/4-, LIN28a-, CD30-, Glypican-3
Gastrointestinal (especially colorectal, gastric)	CDX-2+, SATB2+, CK20+, Vimentin -, MelanA -, SF-1 -	CDX-2+, SATB2+, CK20+, TTF-1 -, Pax-8 -, Thyreoglobulin -, Calcitonin -	CDX-2+, SATB2+, CK20+, SF-1 -, PIT-1 -, TPIT -, Pituitary hormones	CDX-2+, SATB2+, CK20+, PTH-	CDX-2+, SATB2+, CK20+, Pax-8 -, SF-1 -, WT-1 -	CDX-2+, SATB2+, CK20+, SALL-4-, Oct3/4-, LIN28a-, CD30-, Glypican-3

CDX-2, caudal type homeobox 2; GATA-3, GATA binding protein 3; GCDFFP-15, gross cystic disease fluid protein 15; HMB-45, human melanoma black 45; Oct3/4, octamer-binding transcription factor 3/4; PAX-8, paired-box gene 8; PIT1, pituitary-specific positive transcription factor 1; PTH, parathyroid hormone; RCC, renal cell carcinoma; SALL-4, Sal-like protein 4; Sall-like protein 4; special AT-rich sequence binding protein 2; SF-1, steroidogenic factor 1; SOX-10, Sry-related HMG-Box gene 10; TTF-1, thyroid transcription factor-1; WT-1, Wilms' tumour 1.

The presence of DI and/or cranial neuropathies should always point towards pituitary metastases, especially when developing rapidly in patients over 50 years of age (He *et al.* 2015). Symptoms of DI may be masked by concomitant adrenocorticotrophic hormone (ACTH) deficiency, becoming apparent when glucocorticoid replacement therapy is initiated (Castle-Kirsbaum *et al.* 2018). Hypothyroidism and hypoadrenalism are the most frequent anterior pituitary deficiencies, followed by hypogonadism (Morita *et al.* 1998). Hypothalamic metastases are uncommon and are often associated with compression of the pituitary gland and the optic chiasm leading to DI, visual impairment and cognitive defects, and are associated with greater morbidity and mortality (Diallo *et al.* 2017).

Pituitary apoplexy into a pituitary metastasis has been rarely described in patients with melanoma (Masui *et al.* 2013), bronchogenic (Hanna *et al.* 1999, Man & Fu 2014), colorectal (Thewjitcharoen *et al.* 2014) and renal cell carcinoma (Quevedo *et al.* 2000) metastases. Metastases in patients with pre-existing functioning adenomas have also been described, suggesting that the hypervascularity of the pre-existing adenoma may promote metastasis and apoplexy (Hanna *et al.* 1999, Thewjitcharoen *et al.* 2014).

Pituitary biopsy is rarely needed because usually a relevant clinical history, or imaging characteristics, can differentiate an adenoma from a metastatic lesion (Altay *et al.* 2012). Furthermore, biopsy of the sellar area has substantial risks including haemorrhage, infection or hypopituitarism, although stereotactically guided biopsy has a low (0–1.6%) morbidity rate. Thus, in general, pituitary biopsy is reserved for patients with atypical symptoms and a pituitary mass with atypical imaging features and a non-functional syndrome when it is expected to have an impact on clinical management (Weilbaeher *et al.* 2004, Yoon *et al.* 2016).

Imaging

Although it is difficult to differentiate pituitary metastases from other space-occupying lesions of the region, some neuroimaging characteristics are suggestive (He *et al.* 2015). Pituitary metastases may present as contrast-enhanced sellar lesions being iso- or hyperintense on T₁-weighted imaging and moderately hypointense on T₂-weighted imaging showing overall rapid progression (Dutta *et al.* 2011) (Fig. 4). The presence of bony erosion without sellar enlargement indicates a pituitary metastasis rather than an adenoma (Lu *et al.* 2010). Furthermore, the metastatic mass may appear as a dumbbell-shaped lesion due to

Figure 4

T₁-weighted MRI coronal image demonstrating a large (3.2 cm maximum diameter) heterogeneous pituitary metastasis with intense gadolinium-enhanced contrast enhancement (white arrow) infiltrating the sella turcica and compressing the optic chiasm in a 55-year-old male patient with a lung adenocarcinoma. MRI: magnetic resonance imaging.

indentation by the diaphragma sella (Freda & Wardlaw 1999). Micro- or macro-pituitary adenomas can manifest as hypermetabolic foci on ¹⁸FDG-PET imaging, causing confusion when evaluating patients with brain metastases (Ryu *et al.* 2010). Occasionally, pituitary metastases may occur within a pituitary adenoma such that an adenoma and pituitary metastases tissue may coexist (Bret *et al.* 2001, Takei *et al.* 2007).

Pathology

The correct diagnosis of a pituitary metastasis often requires a combination of patient history and molecular pathologic analysis. However, the degree of cytological atypia and mitoses as well as immunochemistry usually point to the correct diagnosis (Larkin & Ansorge 2017) (Table 3).

Treatment and prognosis

Currently available treatment modalities include surgery, radiosurgery, whole brain radiation and chemotherapy, along with replacement of any endocrine hormonal deficiencies (He *et al.* 2015). The prognosis of pituitary metastases is generally related to the histological subtype and the stage of the primary malignancy rather than to the presence of metastases *per se* (Metivier *et al.* 2006). Overall, the management of patients with pituitary

metastases is mostly palliative, as treatments including surgery have not been associated with an improvement in OS (Morita *et al.* 1998). In a recent series, the median survival after the diagnosis of a pituitary metastasis was 10 months, in line with older series demonstrating a 13.6-month mean survival (Javanbakht *et al.* 2018). Adrenal insufficiency is a rare complication of metastatic disease to the hypothalamopituitary axis requiring glucocorticoid replacement, ideally with hydrocortisone (Komninou *et al.* 2004).

Thyroid

Epidemiology

Metastases from non-thyroidal malignancies to the thyroid are found in 1.4–3% of all patients undergoing surgery for suspected thyroid cancer (Wood *et al.* 2004, Calzolari *et al.* 2008) (Table 1). Metastases account for approximately 2% of all thyroid malignancies and are found in 2.3–7.5% of patients submitted to FNA (Papi *et al.* 2007, Straccia *et al.* 2017). Autopsy studies have reported a wide prevalence from 1.9 to 24% (Papi *et al.* 2007, Chung *et al.* 2012), with the most frequent primaries being renal (48.1%), colorectal (10.4%), breast (7.8%) and lung carcinoma (8.3%) and lymphomas (Calzolari *et al.* 2008, Chung *et al.* 2012, Diaconescu *et al.* 2013, Bellecine *et al.* 2015). Approximately 1.9% of cancers that metastasised to the thyroid gland originated from a cancer of an unknown primary (Chung *et al.* 2012).

Metastases to the thyroid are slightly more common in women than men (female/male ratio 1.4/1). Of head and neck cancers, nasopharyngeal carcinoma is the most commonly reported primary lesion metastasising to the thyroid (Lewis *et al.* 2017). Thyroid metastases can present long after the initial diagnosis, the mean interval being 69.9 months and the longest 21 years from a 'foregut' neuroendocrine tumour; in 20% of cases metastases can be synchronous with the diagnosis of the primary cancer (Mattavelli *et al.* 2008, Chung *et al.* 2012, Straccia *et al.* 2017).

Pathogenesis

Thyroid metastases can develop either by direct extension from adjacent structures or from metastatic foci from a distant primary tumour (Wood *et al.* 2004, Calzolari *et al.* 2008). Given the extensive blood supply of the thyroid, the low incidence of thyroid metastases is somewhat surprising (Nixon *et al.* 2017). It has been suggested that metastasis development may be influenced by the

glandular microenvironment; the fast arterial blood flow and the high concentration of oxygen and iodine may prevent the growth of circulating tumour cells (Nixon *et al.* 2017).

Clinical characteristics

The clinical presentation of thyroid metastases is heterogeneous, being clinically evident only in a minority of patients and mostly found incidentally. Thyroid metastases present in the context of widespread metastatic disease; when they are the first presentation of recurrent disease, they usually appear as a palpable neck mass and, less often, can be associated with dysphagia, massive tracheal involvement or dysphonia (Falcone *et al.* 2018). Patients often present with a painless neck mass (Surov *et al.* 2016). The reported interval of presentation for metachronous thyroid metastases may be longer than 10 years (Hegerova *et al.* 2015).

Although there is a relative paucity of data regarding thyroid function, most affected patients were euthyroid. Hypothyroidism, when it occurs, is related to massive infiltration of the thyroid by the tumour (Chung *et al.* 2012). Thyrotoxicosis occurs rarely most likely due to the leakage of the hormones from the thyroid following neoplastic infiltration (Papi *et al.* 2005, 2007).

Imaging

The probability of finding metastases to the thyroid depends on the method of investigation and has recently increased following the application of US, FNA, ¹⁸FDG-PET and ⁶⁸Gallium DOTATATE PET/CT (Diaconescu *et al.* 2013, Kanthan *et al.* 2016).

Ultrasonography is considered the investigation of choice showing either focally or diffusely infiltrating hypoechoic lesions (Fig. 5A). However, no single US feature has enough sensitivity and specificity to reliably indicate that thyroid nodules are benign or malignant, although utilisation of the Thyroid Imaging Reporting and Data System (TI-RADS) identifies suspicious lesions either primary or secondary (Sánchez 2014, Zhuang *et al.* 2018). On US, thyroid metastases appear as homogeneously hypoechoic with indistinct margins, irregular shape and increased vascularity in most cases (Surov *et al.* 2016). On CT thyroid metastases were found to be heterogeneous and hypodense with inhomogeneous enhancement in comparison to the normal thyroid (Surov *et al.* 2016, Straccia *et al.* 2017, Takenobu *et al.* 2018). On MRI T₁-weighted images, most cases appeared as inhomogeneous iso-to-hyperintense lesions in comparison to the normal

thyroid tissue, whereas on T₂-weighted images were slightly hyperintense (Surov *et al.* 2016). Moreover, thyroid metastases present high uptake in ¹⁸FDG-PET in contrast to the normal thyroid gland that usually shows low or absent ¹⁸FDG-PET uptake (Chen *et al.* 2009, Saito *et al.* 2014, Surov *et al.* 2016) (Fig. 5B).

Pathology

Thyroid metastases cannot be differentiated from a primary thyroid cancer based on biochemical or radiological features, and suspicion is thus mainly related to the relevant clinical setting and the histological picture. The diagnostic workup is identical to that used in the assessment of any common thyroid nodule.

FNA has been widely accepted as the most accurate test (Chung *et al.* 2012). Cytology generally shows abundant cellularity and the cells may be typical of the primary site (Chung *et al.* 2012), leading to the correct diagnosis in 74% of cases (Chung *et al.* 2012, Khan *et al.* 2018). However, it exhibits a high false-negative rate in nodules larger than 3 cm (Agcaoglu *et al.* 2013, Nam *et al.* 2017). The most common thyroid metastases for which FNA did not make the correct diagnosis originated from the oesophagus (50%), the cervix (33%), the kidney (28.5%) and melanomas (20%) (Chung *et al.* 2012). The most difficult morphological diagnoses concern renal cell and breast carcinomas. These tumours may show an alveolar/glandular structure resembling the follicular pattern observed in thyroid hyperplastic nodules, necessitating the need for immunohistochemical techniques (Straccia *et al.* 2017) (Table 3). Negative staining with anti-thyroglobulin and anti-calcitonin antibodies favours a diagnosis of metastatic tumour (Chung *et al.* 2012).

Molecular markers have been also applied to identify the presence of the *BRAF* V600E mutation that is a common in thyroid cancer, in contrast to extra-thyroid metastases, occurring in about 45% of papillary thyroid cancer and 25% of anaplastic thyroid cancer (Xing *et al.* 2004).

Treatment and prognosis

The treatment of thyroid metastases depends on the site of the primary tumour, the presence of metastases elsewhere, symptoms caused by the thyroid mass, and/or alterations of thyroid function. Surgery is considered the gold standard treatment; radical treatment of an isolated metastasis can be curative, and an aggressive surgical approach has been recommended, especially in slow-growing tumours such as those originating from the breast or kidney (Wood *et al.* 2004). In contrast, patients with multiple metastases in different organs should be treated with systemic therapy (Takenobu *et al.* 2018). For patients with metastatic sites other than the thyroid, thyroid surgery can still be palliative when metastases are causing compressive symptoms such as airway obstruction and skin ulceration (Calzolari *et al.* 2008). Metastases to the thyroid are associated with a poor prognosis, most patients dying after the diagnosis was made due to disseminated disease (Papi *et al.* 2005, Straccia *et al.* 2017). A recent meta-analysis showed that total thyroidectomy increased both disease-free and OS in patients (33% of operated patients survived for 6–53 months vs 8% of the non-operated who survived for 4–24 months) even when accompanied by disseminated disease, compared to chemotherapy or local radiotherapy (Straccia *et al.* 2017).

Figure 5

(A) Ultrasound of the thyroid demonstrating a metastasis in the right lobe of the thyroid in a 77-year-old patient with a poorly differentiated small-cell lung carcinoma (white arrow). (B) ¹⁸FDG-PET scanning showed increased uptake in the thyroid along with lung lesions in the same patient (white arrows). ¹⁸FDG-PET, ¹⁸Fluoro-deoxyglucose-positron emission tomography.

Parathyroid gland

Epidemiology

Metastases to the parathyroids are rare and are nearly always identified as part of extensive metastatic disease, with only 3.2% of cases reported as isolated metastases (Chrisoulidou *et al.* 2012, Lee *et al.* 2013, Shifrin *et al.* 2015, Bauer *et al.* 2018). Autopsy studies have suggested that the prevalence of the incidental involvement of the parathyroids by metastatic tumours varies between 5.3 and 19%, with breast carcinoma being the most common tumour (Bauer *et al.* 2018) (Table 1). A recent review (Bauer *et al.* 2018) identified that 66.9% of parathyroid metastases originated from breast carcinoma, followed by melanoma (11.8%) and lung carcinoma (5.5%); approximately 5.5% were 'tumour-to-tumour' metastases to a parathyroid adenoma (Chrisoulidou *et al.* 2012, Lee *et al.* 2013, Shifrin *et al.* 2015, Bauer *et al.* 2018). Thymic neuroendocrine tumour metastatic to the parathyroids has been reported in a case of a patient with multiple endocrine neoplasia (MEN1) syndrome and an enlarged parathyroid gland (Shifrin *et al.* 2015).

Clinical characteristics

Symptoms, if present at all, are likely to be non-specific; 40% of patients demonstrated hypercalcemia, 29.3% hypocalcemia, while the remainder were eucalcaemic. Serum parathyroid hormone (PTH) levels were elevated in 75% of patients and reduced in 8.3% (Bauer *et al.* 2018). The inability of the glands to produce PTH could lead to clinical hypocalcaemia, while destruction or infiltration of the gland by a rapidly growing tumour could also lead to the release of stored PTH, causing at least transiently abnormal increased serum calcium levels (Shifrin *et al.* 2015). In most cases diagnosis was confirmed through histology of surgical specimens from parathyroidectomies.

Imaging

The diagnosis was usually based on neck US during follow-up evaluation, and in some cases, such as with biochemically proven hyperparathyroidism, further imaging with Sestamibi radionuclide scanning can be performed although Sestamibi cannot distinguish benign from malignant parathyroid lesions (Cracolici *et al.* 2018). Currently, no imaging modality that could reliably distinguish a parathyroid adenoma from metastases.

Pathology

Widely available immunohistochemical studies such as chromogranin-A, synaptophysin, keratin, parathyroid hormone, thyroglobulin, and TTF1 can help to distinguish parathyroid tumours from metastases from extra-parathyroid tumours (Erickson & Mete 2018) (Table 3).

Treatment

In most cases, once the diagnosis is made no specific treatment is required, although due to the rarity of metastases data are limited. However, in the presence of hypocalcemia standard replacement therapy should be administered (Wilhelm *et al.* 2016).

Pancreas

Epidemiology

Pancreatic metastases are rare, comprising 2% of all malignancies that may affect the pancreas (Reddy & Wolfgang 2009, Apodaca-Rueda *et al.* 2019) including renal cell, lung, colorectal carcinoma and melanoma (Alzahrani *et al.* 2012, Ito *et al.* 2018). Renal cell carcinoma is the most common (Boni *et al.* 2018). In most cases, metastasis develops through haematological and lymphatic dissemination, particularly with renal and lung carcinomas, but can also occur through contiguous invasion of neighbouring organs. Pancreatic involvement from a primary breast neoplasm is rare, occurring in less than 3% of the cases of breast cancer (Apodaca-Rueda *et al.* 2019). The incidence of synchronous disease is approximately 12%. However, pancreatic metastases can develop almost 10 years from initial diagnosis (Chrom *et al.* 2018). Papillary thyroid carcinoma metastasising to the pancreas is extremely rare; a recent review reported 11 cases of pancreatic metastases from papillary thyroid cancer with an average age at diagnosis of 55.3 years (Davidson *et al.* 2019).

Clinical signs and diagnosis

The clinical signs of pancreatic metastatic disease are non-specific, abdominal pain and obstructive jaundice being the main findings (Apodaca-Rueda *et al.* 2019). Diabetes mellitus (DM) may develop in up to 80% of the cases with pancreatic cancer along with exocrine pancreatic insufficiency (Li 2012). In cases of pancreatic metastases from renal carcinoma, DM developed in 61%, attributed to low insulin and pancreatic polypeptide levels, impaired incretin secretion and secondary insulin resistance

(Salvatore *et al.* 2015, Kalra *et al.* 2016). The most accurate diagnostic method is pancreatic biopsy. Some studies have suggested that FNA biopsies guided by endoscopic US (EUS) or percutaneously could be useful (Apodaca-Rueda *et al.* 2017).

Imaging

Ultrasonography, CT and MRI are frequently used radiological tools; however, the radiological features of primary pancreatic tumours and pancreatic metastases are difficult to differentiate (Apodaca-Rueda *et al.* 2019) (Fig. 6A and B). To avoid mis-diagnosis, the routine use of EUS-guided FNA (EUS-FNA) followed by immunocytochemistry establishes the nature of pancreatic tumours with high accuracy and a low incidence of adverse events (Eloubeidi *et al.* 2004, Banafea *et al.* 2016).

Pathology

EUS-FNA followed by immunocytochemistry helps the differentiation of primary and secondary lesions of the pancreas (Table 3). Lung cancer metastases are usually CK20 negative. CD56 can be a better marker for neuroendocrine differentiation when dealing with small-cell neoplasms (Stoos-Veic *et al.* 2017). In general, the suggested primary panel for a small-cell tumour aspirated from the pancreas should employ leucocyte common antigen-A (LCA), TTF-1, CK20, Pan Cytokeratin, CD56, CD117 and possibly one additional neuroendocrine marker. Depending on the medical history, other antibodies may be used (Stoos-Veic *et al.* 2017).

Treatment and prognosis

Surgical resection of pancreatic metastases is performed when metastases are limited to the pancreas, and/or causing obstructive symptoms, and the patient has an otherwise good prognosis (Alzahrani *et al.* 2012). Pancreatic metastases secondary to breast cancer are associated with a 2- and 5-year survival rate of 57.1 and

34.3% respectively (Masetti *et al.* 2010), whereas the 5-year survival rate of patients with pancreatic metastases from renal cell carcinoma was 66% (Reddy & Wolfgang 2009, Ito *et al.* 2018). Patients with only pancreatic metastases from renal cell carcinoma present a more favourable prognosis compared to other metastatic sites (Grassi *et al.* 2016, Kalra *et al.* 2016).

Pancreatectomy for localised metastases can be beneficial, particularly in patients with isolated metastases from tumours with favourable histologic subtypes such as renal carcinoma (Adler *et al.* 2014). Loco-regional treatment of relatively few metastatic sites is possible with less invasive modalities such as stereotactic radiotherapy and highly focused radiation treatment, particularly in patients medically or technically unfit for surgery (Loi *et al.* 2017).

Gonads (ovaries and testes)

Epidemiology

Metastatic involvement of the ovaries is not rare, as 7% of all ovarian masses presenting as primary ovarian tumours are found to be metastatic in origin (Koyama *et al.* 2007). The most common tumours metastasising to the ovaries include colorectal (33%), breast (10%), gastric and appendiceal tumours as well as renal carcinomas (de Waal *et al.* 2009, Bauerová *et al.* 2014) (Table 1). There is also a variation in the incidence of secondary tumours of the ovaries across different geographical regions, with gastric cancers representing 23.4–30.4% of metastatic ovarian tumours in Japan, whereas breast and colorectal primaries are commonest in Western countries (de Waal *et al.* 2009, Kutasovic *et al.* 2018). Colorectal cancers metastasising to the ovaries most commonly originate from the distal colon, especially from the recto-sigmoid area (Kir *et al.* 2010). Around 1.2–14% of all gastrointestinal cancers can metastasise to the ovaries (Kir *et al.* 2010). Krukenberg tumours, defined as ovarian metastases from gastrointestinal tumours, account for only 1–2% of all ovarian tumours (Kammar *et al.* 2017).

Figure 6

(A) T₂-weighted MRI image of the abdomen demonstrating an oval-shaped solid lesion in the pancreatic head-uncinate process of low signal intensity, lying in front of the inferior vena cava, in a 56-year-old male patient with an ileal neuroendocrine tumour (NET) (white arrow). (B) CT of the abdomen with contrast showing a hypervascular round solid lesion in the pancreatic head-uncinate process in contact with the inferior vena cava, in the same patient (white arrow).

Excluding leukaemia and lymphoma, metastases to the testis are rare, ranging from 0.02% to 2.5% in autopsy series (Moriyama *et al.* 2014, Kamble & Agrawal 2017). Metastases represent 1.4% of all testicular tumours biopsied (Dutt *et al.* 2000) with the most common primaries being prostate (35%), lung (19%), malignant melanoma (9%), colon (9%), and kidney tumours (7%) (Dogra *et al.* 2003, Zhou *et al.* 2019). A total of 57 cases of testicular or paratesticular neuroblastoma have been reported in children, and most cases represented metastases (Kebudi *et al.* 2019). Testicular metastases are detected incidentally after orchidectomy or at autopsy in up to 4% cases of prostate cancer (Moriyama *et al.* 2014, Kamble & Agrawal 2017).

Pathogenesis

Lymphogenous, haematogenous and trans-coelomic means of dissemination to ovarian tissue have been proposed (Kubecek *et al.* 2017). Trans-coelomic dissemination refers to the tumour spread via the peritoneal surfaces (Tan *et al.* 2006, Sugarbaker & Liang 2018). Colorectal cancers as well as renal cancer appear to spread mostly haematogenously whereas the lymphogenous route plays an important role in gastric cancers (Yamanishi *et al.* 2011). The renal-ovarian axis appears to play a significant role through the direct drainage of the left ovarian venous outflow into the left renal vein (Anagnostou *et al.* 2009). The most plausible hypothesis for the spread of prostatic cancer to the testis is the retrograde venous extension or embolism, arterial embolism, lymphatic extension and endo-canalicular spread (Kamble & Agrawal 2017). Renal cell carcinoma rarely spreads to the testes. The testes are regarded as a 'tumour sanctuary', as tumour cells are not able to grow easily in that environment due to the relatively low temperature of the scrotum (Moriyama *et al.* 2014). Additionally, the presence of the blood-testis barrier formed by Sertoli cells, to protect spermatozoa, may also prevent testicular metastasis (Moriyama *et al.* 2014).

Clinical symptoms and biochemical markers

Non-specific symptoms, including abdominal pain and fullness, weight loss, post-menopausal bleeding, and signs such as increased abdominal circumference, are commonly observed in ovarian metastases (Moore *et al.* 2004). Ascites is not common, being detected in 39% of cases, in contrast to primary ovarian cancer where it is the most common presenting finding (Bruchim *et al.* 2013). Although there are no data regarding gonadal function in these patients, biomarkers such as Carcinoembryonic Antigen (CEA) and the Cancer Antigen (CA125)/CEA ratio may help distinguish primary ovarian neoplasms from ovarian metastases (Moro *et al.* 2018). Risk factors for predicting ovarian involvement of endometrial cancer include deeper myometrial invasion, positive lymph node metastasis, and high histologic grade (Loi *et al.* 2017). Metastatic breast cancer to the ovaries is typically bilateral, tends to be smaller than 5 cm in size, and usually affects younger women.

In cases of testicular metastases due to prostate cancer, most patients are asymptomatic except from a palpable testicular mass. Non-Hodgkin's lymphoma is more likely to occur in older patients (>60 years old) and to be bilateral compared to seminoma (Appelbaum *et al.* 2013). If a history of extra-testicular lymphoma is not available, lymphoma could potentially be confused with seminoma (Appelbaum *et al.* 2013). Obtaining an adequate patient history may be critical in avoiding an erroneous diagnosis of a seminoma or other primary neoplasm (Emerson & Ulbright 2007).

Imaging

CT characteristics of ovarian malignant masses show bilaterally enlarged ovaries that are completely replaced by malignant tissue; however, MRI may better demonstrate the internal architecture of these masses, where the cystic component most commonly appears as hyperintense on T₂-weighted images (Koyama *et al.* 2007) (Fig. 7A and B).

Figure 7

(A) T₂-weighted MRI image of the abdomen showing a right pelvic lobulated adnexal mass consisting of both solid and cystic parts depicting mixed signal intensity (high, low and intermediate) in a 38 year-old patient with an unknown primary NET (white arrow). (B) T₁-weighted MRI image showing a right heterogeneous pelvic adnexal mass exhibiting low signal intensity due to the presence of the mucous component of the cystic part (white arrow) in the same patient. MRI, magnetic resonance.

After contrast injection, solid parts exhibit avid contrast uptake, an indirect sign of the increased vascularity of the tumours (Ha *et al.* 1995).

Ultrasonography is an initial imaging modality to detect testicular masses with a nearly 100% sensitivity, also indicating whether the mass is intra-testicular or inter-testicular (Appelbaum *et al.* 2013). Contrast-enhanced US (CEUS) and ultrasonic elastography may contribute to differentiation from benign intra-testicular lesions to avoid unnecessary orchidectomy (Auer *et al.* 2017). The main characteristics of the testes with metastases include a bulky, heterogeneous multiple hypoechoic lesions within the testis, and raised vascularity on colour Doppler (Kamble & Agrawal 2017, Kawamoto *et al.* 2018). In CT imaging the testes can be bulky and heterogeneous with significant heterogeneous enhancement on post-contrast analysis.

Pathology

Immunohistochemistry using a panel of markers can help the differential diagnosis of primary and metastatic tumours of the ovary and the testes (Table 3). Cytokeratin-7 (CK7) as well as Wilms' tumour 1 (WT1) antibody staining are helpful markers to differentiate primary ovarian carcinoma from metastatic ones (Kriplani & Patel 2013). Immunostaining for the RCC and leucocyte common antigen (CD45) or (CD20) is positive in clear cell renal

cell carcinoma and in lymphomas respectively, but not in primary germ cell tumours such as seminoma (Avery *et al.* 2000, McGregor *et al.* 2001, Emerson & Ulbright 2007). Prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) may be used to confirm the diagnosis of metastatic prostate carcinoma (Tu *et al.* 2002). Moreover, Octamer-binding transcription factor 4 (OCT4) is positive in seminoma and negative in almost all the other metastatic primaries, although it can rarely be positive in renal cell carcinomas and non-small lung carcinomas (Looijenga *et al.* 2003).

Treatment and prognosis

The treatment and potential responses of ovarian metastases depend on the primary cancer. Patients with ovarian metastases of colorectal origin (Kammar *et al.* 2017, Sugarbaker & Liang 2018) were more resistant in chemotherapy compared to patients with ovarian metastases from gastric cancer (Brieau *et al.* 2016). The prognosis of patients with secondary tumours of the ovaries is generally poor, as they are usually encountered in patients with advanced stage cancer (Petru *et al.* 1992), with those originating from the pancreas and the small bowel having the worst prognosis (de Waal *et al.* 2009).

A metastatic epithelial malignant tumour metastasising to the testes was associated with poor prognosis with a survival of only 9.1 months from

Figure 8

Diagnostic approach of a lesion suspicious of metastasis in endocrine organs. *Adrenal hormones of the adrenal cortex and adrenal medulla, pituitary function (anterior and posterior basal and if needed dynamic), common tumour and markers and neuroendocrine tumour markers. ** See Table 3. CT, computerised tomography; MRI, magnetic resonance imaging; ¹⁸FDG-PET, ¹⁸Fluoro-deoxyglucose-positron emission tomography; DD, differential diagnosis.

diagnosis (Salesi *et al.* 2004). Surgery is the main treatment for testicular metastases (Salesi *et al.* 2004).

Clinical work-flow

In the case of a lesion detected incidentally in the endocrine glands, it is important to obtain a clinical history of any recent malignancy. In most cases, imaging cannot distinguish a primary malignant lesion from a metastatic one, but can help to differentiate benign from malignant lesions. Especially, in the case of an isolated lesion in the adrenal gland in a patient with no history of malignancy, a functioning primary tumour of the adrenal medulla or cortex should be excluded first. Routine imaging (CT/MRI) as well as functional imaging (^{18}F FDG-PET) may help in the distinction between benign and malignant tumours. Adrenal biopsy should be performed only when an ACC or pheochromocytoma have been excluded and should be reserved for the rare cases of a high suspicion of adrenal metastases from an unknown primary tumour. Alternatively, it may sometimes be more appropriate to simply remove the entire lesion laparoscopically. On the contrary, in the thyroid FNA-guided biopsy is a routinely and easily performed diagnostic technique when a suspicious thyroid nodule is detected. Regarding pituitary tumours, biopsy is almost never necessary and the diagnostic approach should be based on a relevant clinical history, hormonal assessment and imaging characteristics. Concerning parathyroid tumours, the diagnosis should be based on clinical history and histological analysis. Similarly, for pancreatic lesions, a clinical history of a known malignancy can be useful although EUS-FNA-guided biopsy can be used to establish the diagnosis. Finally, in cases of bilateral gonadal lesions with suspicious imaging characteristics, metastases should always be suspected.

In general, immunochemistry through biopsy or surgery and the use of specific markers based on the clinical history can be a helpful tool to confirm the metastatic origin of a known malignancy, or to determine the origin of the tumour in the case of unknown primary. A proposed algorithm of a diagnostic approach is presented in Fig. 8.

Conclusions

Although metastases to endocrine organs have been considered to be rare, new imaging modalities and more

intensive and prolonged follow-up have revealed that their prevalence has substantially increased over previous estimates. Breast, lung, clear cell renal carcinoma and melanomas are the most common primary tumours metastasising to endocrine organs. The adrenal is the most common endocrine organ involved in the metastatic process. Although in the great majority of cases there are no specific symptoms and the secretory component of the endocrine gland is usually not affected, when the pituitary and adrenal glands are involved hormonal tests should be performed, even in the absence of clinical suspicion, to exclude primary or secondary adrenal insufficiency. In addition, the presence of diabetes insipidus should always raise the suspicion of pituitary involvement in patients with pituitary lesions. In most cases, prognosis is directly related to the biological behaviour of the primary tumour, and generally with disseminated disease the outlook is relatively poor. However, in the case of mono- or oligo-metastatic disease, surgery may improve overall survival, particularly in the presence of slowly-progressive cancers while adequate hormonal replacement may improve overall outcome and quality of life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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