1. Introduction

Pheochromocytoma (Pheo) is a chromaffin tumor of the adrenal gland. When the tumor arises in the extra-adrenal chromaffin tissue, it is called paraganglioma (PGL). These chromaffin tumors generally synthesize and release catecholamines together with different types of peptides. Adrenal and extra-adrenal chromaffin tumors can be referred to as secreting PGLs. PGLs can arise also in the parasympathetic ganglia located mainly in the head and neck. These PGLs are generally not secreting, their clinical picture is characterized by compression of the local nerves and are referred to as non-secreting PGLs.

Malignant PGLs are rare and, as a whole, they account for about 10% of all PGLs.

At present, the only objective criterion for malignancy is the presence of metastases (i.e. spreading of the tumor in bones, liver, lungs or lymph-nodes where chromaffin tissue is normally absent).

Some features can suggest malignant potential but they cannot be assumed as diagnostic criteria. Among these, an extensive invasion of adjacent tissues, high cellularity, necrosis, vascular/capsular invasion, high Ki-67 immunoreactivity, extra-adrenal localizations, large size and irregular shape.

Metastases can be found at diagnosis or develop after primary surgery, sometimes also after many years. For this reason an annual or bi-annual control visit is recommended in every patient operated for a Pheo/PGL.

2. Biochemistry

Plasma and/or urinary metanephrines are the most sensitive assays for the diagnosis of a secreting PGL. The biochemical profile of malignant Pheo/PGL is generally represented by high levels of norepinephrine and its derivative normetanephrine.

Occasionally, malignant PGLs secrete preferentially dopamine, due to altered catecholamine synthesis. When dopamine is the only product the biochemical marker to be looked for is urinary methoxytyramine. The measurement of urinary dopamine is not useful and can be misleading as urinary dopamine derives almost exclusively from the decarboxylation of l-Dopa in the kidney tubules. In patients with progressive metastatic disease urinary total metanephrine excretion increases with time and can be used as an indirect indicator of tumor burden. Rarely malignant tumors can be non-secreting. In these very rare cases, chromogranin A and neuronal specific enolase can be used as surrogate markers.

3. Genetics

Pheo/PGL can be sporadic or syndromic. The so-far known susceptibility genes include the VHL gene, responsible for the von Hippel-Lindau disease, the RET gene, responsible for the Multiple Endocrine Neoplasia type 2 syndrome, the NF1 gene, responsible for neurofibromatosis type 1 and three of the four nuclear genes encoding the B, C and D subunits of the succinate-dehydrogenase or mitochondrial complex II (SDHB, SDHC and SDHD genes, respectively). It is well established that in patients with a syndromic Pheo/PGL malignancy occurs in about 5% unless they are SDHB mutation carriers where the incidence of metastatic disease ranges from 30 to 60%. The reason for this different clinical behavior are completely unknown at present.

4. Therapy

Malignant pheo/PGL show a clinical course which varies among the different patients. The disease course ranges from indolent to very aggressive. The overall 5 years survival varies from 40 to 74%. Unfortunately, at present the therapy of malignant Pheos/PGLs is palliative. Surgery should always be considered, even in the presence of metastases, as it reduces
catecholamine secretion and may also increase the efficacy of other therapeutic modalities. In fact, surgical debulking, as well as other ablative procedures, ameliorate symptoms and increase the efficacy of radio- and/or chemotherapy.

Radiometabolic therapy using $^{131}$I-MIBG is the first option when metastases result positive at scintigraphy. The efficacy of this therapy depends in part on the ability of the radionuclide to enter the cell membrane and be stored in the chromaffin granules via VMA transporters (VMAT 1 and 2).

Efficacy varies also depending on the scheme of treatment and on the cumulative dose of the radionuclide. It has been reported that a high initial dose (> 500 mCi) results in a longer survival. Maximal doses as high as 900 mCi have been shown to possibly induce disappearance of skeletal and soft tissue metastases but cause bone marrow toxicity and may require stem cell rescue.

In case $^{131}$I-MIBG uptake is less than 1% or absent, an alternative radiotherapy may be permitted by the presence of somatostatin receptors on tumor cells. Chromaffin cell tumors generally express somatostatin receptors which can be the targets of several radiopharmaceuticals such as $^{111}$In-pentetreotide/$^{111}$In-DOTA octreotide, $^{90}$Y-DOTA-octreotide, $^{177}$Lu-DOTA-octreotate, $^{111}$In- and $^{90}$Y-DOTA-lanreotide. When metastatic lesions results positive at $^{131}$I-MIBG scintigraphy and at octreoscan, a combined treatment using both the radionuclides can be considered.

Chemotherapy has been used alone or in association with radionuclide treatment but always with limited results. Limited success has been reported with the combination of cyclophosphamide, vincristine and dacarbazine (CVD), etoposide and cisplatin, temozolomide and thalidomide or with the HSP 90 inhibitor geldanamycin.

Therapy with other anti-angiogenetic drugs is a putative option that might be tested in the next future.

**Further reading**


