# FOREWORD

Paragangliomas and pheochromocytomas are rare tumors of the autonomic nervous system that pose important clinical questions. Their presentation may be extremely variable. Classic sites of origin, such as the adrenal medulla and the autonomic branches of the lower cranial nerves, are the most frequent locations, but other sites may also be involved. Paragangliomas may indeed arise in connection with autonomic neural branches almost anywhere in the thoracic, abdominal, and head and neck regions. Some of these locations are accessible only by surgeons with special skills, not easy to acquire, given the rarity of the disease in general and of the specific locations, in particular.

Early diagnosis may be problematic, particularly when patients are seen by physicians who do not have specific experience. This may have relevant consequences, as surgical resection, which must be radical, is still the mainstay therapy, and late diagnosis may complicate surgery. In fact, paragangliomas, despite their slow growth, in most cases they do not grow more than few a millimeters in diameter per year, tend to relentlessly infiltrate adjacent anatomical structures, most often extending along regional neurovascular bundles. With time, this behavior makes their resection difficult and, in some instances, even impossible. Such is often the case for those paragangliomas that, arising at the skull base, extend within the skull, either through neurovascular foramina or by direct bone erosion. Another challenge is represented by the possible secretion of catecholamines, more frequent in pheochromocytomas and sympathetic thoracoabdominal paragangliomas. This may per se entail life-threatening cardiovascular complications. Such tumors require cautious surgical approaches and well-trained multidisciplinary surgical teams.

A critical, but still poorly understood, characteristic of paragangliomas seems to be their resistance to radiotherapy and chemotherapy. In this regard, the search for effective nonsurgical therapeutic approaches is made even more difficult by the rarity of the patients, which makes comparative evaluation of treatment modalities challenging or impossible. This is compounded by marked differences in tumor location, size, and type among treated cases. Slow growth complicates the assessment of therapeutic results, as, dealing with tumors that may naturally grow at most a few millimeters per year, it is difficult to distinguish the effect of therapies. It cannot be excluded that inappropriate therapeutic interventions, particularly with radiotherapy, could contribute to aggressive evolution and/or increased difficulties in case of later surgery. Timely surgery is indeed the safer option, considering also that metastatic spread, even if extremely rare, can never be completely excluded, even for well-differentiated paragangliomas.

The abovementioned surgical and clinicopathological issues are not the only factors that contribute to the important place that paragangliomas and pheochromocytomas occupy in oncology. In fact, these are the tumor types in which the impact of genetic predisposition factors is the highest. Germline or somatic mutations in at least 20 different genes have been implicated in the pathogenesis of paragangliomas and pheochromocytomas, and as much as 40% of the patients carry germline predisposing mutations, most notably in the five genes that encode

the protein components of complex 2 of the mitochondrial respiratory chain. In this regard, paragangliomas and pheochromocytomas have been hailed as "Warburg's tumors", that is, prototypic tumors that fulfill Warburg's concept on the role of deficient mitochondrial respiration in cancer. Beyond the scientific relevance, this impacts on patient management, as some mutations are linked to more aggressive and even metastatic tumor behavior. Furthermore, constitutional predisposition means that a patient with paraganglioma may develop, throughout life, multiple independent tumors. Such event heavily impacts on the quality of life, and may pose specific surgical challenges, for example, when distinct paragangliomas involve bilaterally the carotid arteries. In addition, despite the unpredictable penetrance of the mutations, an increased risk for relatives can never be ruled out.

All these issues highlight the importance of paragangliomas and pheochromocytomas. In spite of this, even today, there is a relative scarcity of comprehensive therapies for these tumors. This book, although small, intends to fill the gap of knowledge on these diseases, making a series of chapters readily available, which address several critical questions that concern the genetics, pathology and treatment of paragangliomas and pheochromocytomas. With enhanced knowledge, hope emerges that the development of new therapies is within reach for these patients.

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May 2019
Doi:http://dx.doi.org/10.15586/paraganglioma.2019.fr