The risk of tumor recurrence and the need for follow-up in patients operated on a pheochromocytoma or paraganglioma

Setting

The clinical committee of the European Society of Endocrinology (ESE) and the endocrine hypertension working group (WG) of the European Society of Hypertension (ESH) agreed to create a Special Interest Group (SIG) to assess the risk of tumor recurrence and the need for follow-up in patients operated on a pheochromocytoma or paraganglioma (PPGL). The ENS@T (European Network for the Study of Adrenal Tumors) PPGL WG also agreed to participate.

Background

Current knowledge concerning long term postoperative outcome can be summarized as follows:[1]

- There is evidence that at least 15% of patients undergoing surgery for PPGL develop new tumors or recurrences and that most recurrences are metastatic.
- Although there are reports of the prognostic value of various clinical, biochemical, genetic, imaging and pathological features, there are no robust prognostic indices of tumor recurrence in individual patients with PPGL other than the higher probability of new events in patients with inherited tumors and, probably, in patients with extraadrenal or large tumors.
- The duration of follow-up required remains unclear, as new events may occur decades after initial surgery.
- The combination and sequence of biochemical and imaging tests to detect and monitor recurrences is poorly defined.
- Kaplan-Meier estimates of the incidence of recurrences in inherited PPGL syndromes are required, together with determinations of the distribution of events between metastatic recurrences and new tumors.

CLINICAL QUESTION BUILDING

Key questions

1. What is the incidence of documented recurrences (local or metastatic) or new tumors in patients operated on for PPGL with apparently complete tumor resection?
2. Which are the factors associated with documented recurrences (local or metastatic) or new tumors in patients operated on for PPGL with apparently complete tumor resection?

COMPILATION OF EXISTING PPGL DATABASES

This compilation is a necessary complement to the systematic review of the literature as many published papers could not take into account the presence or absence of inherited diseases. Many

[1] See the review prepared by the Pheochromocytoma Research Support Organization (PRESSOR) following the 3rd International Symposium on Pheochromocytoma: Amar L et al, Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. Horm Metab Res 2012;44:385-9

genes have been described recently, and the presence or absence of a germline mutation in one PPGL susceptibility gene is a critical predictor of long term outcome. Most patients in the existing ENS@T PPGL database have been screened for the major known inherited diseases involving PPGL and have a standardized comprehensive data set. We also consider importing data from other existing databases into the ENS@T database

Patient selection

Inclusion criteria are (i) resection of the primary tumor, (ii) no evidence of persistent disease at postoperative assessment (negative biochemical tests in patients with functioning tumors, negative imaging tests in patients with non-functioning tumors), and (iii) documented follow-up of one year or more. For the ENS@T PPGL database, this converts into the need for the following forms:

Form	Timing or scope
Identification	-
Genetics	-
Clinical assessment	before initial surgery
Surgery	regarding initial surgery
Tumor	regarding the primary tumor
Biochemical assessment	at least two for functioning tumors: before and in the year following initial surgery
Imaging test	at least two for non-functioning tumors: before and in the year following initial surgery
Follow-up	most recent follow-up

Numbers

A cohort of 1000 subjects, a mean accrual interval of 15 years plus an additional follow-up after the accrual interval of one year, and a 10-year probability of event of 15% (the expected incidence) will enable to detect hazard ratios of approximately 2 for risk factors with a prevalence of 10% (e.g. presence of a mutation, of an extraadrenal tumor or of a tumor with a diameter of 8 cm or more). We expect 150 events (recurrence, new tumor or death), which should enable a multivariate analysis with approximately 15 variables.

INTELLECTUAL PROPERTY

The ENS@T policy regarding publication and data usage is as follows (ENS@T Regulatory issues, Version 08.07.2011)

Publication policy

Recipient scientist formally agrees with the provider(s) [of data for the present compilation] - *at the time of the request or soon after the provider(s) have accepted the collaboration - the (ir) presence (if any) as co-authors in the publications originating from the collaboration.*

Number of authors per center and order of authorships are specified as follows:
We suggest naming all participants who included 100 valid cases or more, plus PF Plouin (coordinator) and O Steichen (methodologist)

Depending on the contribution of each center or if number of authors has to be limited on the basis of a specific journal style co-authors will be represented as "on behalf of ENS@T" and placed in an appropriate list depending on the Journal format(acknowledgment or collaborators list). In this case the recipient scientist will contact all provider(s) and obtain agreement.

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We shall also acknowledge the European Societies of Endocrinology and Hypertension and the PPGL Special interest Group (to be detailed by the ESE)

Conditions of data usage

The Recipient scientist will use the data for research purposes only. The data will be used by the Recipient scientist solely in connection with the Research Project as outlined above. The Recipient scientist shall use the data in compliance with all applicable laws and government regulations of the Recipient's country. The Recipient Scientist shall not release the data to any person other than the personnel under the Recipient Scientist's direct supervision. When the Research Project is completed, a detailed description of the use of the data will be made available to the appropriate ENS@T Working Group. In the event that a journal publication or scientific article is published based on use of the data, the Recipient Scientist will send a copy of such publication, or the publication cite, promptly after it becomes available to the Recipient, to the appropriate ENS@T Working Group.