MANAGEMENT OF ENDOCRINE DISEASE

Recurrence or new tumors after complete resection of pheochromocytomas and paragangliomas: a systematic review and meta-analysis

Laurence Amar^{1,2,3,*}, Charlotte Lussey-Lepoutre^{2,3,*}, Jacques W M Lenders^{4,5}, Juliette Djadi-Prat⁶, Pierre-Francois Plouin^{1,2,3} and Olivier Steichen^{7,8,9}

¹Faculty of Medicine, Université Paris-Descartes, Paris, France, ²Hypertension Unit, AP-HP, Hôpital Européen Georges Pompidou, Paris, France, ³Paris Cardiovascular Research Center, INSERM UMR970, Paris, France, ⁴Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands, ⁵Department of Internal Medicine III, Technische Universität Dresden, University Hospital Carl Gustav Carus, Dresden, Germany, ⁶Clinical Research Unit, AP-HP, Hôpital Européen Georges Pompidou, Paris, France, ⁷Faculty of Medicine, Sorbonne Universités, UPMC Univ Paris 06, Paris, France, ⁸INSERM, U1142, LIMICS, Paris, France, and ⁹Department of Internal Medicine, AP-HP, Hôpital Tenon, Paris, France

* (L Amar and C Lussey-Lepoutre contributed equally to this work)

Correspondence
should be addressed
to O Steichen
Email
olivier.steichen@aphp.fr

Abstract

Objectives: To systematically review the incidence and factors associated with recurrences or new tumors after apparent complete resection of pheochromocytoma or thoraco–abdomino–pelvic paraganglioma.

Design: A systematic review and meta-analysis of published literature was performed.

Methods: Pubmed and Embase from 1980 to 2012 were searched for studies published in English on patients with non-metastatic pheochromocytoma or thoraco–abdomino–pelvic paraganglioma, complete tumor resection, postoperative follow-up exceeding 1 month, and recurrence or new tumor documented by pathology, hormonal dosages, or imaging tests. Incidence rates of new events after curative surgery were calculated for each study that had sufficient information and pooled using random-effect meta-analysis.

Results: In total, 38 studies were selected from 3518 references, of which 36 reported retrospective cohorts from the USA, Europe, and Asia. Patient follow-up was neither standardized nor exhaustive in the included studies. A clear description of patient retrieval methods was available for nine studies and the follow-up protocol and patient flow for four studies. Only two studies used multivariable methods to assess potential predictors of postoperative events. The overall rate of recurrent disease from 34 studies was 0.98 events/100 person-years (95% confidence interval 0.71, 1.25). Syndromic diseases and paragangliomas were consistently associated with a higher risk of a new event in individual studies and in meta-regression analysis.

Conclusions: The risk of recurrent disease after complete resection of pheochromocytoma may be lower than that previously estimated, corresponding to five events for 100 patients followed up for 5 years after complete resection. Risk stratification is required to tailor the follow-up protocol after complete resection of a pheochromocytoma or paraganglioma. Large multicenter studies are needed to this end.

European Journal of
Endocrinology
(2016) **175**, R135–R145

Review	L Amar, C Lussey-Lepoutre and others	Recurrent disease after PH/PG resection	175:4	R136
---------------	--------------------------------------	---	--------------	-------------

Introduction

Pheochromocytomas and paragangliomas (PH/PG) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or sympathetic and parasympathetic paraganglia respectively. Following resection of the primary tumor, most patients are free of tumor with no clinical, biochemical, or imaging evidence of persistent disease. However, tumor-free patients are at a risk of long-term recurrence, defined as the reappearance of disease after complete surgical eradication of the tumor (1). Recurrences may arise at the operated site or may be metastatic, developing in non-chromaffin organs, mainly the lymph nodes, bones, lungs, and liver (2, 3). Patients with inherited tumors may also develop new PH/PGs in the contralateral adrenal gland or in other paraganglia (3, 4). At least 15% of patients undergoing surgery for PH/PG develop new tumors or recurrences, most of which are metastatic (4). Consequently, long-term follow-up is recommended for patients who have undergone surgery for PH/PG (5).

Although there are reports of the prognostic value of various clinical, genetic, and pathological features, there are no robust prognostic indices of recurrence other than the higher probability of new events in patients with inherited tumors and possibly in patients with extra-adrenal or large tumors (4, 5). The total duration of follow-up that is required remains unclear, as new events may occur decades after initial surgery. The optimal combination and sequence of biochemical and imaging tests to detect and monitor recurrences are poorly defined. There have been no comprehensive systematic reviews assessing the incidence of recurrences or new tumors following surgery for PH/PG.

Our primary objective is to systematically review the incidence of local or metastatic recurrences or new tumors in patients who have undergone apparently complete resection of a non-metastatic PH/PG. A secondary objective is to assess the factors associated with recurrences (local or metastatic) or new tumors.

Methods

Eligibility criteria

We searched randomized or non-randomized controlled trials, prospective or retrospective cohort studies, and case-control studies published in English in 1980 or later (computed tomography and metanephrine determinations were not universally available before 1980). Studies were eligible if (i) they enrolled at least 20 patients with PH/PG; (ii) patients had reportedly undergone complete tumor resection; (iii) postoperative follow-up exceeded

1 month (arbitrarily); and (iv) the number of patients with recurrence or new tumor could be identified.

Information sources and search

We searched Medline and Embase databases from 01/01/1980 to 10/19/2012. We developed a specific search strategy for each database and is presented in [Supplementary Methods](#) (see section on [supplementary data](#) given at the end of this article).

Study selection

Two physicians, experts in endocrine hypertension (L A and C L), independently made a first selection using the titles, abstracts, and keywords to exclude studies that clearly did not fulfill the inclusion criteria. They independently read the full text of the remaining papers to identify eligible articles. At each stage, disagreements between readers were resolved by discussion or, if necessary, by a third reader (P F P or J L). Journals and authors were not blinded during study selection. In cases of overlapping publications by a given team, only the most comprehensive or most recent was included.

The studies were then further subdivided into two categories: (i) studies on head and neck paraganglioma only and (ii) studies on pheochromocytoma and thoraco-abdomino-pelvic paraganglioma. This review reports only the results of the latter category of studies.

Data collection

A standardized form was tested on ten articles and two senior experts (P F P and J L) to homogenize further data collection. The form was then used by two abstractors (L A and C L) to extract methodological and clinical data from all included studies. Records were reviewed by a third reader and issues were resolved by discussion. Journals, titles, and authors were not blinded during data abstraction.

The following data were collected from each study: first author and publication year; study design and settings; number of centers, total number and number of operated patients with complete tumor resection; risk of bias; percentage of female patients, mean age, percentage of hypertensive patients, percentage of patients with pheochromocytoma, location of paragangliomas, mean tumor size, percentage of secreting tumors, and percentage of genetic or syndromic diseases; number of patients with follow-up and duration of follow-up; incidence of recurrence, timing of recurrence, and attributable deaths.

Quality assessment

No agreed criteria exist for assessing the risk of bias of prognostic studies. We used several resources to compile a list of criteria to assess the risk of bias regarding study participants, prognostic factors, outcome, follow-up, and reporting. Further details are provided in the [Supplementary Methods](#).

Summary measures

Incidence rates of recurrence or new tumor over the entire duration of the follow-up were calculated by dividing

the number of events by the number of person-years of follow-up, and then standardized to the number of events/100 person-years. The mean duration of follow-up was multiplied by the number of patients when the number of person-years of follow-up was not reported. When the mean duration of follow-up was not reported, it was approximated by a formula using the median and range when available (6, 7), or by the median in other cases. We assumed the Poisson distribution to estimate 95% confidence intervals for the rate of events presented in forest plots. Meta-analysis was performed on rates and their confidence interval limits. Heterogeneity was

Figure 1

Study flow diagram. FU, follow-up; HN, head and neck; PH/PG, pheochromocytomas and paragangliomas; PG, paragangliomas.

assessed using Cochran statistic and the I^2 inconsistency coefficient. An I^2 value greater than 50% was considered to be indicative of substantial heterogeneity. Study results were pooled using random-effect meta-analysis. We used Stata SE/MP version 9.2 (StataCorp) for the analyses.

Additional analyses

We performed sensitivity analyses based on the availability of the mean duration of follow-up (allowing to compute the exact incidence rate) and by risk of bias. A funnel plot of the event rate according to the number of person-years of follow-up (a substitute for the precision of estimates) was used to assess publication bias.

Meta-regression analysis was used to assess the impact of the following variables on the logarithm of incidence rates: operation year of the first patient, specialty of the author team (surgery vs others), percentage of females, mean age, percentage of familial diseases (genetic or syndromic), percentage of pheochromocytomas, mean size of the tumor, and mean duration of follow-up.

Results

Study selection

The details of the selection process and reasons for exclusions are depicted in the flow chart (Fig. 1).

Table 1 Overview of included studies.

Study	Country	Period	Design	Settings	Number of centers	Total number of patients	Number of curative surgeries
Agarwal 2012 (8)	India	1990–2010	Retrospective	Surgery	1	101	100
Amar 2005/2006 (9, 10)	France	1975–2006	Retrospective	Medicine	1	261	242
Beatty 1996 (11)	Ireland	1970–1991	Retrospective	Mixed	1	41	38
Benhammou 2010 (12)	USA	1995–2003	Retrospective	Surgery	1	26	26
Brunt 2001/2002 (13, 14)	USA	1993–2000	Retrospective	Surgery	1	35	35
Castilho 2009 (15)	Brazil	1995–2006	Retrospective	Surgery	1	24	24
Cotesta 2009 (16)	Italy	1992–2008	Retrospective	Medicine	1	91	91
de Wailly 2012 (17)	France	1993–2009	Retrospective	Medicine	1	53	48
Diner 2005 (18)	USA	1995–2004	Retrospective	Surgery	1	33	33
Edström Elder 2003 (19, 20)	Sweden	1976–1999	Retrospective	Mixed	1	85	80
Favia 1998 (21)	Italy	1977–1996	Retrospective	Surgery	1	55	50
Geoghegan 1998 (22)	UK	1978–1992	Retrospective	Surgery	1	43	42
Grozinsky-Glasberg 2010 (23)	Israel	1989–2009	Retrospective	Medicine	2	43	41
van der Harst 2002 (24)	The Netherlands	1983–2001	Retrospective	Mixed	1	87	87
Hayry 2009 (25)	Finland	1985–2008	Retrospective	Laboratory	1	42	36
Iacobone 2011 (26)	Italy	1985–2010	Retrospective	Medicine	1	71	70
Jaroszewski 2003 (27)	USA	1992–2001	Retrospective	Surgery	1	47	47
Kercher 2002 (28)	USA	1995–2000	Retrospective	Surgery	1	39	39
Khorram-Manesh 2005 (29)	Sweden	1950–1997	Retrospective	Medicine	1	121	118
Lairmore 1993 (30)	USA	1956–1990	Retrospective	Mixed	3	58	55
Zhang 2007/Lang 2008 (31, 32)	China	1998–2005	Retrospective	Surgery	1	103	103
Lucon 1997 (33)	Brazil	1974–1994	Retrospective	Mixed	1	50	41
Lumachi 1998 (34)	Italy	1977–1996	Retrospective	Surgery	1	55	50
Neumann 1999 (35)	Germany	1985–1995	Retrospective	Mixed	1	39	39
Noshiro 2000 (36)	Japan	1957–1995	Retrospective	Medicine	1	95	91
Obara 1995 (37)	Japan	1981–1994	Retrospective	Surgery	1	87	83
Pan 2005 (38)	China	1990–2004	Retrospective	Surgery	1	26	25
Park 2011 (39)	Korea	1989–2008	Retrospective	Surgery	1	152	147
Pomares 1998 (40)	Spain	1979–1995	Retrospective	Medicine	1	44	43
Rodriguez 2008 (41)	Spain	–	Retrospective	Surgery	2	54	54
Scholten 2011 (42)	The Netherlands	1959–2010	Retrospective	Surgery	1	61	61
Scott 1984 (43)	USA	1950–1983	Retrospective	Surgery	3	69	53
Stenström 1988 (44)	Suede	1956–1982	Prospective	Mixed	1	64	64
Tiberio 2008 (45)	Italy	2000–2006	RCT	Surgery	1	22	22
Timmers 2008 (46)	The Netherlands	1966–2000	Retrospective	Medicine	1	69	64
Tormey 2002 (47)	Ireland	1989–2000	Retrospective	Medicine	21	39	32
Wilhelm 2006 (48)	USA	1995–2005	Retrospective	Surgery	3	65	64
Yip 2004 (49)	USA	1962–2003	Retrospective	Surgery	1	59	58

Review	L Amar, C Lussey-Lepoutre and others	Recurrent disease after PH/PG resection	175:4	R139
---------------	--------------------------------------	---	-------	-------------

Bibliographic searches yielded 3518 references, among which 42 on pheochromocytoma and thoraco-abdomino-pelvic paraganglioma were finally selected, reporting 38 different cohorts.

Study characteristics

The characteristics of the included studies are reported in Table 1.

All studies were on retrospective cohorts except one on a prospective cohort (44) and one that was a randomized controlled trial (45). Of the 38 studies, 20 were performed in Europe, nine in North America, six in Asia, two in South America, and one in the Middle East. The inception year ranged from 1950 to 2000 (median 1985). Studies involved 1–21 centers; 20 studies were performed by surgical teams, ten by medical teams, seven by both, and one by laboratory physicians.

Table 2 Overview of patient and disease characteristics.

Study	Females (%)	Age (years)	HTN (%)	Pheo (%)	PHPG size (mm)	Secreting tumors (%)	Genetic diseases ^a (%)
Agarwal 2012 (8)	43	Mean 36 (s.d. 14.6)	81	82	Mean 71 (s.d. 25)	–	–
Amar 2005/2006 (9, 10)	52	Mean 42.5 (s.d. 15)	89	87	Mean 54 (s.d. 27)	–	21
Beatty 1996 (11)	54	–	90	84	–	–	24
Benhammou 2010 (12)	–	Mean 27	–	100	Mean 25	–	100
Brunt 2001/2002 (13, 14)	51	Mean 42 (s.d. 17)	54	100	Mean 34 (s.d. 13)	–	57
Castilho 2009 (15)	42	Median 46.5 (range 10–75)	83	100	Median 37 (range 5–120)	–	13
Cotesta 2009 (16)	52	Mean 48 (range 8–77)	–	92	Mean 43 (range 10–110)	–	23
de Wailly 2012 (17)	55	Mean 53 (range 13–88)	–	100	Mean 46 (s.d. 13)	96 ^b	15
Diner 2005 (18)	–	Mean 38 (range 10–79)	–	100	Mean 23 (range 8–50)	–	94
Edström Elder 2003/2003 (19, 20)	56	Range 14–77	61	82	Range 10–140	–	18
Favia 1998 (21)	49	Median 41 (range 10–63)	58	91	Mean 58 (s.d. 30)	–	7
Geoghegan 1998 (22)	67	Mean 42 (range 16–73)	56	100	Mean 49 (range 20–130)	–	28
Grozinsky-Glasberg 2010 (23)	49	Mean 52.6 (range 16–77)	47	88	Mean 49 (s.d. 20)	–	–
van der Harst 2002 (24)	55	Mean 46 (range 9–78)	66	89	Mean 54 (s.d. 31)	–	31
Häyry 2009 (25)	–	Mean 46.5	–	95	Mean 47 (s.d. 26)	86 ^c	–
Iacobone 2011 (26)	52	Mean 44.8 (range 15–80)	–	93	Mean 54 (s.d. 30)	–	24
Jaroszewski 2003 (27)	51	Mean 53.1 (range 16–81)	–	100	Mean 43 (range 10–85)	–	13
Kercher 2002 (28)	64	Mean 43 (range 19–59)	95	97	Mean 52 (range 20–121)	95 ^b	10
Khorram-Manesh 2005 (29)	56	Mean 47.2 (s.d. 16.8)	84	93	Mean 49 (s.d. 24)	88 ^b	25
Lairmore 1993 (30)	57	Mean 32.8 (s.d. 12.2)	57	100	Mean 43 (s.d. 27)	–	100
Zhang 2007/Lang 2008 (31, 32)	49	Mean 35.8 (s.d. 13.3)	–	100	Mean 47 (s.d. 23)	–	–
Lucon 1997 (33)	56	Median 33 (range 10–64)	86	84	Median 70 (range 30–200)	97 ^b	12
Lumachi 1998 (34)	49	Mean 41 (range 10–63)	45	90	–	–	7
Neumann 1999 (35)	59	Mean 40 (range 10–76)	–	100	Mean 40 (range 10–90)	–	67
Noshiro 2000 (36)	55	Mean 40 (s.d. 14)	88	–	–	–	15
Obara 1995 (37)	56	Median 40 (range 11–67)	–	84	Mean 62 (s.d. 26)	92	14
Pan 2005 (38)	58	Mean 39.5 (s.d. 8.9)	–	85	Mean 73 (s.d. 35)	0	–
Park 2011 (39)	47	Mean 46.5 (range 18–76)	62	90	Mean 67 (s.d. 35)	–	2
Pomares 1998 (40)	54	Mean 43 (s.d. 13.7)	37	98	Mean 49 (s.d. 26)	84 ^b	52
Rodriguez 2008 (41)	57	Mean 37.4 (range 14–71)	24	100	Mean 45 (range 10–120)	89	100
Scholten 2011 (42)	39	Mean 33 (s.d. 12.7)	3	100	–	67	100
Scott 1984 (43)	58	Range 9–79	98	77	–	–	12
Stenström 1988 (44)	53	Mean 45 (range 15–79)	47	94	–	–	20
Tiberio 2008 (45)	36	Mean 51 (range 34–74)	–	100	Mean 40 (range 22–60)	–	–
Timmers 2008 (46)	64	Mean 46.1 (s.d. 15.6)	78	88	–	–	20
Tormey 2002 (47)	38	Median 36 (range 8–76)	89	87	–	–	59
Wilhelm 2006 (48)	62	Mean 48.5 (s.d. 16.1)	68	100	Mean 40 (s.d. 15)	–	14
Yip 2004 (49)	58	Median 36	–	95	–	–	97

^aFamilial or syndromic disease or germline mutation; ^bMethoxylated derivatives only; ^cCalculated using urinary normetanephrine+metanephrine: abnormal if ≥ 4.5 $\mu\text{mol}/24$ h.

Risk of bias within studies

Detailed risks of bias of the included studies are reported in the [Supplementary Table 1](#). Only nine studies explained how they ensured the completeness of patient retrieval (for instance, through a prospectively maintained research database or administrative databases with diagnostic coding). Only four studies provide a clear and specific description of patient flow (inclusion, operation, cure, and follow-up). Fourteen studies looked for prognostic factors, but only two performed multivariate analyses.

Patient and disease characteristics

Patient and disease characteristics are reported in [Table 2](#). The percentage of females was reported in 35 studies and was between 36 and 67% (median 54%). The mean or median age was reported in 35 studies and was between 27 and 53 years (median 42 years). The percentage of hypertensive patients was reported in 25 studies and was between 3 and 98% (median 66%). The percentage of syndromic or genetic disease was reported in 32 studies. Of the 32 studies, four involved only patients with a syndromic disease (VHL, NF1, or MEN2). In the

Table 3 Overview of treatment and outcomes.

Study	Cured and followed up	Follow-up duration (months)	Same-site recurrences	Other-site recurrences	Metastases	Attributable death
Agarwal 2012 (8)	100	Mean 44 (range 3–160)	0	0	1	0
Amar 2005/2006 (9, 10)	242	Mean 102 (range 45.6–158.4)	18	0	18	0
Beatty 1996 (11)	38	Mean 84	2	0	4	4
Benhammou 2010 (12)	26	Mean 111	3	3	0	0
Brunt 2001/2002 (13, 14)	34	Mean 46 (range 2–85)	0	3	0	0
Castilho 2009 (15)	24	Mean 74 (range 18–150)	0	0	0	0
Cotesta 2009 (16)	43	Range 6–192	2	0	1	2
de Wailly 2012 (17)	48	Mean 86	0	1	1	0
Diner 2005 (18)	33	Mean 36 (range 3–108)	2	0	0	0
Edström Elder 2003 (19, 20)	80	Median 144	2	0	3	2
Favia 1998 (21)	50	Mean 88 (range 6–232)	1	1	0	0
Geoghegan 1998 (22)	41	Mean 31 (range 9–120)	0	0	0	1
Grozinsky-Glasberg 2010 (23)	41	–	0	0	0	0
van der Harst 2002 (24)	87	Median 120 (range 3–192)	0	1	14	10
Hayry 2009 (25)	36	Mean 103 (range 20–284)	1	0	3	0
Iacobone 2011 (26)	70	Median 126 (range 6–300)	2	0	1	–
Jaroszewski 2003 (27)	45	Mean 41 (range 10–89)	0	1	0	0
Kercher 2002 (28)	39	Mean 14 (range 1–40)	0	0	0	0
Khorram-Manesh 2005 (29)	121	Mean 180	2	1	6	4
Lairmore 1993 (30)	55	Mean 112.8 (range 8.4–342)	0	12	0	0
Zhang 2007/Lang 2008 (31, 32)	103	Range 5–36	0	0	0	0
Lucon 1997 (33)	35	Mean 33 (range 0.33–192)	0	0	0	0
Lumachi 1998 (34)	50	Mean 88.2 (range 6–232)	1	0	0	0
Neumann 1999 (35)	33	Mean 73 (range 16–179)	1	7	0	–
Noshiro 2000 (36)	74	Mean 117	1	2	5	4
Obara 1995 (37)	83	Median 58 (range 1–164)	0	4	0	1
Pan 2005 (38)	25	Median 66 (range 24–132)	0	0	0	0
Park 2011 (39)	147	Mean 41.5 (range 0.9–298)	0	0	12	12
Pomares 1998 (40)	42	Mean 96 (range 24–216)	0	0	1	0
Rodriguez 2008 (41)	54	Mean 92.5 (range 12–178)	0	5	0	0
Scholten 2011 (42)	61	Mean 160.8 (range 1.2–501.6)	3	18	0	–
Scott 1984 (43)	53	Mean 103 (range 12–348)	0	0	5	4
Stenström 1988 (44)	64	Mean 139.2 (range 12–324)	0	2	2	0
Tiberio 2008 (45)	22	Mean 35 (range 18–84)	0	0	0	0
Timmers 2008 (46)	64	Mean 132 (range 12–456)	2	0	7	7
Tormey 2002 (47)	32	–	2	3	0	2
Wilhelm 2006 (48)	46	Mean 24 (range 1–84)	1	0	0	0
Yip 2004 (49)	58	Median 71	7	3	1	0

remaining 28 studies with phenotypic and/or genetic information, a syndromic or familial disease and/or a mutation in a gene predisposing to PH/PG was between 2 and 97% (median 20%).

The percentage of pheochromocytoma was reported in 37 studies and was between 77 and 100% (median 94%). Of these, 14 studies involved only patients with pheochromocytomas, and the percentage of patients with pheochromocytoma was between 77 and 98% (median 89%) in the 23 remaining studies with information on tumor location. The mean or median tumor size was reported in 28 studies and was between 23 and 73 mm (median 48 mm).

Results of individual studies

Raw results of individual studies are reported in Table 3. The number of patients followed up after complete surgical resection was between 22 and 242 (median 52). The mean or median duration of follow-up was available for 34 studies and was between 14 and 180 months (median 84 months). The percentage of recurrent disease over the entire follow-up was between 1 and 34% (median 6%). Eleven studies (51 events) provided individual data on the time from surgery to recurrent disease, with an overall median time to event of 60 months (range 3–204), and two studies (26 events) provided summary results with median times to event of 17 and 29 months

Figure 2

Forest plot of new event rates.

(range 5–195). Two studies (7 events) did not provide any information on the time to the recurrent event.

Candidate prognostic markers assessed by one or more individual studies are reported in [Supplementary Table 2](#). Paragangliomas (hazard ratios 11 and 8.8 compared with pheochromocytomas) and syndromic diseases (hazard ratios 3.4 and 14 compared with sporadic diseases) were independently associated with an increased risk of a new event after curative surgery in two studies (9, 37) and larger tumor size in one study (hazard ratio 1.2 for each supplementary centimeter in tumor diameter) (9). Paragangliomas were also associated with new events by univariate analyses in one additional study but not in two others. Larger tumor size was also associated with an increased risk of a new event by univariate analysis in an additional study but not in three others.

Synthesis of results

The new event rate estimates of 34 studies with follow-up duration data showed significant heterogeneity (I^2 51%, $P < 0.001$; [Fig. 2](#)). Random-effect meta-analysis produced an overall new event rate estimate of 0.95 events/100 person-years (95% confidence interval (CI) 0.68, 1.21). Assuming a steady incidence over time, this converts into a 5-year cumulative incidence of 4.7% (95% CI: 3.4, 6.1; [Fig. 2](#)), distributed as follows: new tumors 22%, local recurrences 23%, and metastatic recurrences 55%.

The pooled estimate of event rate was as follows:

- 0.98 events/100 person-years (95% CI: 0.68, 1.29) across studies allowing the calculation of the exact number of person-years of follow-up;
- 1.18 events/100 person-years (95% CI: 0.71, 1.66) across studies with the lowest risk of bias (at most five risks regarding participants, outcome, follow-up, or results);
- 1.11 events/100 person-years (95% CI: 0.56, 1.66) across studies fulfilling both conditions.

Risk of bias across studies

The funnel plot of incidence rate against person-years of follow-up shows that the estimated incidence rate of several studies deviates from the overall estimate ([Supplementary Fig. 1](#)).

Meta-regression analysis

The percentage of genetic or syndromic disease was associated with the rate of new events ([Fig. 3](#) and [Supplementary Fig. 2](#)). The pooled event rate estimate was 0.79 events/100 person-years (95% CI: 0.53, 1.04) for

Figure 3

Meta-regression analysis of event rates according to the proportion of genetic or syndromic diseases.

studies with less than 60% genetic or syndromic diseases (I^2 40%, $P = 0.03$) and 2.24 events/100 person-years (95% CI: 1.62, 2.87) for studies with 60% or higher genetic or syndromic diseases (I^2 0%, $P = 0.51$). A younger mean age was also associated with a higher rate of new events; however, this association disappeared in a multivariate model including both the mean age and the percentage of genetic or syndromic disease. Other variables were not associated with the new event rate in meta-regression analyses ([Supplementary Table 3](#)).

Discussion

Summary

Our review suggests that the risk of recurrent disease following complete resection of a pheochromocytoma or a thoraco-abdomino-pelvic paraganglioma is lower than that previously estimated. However, the risk remains non-negligible, approximately 5% per 5 years of follow-up, and late events are possible, up to 15 years after surgery in the included studies. Paragangliomas and familial disease are the two main independent risk factors of recurrent disease identified by several studies and by meta-regression analyses across studies. The association between the size of the primary tumor and the risk of recurrence after complete removal was weaker.

Limitations of evidence

The reporting of methodological details and clinical results of the included studies was very heterogeneous.

Most studies were retrospective, and patient follow-up was neither standardized nor exhaustive. The time pattern of recurrence risk (early vs late) was not assessed, and data were scarce after the first 10 years of follow-up, precluding any firm conclusion beyond this horizon, although recurrent disease is clearly still possible. Risk factors were not consistently assessed across studies and only a few had available genetic data. It is now estimated that around 40% of all PH/PG arise in patients carrying a germline mutation in one of the 13 susceptibility genes identified so far (50). Individual patient data were not available, and meta-regression analyses were limited by an incomplete description of patients and disease in individual studies.

Implications

The overall low frequency of recurrent disease after complete resection of a PH/PG calls into question the need for lifelong follow-up after surgery for all patients. This contradicts the estimates from a previous review of published studies that did not take the varying mean duration of follow-up into account (3). Nonetheless, recurrent disease remains possible even after a long and uneventful follow-up and appears to be more frequent in patients with paragangliomas or familial disease than patients with sporadic pheochromocytoma. The follow-up protocol may need to be tailored according to these and other patient and disease characteristics. In particular, several studies that did not meet our inclusion criteria consistently show that germline mutations, even in apparently sporadic cases, are also associated with more aggressive disease and would benefit from intensive follow-up (5).

The results of this systematic review do not allow any conclusion concerning the necessary length and frequency of follow-up after surgery and further research is warranted. Given the rarity of the disease and the number of candidate risk factors, multicenter studies with consistent documentation of the phenotype and genotype of included patients are needed to overcome the limitations of available evidence and reach the power necessary for multivariate prognostic analyses.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0189>.

Declaration of interest

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

Funding

This research was partly funded by the European Society of Endocrinology.

References

- 1 Miller AB, Hoogstraten B, Staquet M & Winkler A. Reporting results of cancer treatment. *Cancer* 1981 **47** 207–214. (doi:10.1002/(ISSN)1097-0142)
- 2 DeLellis RA, Lloyd RV, Heitz PU & Eng C. *Pathology and Genetics of Tumours of Endocrine Organs*. Lyon, France: IARC, 2004.
- 3 Amar L, Fassnacht M, Gimenez-Roqueplo A-P, Januszewicz A, Prejbisz A, Timmers H & Plouin P-F. Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. *Hormone and Metabolic Research* 2012 **44** 385–389. (doi:10.1055/s-0031-1301339)
- 4 Plouin P-F, Fitzgerald P, Rich T, Ayala-Ramirez M, Perrier ND, Baudin E & Jimenez C. Metastatic pheochromocytoma and paraganglioma: focus on therapeutics. *Hormone and Metabolic Research* 2012 **44** 390–399. (doi:10.1055/s-0031-1299707)
- 5 Lenders JWM, Duh Q-Y, Eisenhofer G, Gimenez-Roqueplo A-P, Grebe SKG, Murad MH, Naruse M, Pacak K, Young WF & Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 1915–1942. (doi:10.1210/jc.2014-1498)
- 6 Hozo SP, Djulbegovic B & Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005 **5** 13. (doi:10.1186/1471-2288-5-13)
- 7 Wan X, Wang W, Liu J & Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014 **14** 135. (doi:10.1186/1471-2288-14-135)
- 8 Agarwal G, Sadacharan D, Aggarwal V, Chand G, Mishra A, Agarwal A, Verma AK & Mishra SK. Surgical management of organ-contained unilateral pheochromocytoma: comparative outcomes of laparoscopic and conventional open surgical procedures in a large single-institution series. *Langenbeck's Archives of Surgery* 2012 **397** 1109–1116. (doi:10.1007/s00423-011-0879-3)
- 9 Amar L, Servais A, Gimenez-Roqueplo A-P, Zinzindohoue F, Chatellier G & Plouin P-F. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 2110–2116. (doi:10.1210/jc.2004-1398)
- 10 Amar L, Peyrard S, Rossignol P, Zinzindohoue F, Gimenez-Roqueplo A-P & Plouin P-F. Changes in urinary total metanephrine excretion in recurrent and malignant pheochromocytomas and secreting paragangliomas. *Annals of the New York Academy of Sciences* 2006 **1073** 383–391. (doi:10.1196/annals.1353.042)
- 11 Beatty OL, Russell CF, Kennedy L, Hadden DR, Kennedy TL & Atkinson AB. Pheochromocytoma in Northern Ireland: a 21 year review. *European Journal of Surgery* 1996 **162** 695–702.
- 12 Benhammou JN, Boris RS, Pacak K, Pinto PA, Linehan WM & Bratslavsky G. Functional and oncologic outcomes of partial adrenalectomy for pheochromocytoma in patients with von Hippel-Lindau syndrome after at least 5 years of followup. *Journal of Urology* 2010 **184** 1855–1859. (doi:10.1016/j.juro.2010.06.102)
- 13 Brunt LM, Moley JF, Doherty GM, Lairmore TC, DeBenedetti MK & Quasebarth MA. Outcomes analysis in patients undergoing laparoscopic adrenalectomy for hormonally active adrenal tumors. *Surgery* 2001 **130** 629–634. (doi:10.1067/msy.2001.116920)
- 14 Brunt LM, Lairmore TC, Doherty GM, Quasebarth MA, DeBenedetti M & Moley JF. Adrenalectomy for familial pheochromocytoma in the laparoscopic era. *Annals of Surgery* 2002 **235** 713–720. (doi:10.1097/0000658-200205000-00014)

Review	L Amar, C Lussey-Lepoutre and others	Recurrent disease after PH/PG resection	175:4	R144
--------	--------------------------------------	---	-------	------

- 15 Castilho LN, Simoes FA, Santos AM, Rodrigues TM & dos Santos Junior CA. Pheochromocytoma: a long-term follow-up of 24 patients undergoing laparoscopic adrenalectomy. *International Brazilian Journal of Urology* 2009 **35** 24–31. (doi:10.1590/S1677-55382009000100005)
- 16 Costeta D, Petramala L, Serra V, Pergolini M, Crescenzi E, Zinnamosca L, De Toma G, Ciardi A, Carbone I, Massa R *et al.* Clinical experience with pheochromocytoma in a single centre over 16 years. *High Blood Pressure & Cardiovascular Prevention* 2009 **16** 183–193. (doi:10.2165/11530430-000000000-00000)
- 17 de Wailly P, Oragano L, Radé F, Beaulieu A, Arnault V, Levillain P & Kraimps JL. Malignant pheochromocytoma: new malignancy criteria. *Langenbeck's Archives of Surgery* 2012 **397** 239–246. (doi:10.1007/s00423-011-0850-3)
- 18 Diner EK, Franks ME, Behari A, Linehan WM & Walther MM. Partial adrenalectomy: the National Cancer Institute experience. *Urology* 2005 **66** 19–23. (doi:10.1016/j.urol.2005.01.009)
- 19 Edström Elder E, Hjelm Skog AL, Hoog A & Hamberger B. The management of benign and malignant pheochromocytoma and abdominal paraganglioma. *European Journal of Surgical Oncology* 2003 **29** 278–283. (doi:10.1053/ejso.2002.1413)
- 20 Edström Elder E, Xu D, Höög A, Enberg U, Hou M, Pisa P, Gruber A, Larsson C & Bäckdahl M. KI-67 AND hTERT expression can aid in the distinction between malignant and benign pheochromocytoma and paraganglioma. *Modern Pathology* 2003 **16** 246–255. (doi:10.1097/01.MP.0000056982.07160.E3)
- 21 Favia G, Lumachi F, Polistina F & D'Amico DF. Pheochromocytoma, a rare cause of hypertension: long-term follow-up of 55 surgically treated patients. *World Journal of Surgery* 1998 **22** 689–693. (doi:10.1007/s002689900454)
- 22 Geoghegan JG, Emberton M, Bloom SR & Lynn JA. Changing trends in the management of phaeochromocytoma. *British Journal of Surgery* 1998 **85** 117–120.
- 23 Grozinsky-Glasberg S, Szalat A, Benbassat CA, Gorshtein A, Weinstein R, Hirsch D, Shraga-Slutsky I, Tsvetov G, Gross DJ & Shimon I. Clinically silent chromaffin-cell tumors: tumor characteristics and long-term prognosis in patients with incidentally discovered pheochromocytomas. *Journal of Endocrinological Investigation* 2010 **33** 739–744. (doi:10.1007/BF03346680)
- 24 van der Harst E, de Herder WW, de Krijger RR, Bruining HA, Bonjer HJ, Lamberts SWJ, van den Meiracker AH, Stijnen TH & Boomsma F. The value of plasma markers for the clinical behaviour of phaeochromocytomas. *European Journal of Endocrinology* 2002 **147** 85–94. (doi:10.1530/eje.0.1470085)
- 25 Häyry V, Salmenkivi K, Arola J, Heikkilä P, Haglund C & Sariola H. High frequency of SNAIL-expressing cells confirms and predicts metastatic potential of phaeochromocytoma. *Endocrine-Related Cancer* 2009 **16** 1211–1218. (doi:10.1677/ERC-09-0049)
- 26 Iacobone M, Schiavi F, Bottussi M, Taschin E, Bobisse S, Fassina A, Opocher G & Favia G. Is genetic screening indicated in apparently sporadic pheochromocytomas and paragangliomas? *Surgery* 2011 **150** 1194–1201. (doi:10.1016/j.surg.2011.09.024)
- 27 Jaroszewski DE, Tessier DJ, Schlinkel RT, Grant CS, Thompson GB, van Heerden JA, Farley DR, Smith SL & Hinder RA. Laparoscopic adrenalectomy for pheochromocytoma. *Mayo Clinic Proceedings* 2003 **78** 1501–1504. (doi:10.4065/78.12.1501)
- 28 Kercher KW, Park A, Matthews BD, Rolband G, Sing RF & Heniford BT. Laparoscopic adrenalectomy for pheochromocytoma. *Surgical Endoscopy* 2002 **16** 100–102. (doi:10.1007/s00464-001-8171-1)
- 29 Khorram-Manesh A, Ahlman H, Nilsson O, Friberg P, Odén A, Stenström G, Hansson G, Stenquist O, Wängberg B, Tisell L-E *et al.* Long-term outcome of a large series of patients surgically treated for pheochromocytoma. *Journal of Internal Medicine* 2005 **258** 55–66. (doi:10.1111/jim.2005.258.issue-1)
- 30 Lairmore TC, Ball DW, Baylin SB & Wells SA. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. *Annals of Surgery* 1993 **217** 595–601. (doi:10.1097/0000658-199306000-00001)
- 31 Zhang X, Lang B, Ouyang J-Z, Fu B, Zhang J, Xu K, Wang B-J & Ma X. Retroperitoneoscopic adrenalectomy without previous control of adrenal vein is feasible and safe for pheochromocytoma. *Urology* 2007 **69** 849–853. (doi:10.1016/j.urol.2007.01.078)
- 32 Lang B, Fu B, Ouyang J-Z, Wang B-J, Zhang G-X, Xu K, Zhang J, Wang C, Shi T-P, Zhou H-X *et al.* Retrospective comparison of retroperitoneoscopic versus open adrenalectomy for pheochromocytoma. *Journal of Urology* 2008 **179** 57–60. (doi:10.1016/j.juro.2007.08.147)
- 33 Lucon AM, Pereira MA, Mendonça BB, Halpern A, Wajchenbeg BL & Arap S. Pheochromocytoma: study of 50 cases. *Journal of Urology* 1997 **157** 1208–1212. (doi:10.1016/S0022-5347(01)64925-5)
- 34 Lumachi F, Polistina F, Favia G & D'Amico DF. Extraadrenal and multiple pheochromocytomas. Are there really any differences in pathophysiology and outcome? *Journal of Experimental & Clinical Cancer Research* 1998 **17** 303–305.
- 35 Neumann HP, Bender BU, Reincke M, Eggstein S, Laubenberg J & Kirste G. Adrenal-sparing surgery for phaeochromocytoma. *British Journal of Surgery* 1999 **86** 94–97. (doi:10.1046/j.1365-2168.1999.00974.x)
- 36 Noshiro T, Shimizu K, Watanabe T, Akama H, Shibukawa S, Miura W, Ito S & Miura Y. Changes in clinical features and long-term prognosis in patients with pheochromocytoma. *American Journal of Hypertension* 2000 **13** 35–43. (doi:10.1016/S0895-7061(99)00139-9)
- 37 Obara T, Kanbe M, Okamoto T, Ito Y, Yamashita T, Ito K, Hirose K, Yamazaki K, Hagihara J & Kusakabe K. Surgical strategy for pheochromocytoma: emphasis on the pledge of flank extraperitoneal approach in selected patients. *Surgery* 1995 **118** 1083–1089.
- 38 Pan D, Li H, Zeng Z, Li F & Cui Q. Twenty-six patients with nonfunctional pheochromocytomas. *Chinese Medical Journal* 2005 **118** 866–868.
- 39 Park J, Song C, Park M, Yoo S, Park SJ, Hong S, Hong B, Kim C-S & Ahn H. Predictive characteristics of malignant pheochromocytoma. *Korean Journal of Urology* 2011 **52** 241–246. (doi:10.4111/kju.2011.52.4.241)
- 40 Pomares FJ, Cañas R, Rodriguez JM, Hernandez AM, Parrilla P & Tebar FJ. Differences between sporadic and multiple endocrine neoplasia type 2A phaeochromocytoma. *Clinical Endocrinology* 1998 **48** 195–200. (doi:10.1046/j.1365-2265.1998.3751208.x)
- 41 Rodriguez JM, Balsalobre M, Ponce JL, Ríos A, Torregrosa NM, Tebar J & Parrilla P. Pheochromocytoma in MEN 2A syndrome. Study of 54 patients. *World Journal of Surgery* 2008 **32** 2520–2526. (doi:10.1007/s00268-008-9734-2)
- 42 Scholten A, Valk GD, Ulfman D, Borel Rinkes IHM & Vriens MR. Unilateral subtotal adrenalectomy for pheochromocytoma in multiple endocrine neoplasia type 2 patients: a feasible surgical strategy. *Annals of Surgery* 2011 **254** 1022–1027. (doi:10.1097/SLA.0b013e318237480c)
- 43 Scott HW & Halter SA. Oncologic aspects of pheochromocytoma: the importance of follow-up. *Surgery* 1984 **96** 1061–1066.
- 44 Stenström G, Ernest I & Tisell LE. Long-term results in 64 patients operated upon for pheochromocytoma. *Acta Medica Scandinavica* 1988 **223** 345–352. (doi:10.1111/j.0954-6820.1988.tb15883.x)
- 45 Tiberio GAM, Baiocchi GL, Arru L, Agabiti Rosei C, De Ponti S, Matheis A, Rizzoni D & Giulini SM. Prospective randomized comparison of laparoscopic versus open adrenalectomy for sporadic pheochromocytoma. *Surgical Endoscopy* 2008 **22** 1435–1439. (doi:10.1007/s00464-008-9904-1)
- 46 Timmers HJLM, Brouwers FM, Hermus ARMM, Sweep FCGJ, Verhofstad AAJ, Verbeek ALM, Pacak K & Lenders JWM. Metastases but not cardiovascular mortality reduces life expectancy following surgical resection of apparently benign pheochromocytoma. *Endocrine-Related Cancer* 2008 **15** 1127–1133. (doi:10.1677/ERC-08-0049)

Review	L Amar, C Lussey-Lepoutre and others	Recurrent disease after PH/PG resection	175:4	R145
---------------	--------------------------------------	---	--------------	-------------

- 47 Tormey WP, Fitzgerald RJ, Davis WG & Thompson CJ. Twelve-year experience in the investigation and treatment of paragangliomas. *International Journal of Clinical Practice* 2002 **56** 739–745.
- 48 Wilhelm SM, Prinz RA, Barbu AM, Onders RP & Solorzano CC. Analysis of large versus small pheochromocytomas: operative approaches and patient outcomes. *Surgery* 2006 **140** 553–559. ([doi:10.1016/j.surg.2006.07.008](https://doi.org/10.1016/j.surg.2006.07.008))
- 49 Yip L, Lee JE, Shapiro SE, Waguespack SG, Sherman SI, Hoff AO, Gagel RF, Arens JF & Evans DB. Surgical management of hereditary pheochromocytoma. *Journal of the American College of Surgeons* 2004 **198** 525–534. ([doi:10.1016/j.jamcollsurg.2003.12.001](https://doi.org/10.1016/j.jamcollsurg.2003.12.001))
- 50 Favier J, Amar L & Gimenez-Roqueplo A-P. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. *Nature Reviews Endocrinology* 2015 **11** 101–111. ([doi:10.1038/nrendo.2014.188](https://doi.org/10.1038/nrendo.2014.188))

Received 1 March 2016

Revised version received 11 April 2016

Accepted 13 April 2016