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

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MANAGEMENT OF ENDOCRINE DESEASE : Recurrence or new tumors after complete resection of phaeochromocytomas and paragangliomas. A systematic review and meta-analysis

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Abstract

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

Design. Systematic review and meta-analysis.

Methods. Pubmed and Embase from 1980 to 2012 were searched for studies published in English on patients with: non-metastatic phaeochromocytoma or thoraco-abdomino-pelvic paraganglioma; complete tumor resection; postoperative follow-up exceeding one month; 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. Thirty-eight 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 phaeochromocytoma may be lower than previously thought, although late events occur. Risk stratification is required to tailor the follow-up protocol after complete resection of a phaeochromocytoma or paraganglioma. Large multicentric studies are needed to this end.

Introduction

Pheochromocytomas and paragangliomas (PH/PG) are rare neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or sympathetic and parasympathetic paraganglia respectively. Following resection of the primary tumor, most patients are tumor-free with no clinical, biochemical or imaging evidence of persistent disease. However, tumor-free patients are at risk of long term recurrence, defined as the reappearance of disease after complete surgical eradication of the tumor (1). Recurrences may arise et the operated site or may be metastatic, developing in non-chromaffin organs, mainly lymph nodes, bones, lungs and the 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 is 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 was 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 was 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 undergone complete tumor resection;

(iii) postoperative follow-up exceeded one month; (iv) the numbers of patients with recurrence or new tumor could be identified.

Information sources and search

We searched *Medline* and *Embase* from 01/01/1980 to 10/19/2012. We developed a specific search strategy for each database (Supplementary Methods).

Study selection

Two physicians, expert in endocrine hypertension (LA and CL), independently made a first selection using the titles, abstracts, and keywords to exclude studies that clearly did not fulfill inclusion criteria. They independently read the full text of remaining papers to identify eligible articles. At each stage, disagreements between readers were resolved by discussion or, if necessary, by a third reader (PFP or JL). 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; (ii) studies on phaeochromocytoma 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 (PFP and JL) to homogenize further data collection. The form was then used by two abstractors (LA and CL) 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 phaeochromocytoma, location of paragangliomas, mean tumor size, percentage of secreting tumors, percentage of genetic or syndromic diseases; number of patients with follow-up and duration of follow-up; incidence of recurrence, timing of recurrence, 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 disease 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 w he 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 quartiles when available (6,7), or by the median in other cases. We assumed the Poisson distribution to estimate 95 percent confidence intervals for the rate of events presented in forest plots. Meta-analysis was performed on rates and their confidence interval limits. Heterogeneity was 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, College Station, TX) for analyses.

Additional analyses

We performed sensitivity analyses based on the availability of the mean duration of follow-up and by risk of bias. A funnel plot of the event rate according to the number of person-years of follow-up was used to assess publication bias.

Meta-regression 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 phaeochromocytomas, mean size of the tumor, mean duration of follow-up.

Results

Study selection

The details of the selection process and reasons for exclusions are depicted in the flow chart (Figure 1). Bibliographic searches yielded 3518 references, among which 42 on phaeochromocytoma 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). Twenty studies 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 one to 21 centers; 20 studies were performed by surgeons, 10 by physicians, seven by both and one by laboratory physicians.

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 three and 98% (median 66%). The percentage of syndromic or genetic disease was reported in 32 studies. Four studies involved only patients with a syndromic disease (VHL, NF1 or MEN2). In the 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 two and 97% (median 20%).

The percentage of phaeochromocytoma was reported in 37 studies and was between 77 and 100% (median 94%). Fourteen studies involved only patients with phaeochromocytomas and the percentage of patients with phaeochromocytoma 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 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 one 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 three to 204), and two studies (26 events) provided summary results with median times to event of 17 and 29 months (range 5 to 195). Two studies (seven 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 the Supplementary Table 2. Paragangliomas (compared to phaeochromocytomas) and syndromic 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 (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%, $p < 0.001$). 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 incidence of 4.7% [95% CI: 3.4, 6.1], distributed as follows: new tumors 22%, local recurrences 23%, and metastatic recurrences 55%.

The pooled estimate of event rate was:

- 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 Figure 1).

Meta-regression analysis

The percentage of genetic or syndromic disease was associated with the rate of new events (Figure 3 and Supplementary Figure 2). The pooled event rate estimate was 0.79 events/100 person-years (95% CI 0.53, 1.04) for 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). Other variables were not associated with the new event rate in meta-regression analyses.

Discussion

Summary

Our review suggests that the risk of recurrent disease following complete resection of a phaeochromocytoma or a thoraco-abdomino-pelvic paraganglioma is lower than previously thought. 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 was 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 previous estimates that did not take the varying time 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 phaechromocytoma. 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, multicentric 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.

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Figure legends

Figure 1. Study flow diagram
FU: follow-up; HN: head and neck; PH/PG: phaeochromocytomas and paragangliomas; PG: paragangliomas

Figure 2. Forest plot of new event rates

Figure 3. Meta-regression of event rates according to the proportion of genetic or syndromic diseases

Table 1. Overview of included studies

Study	Country	Period	Design	Settings	Number of centers	Total number of patients	Number of curative surgeries
Agarwal 2011 (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)	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)	Netherlands	1959-2010	Retrospective	Surgery	1	61	61
Scott Jr 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)	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

Table 2. Overview of patient and disease characteristics

Study	Females	Age (years)	HTN	Pheo	PHPG size (mm)	Secreting tumors	Genetic diseases[#]
Agarwal 2011	43%	Mean 36 (SD 14.6)	81%	82%	Mean 71 (SD 25)	-	-
Amar 2005/2006	52%	Mean 42.5 (SD 15)	89%	87%	Mean 54 (SD 27)	-	21%
Beatty 1996	54%	-	90%	84%	-	-	24%
Benhammou 2010	-	Mean 27	-	100%	Mean 25	-	100%
Brunt 2001/2002	51%	Mean 42 (SD 17)	54%	100%	Mean 34 (SD 13)	-	57%
Castilho 2009	42%	Median 46.5 (Range 10-75)	83%	100%	Median 37 (range 5-120)	-	13%
Cotesta 2009	52%	Mean 48 (Range 8-77)	-	92%	Mean 43 (range 10-110)	-	23%
DeWailly 2012	55%	Mean 53 (Range 13-88)	-	100%	Mean 46 (SD 13)	96%[§]	15%
Diner 2005	-	Mean 38 (Range 10-79)	-	100%	Mean 23 (range 8-50)	-	94%
EdstromElder 2003/2003	56%	Range 14-77	61%	82%	Range 10-140	-	18%
Favia 1998	49%	Median 41 (Range 10-63)	58%	91%	Mean 58 (SD 30)	-	7%
Geoghegan 1998	67%	Mean 42 (Range 16-73)	56%	100%	Mean 49 (range 20-130)	-	28%
Grozinsky-Glasberg 2010	49%	Mean 52.6 (Range 16-77)	47%	88%	Mean 49 (SD 20)	-	-
van der Harst 2002	55%	Mean 46 (Range 9-78)	66%	89%	Mean 54 (SD 31)	-	31%
Hayry 2009	-	Mean 46.5	-	95%	Mean 47 (SD 26)	86%*	-
Iacobone 2011	52%	Mean 44,8 (Range 15-80)	-	93%	Mean 54 (SD 30)	-	24%
Jaroszewski 2003	51%	Mean 53.1 (Range 16-81)	-	100%	Mean 43 (range 10-85)	-	13%
Kercher 2002	64%	Mean 43 (Range 19-59)	95%	97%	Mean 52 (range 20-121)	95%[§]	10%
Khorram-Manesh 2005	56%	Mean 47.2 (SD 16.8)	84%	93%	Mean 49 (SD 24)	88%[§]	25%
Lairmore 1993	57%	Mean 32.8 (SD 12.2)	57%	100%	Mean 43 (SD 27)	-	100%
Zhang2007/Lang 2008	49%	Mean 35.8 (SD 13.3)	-	100%	Mean 47 (SD 23)	-	-
Luccon 1997	56%	Median 33 (Range 10-64)	86%	84%	Median 70 (range 30-200)	97%[§]	12%
Lumachi 1998	49%	Mean 41 (Range 10-63)	45%	90%	-	-	7%
Neumann 1999	59%	Mean 40 (Range 10-76)	-	100%	Mean 40 (range 10-90)	-	67%
Noshiro 2000	55%	Mean 40 (SD 14)	88%	-	-	-	15%
Obara 1995	56%	Median 40 (Range 11-67)	-	84%	Mean 62 (SD 26)	92%	14%

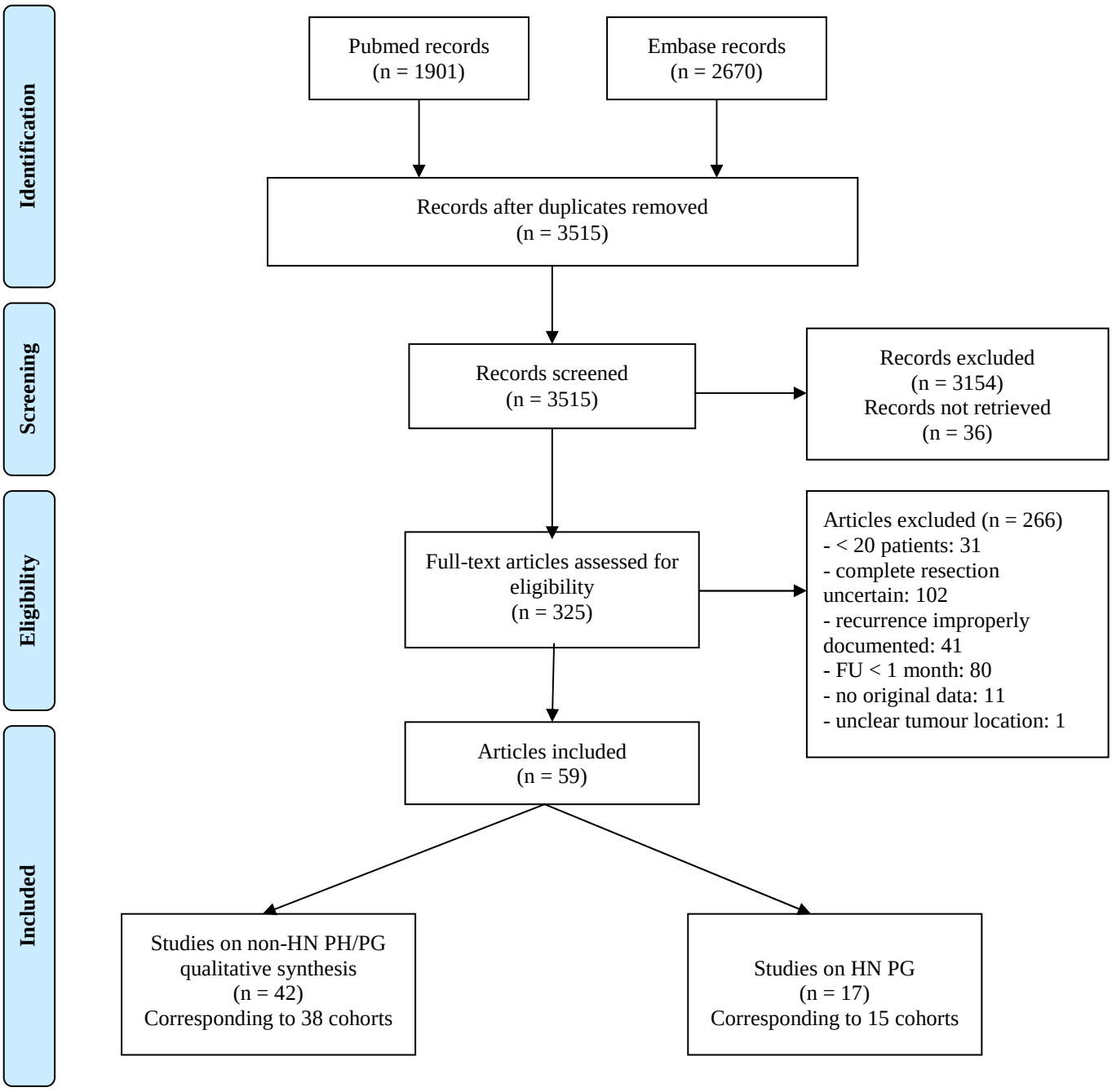
Pan 2005	58%	Mean 39,5 (SD 8,9)	-	85%	Mean 73 (SD 35)	0%	-
Park 2011	47%	Mean 46.5 (Range 18-76)	62%	90%	Mean 67 (SD 35)	-	2%
Pomares 1998	54%	Mean 43 (SD 13.7)	37%	98%	Mean 49 (SD 26)	84%[§]	52%
Rodriguez 2008	57%	Mean 37,4 (Range 14-71)	24%	100%	Mean 45 (range 10-120)	89%	100%
Scholten 2011	39%	Mean 33 (SD 12.7)	3%	100%	-	67%	100%
ScottJr 1984	58%	Range 9-79	98%	77%	-	-	12%
Stenstrom 1988	53%	Mean 45 (Range 15-79)	47%	94%	-	-	20%
Tiberio 2008	36%	Mean 51 (Range 34-74)	-	100%	Mean 40 (range 22-60)	-	-
Timmers 2008	64%	Mean 46.1 (SD 15.6)	78%	88%	-	-	20%
Tormey 2002	38%	Median 36 (Range 8-76)	89%	87%	-	-	59%
Wilhelm 2006	62%	Mean 48.5 (SD 16.1)	68%	100%	Mean 40 (SD 15)	-	14%
Yip 2004	58%	Median 36	-	95%	-	-	97%

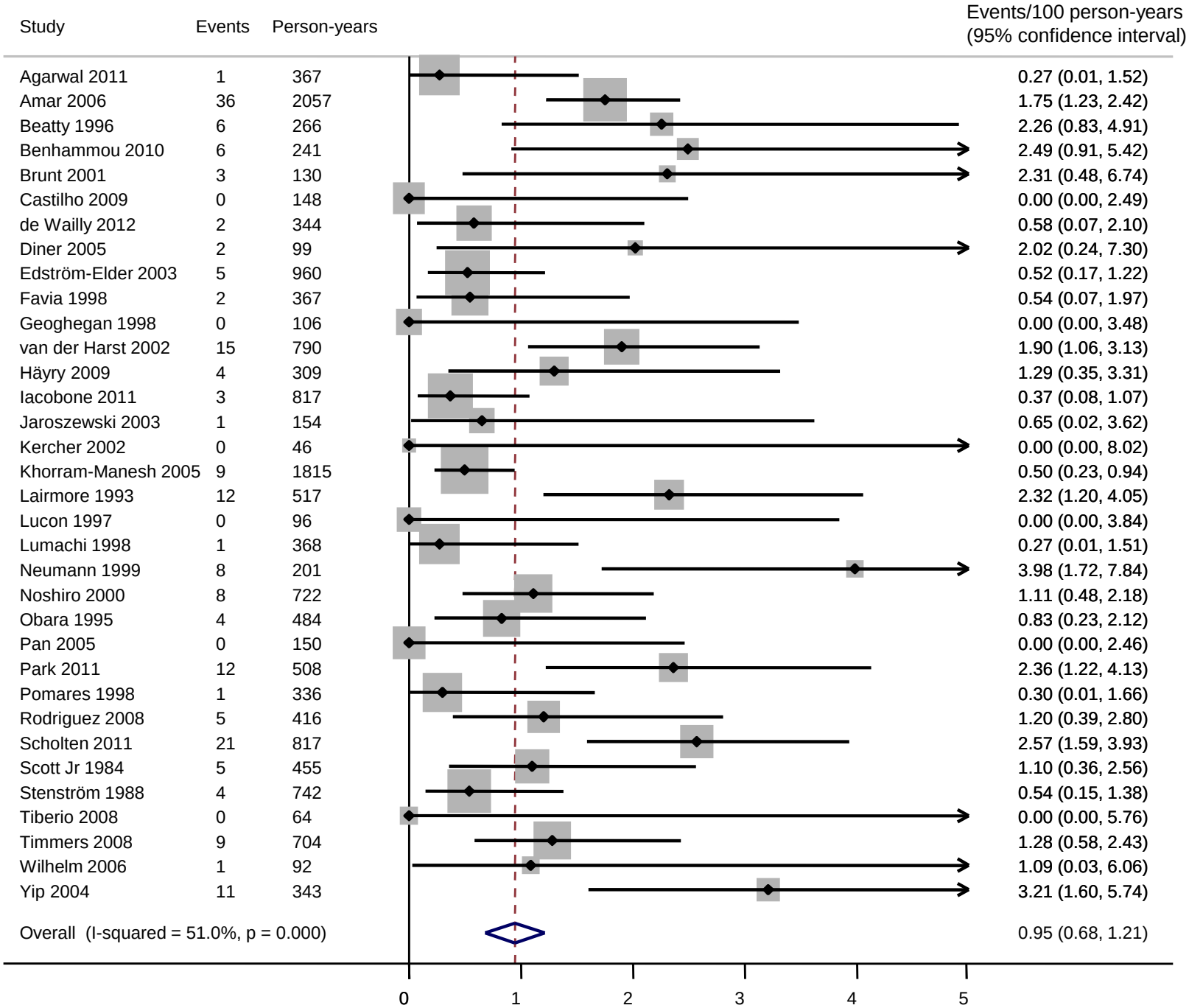
[#] familial or syndromic disease, or germline mutation
[§] metoxylated derivatives only
*calculated using urinary normetanephrine + metanephrine: abnormal if ≥ 4.5 µmol/24h

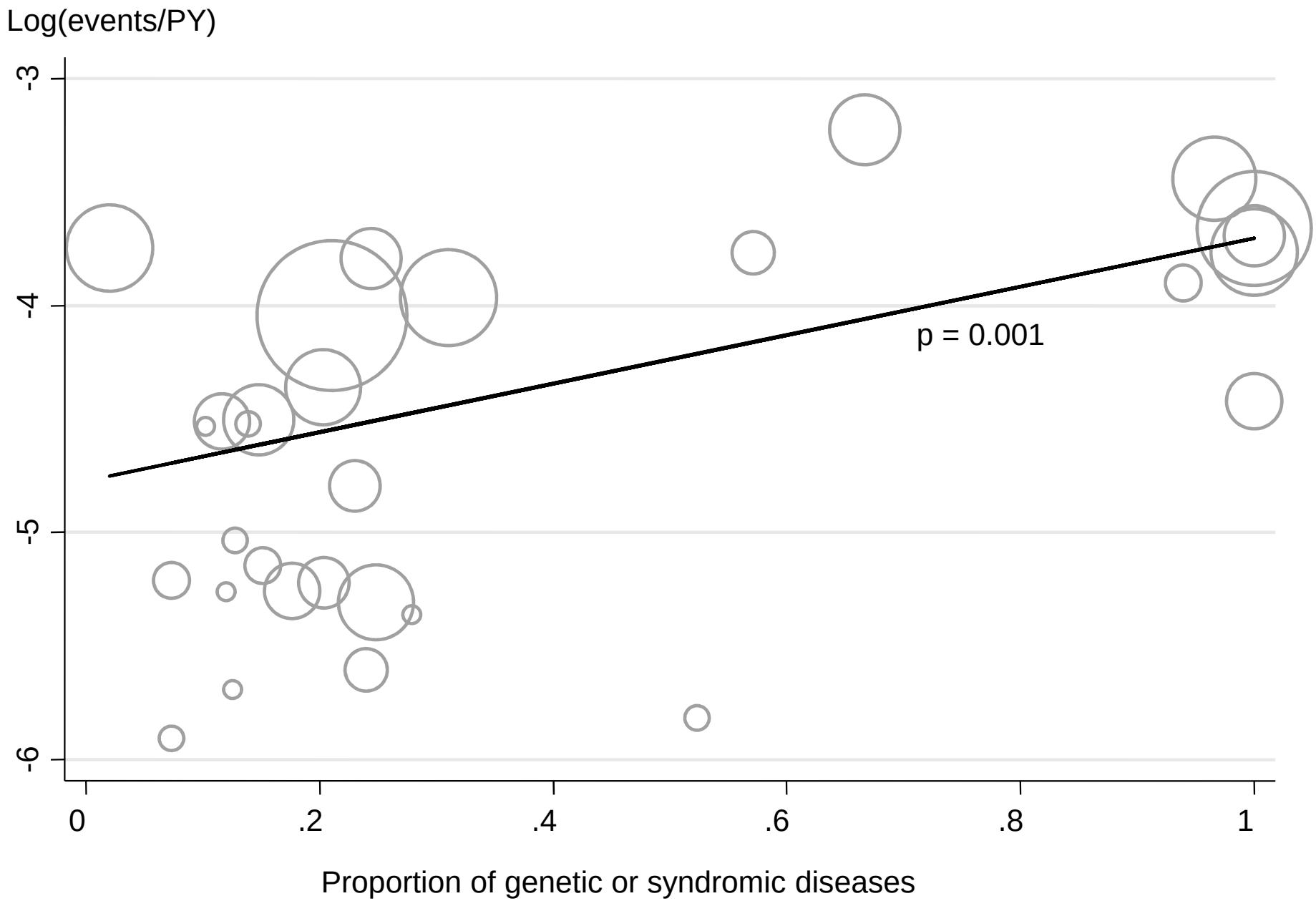
Table 3. Overview of treatment and outcomes

Study	Cured and followed-up	Follow-up duration (months)	Same site recurrences	Other site recurrences	Metastases	Attributable death
Agarwal 2011 (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 Jr 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


Identification
Screening
Eligibility
Included
Pubmed records
(n = 1901)
Embase records
(n = 2670)
Records after duplicates removed
(n = 3515)
Records screened
(n = 3515)
Records excluded
(n = 3154)
Records not retrieved
(n = 36)
Full-text articles assessed for eligibility
(n = 325)
Articles excluded (n = 266)
- < 20 patients: 31
- complete resection uncertain: 102
- recurrence improperly documented: 41
- FU < 1 month: 80
- no original data: 11
- unclear tumour location: 1
Articles included
(n = 59)
Studies on non-HN PH/PG
qualitative synthesis
(n = 42)
Corresponding to 38 cohorts
Studies on HN PG
(n = 17)
Corresponding to 15 cohorts


Study
Events
Person-years
Events/100 person-years
(95% confidence interval)
Agarwal 2011 1 367 0.27 (0.01, 1.52)
Amar 2006 36 2057 1.75 (1.23, 2.42)
Beatty 1996 6 266 2.26 (0.83, 4.91)
Benhammou 2010 6 241 2.49 (0.91, 5.42)
Brunt 2001 3 130 2.31 (0.48, 6.74)
Castilho 2009 0 148 0.00 (0.00, 2.49)
de Wailly 2012 2 344 0.58 (0.07, 2.10)
Diner 2005 2 99 2.02 (0.24, 7.30)
Edström-Elder 2003 5 960 0.52 (0.17, 1.22)
Favia 1998 2 367 0.54 (0.07, 1.97)
Geoghegan 1998 0 106 0.00 (0.00, 3.48)
van der Harst 2002 15 790 1.90 (1.06, 3.13)
Häyry 2009 4 309 1.29 (0.35, 3.31)
Iacobone 2011 3 817 0.37 (0.08, 1.07)
Jaroszewski 2003 1 154 0.65 (0.02, 3.62)
Kercher 2002 0 46 0.00 (0.00, 8.02)
Khorram-Manesh 2005 9 1815 0.50 (0.23, 0.94)
Lairmore 1993 12 517 2.32 (1.20, 4.05)
Lucon 1997 0 96 0.00 (0.00, 3.84)
Lumachi 1998 1 368 0.27 (0.01, 1.51)
Neumann 1999 8 201 3.98 (1.72, 7.84)
Noshiro 2000 8 722 1.11 (0.48, 2.18)
Obara 1995 4 484 0.83 (0.23, 2.12)
Pan 2005 0 150 0.00 (0.00, 2.46)
Park 2011 12 508 2.36 (1.22, 4.13)
Pomares 1998 1 336 0.30 (0.01, 1.66)
Rodriguez 2008 5 416 1.20 (0.39, 2.80)
Scholten 2011 21 817 2.57 (1.59, 3.93)
Scott Jr 1984 5 455 1.10 (0.36, 2.56)
Stenström 1988 4 742 0.54 (0.15, 1.38)
Tiberio 2008 0 64 0.00 (0.00, 5.76)
Timmers 2008 9 704 1.28 (0.58, 2.43)
Wilhelm 2006 1 92 1.09 (0.03, 6.06)
Yip 2004 11 343 3.21 (1.60, 5.74)
Overall (I-squared = 51.0%, p = 0.000) 0.95 (0.68, 1.21)
0
1
2
3
4
5


Log(events/PY)
-3
-4
-5
-6
p = 0.001
0
.2
.4
.6
.8
1
Proportion of genetic or syndromic diseases

Supplementary Methods.

Information sources and search

We searched *Medline, Embase* from 1980 to 2012. We developed a specific search strategy for each database.

The following query was run in PubMed:

```
("Phaeochromocytoma"[mh] OR "Paraganglioma"[mh])
AND ("follow-up studies"[mh] OR "Recurrence"[mh] OR "mortality"[mh] OR
"Treatment Outcome"[mh] OR "Outcome Assessment (Health Care)"[mh] OR
"Prognosis"[mh] OR "Disease Progression"[mh] OR prognos* OR predict* OR
course* OR cohort OR "follow-up" OR "neoplasm metastasis"[mh] OR metastas*
OR metastat*)
AND "Humans"[Mesh] AND "1980/01/01"[PDAT] : "2013/12/31"[PDAT] AND
English[lang]
NOT "case reports"[ptyp]
```

The following query vas run in Embase:

```
('pheochromocytoma'/exp OR 'paraganglioma'/exp OR 'chemodectoma'/exp)
AND ('cohort analysis'/exp OR 'cancer recurrence'/exp OR 'tumor
recurrence'/exp OR 'recurrent disease'/exp OR 'survival'/exp OR
'mortality'/exp OR 'treatment outcome'/exp OR 'prognosis'/exp OR
'metastasis'/exp OR prognos* OR predict* OR course* OR cohort* OR 'follow-
up'/exp OR metastas* OR metastat*)
AND [humans]/lim AND [english]/lim AND [1980-2013]/py AND [embase]/lim
NOT 'case report'/exp
```

Risk of bias of individual studies

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 in our studies:

- Newcastle Ottawa: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
- GRADE: Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, McGinn T, Hayden J, Williams K, Shea B, Wolff R, Kujpers T, Perel P, Vandvik PO, Glasziou P, Schunemann H, Guyatt G. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015;350:h870.

- QUIPS: Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
- Cochrane Handbook, Section 13.5: Assessing risk of bias in non-randomized studies

Two raters used the following criteria to evaluate individual studies. A third rater checked all ratings and resolved potential disagreements.

A- Study participants:

1- Appropriate method used to identify patients: yes, if prospective study, or retrospective study using an administrative, clinical or research database;
2- Restrictive inclusion criteria: yes, if population restricted according to any characteristic (location of the tumor, familial history, catecholamine secretion, available follow up...);
3- Consecutive sample of patients: yes, if stated that all patients responding to the inclusion criteria during the study period were included;
4- Cure after surgery ascertained: yes, if cure ascertained early ($\leq$ 6 months) with systematic hormonal or imaging studies.

B- Outcome:

5- Adequate outcome definition: yes, if definition of recurrence or malignancy or metastasis;
6- Valid identification method: yes, if events ascertained by hormonal or imaging studies.

C- Follow up:

7- Standardized follow-up: yes, if an institutional follow-up protocol was applied or if all patients were contacted at the time of the study;
8- Sufficient length of follow up: yes, if mean or median follow up $\geq$ 12 months;
9- Complete follow up: yes, if $\geq$ 80% of those operated on (and cured) were followed-up.

D- Reporting:

10- Adequate description of the inclusion process: yes, if flow diagram showing the numbers of individuals at all stages of the study;
11- Baseline characteristics of cured patients appropriately described: yes, if at least sex, age, syndromic phenotype and tumor location either for cured patients or for all patients if over 90% were cured;
12- Cause of losses to follow-up reported;
13- Adequate statistical analysis: yes, if survival analysis was performed on censored data.

E- Prognostic factors:

14- Adequate definition: yes, if the main prognostic factor was clearly defined;
15- Adequate measurement: yes, if the main prognostic factors were reliably searched or measured in all patients;
16- Multivariable analysis: yes, if multivariable models were used to assess the independence of prognostic factors.

Supplementary Table 1. Risk of bias of individual studies.

	Participants				Outcome		Follow-up			Results				Prognostic factors		
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Agarwal 2011 (8)	Yes	No	Yes	Yes	No	Uncl	Uncl	Yes	Yes	No	No	No	No	-	-	-
Amar 2005/2006 (9,10)	Yes	Yes[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Beatty 1996 (11)	No	No	Uncl	Uncl	No	Yes	Uncl	Yes	Yes	No	No	Yes	No	-	-	
Benhammou 2010 (12)	No	Yes[b]	Uncl	Uncl	Yes	Uncl	Uncl	Yes	Uncl	No	No	No	No	-	-	-
Brunt 2001/2002 (13,14)	No	Yes[c]	Uncl	Yes	No	Yes	Uncl	Yes	Yes	No	Yes	No	No	-	-	-
Castilho 2009 (15)	No	Yes[c]	Uncl	Yes	No	Yes	Yes	Yes	Yes	No	Yes	-[o]	No[m]	-	-	-
Cotesta 2009 (16)	No	No	Uncl	Uncl	Yes	Uncl	Uncl	Yes	No	No	Yes	No	No	-	-	-
de Wailly 2012 (17)	No	Yes[c]	No[l]	Uncl	Yes	Uncl	Uncl	Yes	Yes	No	Yes	-[o]	No	-	-	-
Diner 2005 (18)	No	Yes[c]	Uncl	Yes	No	Yes	Yes	Yes	Yes	No	No	-[o]	No	-	-	-
Edström Elder 2003 (19,20)	No	No	Uncl	Yes	No	Yes	Uncl	Yes	Yes	No	Yes	-[o]	No[m]	Yes	Yes	No
Favia 1998 (21)	No	No	Yes	Yes	No	Yes	Yes	Yes	Uncl	No	Yes	No	No	-	-	-
Geoghegan 1998 (22)	No	Yes[c]	Yes	Yes	No	Uncl	Uncl	Yes	Uncl	No	Yes	No	No	-	-	-
Grozinsky-Glasberg 2010 (23)	Yes	Yes[d]	Yes	Yes	No	Yes	Yes	Yes	Uncl	No	No	No	No	Yes	Yes	No
van der Harst 2002 (24)	No	Yes[e]	Uncl	Yes	Yes	Yes	Yes	Yes	Yes	No	No	-[o]	Yes	Yes	Yes	No
Hayry 2009 (25)	No	Yes	Uncl	Uncl	No	Uncl	Uncl	Yes	Yes	No	No	-[o]	No[m]	-	-	-
Iacobone 2011 (26)	No	Yes[f]	Yes	Uncl	Yes	Yes	Uncl	Yes	Uncl	No	Yes	No	No	Yes	Yes	No
Jaroszewski 2003 (27)	No	Yes[c]	Yes	Uncl	No	Uncl	Yes	Yes	Yes	No	Yes	No	No	-	-	-
Kercher 2002 (28)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	-[o]	No	-	-	-
Khorram-Manesh 2005 (29)	No	No	Yes	Uncl	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	-	-	-
Lairmore 1993 (30)	No	Yes[g]	Yes	Uncl	No	Uncl	Yes	Yes	Yes	No	Yes	-[o]	No	Yes	Yes	No
Zhang 2007/Lang 2008 (31,32)	No	Yes[c]	Uncl	Uncl	No	Uncl	Uncl	Uncl	Yes	No	No	-[o]	No	-	-	-
Lucon 1997 (33)	No	No	Uncl	Uncl	No	Uncl	Uncl	Yes	Yes	No	No	No	No	-	-	-
Lumachi 1998 (34)	No	Yes	Uncl	Yes	No	Uncl	Yes	Yes	Yes	No	Yes	-[o]	No	-	-	-
Neumann 1999 (35)	No	Yes[h]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	-	-	-
Noshiro 2000 (36)	No	Uncl [c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Obara 1995 (37)	No	No	Uncl	Uncl	No	Yes	Yes	Yes	Uncl	No	Yes	-[o]	Yes	Yes	Yes	Yes
Pan 2005 (38)	No	Yes[i]	Yes	No	No	Uncl	Yes	Yes	Yes	No	No	-[o]	No	-	-	-

Park 2011 (39)	Yes	No	Uncl	Uncl	Yes	Yes	Yes	Yes	Yes	No	Yes	-[o]	Yes	Yes	Yes	No
Pomares 1998 (40)	No	No	Uncl	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	-	-	-
Rodriguez 2008 (41)	No	Yes[g]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	-[o]	No	Yes	Yes	No
Scholten 2011 (42)	Yes	Yes[j]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	-[o]	No	Yes	Yes	No
Scott Jr 1984 (43)	No	No	Uncl	Uncl	No	Yes	Uncl	Yes	Yes	No	No	Yes	No[m]	-	-	-
Stenström 1988 (44)	No	No	Yes	Uncl	No	Uncl	Yes	Yes	Yes	No	Yes	Yes	No	-	-	-
Tiberio 2008 (45)	Yes	Yes[c]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	-[o]	No[n]	-	-	-
Timmers 2008 (46)	No	No	Uncl	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Tormey 2002 (47)	No	No	Yes	Uncl	No	Uncl	Uncl	Yes	Yes	No	No	No	No	-	-	-
Wilhelm 2006 (48)	Yes	Yes[c]	Yes	Yes	Yes	Yes	Uncl	Yes	No	No	Yes	No	No	Yes	Yes	No
Yip 2004 (49)	Yes	Yes[k]	Yes	Yes	Yes	Uncl	Uncl	Yes	Yes	Yes	Yes	-[o]	No	Yes	Yes	No
Number of studies with																
low risk of bias	9	15	20	21	14	24	22	37	30	4	25	24	12	14	14	2
unclear risk of bias	0	1	17	16	0	14	0	1	6	0	0	0	0	0	0	0
high risk of bias	29	12	1	1	24	0	16	0	2	34	13	14	26	0	0	12

[a] Follow-up in the center
[b] Von Hippel Lindau and > 5 years follow-up
[c] Pheochromocytoma (adrenal tumor)
[d] Follow-up in an endocrine clinic
[e] Pheochromocytoma or abdominal paraganglioma
[f] Genetic pheochromocytoma or thoraco-abdominal paraganglioma with complete follow-up data
[g] MEN2 with pheochromocytoma
[h] Pheochromocytoma with adrenal sparing surgery
[i] Non-secreting pheochromocytoma
[j] MEN2A with pheochromocytoma
[k] Familial pheochromocytoma or paraganglioma
[l] Malignant pheochromocytoma each matched with two benign ones
[m] No, but raw data provided, allowing a survival analysis
[n] No, but same duration of follow-up for all participants, obviating the need for censoring
[o] All included patients were followed-up

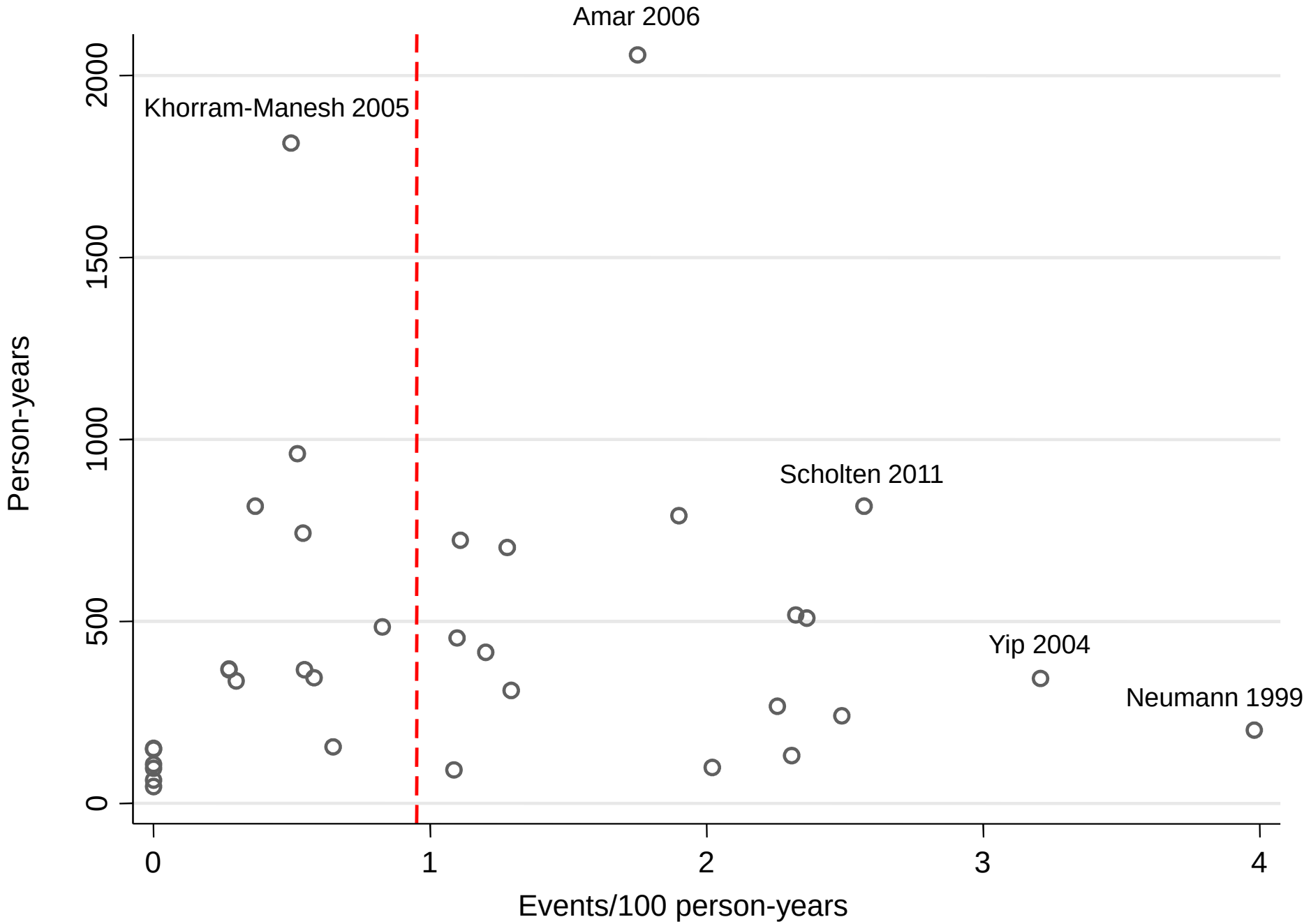
Table 4. Risk factors of new events following curative surgery assessed in individual studies.

Risk factor	Associated by univariate analysis	Associated by multivariate analysis	Not associated
Syndromic disease	Iacobone 2011 (PH/PG)	Amar 2005/2006 (PH/PG) Obara 1995 (PH/PG)	
Nature of MEN2A mutation			Rodriguez 2008 (PH – MEN2A)
Tumor size	Park 2011 (> 5.5 cm, PH)	Amar 2005/2006 (> 5 cm, PH/PG)	Obara 1995 (> 5 cm, PH/PG) Rodrigues 2008 Wilhelm 2006 (> 6 cm, PH)
Tumor weight	Noshiro 2000 (> 60 g, PH/PG)		
Paraganglioma (vs PH)	Edstrom Elder 2003 (PH/PG)	Amar 2005/2006 (PH/PG) Obara 1995 (PH/PG)	Timmers 2008 (PH/PG) Noshiro 2000 (PH/PG)
Age	Obara 1995 (< 20 years, PH/PG)		Amar 2005/2006 (PH/PG) Rodriguez 2008 (PH – MEN2A) Timmers 2008 (PH/PG)
Sex			Amar 2005/2006 (PH/PG) Rodriguez 2008 (PH – MEN2A) Timmers 2008 (PH/PG)
Resistant hypertension			Amar 2005/2006 (PH/PG)
Level of urinary metanephrines	Park 2011 (higher risk with lower urinary excretion of adrenaline, noradrenaline and VMA/cm of tumor diameter, PH)		Amar 2005/2006 (PH/PG)
Lack of catecholamine secretion			Grozinsky-Glasberg 2010 (PH/PG)
Type of secreted catecholamine			Obara 1995 (PH/PG) Timmers 2008 (PH/PG)
Subtotal adrenalectomy (vs total)			Scholten 2011 (PH – MEN2)

Unilateral adrenalectomy (vs bilateral) in syndromic PH	Lairmore 1993 (MEN2) Yip (RET/MEN2/VHL)
Ki67 tissue expression	Edstrom Elder 2003 (PH/PG)

PH: pheochromocytoma; PG: paraganglioma; MEN: multiple endocrine neoplasia; VMA: vanilmandelic acid; RET: Recklinghausen disease; VHL: von Hippel Lindau disease

Supplementary Figure 1. Event rate according to the number of person-years of follow-up



Supplementary Figure 2. Forest plot of new event rates according to the proportion of patients with genetic or syndromic disease