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ORIGINAL ARTICLE

Malignant pheochromocytoma: predictive factors of malignancy and clinical course in 16 patients at a single tertiary medical center

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Abstract Metastases appear in approximately 10% of patients with pheochromocytoma. There is no predictive marker of malignancy. The aim is to describe clinical course of patients with malignant pheochromocytoma and to identify predictive features of malignancy. The method involves retrospective analysis of patients files diagnosed with malignant pheochromocytoma at our institution between January 1, 1980 and December 31, 2008. We identified 16 patients with malignant pheochromocytoma. There were more men than women (10/6). Mean age of patients at time of diagnosis was 37.75-year-old. Time of occurence of metastases ranged from 0 to 22 years after first diagnosis of pheochromocytoma. The mean size of the primary tumor was 12.1 cm. High levels of chromogranin A at the time of diagnosis were associated with the presence of metastases. The pheochromocytoma of the adrenal gland scoring scale (PASS) histological evaluation in adrenal primary tumors was above four in all cases but one. All patients had initial surgery, followed in most cases by palliative therapy: chemotherapy (streptozocin, cyclophosphamide-vincristine-dacarbazine, thalidomide, imatinib, everolimus) or ^{131}I-MIBG; only the latter had replicable encouraging response evaluation criteria in solid tumor response rates. We observed a 10-year survival rate of 50% after initial diagnosis of pheochromocytoma, and 25% after diagnosis of metastasis. Metastasis can occur very late after the initial diagnosis of pheochromocytoma. High chromogranin A levels may be associated with the presence of metastases and poor prognosis. Histological adrenal PASS higher than 4 appears to be suggestive of malignancy. The best therapeutic approach remains to be established.

Keywords Pheochromocytoma · PASS · Chromogranin A · MIBG · Tyrosine-kinase inhibitor

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Introduction

Malignant pheochromocytoma is defined as the occurrence or development of chromaffin tissue metastases at non-chromaffin sites in patients with adrenal pheochromocytoma or extra-adrenal tumor (paraganglioma). It is a rare disease, estimated to occur in 10% of all pheochromocytomas [1]. When the diagnosis of malignant pheochromocytoma is established, there is no uniformly effective treatment for all patients and invariably various modes of therapy are explored [2]. Thus, management of such patients presents a challenge to their medical teams. Moreover, prediction of the malignant potential of a pheochromocytoma before the occurrence of metastases is difficult to ascertain: it is admitted that genetic background, especially mutation in the succinate dehydrogenase B (SDHB) gene is associated with malignancy whereas the extra-adrenal location, biological markers as urinary catecholamines and plasma chromogranin A (CgA), the size, or the histopathological evaluation of the primary tumor remain controversial predictive factors of malignancy. The aim of this report is to evaluate the value of the latter in

patients diagnosed with malignant pheochromocytoma at our institution, and to describe our local experience regarding clinical course and treatment of this rare entity.

Results

We identified 16 patients with a diagnosis of malignant pheochromocytoma (Table 1) based on the presence of metastases at the time of diagnosis or during the follow-up. Fifty-one patients with a diagnosis of pheochromocytoma without mention of metastases were registered in the archives of our institution and were not included in our observation.

Each included patient had a clinical follow-up either in-hospital or outpatient clinical consultation. Those with a tumor size >4 cm or familial syndromes underwent periodic imaging follow-up, usually once a year, less commonly once at 2–3 years. For other patients, laboratory and imaging follow-up was guided by the recurrence of clinical symptoms.

We observed a higher proportion of men than women (men/women: 10/6).

The mean age of the first diagnosis of pheochromocytoma was 37.75 years (range 13–55). Two patients had a genetic syndrome: patient 3 had a VHL and patient 6 had a MEN IIb (Table 1).

Biochemical patterns of catecholamine hypersecretion were available in 15 patients: urinary norepinephrine (NE) was elevated in nine patients (60%) alone or in association with other markers; to note, epinephrine (E) was elevated only in one case (patient 15). A few of our patients had results of urinary metanephrine (M) or normetanephrine (NM). Levels of plasma CgA were available in only eight patients and were elevated in 89%; kidney function was normal in all. The two patients with the highest levels (patients 13 and 14) had metastases at the time of initial diagnosis of pheochromocytoma. They also had very large tumors (more than 20 cm in both). No other patients with metastases at the time of the diagnosis of pheochromocytoma had available levels of CgA.

The mean size of the tumor at the time of first diagnosis of pheochromocytoma was available in nine patients and was 12.1 cm (range 4.4–22 cm). 90% of patients had a tumor diameter more than 5 cm. There were four extra-adrenal tumors (Table 1, patients 4, 9, 15, and 16).

The first step diagnostic imaging studies as well as periodic follow-up were computed tomography (CT) and/or magnetic resonance imaging (MRI) in all patients. Tumoral staging was performed if metastases were suspected on the first imaging test and included: ^{123}Iodine-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy, positron emission tomography (PET) with [18F]-fluorodeoxy-D-glucose (FDG), PET with [18F]-fluorohydroxyphenylalanine (DOPA). The CT and/or MRI were accurate for the initial localization of the tumor and were positive in all the cases; they could also identify some metastases, but the latter were significantly more clearly visualized on ^{123}I-MIBG scintigraphy, FDG-PET or DOPA-PET.

Histological analysis was available in eight patients (Table 1): the primary tumor was in the adrenal in seven cases and extra-adrenal in one (patient 15); all cases but one (patient 10) had a PASS above 4.

Metastases were diagnosed at the time of initial diagnosis of pheochromocytoma in five cases, and within 5 years in another six patients (Table 1). Overall, close to 70% of patients presented with metastases within 5 years of the diagnosis of pheochromocytoma. The occurrence of metastasis was delayed beyond 10 years of follow-up in three patients (Table 1, patients 7, 8, and 15), and had a latency of more than 20 years in one patient (Table 1, patient 3). All sites in the body were involved with metastases with the exception of the central nervous system: the more frequently involved sites were intra-abdominal solid tumors, lymph nodes, liver, lungs, bones, and kidneys. More than 50% of patients had more than two sites simultaneously involved with metastases.

All patients had a large resection of the tumor at the time of the diagnosis of pheochromocytoma, and 14 out of 16 patients (87.5%) had a second procedure when metastases were diagnosed (Table 2). Then, a palliative therapy was usually instituted; results of these therapeutic endeavors and their response evaluation criteria in solid tumor (RECIST) classification are summarized in Table 2. Kaplan–Meier survival curves commencing at the initial diagnosis of pheochromocytoma (Fig. 1a) and at the diagnosis of metastasis (Fig. 1b) show a 5-year survival rate of 80 and 55%, respectively. The 10-year survival rate was 50 and 25%, respectively.

Discussion

Our study has several limitations inherent to retrospective design and the relatively low number of patients; the lack of systematic molecular genetic testing could not lead to a genetic-oriented interpretation of the biochemical profile of catecholamine over-expression [3], nor identification of known susceptible genes associated with sporadic pheochromocytoma in 14–20% of cases [4, 5], or proportions of patients with mutation in the SDHB gene which is usually highly associated with malignancy [6]. However, we expose epidemiologic data and medical follow-up beyond 20 years in 16 patients. Our observations raise several issues for discussion.

Table 1 Characteristics of patients with malignant pheochromocytoma

	Gender	Age at 1st diagnosis of patient (years)	Localization, Size (cm) of tumor at 1st diagnosis of Pheo	PASS	Elapsed time at diagnosis of MP since 1st diagnosis of patient (years)	Survival since diagnosis of MP (years)	Biological markers	Familial or syndrome
1	F	51	Lt adrenal, 8 cm	8	6	2	E: WNR NE: 22xN	
2	F	37	Rt adrenal, 10 cm	16	1	9	Normal (non secreting)	
3	M	13	Rt adrenal, (?)	5	22	0	E: WNR NE: 2xN	NF1
4	M	49	Zuckerkandel 4.4 cm	NA	0	3	E: WNR NE: 12xn	
5	M	20	Lt adrenal, 9 cm	NA	0	6	E: WNR NE: 1.3xN VMA: (?)	
6	F	24	Bilateral, (?)	11	5	8	?	MEN2b
7	M	34	Rt adrenal, 22 cm		10	FU—18 years	E: WNR NE: 2xN CGA: 4xN	
8	M	24	Lt adrenal, (?)		11	FU—12 years	E:WNR NE: 1.5xN CGA: 1.2xN	
9	M	45	Paraganglioma, (?)		0	2	E: WNR NE: 21xN	
10	F	48	Lt adrenal, (?)	1	4	FU—5 years	NE: (?) E: WNR NM: (?) CGA: 4.9xN	
11	M	39	Rt adrenal, (?)	11	3	FU—4 years	M: 2.5xN NM: 100xN CGA: WNR	
12	M	55	Rt adrenal, 9 cm		4	FU—2 years	M: 2.5xN NM: 4.5xN CGA: 1.5xN	
13	M	37	Rt adrenal, 22 cm	11	0	FU—1 years	CGA: 230xN	
14	F	20	Lt adrenal, 20 cm		0	5	CGA: 260xN	
15	F	52	Lt supra-renal, (?)	6	13	FU—2 years	E: 1.4xN NE: 10xN CGA: 5.8xN	
16	M	54	Rt supra-renal, 5 cm		5	FU—1 years	VMA: (?) MN: (?)	

All biological markers of pheochromocytoma are results of urine collection for 24 h but results of chromogranin A (CgA) which are measured from blood samples

Results are given in number folds of the upper limit of the normal range

PASS Pheochromocytoma of the Adrenal Gland Scoring Scale, checking and scoring 12 histomorphologic features to a maximal score of 20 (Expanded large and confluent nests or diffuse growth, necrosis, increased cellularity, cellular monotony, tumor cell spindling, increased mitotic figures, any atypical mitotic figures, extension into the periadrenal adipose tissue, capsular invasion, vascular invasion, profound cellular and nuclear pleomorphism, and nuclear hyperchromasia)

WNR within the normal range, *E* epinephrine, *NE* norepinephrine, *M* metanephrine, *NM* normetanephrine, *VMA* vanillyl-mandelic acid, *FU* follow-up, *MEN 2b* multiple endocrine neoplasia 2b, *NF1* neurofibromatosis 1

(?), unknown size in column 3; non available PASS in column 4; elevated above upper limit of normal without specific number in column 6

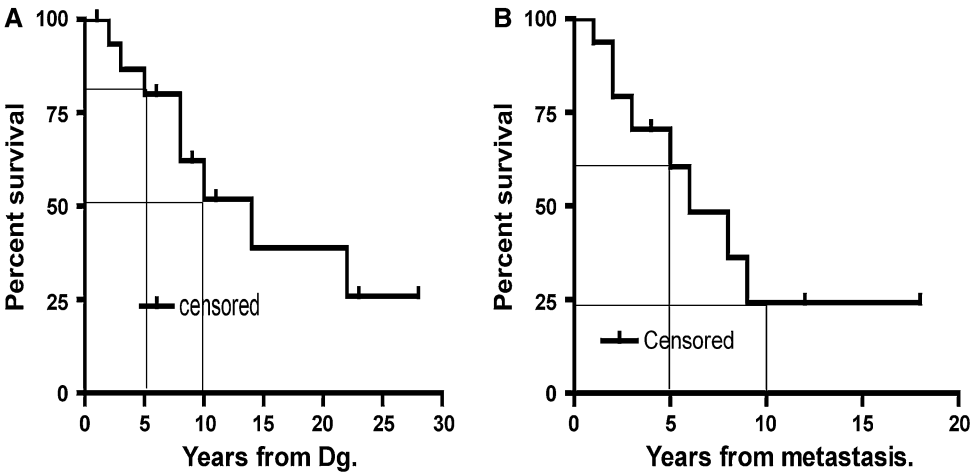

Fig. 1 Kaplan–Meier survival curve in patients with malignant pheochromocytoma since first diagnosis of pheochromocytoma (**a**) and since first diagnosis of metastases (**b**)

Epidemiologic data

We found that men were afflicted more frequently than women. Gender-specific predilection has been described [7, 8] but is not always found; neither is difference in age of onset in benign or malignant pheochromocytoma [9, 10].

Biochemical markers

NE levels were elevated in most patients; at the opposite, E was mildly elevated in only one patient (patient 15). This may be explained by defective catecholamine synthetic enzymes with down-regulation of the phenylethanolamine *N*-methyltransferase (PNMT) in malignant pheochromocytoma, as observed in mice [11], which converts NE to E. Although controversial, a lower ratio of E/NE + E may be a predictive marker of malignant pheochromocytoma [12]. We had no routine measures of plasma dopamine, urinary HVA, or M and NM levels, and thus could not evaluate their potential role for differentiation between malignant and benign pheochromocytoma [1].

We found that very high levels of CgA are associated with the concomitant presence of metastases, and thus may predict the diagnosis of malignancy. This finding is corroborated in other studies [13] but remains controversial [12, 14]. Moreover, the prognosis of such patients may be affected. In the meantime, the high sensitivity and specificity of the tests reported to be 91–95% for the former whether alone or in combination with urinary catecholamines or metanephrine [14, 15] warrants its use as an easy, useful, and reliable test for the follow-up of patients with pheochromocytomas.

Size and laterality of tumors

In our series, most of tumors were larger than 5 cm in diameter, and had no particular sided adrenal localization. In Thompson's series, benign pheochromocytoma was more frequently right-sided, but there is neither side nor size inherent to malignant tumors [8]. At best, one can say that malignant pheochromocytomas are slightly larger than benign tumors. Of note, we had four cases of extra-adrenal malignant pheochromocytoma (Table 1, patients 4, 9, 15, and 16), considered a risk factor for malignancy [16] and often associated with SDHB mutations [6].

Microscopic evaluation

The PASS, as a histomorphologic tool characterizing adrenal tumors, seems to be an accurate prognostic marker of malignancy, as all patients but one (patient 10) had a score above 4, in accordance with findings described in Thompson's series [8]. To note, the elevated PASS in patient 15 is related to an extra-adrenal tumor and should thus be interpreted with caution: there is no data concerning the value of PASS for tumors not localized into adrenal glands. In our institution, an analysis of 19 patients with benign pheochromocytoma who had no metastases after a follow-up of 5 years after the initial diagnosis of pheochromocytoma, showed that the PASS was below 4 in all (data not shown), confirming the interest of this evaluation to suggest potential of malignancy of an adrenal tumor. There are two major limitations with regard to use of PASS as a prognostic marker of malignant pheochromocytoma: first, it has never been applied to large series, but only to a small number of cases; second, some parameters of the PASS are subjective and pathologist-dependant, (such as scoring of hyperchromasia or profound nuclear pleomorphism), thus warranting additional, more objective, histological markers [1]. In his study, Thompson reports that the immunohistologic marker S100 was positive in 100% of benign tumors but only in 18% of malignant tumors and may be thus a marker of interest to distinguish between benign and malignant pheochromocytoma. Interestingly, the retinoblastoma protein

Table 2 Efficacy of treatment in patients with malignant pheochromocytoma

Patients	Survival since diagnosis (years)	Surgery (*n*)	Chemotherapy			Other	Cause of death
			Drug (for each patient, the mentioned therapies are in chronologic order)	Number of courses or length of time	RECIST		
1	2	2	CVD				CVA
2	9	4	Mitotane		PR	XRT to spinal metastases and to IVC compressing tumor	Pheo
			CVD		PD		
						Chemo	
						RFA	
3	0	2					Post-operative sepsis
4	3	2	CVD		PD	XRT to bone metastasis and pelvis SOL	Pheo
5	6	2	Imatinib (Glivec)		PD		Post-operative sepsis
6	8	2					Pheo
7	FU—18 years	6	Thalidomide-IFN-indomethacine	24 months	Clinical and biological SD	RFA to liver lesions	
					severe polyneuropathy		
			Imatinib (Glivec)	4 months	PD		
			MIBG	4 courses	SD during 3 courses (48 months) then PD		
8	FU—12 years	2	MIBG	2 courses	SD		
9	2	1	Streptozotocin		PD		Pheo
10	FU—5 years	3	MIBG	1 courses	SD		
11	FU—4 years	2	CVD	6 courses	PD		
			RAD 001		SD for 3 months, then PD		
12	FU—2 years	2			PD		
13	FU—1 year	2	MIBG	2 courses	SD		
14	5	1	MIBG	4 courses	PD	XRT to lower spine	Pheo
			CVD	7 courses	PR but Severe myelotoxicity		
			RAD 001	3 months	PD		
15	FU—1 year	2	MIBG	2 courses	SD		
16	FU—1 year	2					

FU follow-up, *CVD* cyclophosphamide-vincristine-dacarbazine, *IFN* interferon, *XRT* radiotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *SVC* superior vena-cava, *RFA* radio-frequency ablation, *Chemo* chemo-embolization, *CVA* cerebrovascular accident, *Pheo* pheochromocytoma (progressive disease)

immunohistochemical marker could point a statistical difference between tumors with PASS below 3 from those with PASS above 4, suggesting early S phase mitotic difference between benign and malignant diseases [17]. Of note, it seems that the reproducibility of the evaluation is limited with inter-observer variations [18]. In our study, we addressed this limiting factor, and only a single experienced pathologist reported the histopathologic findings.

Metastases

The occurrence of metastases in our population conforms to the data published in the literature, namely usually within 5 years but sometimes at a much longer interval after the initial diagnosis [1]. Indeed we noted four cases of occurrence of metastasis 10 years after the initial diagnosis of pheochromocytoma, including one patient after 22 years (Table 1, patient 3). Other publications report late-onset occurrence of metastases up to 13 [10] or 15 years after initial diagnosis [19]. Our protocol of follow-up included a systematic outpatient or in-hospital clinical consultation, with laboratory and imaging studies guided by the initial size of the tumor or the presence of familial disease. Patients 8, 10, 11, and 15, had diagnosed metastases from 3 to 13 years after initial diagnosis (Table 1), but might have been diagnosed earlier if a more stringent follow-up had been performed. The best means and periodicity for follow-up, particularly in patients with an a priori benign sporadic tumor remains an issue: beyond clinical and laboratory (catecholamines and/or metanephrines) evaluation, the roles of conventional imaging studies with CT or MRI, and functional imaging studies with ^{123}I-MIBG scintigraphy or FDG/DOPA-PET scanning remain to be defined [20, 21].

Survival and treatment

Our data are in keeping with the well-established fact that there is no curative therapy for malignant pheochromocytoma. A 5-year survival rate from the time of diagnosis of metastatic disease of less than 50% is found in the literature but there is a wide individual variation correlating with the aggressive pattern of the tumors [1, 22–24]. In our series, two patients have been followed for more than 10 years after the diagnosis of metastases, without any distinguishing clinical, laboratory or histologic findings; this suggests that the malignant pattern should also be graded according to the aggressiveness of the tumor, which requires further research.

Principles of treatment for malignant pheochromocytoma are focused on control of hypertensive symptoms and tumor cytoreduction which begins with removal of the tumor; however, radical surgery is rarely feasible when there are diffuse metastases [1, 2], warranting the use of palliative cytoreductive therapies.

It is today accepted that when ^{123}I MIBG uptake is sufficient, then ^{131}I MIBG should be the first line palliative therapy [2]. Overall, in our series, it is the only treatment which led repetitively and for a notable period of time to a stable disease according to RECIST criteria (Table 2): six patients received ^{131}I-MIBG with stable disease being achieved in four (patients 8, 10, 13, and 15); these patients have ongoing follow-up ranging from 1 to 12 years; in another one there was progression after three courses performed within 4 years of treatment (patient 7), and in one patient with very aggressive disease, it was not efficient (patient 14). Other therapeutic approach has also been described: streptozotocin (Table 2, patient 9 [25]) could not help our patient whereas the use of the cyclophosphamide–vincristine–dacarbazine combination in five of our patients (1, 2, 4, 11, and 14) had limited efficacy, as reported in the literature [24]. One patient (patient 2) received a therapeutic dose of mitotane to enhance the cytotoxic effect of chemotherapy [26]. The use of everolimus (RAD001), an inhibitor of the mTOR pathway, in two of our patients (Table 2, patients 11 and 14) led to disappointing results, as reported in four patients with malignant pheochromocytomas including ours [27]. One of our patients was treated with thalidomide (Table 1, patient 7) with a beneficial response characterized by laboratory and radiological stabilization of the disease but stopped the treatment because of severe neurologic side effects (peripheral sensory neuropathy). Recently, the use of tyrosine-kinase inhibitors (TKI) has been described in neuroendocrine tumor (NET): two of our patient treated with imatinib did not show significant improvement [28], however interestingly, one (Table 1, patient 7) became positive for ^{123}MIBG uptake, allowing subsequent effective therapy with the compound. This may have been the effect of chance, but more studies could help to explore a direct effect of Imatinib on the differentiation of pheochromocytoma tumor cells.

In conclusion, metastatic disease can occur at a delayed interval after the diagnosis of so-called "benign pheochromocytoma", and the course of the disease is highly variable from case to case. The prediction of malignancy is a challenge, and may be suggested by the following parameters: extra-adrenal/paraganglioma localization of the tumor; very high levels of chromogranin A at the time of the diagnosis; a PASS histological evaluation with a score above 4. Thus, clinical, biochemical, and imaging follow-up should be mandatory for an extended period of time in any patient diagnosed with pheochromocytoma, particularly those with the previously mentioned criterions suggestive of potential malignancy. A consensual recommended follow-up remains to be established. When metastases are diagnosed, the 5-year survival rate is today 50%; in this situation, surgery or less invasive cytoreduction (chemoembolization, radiofrequency ablation) can be employed followed by palliative treatments as ^{131}I-MIBG with or without chemotherapy. Cure is seldom achieved, placing the development of new effective drugs for management of malignant pheochromocytoma as a major challenge for the coming years.

Methods

We reviewed the files of all patients with a diagnosis of malignant pheochromocytoma and/or pheochromocytoma who attended our institution from January 1, 1980 to December 31, 2008. We had free access to laboratory results and imaging studies performed at our institution as well as discharge letters. The biologic markers of pheochromocytoma were urinary catecholamines (E, NE, vanillylmandelic acid (VMA), M, NM) and serum levels of CgA). The CgA radioimmunoassay was routinely performed using the CGA-KIT (Cisbio bioassays) on human plasma or serum from year 2005. Imaging studies include: CT with contrast product, MRI, ^{123}I-MIBG scintigraphy, PET-FDG, DOPA-PET. The histological evaluation of the tumors was conducted by a pathologist specialized in assessment of NET and was performed according to the classification based on the PASS [8]. This evaluation was performed both in cases of adrenal and extra-adrenal tumors, despite it is not validated in the latter. The follow-up of the patients and the tumor response to therapies were based on clinical, biochemical, and imaging studies available in patients' files, the latter in accordance with the RECIST classification [29]: complete response; partial response; stable disease; and progressive disease.

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