Prognostic value of Pheochromocytoma of the Adrenal gland Scaled Score (PASS score) tests to separate benign from malignant neoplasms

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La valeur pronostique du PASS score dans la distinction entre phéochromocytome bénin et malin

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RÉSUMÉ

Prérequis : La distinction entre phéochromocytome bénin et malin peut se révéler délicate sur le plan morphologique. Cette difficulté découle de la définition même des phéochromocytomes malins dont le diagnostic repose sur la présence de métastases. Un score de PASS a été développé afin de contribuer à cette distinction. Un score de PASS >4 est corrélé à un haut potentiel de malignité.

But: Etudier la valeur pronostique du score de PASS afin de différencier les phéochromocytomes bénins et les phéchromocytomes malins.

Méthodes: Nous rapportons une étude à propos de 11 patients présentant des phéochromocytomes diagnostiqués entre 1970 et 2010. Des courbes ROC ont été utilisées afin d'évaluer le potentiel diagnostique du score de PASS. Ce modèle logistique a été développé en utilisant 11 variables prédictives. Sa performance a été évaluée en calculant l'aire comprise sous la courbe ROC.

Résultats: Dans les tumeurs bénignes, le sore de PASS était <4 dans 3 cas et ≥4 dans 6 cas. Dans les tumeurs malignes, le score de PASS était ≥4 dans les 2 cas. L'analyse de la courbe ROC a permis d'établir qu'un score ≥ à 4 permettait d'identifier les phéochromocytomes malins avec une sensibilité de 50% et une spécificité de 45%.

Conclusion: Le score de PASS peut contribuer au diagnostic des phéochromocytomes malins et ce malgré sa faible sensibilité. Cependant, ce score pourrait être enrichi par de nouveaux items tel que les données imunohistochimiques permettant ainsi d'améliorer sa sensibilité.

Mots-clés
Score de PASS, pheochromocytome, pronostic, microscopie

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Prognostic value of pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms

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SUMMARY

Background: Differentiating malignant from benign pheochromocytoma has been challenging when based on histologic features. This is due to the definition of malignant pheochromocytoma which are defined by the presence of metastases. A PASS score was developed and according to many authors, a PASS score> =4 identified potentially malignant tumors.

Aim: To assess the prognostic value of PASS score in differentiating benign pheochromocytomas from malignant ones.

Methods: The records of 11 patients with tumors diagnosed as "pheochromocytoma" were identified from 1970 to 2010 in the files of the pathology, intern medicine and biochemistry departments of the Charles Nicolle hospital and Pasteur Institute. Receiver operating characteristics (ROC) curve analysis was performed to evaluate the diagnostic performance of PASS. The logistic model was developed using the 11 predictive variables. Its performance was evaluated by calculating the area under the ROC curve and comparing it with that of the PASS.

Results: In benign tumors, The PASS score was <4 in 3 cases and >=4 in 6 cases. In malignant tumors, the PASS score was >=4 in both cases. According to the ROC curve analysis, a PASS equal or superior to 4 identifies malignant pheochromocytoma with a sensitivity of 50% and a specificity of 45%.

Conclusion: I think that PASS score, despite its low sensitivity, may help to reserve the more aggressive treatment and narrow follow up for potentially malignant tumors. Widespread of this called score with complete clinical data will help to validate these findings and to add other prognostic factors of value that could be a part of this scaled score such as immunohistochemical findings.

Key-words
PASS score, pheochromocytoma, prognosis, microscopy

The term pheochromocytoma, a catecholamine-secreting tumor arising from the chromaffin cells of the sympathoadrenal system, was coined by Poll in 1905 to describe the dusky color of the cut surface of the tumor when exposed to dichromate (1). The vast majority of pheochromocytomas arise from the adrenal medulla where the largest collections of chromaffin cells are found (2). The term paraganglioma is used for this same tumor in other anatomic sites except for the organs of zuckerkandl. According to the World Health Organization definition, malignant pheochromocytoma is currently defined by the presence of metastases (3). These metastases may be present at referral or during the follow-up. It is currently accepted that the biologic behavior of these tumors can't be predicted based on prospective diagnosis. We searched to make a retrospective analysis in order to assess the importance of PASS score and laboratory tests in predicting the behavior of these tumors.

Our aim is to provide a study of pheochromocytomas encompassing the use of clinical features, morphologic findings and patient follow up information applied to a group of 11 patients.

PATIENTS AND METHODS

The records of 11 patients with tumors diagnosed as "pheochromocytoma", "malignant pheochromocytoma" and "atypical pheochromocytoma" were identified from 1970 to 2010 in the files of the pathology, intern medicine and biochemistry departments of the Charles Nicolle hospital and Pasteur Institute. The few number of the cases reported is due to the rarity of the complete adequate follow up information and hematoxylin and eosin-stained slides to make a definitive diagnosis. Materials were supplemented by a review of the patient demographics (gender, age), symptoms and physical findings at presentation (diaphoresis, headaches, palpitations, weakness, syncope or dizziness, anxiety, flushing, chest pain, nausea, hypertension including paroxysmal type, vomiting and weight loss), including duration, medical and surgical history. Laboratory values, specifically related to catecholamines (serum or urine) and their various metabolites, were obtained in all cases. In addition, we reviewed radiographic, surgical pathology and obtained follow up information when available. Hematoxylin and eosin-stained slides from all patients were reviewed for morphologic assessment of malignant and benign pheochromocytoma. A pathologist blinded to clinical outcome, reviewed the histopathologic characteristics of all cases using the PASS system. A number of macroscopic and histologic observations were recorded for each tumor as follows : tumor size, encapsulation (present or absent), capsular invasion, vascular invasion defined by direct extension into the vessel lumen, intravascular attached tumor thrombi, and/or tumor nests covered by endothelium identified in a capsular or extra capsular vessel with no distinction between veins and lymphatic channels, extension into the periadrenal adipose tissue, cell nests (small, zellballen type nests to large, confluent nests which are defined as 3 to 4 times the size of a zellballen or the normal size of the medullary paraganglia nests or diffuse growth, necrosis identified in the center of large nests, fibrosis, degenerative changes, calcifications, cellularity, cytoplasmic quality (clear, basophilic, eosinophilic, amphophilic), tumor spindling, cellular pleomorphism, cellular monotony, nuclear hyperchromasia, piknosis, macronucleoli (defined as >4 um in diameter, eosinophilic-magenta or irregular in shape), intranuclear cytoplasmic inclusions, mitotic figures (number of mitoses per 10 higher power fields with magnification at x40 using a Zeiss microscope), atypical mitotic figures (present or absent and defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms or indescribably bizarre). A PASS score was performed in all cases identifying presumably benign tumors with a PASS score less than 4 and malignant ones with a PASS score equal or superior to 4. If recurrent disease was present, it was established whether it was histologically similar to the primary tumor. Malignant recurrence was defined as the appearance of metastasis after complete tumor eradication. Distant metastases were documented by histology in all cases.

The informed and written consent was obtained from all patients.

Statistical analysis

Receiver operating characteristics (ROC) curve analysis was performed to evaluate the diagnostic performance of PASS. The logistic model was developed using the 11 predictive variables. Its performance was evaluated by calculating the area under the ROC curve and comparing it with that of the PASS. Survival was analyzed as the number of months from the diagnosis of the first metastasis to last follow up. Comparison of means between groups was made with bilateral student test.

RESULTS

1. Clinical demographics and presentation

A summary of the clinical information on the patients is provided in table 1. The mean age of the patients at the presentation for the patients who had an association syndrome or genetic abnormality was 32, 5 years and 45.44 years in patients with sporadic pheochromocytoma. Statistical analysis proved the absence of a significant difference between the 2 means. Patients presented with a variety of symptoms and physical findings but the most frequently identified physical finding was hypertension which was variably described as episodic, labile, paroxysmal or associated with postural changes. Most patients presented with other findings as noted in the Table 1. When pain was encountered, it was lumbar in all cases. No patient was asymptomatic. We describe a female predominance with a sex ration F/M of 10/1. Two patients had what was considered to be a non sporadic tumor: an association with a syndrome known to include an increase incidence of adrenal pheochromocytoma. These patients were 2 women aged respectively 31 and 34 years. The first patient presented a NEM 2a and the second a neurofibromatosis. The first one presented a malignant recurrence discovered after 11 years of follow up.

The second one presented a benign pheochromocytoma with a benign recurrence after 24 months of follow up.

Benign

We define benign tumors as tumors without clinical metastases at presentation or during follow up. The mean age of the patients at presentation was 47, 44 years. All the patients were symptomatic with hypertension being the most frequent symptoms (100%). 8 patients presented sporadic pheochromocytoma and 1 patient presented hereditary pheochromocytoma. Laboratory values were available in all patients. All patients had elevated levels in either their serum or urine of catecholamines, norepinephrine, epinephrine, metanephrine, dopamine, vanillylmandelic acid or other metabolites. As 24-hour urine measurements seem to be more reliable than plasma catecholamine measurements, we analyzed their values and compared them with the normal rates. The table 2 shows the different results in benign and malignant pheochromocytoma.

Malignant

A summary of the clinical information on the patients in this series is provided in table 1. Malignant tumors are defined as tumors with metastases at referral or follow up. The mean age at presentation was 26 years. Both patients were female. The 2 patients presented malignant recurrences. The first one presented MEN2 syndrome and a malignant recurrence with abdominal lymph nodes and liver metastases after 5 years of follow up. The second patient presented hepatic metastases after 33 years of follow up. Laboratory values were available in the 2 cases. Both patients had increased levels in either their serum or urine of catecholamines, norepinephrine, epinephrine, metanephrine, dopamine, vanillylmandelic acid or other metabolites. The levels were often elevated to>4 and 1,5 times the normal range (Table 2).

Table 2: Urine levels of catecholamines

Clinical nature		Urine levels of catecholamines N (40 - 250 umol/24H)
Benign tumors	1	1000 (4 x N)
	2	1250 (5 x N)
	3	1500 (6 x N)
	4	2250 (9 x N)
	5	2500 (10 x N)
	6	9250 (37 x N)
	7	2500 (10 x N)
	8	2000 (8 x N)
	9	2250 (9 x N)
Malignant tumors	10	1000 (4 x N)
	11	375 (1,5 x N)

2. Radiographic study

All the patients had abdominal ultra-sound sonography, CT-scan and MRI before surgery. Only 4 patients had I-meta-iodobenzylguanine (MIBG) scintigraphy. Two patients presented a malignant pheochromocytoma and the other patients presented benign tumors. In general, varied-sized suprarenal masses were identified, often displacing the kidneys. In general, the lesion was described as heterogeneous, demonstrating an increased signal on T2-weighted images.

Table 1: Patients characteristics

	All cases	Benign clinically	Malignant clinically
Gender			
W	10	8	2
M	1	1	0
Age at presentation			
Range		22-78	16-36
Mean	43.54	47.44	26
Females (Mean)		46.88	26
Males (Mean)		52	-
Patient with associated syndrome	32.5	34	31
Symptoms			
-Hypertension	11	9	2
-Diaphoresis, flushing, nausea, vomiting, headache	10	8	2
-Pain	3	2	1
-Other (weakness, anxiety, regurgitation, diarrhea, weight loss, diabetes mellitus)	8	7	1
-Asymptomatic	0	0	0
Patients with syndrome			
MEN2 syndrome	1	0	1
NF syndrome	1	1	0
Follow up period			
-Range		(15 days, 48 months)	(11 years, 33 years)
-Mean		16 months	22 years

W: women, M: Male

MIBG scintigraphy showed in all the patients a remarkable affinity for the adrenal medullary tissue (in 3 cases) and in hepatic tissue (in one case presenting hepatic metastases). In two cases, hypervascular masses in the liver and lymph nodes were noted and presumed by the radiologist to represent metastatic disease. This fact was attested by the histologic examination.

3. Pathology

3-1 Macroscopic findings

Benign: the majority of the patients presented with unilateral disease (n= 8). One tumor was described as bilateral and occurred in a patient with syndromic association (neurofibromatosis). The tumors involved the right adrenal gland (n= 5 tumors) more frequently than the left adrenal gland (n=3). The mean size of the tumors was 3 cm. The tumors were described as encapsulated or well-circumscribed masses with variegated cut surface showing areas of hemorrhage. The tumors were soft, gray-tan to brow-red with extensive cystic degeneration in one case.

Malignant: both patients presented with unilateral disease. One tumor occurred in a patient with syndromic association. One patient presented a tumor of the right adrenal gland and the second the left adrenal gland. The mean tumor size was 7.54 cm. The tumors were encapsulated or well circumscribed, nodular, lobular or bosselated masses with a variegated cut surface. The tumors were soft, gray-tan with calcification. It wasn't noted an infiltration into the substance of the adrenal cortex or periadrenal adipose tissue.

3-2 Microscopic findings

Benign

The tumors were well circumscribed and separated from the remaining adrenal cortex by a well -formed capsule in most cases (n=8). Focal vascular invasion was noted in 3 cases. Capsular invasion was noted in one case while invasion into the periadrenal soft tissue was not noted in any tumors. The tumor cells were arranged in the characteristic "zellballen" architecture in 3 cases whereas, 6 cases demonstrated diffuse architecture. The tumors were of low to medium cellularity with 3 tumors showing high cellularity. Tumor cell monotony was identified in 3 cases. Pyknosis was noted in 1 case and focal, central, confluent or diffuse necrosis was noted in 1 case. The majority of tumors showed areas of degenerative changes, including cyst formation, hemorrhage and fibrosis. No focal spindle cell architecture was found. Mitotic figures were inconspicuous or absent in all cases. Atypical mitotic forms weren't found.

Malignant

The tumors were well circumscribed and distinctly separated from the remaining adrenal cortical parenchyma by a capsule. A well-formed tumor capsule was present in both cases. Tumor cells were seen transgressing the capsule in 1 case. Vascular invasion wasn't identified. There was varied histologic pattern with a focal "zellballen" architecture and a predominance of large nests in both cases. Necrosis, identified in individual cells (piknosis), focal and confluent or diffuse was identified in no cases. Both tumors were highly cellular with cellular monotony. Tumor cell spindling wasn't noted. Profound nuclear pleomorphism was found in 1 case. Mitotic figures and atypical mitotic forms weren't identified. The histology of the recurrence and of the metastatic tumor deposits was identical to the primary tumor in one patient. In the second case, the histology of the recurrence was different from the primary tumor and was characterized by the presence of features predictive of malignancy.

All microscopic findings are illustrated in table 3.

Table 3: Histologic characteristics of the different tumors

	Benign clinically	Malignant clinically
Vascular invasion	3	-
Capsular invasion	1	-
Extension to the periadrenal tissue	-	1
Large nest size/diffuse architecture	6	2
Necrosis	1	-
High cellularity	3	2
Tumor cell spindling	-	-
Cellular monotony	-	1
> 3 mitoses/ 10 HPF	-	-
Atypical mitotic figures	-	-
Nuclear pleomorphism	5	1
Tumor cell hyperchromasia	1	-

4. PASS score

According to the histologic features, a PASS score was performed for each tumor, primary as well as recurrent ones. In the three cases of recurrent tumors, the PASS score was constant in 1case of malignant pheochromocytoma. It increased in one case of malignant pheochromocytoma and decreased in one case of benign pheochromocytoma. Table 4 shows the different PASS scores.

In benign tumors, The PASS score was <4 in 3 cases and >=4 in 6 cases. In malignant tumors, the PASS score was >=4 in both cases. The ROC curve is represented in figure 1. The area under the ROC curve was estimated to 0,417. According to the ROC curve analysis, a PASS equal or superior to 4 identifies malignant pheochromocytoma with a sensitivity of 50% and a specificity of 45%. These results are illustrated in the table 5.

Table 4: PASS scores of the different tumors

Cases	Clinical nature	PASS score primary tumor	PASS score recurrent tumor
1	Benign	2	-
2	Malignant	4	8
3	Malignant	5	5
4	Benign	9	5
5	Benign	4	-
6	Benign	3	-
7	Benign	7	-
8	Benign	6	-
9	Benign	6	-
10	Benign	3	-
11	Benign	6	-

Table 5: Coordinates of the ROC curve

Positive if Greater Than or Equal To(a)	Sensitivity	1 - Specificity
1.00	1.000	1,000
2.50	1.000	.889
3.50	1.000	.667
4.50	.500	.556
5.50	.000	.556
6.50	.000	.222
8.00	.000	.111
10.00	.000	.000

Test Result Variable(s): score

The test result variable(s): score has at least one tie between the positive actual state group and the negative actual state group.
a The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

5. Clinical therapy and patient outcome

All tumors were managed by surgery with pre-operative adrenergic blockage to decrease intraoperative hypertensive episodes. The surgery included adrenalectomy in 6 cases, double adrenalectomy in 1 case, adrenalectomy and partial liver resection in one case, adrenalectomy, lymph node dissection and partial liver dissection in one case. Seven patients had adrenalectomy alone without adjuvant therapy and 2 patients with malignant pheochromocytomas had surgery followed by chemotherapy.

Benign

All patients with benign tumors were managed by surgery alone. No patients died during the follow up period with a mean follow up period of 16 months

Malignant

Both patients were managed by surgery followed by chemotherapy and no patients died after a follow up period of 3 years and 1 year.

DISCUSSION

The first description of pheochromocytoma in 1886 has been attributed to Felix Frankel in an 18-year-old woman with bilateral adrenal tumors (4). This publication was reviewed by Hartmut and colleagues who assessed the patient's relatives and demonstrated that the original patient and her family had multiple endocrine neoplasia type 2 by providing molecular evidence (5). Pheochromocytomas are divided into hereditary and sporadic tumors. Our understanding of the pathogenesis of pheochromocytomas has tremendously grown during the last years along with the increasing advances of molecular genetics. Multiple genetic alterations have been found to be associated with pheochromocytomas most often inherited than sporadic forms. Some pheochromocytomas are inherited and can be subdivided into a variety of groups: multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), hereditary paraganglioma and SDHD gene-related tumors and hereditary pheochromocytomas (6). MEN2 was observed in our study in one patient with malignant pheochromocytoma. It is an autosomal dominant cancer syndrome with germline mutations in the RET proto-oncogene. VHL disease is an autosomal inherited tumor syndrome with mutations in the VHL tumor suppressor gene. NF is the most common familial cancer syndrome with a risk of pheochromocytoma estimated to 2%. It is related to mutations in NF1 tumor suppressor genes (6). It was diagnosed in our study in one patient with benign pheochromocytoma. The diagnosis is made in the presence of two or more of these criteria: six or more café au lait macules, the greatest diameter of which is more than 5 mm in pre-pubertal patients and more than 15 mm in post-pubertal patients, two or more neurofibromas, axillary or inguinal freckling, optic glioma, two or more lisch nodules, a distinctive osseous lesion such as sphenoid dysplasia or pseudoarthrosis, a first-degree relative with NF1 according to the preceding criteria (3). Familial pheochromocytoma syndromes are related to mutations in the genes encoding mitochondrial succinate dehydrogenase subunit B (SDHB), subunit D (SDHD) and also rarely subunit C (SDHC) (7). Patients with apparently sporadic pheochromocytoma may have germline mutations including RET, VHL, SDHD and SDHB estimated to be as high as 15% to 24% (8, 9). Other germline mutations have been identified. For example, Qin and coworkers reported mutations in TMEM127 tumor suppressor gene in 30% of familial tumors and 3% of sporadic-appearing pheochromocytomas (10). The true incidence of MPA is difficult to determine but they seem to account for 6.5% of all adrenal gland tumors (11-14). The prevalence of malignant pheochromocytoma in familial syndromes varies depending on the familial syndrome and the follow -up period. In MEN2 and VHL-related pheochromocytomas, about 25% are reported as malignant on up to 25 year follow up (6). It is estimated that hereditary tumors are observed in 30 to 40% of cases (15), in the other side, sporadic tumor have a 10 to 15% risk of developing a hereditary tumor when the age at onset is < 45 years (15). Extensive studies on the genetics of pheochromocytomas confirmed the definite death of the 10% rule concerning the genetics of pheochromocytomas. Many authors report the absence of gender predilection of pheochromocytomas (16). In our study, a female predominance was noted. The mean age at presentation ranges from 32 to 61 years (11, 13, 17-20). In this study, the mean age was 43 years. The mean age in patients with syndromic presentation is generally younger than in patients with sporadic forms. In our study, the difference wasn't statistically significant. Bilateral disease is generally associated to syndromic presentation. In our study, one patient presenting syndromic presentation had unilateral tumor, in the other hand, another one presented bilateral tumours without other special findings, but an additional genetic study seems to be compulsory in order to rule it out. In general, the pheochromocytomas associated with syndromes behave in a benign fashion (21, 22). Nevertheless, in our study one patient

with MEN2 presented a malignant recurrence after a follow up period of 11 years. The usual prognosis of malignant pheochromocytoma is poor related to metastatic disease and to the relative excess of catecholamine in the circulation with a 5 year survival rate varying between 44 to 57% (17, 19, 23-25). Many prognostic factors have been studied in the literature without a real consensus. This is due to the rarity of comprehensive analyses with complete clinical, radiographic, histologic and follow up information. Many authors studied the prognostic importance of the size and weight of the tumors and many of them proved the absence of difference in patient outcome based in these parameters (16). Other non consensual prognostic factors have been studied such as the expression of the 3 angiogenesis, metastasis related genes VEGF, Cox-2 and MVD, immunostaining of CD-44, p53, Bcl2, mdm2, cyclin D1, P21, p27, MIB-1 or CGH (23). Some authors reported that tumors with SDHB mutations are associated with shorter survival (24). Pheochromocytomas, whether benign or malignant, have nonspecific symptoms and signs (16). No imaging features can reliably distinguish common benign from rare malignant pheochromocytomas unless the evidence of direct local invasion into the liver, kidney or pancreas or distant metastases. Bone scan and radiographs are useful for the evaluation of skeletal metastases or I-metaiodobenzyl-guanidine (MIBG) is useful for the detection of metastatic or locally recurrent disease (3). In our study, both MPA showed liver metastases. The most common metastatic sites are the axial skeleton, lymph nodes, liver, lung and kidney. Rarely, metastases are reported in the pericardium, the brain and spleen (16). Laboratory tests reveal remarkably elevated levels of serum and/or urine catecholamines, norepinephrine, epinephrine, metanephrine, normetanephrine, dopamine, vanillylmandelic acid (VMA). It has been suggested that dopamine values may correlate with malignant pheochromocytoma (23). In our study, it was confusing to find that the levels in malignant pheochromocytoma were lower than those in benign pheochromocytoma. This fact points out the absence of relevant importance of these markers to make the difference between benign and malignant pheochromocytomas. For some unknown reason, pheochromocytomas, whether benign or malignant, seem to be more commonly found in the right adrenal gland, a finding also noted in our study (16, 11, 17, 20, 25). The positive diagnosis is based on histologic examination. Pheochromocytomas are made up of a dual cell population. The main cell is the chief cell or pheochromocyte which can be detected on routine hematoxylin and eosine-stained slides. The second population is the sustenticular cell which is thought to be a supporting cell similar to the glial cells in the central nervous system. They are slender, with thin wisps of cytoplasm encompassing the chief cells (16). A number of different tumors need to be considered in the differential diagnosis. An adrenal cortical carcinoma have not the same architecture, the cells tend to contain eosinophilic cytoplasm and have vesicular cytoplasm with more mitotic activity; metastatic tumors, which are more frequent than primary one, should be ruled out by immunohistochemical studies. Moreover, in pheochromocytoma with diffuse spindle cell formation, the diagnoses of malignant peripheral nerve sheath tumors, which express also S-100 protein must be ruled out. After ruling out these differential diagnoses, the most difficult distinction is between benign versus malignant pheochromocytoma. In fact, in our study, we found some features predictive of a malignant behavior such as the extension to the adipose tissue or vascular invasion only in benign pheochromocytomas. Facing the difficulty in diagnosing MPH, their challenging management and the absence of consensus concerning the prognostic factors, a PASS score was developed by taking the patients whose tumors were clinically and histologically malignant and identifying the histologic features that were uniquely present or present in a greater frequency than in the patients whose tumors were clinically and histologically benign. Features that were present in both benign and malignant tumors were given a lower weight, whereas those identified more frequently in malignant tumors were given a heavier weight. With this endpoint in mind, the weighted scale (PASS) included vascular invasion (1 pt), capsular invasion (1 pt), extension into the periadrenal adipose tissue (2 pt), large nest size or diffuse architecture (2 pts), presence of focal or confluent necrosis (2 pts), high cellularity (2 pts), tumor cell spindling (2 pts), cellular monotony (2 pts), > 3 mitoses per 10 HPF (2 pts), presence of atypical mitotic figures (2 pts), profound nuclear pleomorphism (1 pt), and increased tumor cell hyperchromasia (1 pt). According to many authors, a PASS < 4 identified potential benign tumors and a PASS> =4 identified potentially malignant tumors. Many authors claim that PASS score doesn't allow for clear-cut histological diagnosis of benign and malignant tumors putting emphasis, in some cases, on the significant inter observer and intra observer variation in assignment of PASS with variable interpretation of pathology (23). Others, suppose that tumors with PASS score >= 4 should be followed closely for recurrence and those with PASS score >= 6 are potentially malignant (23). Many authors support the hypothesis that PASS score can help to predict which tumors may portend a more aggressive clinical course by knowing that pheochromocytomas may develop metastases many years after the first tumor. Moreover, some of them believe that there is a lack of an intermediate category in this classification (tumors with intermediate malignant potential) which may be a potential drawback to its application in the clinical setting. In our study, the cutoff value of 4 showed a low sensitivity and specificity. This fact may be secondary to the few number of cases and the low surface area under the ROC curve. Although special studies weren't included in the PASS, the S-100 protein reaction was of interest in the diagnosis of MPA. S100 protein Immunoreactivity was identified in both the nucleus and cytoplasm of the sustentacular cells surrounding the chromaffin cells. Many authors reported a remarkable decrease in the immunohistochemical reactivity of S-100 protein positive cells in malignant cases. Moreover, many authors suppose that the absence of sustenticuar cells in pheochromocytoam is indicative of a greater potential for malignant behavior. Treatment modalities are based on surgical resection followed in some cases by chemotherapy and/or radiation therapy. It is reported that chemotherapy and radiation therapy (including

treatment with I-MIBG) are only of benefit in palliation by improving the hypertensive effects and not in cure or complete remission (16).The management of pheochromocytoma varied according to the genetic evolution. Prior to 2002, germline mutation testing in patients with apparently sporadic pheochromocytoma was not strongly recommended. Current practice recommends the offering of genetic testing to all patients with pheochromocytoma with the following features: relevant family history, younger than 30 y of age, multiple tumors, malignancy and extra-adrenal pheohromocytoma (26). The recognition of a germline mutation is an important part of the overall management of a patient since it directs investigation for other tumors such as hemangioblastoma and renal cell carcinoma in VHL syndrome. The detection of germline mutations will improve postoperative management by providing the clinicians with information on which to base frequency, length of follow up and the most appropriate follow up investigations. PCR and sequencing analysis of a gene of interest remains the current gold standard for the detection of mutations but other less expensive methods have been reported such as the denaturing high performance liquid chromatography (dHPLC) (7). Recently, techniques of immunohistochemistry with antibodies against SDHB have been validated with a sensitivity of 95% and specificity of 84% (27). A decisional diagram has been proposed in order to point out the most reliable gene to analyze in every case (28).

CONCLUSION

The management of malignant pheochromocytoma remains challenging because of the absence of reliable diagnostic histologic features of malignancy. Laboratory tests seem unreliable in making this difference. I think that PASS score, despite its low sensitivity, may help to reserve the more aggressive treatment and narrow follow up for potentially malignant tumors. Widespread of this called score with complete clinical data will help to validate these findings and to add other prognostic factors of value that could be a part of this scaled score such as immunohistochemical findings. The exploration of prognostic factors and the improvement of molecular approach to cancer will help managing these tumors by deciding prophylacting procedures, diagnostic investigations and selecting targeting therapy.

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