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Retrospective application of the pathologic tumor-node-metastasis classification system for pheochromocytoma and abdominal paraganglioma in a well characterized cohort with long-term follow-up

Adam Stenman, MD, PhD[a,b,c,*], Jan Zedenius, MD, PhD[b,c], Carl Christofer Juhlin, MD, PhD[a,d]

[a] Department of Oncology-Pathology, Karolinska Institutet, Karolinska University Hospital, CCK, Stockholm, Sweden
[b] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[c] Department of Breast, Endocrine Tumours and Sarcoma, Karolinska University Hospital, Stockholm, Sweden
[d] Department of Pathology and Cytology, Karolinska University Hospital, Stockholm, Sweden

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ABSTRACT

Background: A pathologic tumor-node-metastasis staging algorithm for pheochromocytoma and sympathetic paraganglioma was introduced recently in the 8th Edition of the cancer staging manual of the American Joint Committee on Cancer. There is no information, however, as to how this staging correlates to well-established clinical cohorts of pheochromocytoma and sympathetic paraganglioma with extensive follow-up.
Methods: We applied the pathologic tumor-node-metastasis staging retrospectively to a cohort of 118 patients with pheochromocytoma and sympathetic paraganglioma, in which the majority has been characterized for susceptibility gene mutations and global mRNA expressional patterns as well as histologic risk criteria using the pheochromocytoma of the adrenal gland scaled score (PASS).
Results: The overall tumor stage correlated with the presence of metastases, disease-related death, and PASS scores as well as established mutational and expressional clusters.
Conclusion: Stage III to IV pheochromocytomas and sympathetic paragangliomas are associated with increased mortality, increased PASS scores, and mutational and expressional aberrancies in the pseudohypoxia pathway cluster. These findings validate the stratification proposed by the American Joint Committee on Cancer staging manual by linking malignancy-associated pheno- and genotypes to more advanced stages. Moreover, because few pheochromocytomas and sympathetic paragangliomas are metastatic at the time of the original presentation, the staging relies heavily on identifying histologic signs of extra-adrenal invasion.

Tumor staging is one of the fundamental cornerstones of modern oncology, and the general concept is based on systematically appreciating the extent of tumors to allow for precise prognostication and treatment. The staging is based on the extent of the primary tumor (T stage), the extent of lymph node metastases (N stage), and the presence of distant metastases (M stage); these factors are then incorporated to a combined tumor-node-metastasis (TNM) system. There are several ways of staging a particular tumor, of which the clinical and pathologic staging types constitute the most commonly used algorithms. In the former (entitled clinical TNM), investigations are based on physical and radiologic examinations, while the latter (pathologic TNM) relies on the pathologic classification via microscopic analyses of excised tumor material. All malignancies have their unique TNM classification, and the combinations of the T, N, and M stages are merged into an overall stage ranging from 0 to IV, in which stage IV identifies patients with the worst prognosis. The staging is developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control.[1,2]

Pheochromocytoma (PCC) and abdominal paraganglioma (PGL), together abbreviated PPGL, are neuroendocrine neoplasms of the adrenal medulla and sympathetic ganglia, respectively. Historically, PPGLs were considered either benign or malignant, although the current World Health Organization classification of endocrine tumors from 2017 recently dictated that all PPGL exhibit malignant potential and suggests that the term malignant

* Reprint requests: Adam Stenman, MD, PhD, Departments of Oncology-Pathology and Molecular Medicine and Surgery, BioClinicum J6:20, Visionsgatan 4, 17164 Solna, Sweden.
E-mail address: Adam.Stenman@ki.se (A. Stenman).

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PPGL should be replaced with metastatic PPGL, because the occurrence of disseminated disease is the only clear-cut evidence of malignancy.[3]

From a genetic standpoint based on mRNA expression analyses in 2011, a 2-cluster, molecular taxonomy system was suggested originally based on the molecular underpinnings, including the pseudohypoxic PPGL in cluster 1 and the kinase-signaling PPGL in cluster 2.[4] This system has been expanded on recently using a comprehensive analysis of the database of the Cancer Genome Atlas that added a Wnt signaling PPGL cluster and other genomic markers that were found associated with metastatic disease, for instance *SDHB, SETD2,* and *ATRX* mutations.[5–7] Moreover, a hypermethylation subtype, *TERT* promoter mutations, telomerase activation, and structural rearrangements of the *TERT* gene have also been described as associated with malignant disease.[7–9]

Building on this taxonomy system, a staging system for PPGLs was introduced recently in the 8th Edition of the AJCC Cancer Staging Manual (Table I),[1] based on a number of studies creating different levels of evidence.[10–14] In this algorithm, the size of the primary tumor was identified as a prognostic risk factor of developing metastases, and a cut-off of 5 cm was chosen to upstage PCCs from T1 to T2. PGLs are automatically assigned a T2 stage irrespectively of tumor size, reflecting the increased risk of malignancy in these neoplasms compared to PCCs.[10,11] In addition, extra-adrenal invasion was recognized as a negative prognostic factor (even stronger than the size of the primary tumor) based on previous publications and thus resulting in a T3 stage. Extra-adrenal invasion includes invasion of the periadrenal adipose tissue as well as direct overgrowth into adjacent organs, such as the liver, pancreas, spleen, or kidneys.[1]

The definition of regional lymph node (N) stage was conventional (N0 for absence of metastases and N1 for presence of metastases), and the distant metastasis staging (M) was constructed similarly, but with a sub-tier in the M1 category depending on location of the metastases (M1a for bone only, M1b for distant lymph nodes, liver, or lung, and M1c for bone plus multiple other sites). Even so, all M1 PPGLs are assigned stage IV irrespectively of the M1 subcategory (Table I).[1] Because patients with PPGLs metastatic to bone only have been found to display improved 10-year survival rates compared to patients with other metastatic sites, this is a plausible effort to stratify the prognosis, not least because the majority of M1a patients are alive 10 years after diagnosis compared to only half of M1b patients and a third of all M1c patients.[12]

Although a most-welcome stratification model, currently there are no large prospective analyses of the current TNM staging of PPGLs available. Here, we retrospectively applied the TNM criteria as proposed by the 8th edition of the Cancer Staging Manual of the AJCC to a cohort of PPGLs with data regarding long-term follow-up data and molecular aberrancies available, with the aim to establish how well the staging correlated with patient outcome.

Table I
Definitions of AJCC TNM (adapted from the AJCC Cancer Staging Manual, 8th edition)

T category	**T criteria**		
TX	Primary tumor cannot be assessed		
T1	PCC <5 cm in greatest dimension, no extra-adrenal invasion		
T2	PCC ≥5 cm or sympathetic PGL of any size, no extra-adrenal invasion		
T3	Tumor of any size with invasion into surrounding tissues		
N category	**N criteria**		
NX	Regional lymph nodes cannot be assessed		
N0	No lymph node metastasis		
N1	Regional lymph node metastasis		
M category	**M criteria**		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Distant metastasis to only bone		
M1b	Distant metastasis to only distant lymph nodes or liver or lung		
M1c	Distant metastasis to bone plus multiple other sites		
When T is…	**And N is…**	**And M is…**	**Then the AJCC stage group is**
T1	N0	M0	I
T2	N0	M0	II
T1	N1	M0	III
T2	N1	M0	III
T3	Any N	M0	III
Any T	Any N	M1	IV

Materials and Methods

The cohort consists of 118 PPGLs (107 PCCs and 11 abdominal PGLs) operated at the Karolinska University Hospital between 1986 to 2017, and an overview of the case series is presented in Table II. All cases were verified by histopathologic investigations performed by an experienced endocrine pathologist. Seven cases (6%) were metastatic either synchronous or metachronous to the diagnosis date. The average follow-up time was almost 11 years (median 8 years), and 76 patients (64%) had a follow-up time exceeding 7 years. Twenty patients were deceased, of whom 5 were associated with advanced disease and the remaining 15 secondary to other causes. Comprehensive molecular data regarding PPGL susceptibility gene mutational status and mRNA expressional profiles (GeneChip Human Gene 1.0 ST arrays, Affymetrix) have been published previously and were available for 71 (60%) of the tumors.[15–17] AJCC stage for each case from the current study was entered into the dataset and differentially expressed genes were identified using the Qlucore Omics Explorer 3.2 software (Lund, Sweden). Additionally, 9 cases with known mutation in the *RET* were included together with 32 sporadic controls in which no mutational screening had been performed.[18] Information regarding individual pheochromocytoma of the adrenal gland scaled score (PASS) was retrieved from previous publications.[18,19]

In this study, we defined malignant behavior as dictated by distant metastases or locally recurrent, grossly infiltrative disease. Metastatic disease was defined as the presence of chromaffin cells in locations not normally harboring these cells (eg, bone, liver, or lung). In our group of PPGLs with malignant behavior (4 PCCs and 4 PGLs), 7 of 8 cases were diagnosed with metastases. Six of the 7 metastatic cases were verified with histology or cytology, and one case with disseminated bone metastases was verified using a highly specific, 11C-metahydroxyephedrine PET scan (Supplementary Table I). We denoted cases as metastatic irrespectively of whether information regarding disseminated disease was acquired synchronously or metachronously to the initial diagnosis to increase the number of stage IV cases. The authors, however, recognize the rather unrealistic setting in which a retrospective TNM classification is suggested for cases with long-term follow-up regarding future metastatic disease; therefore, information regarding a simulated upfront TNM was included in which data for synchronous metastatic disease only was considered (Table II).

Results

Cohort description

The results of the retrospective TNM application are summarized in Table II and illustrated in Figs 1 and 2. In total, 54 PPGLs

Table II
Clinical characteristics and AJCC staging analysis in PPGL

Parameter	No.	AJCC			
		Stage I	Stage II	Stage III	Stage IV
Tumor type					
PPGL	118	54	47	10	7
PCC : PGL	107 : 11	54 : 2	44 : 3	5 : 5	4 : 3
Evidence of metastasis					
PPGL, no : yes	111 : 7	54 : 0	47 : 0	10 : 0	0 : 7
PCC, no : yes	103 : 4	54 : 0	44 : 0	5 : 0	0 : 4
PGL, no : yes	8 : 3	0 : 0	3 : 0	5 : 0	0 : 3
Evidence of synchronous metastasis					
PPGL, no : yes	111 : 7	54 : 0	47 : 0	10 : 4	0 : 3
PCC, no : yes	103 : 4	54 : 0	44 : 0	5 : 3	0 : 1
PGL, no : yes	8 : 3	0 : 0	3 : 0	5 : 1	0 : 2
Outcome					
Dead of disease : alive or dead of other cause	5 : 113	0 : 54	0 : 47	0 : 10	5 : 2
PASS					
PASS mean (range)	2.9 (0–12)	2.3 (0–7)	2.4 (0–8)	4.5 (2–9)	8.4 (4–12)
PASS <4 : ≥4	79 : 39	41 : 13	35 : 12	3 : 7	0 : 7
Tumor size					
PPGL, <5 cm : >5 cm	64 : 54	54 : 0	2 : 45	6 : 4	2 : 5
PCC, <5 cm : >5 cm	57 : 50	54 : 0	0 : 44	3 : 2	0 : 4
PGL, <5 cm : >5 cm	7 : 4	0 : 0	2 : 1	3 : 2	2 : 1
Mean (range) mm	50 (20–160)	32 (10–45)	68 (45 –160)	44 (20–40)	78 (30–120)
Follow-up time					
Mean, y	11	11	11	14	7
Median (range), y	8 (0–31)	8 (0–30)	9 (0–31)	15 (3–26)	7 (0–13)
Age at diagnosis					
Mean, y	55	54	57	59	47
Median (range), y	57 (14–83)	54 (24–82)	57 (14–83)	63 (25–76)	42 (26–80)
Sex					
Female : male	64 : 54	27: 27	30 : 17	4 : 6	3 : 4

were assigned as pT1 (acquiring stage I), 47 were assigned as pT2 (stage II), and 10 were assigned pT3 (stage III) due to extra-adrenal invasion. Moreover, 7 cases were assigned as stage IV tumors (pT1 tumors; $n = 0$, pT2 tumors; $n = 5$, and pT3 tumors; $n = 2$), all with synchronous or metachronous distant metastatic disease (M1a; 2 cases, M1b; 4 cases, M1c; 1 case, Supplementary Table I).

The upfront TNM (only including synchronous evidence of distant metastases as an accepted criterion for an M1 stage) is summarized in Table II. Using this approach, 4 cases designated previously as stage IV PPGLs were downgraded to stage III (Table II).

Coupling of clinical and molecular parameters to the retrospective TNM application

As expected, the AJCC overall cancer stage correlated with the presence of metastatic disease and death of disease (Pearson χ^2 $P <$ .001 for both associations). Additionally, correlations were noted for both mutational and expressional clusters (Pearson χ^2 $n = 86$, $P = .0014$ and $n = 71$, $P = .0010$, respectively), indicating an overrepresentation of aberrancies in cluster 1 (pseudohypoxia cluster) among high-stage PPGLs (stage III and IV). Moreover, the overall stage was also coupled to the total PASS, in which low-stage PPGLs displayed lesser scores than high-stage PPGLs (Kruskal-Wallis $P <$ .001, Fig 1, *A*), which also was present in PCCs alone (Kruskal-Wallis $P = .007$, Fig 1, *B*). There was also a correlation between low stages and *RET* mutations (Pearson χ^2 $P =$ .034), indicating that mutations in this gene were associated with low stage PPGLs. No correlations were found between overall stage and sex, age at diagnosis, or other commonly mutated genes (*SDHB*, *EPAS1*, *NF1*). When assessing a possible coupling between preoperative biochemical status to patient outcome, a correlation between dopamine production and death from disease was found ($P = .026$, $n = 22$, Fisher exact test). Indeed, 2 of 4 patients with dopamine-producing tumors succumbed to the disease. No correlations between biochemical status and outcome were seen for epinephrine or norepinephrine ($P = 1$ for both analyses, Fisher exact test).

The mRNA expression data from 71 PPGL were analyzed with multiple linear regression analysis for correlation with AJCC stages I to IV. Of all analyzed genes, *Chromogranin B (CHGB)* had the strongest correlation to AJCC stage (noncorrected $P <$ .001, linear regression analysis, Fig 1, *E*), with lesser expression with increasing AJCC stage. Other genes found top correlate with correlation to AJCC stage include *PCSK2*, *MAPK13*, and *PCHD9* (downregulated), together with *NRIP1*, *FRMD5*, and *REN* (upregulated; Fig 1, *E*) to name a few.

Kaplan-Meier analyses are demonstrated in Fig 2, displaying worse survival in stage IV PPGLs compared to all other stages (Fig 2, *A*, log-rank $P <$ .001), as well as for PCCs alone (Fig 2, *B*, log-rank $P <$ .001 for both).

Coupling of clinical and molecular parameters to the simulated upfront TNM application

By staging the PPGL cohort without information regarding subsequent distant metastatic disease, 4 cases designated previously as stage IV PPGLs were downgraded to stage III (Table II). The AJCC overall tumor stage correlated with the presence of metastatic disease and death of disease (Pearson χ^2 $P <$ .001 for both associations), and correlations were found for both mutational and expressional clusters (Pearson χ^2 $n = 86$, $P = .0019$ and $n = 71$, $P =$ .0012, respectively) also with the upfront TNM approach. Furthermore, the overall stage was coupled to the total PASS, (Kruskal-Wallis $P <$ .001, Fig 1, *C*), which also was present in PCCs alone (Kruskal-Wallis $P = .013$, Fig 1, *D*). A Kaplan-Meier analysis was also performed, indicating worse survival in stage III and IV PPGLs compared with stage I and II cases (log-rank $P <$ .001, Fig 2, *C* and *D*).

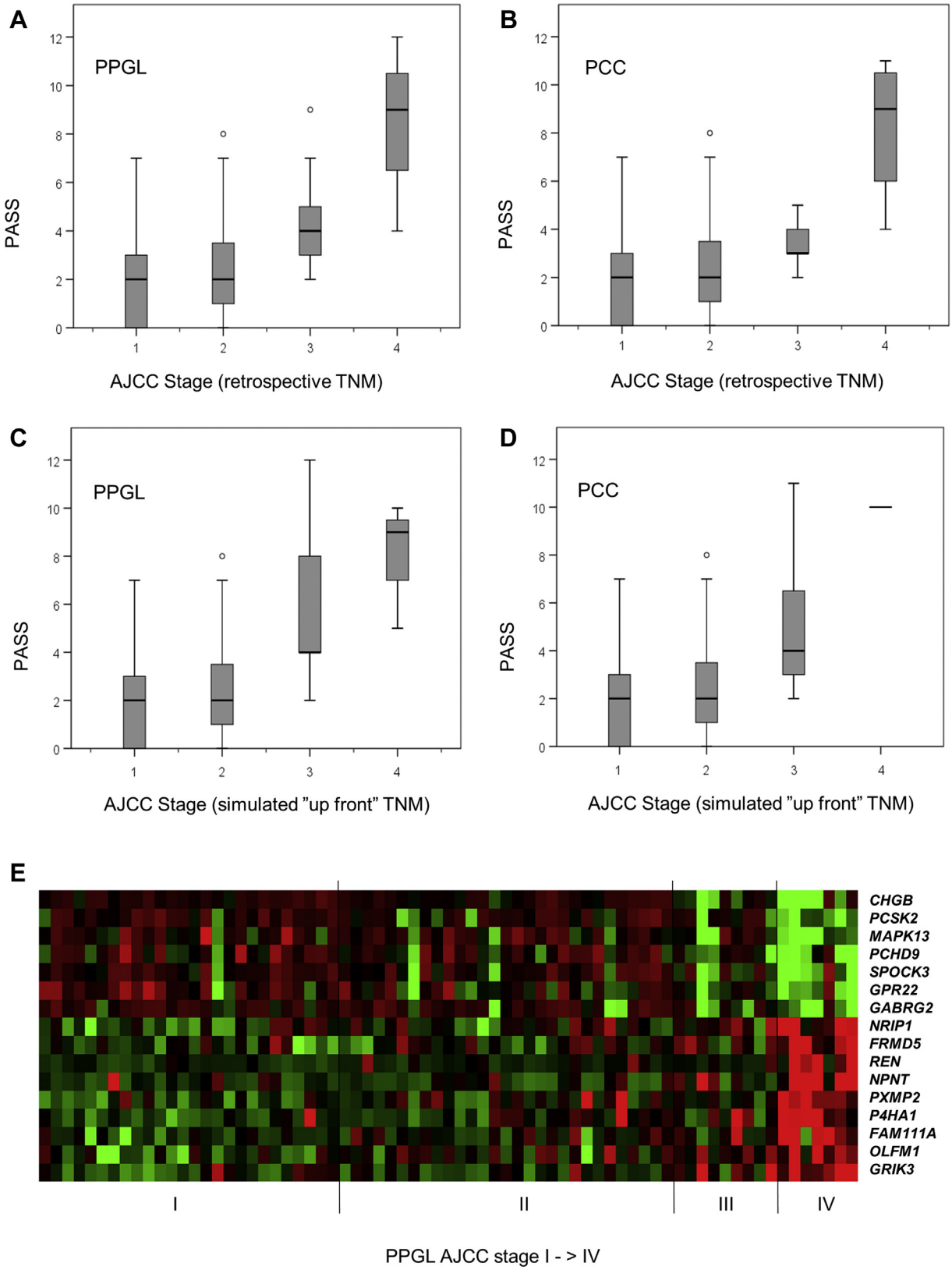

Fig 1. Associations between histologic prediction of malignant potential using the PASS algorithm and AJCC overall staging of PPGLs. (*A*) Retrospective application of cancer staging to PPGLs is significantly coupled to PASS scores. Low-stage PPGLs display lesser scores than high-stage PPGLs (Kruskal-Wallis $P < .001$). (*B*) Same correlation but only including PCCs for which the PASS algorithm was originally designed (Kruskal-Wallis $P = .007$). (*C*) Simulated upfront application of the TNM criteria only counting synchronous (and not future) metastases, with the overall stage coupled to PASS scores, (Kruskal-Wallis $P < .001$). (*D*) Same approach for PCCs alone (Kruskal-Wallis $P = .013$). (*E*) mRNA expression profiles of 71 PPGLs, presented in a heatmap made by linear regression analysis by AJCC stage, and sorted by AJCC stage from I (left) to IV (right) and by the difference for the most significantly up- and downregulated genes. *PASS*, pheochromocytoma of the adrenal gland scaled score; *PCC*, pheochromocytoma; *PPGL*, pheochromocytoma and abdominal paraganglioma; *AJCC*, American Joint Committee on Cancer; *TNM*, tumor-node-metastasis.

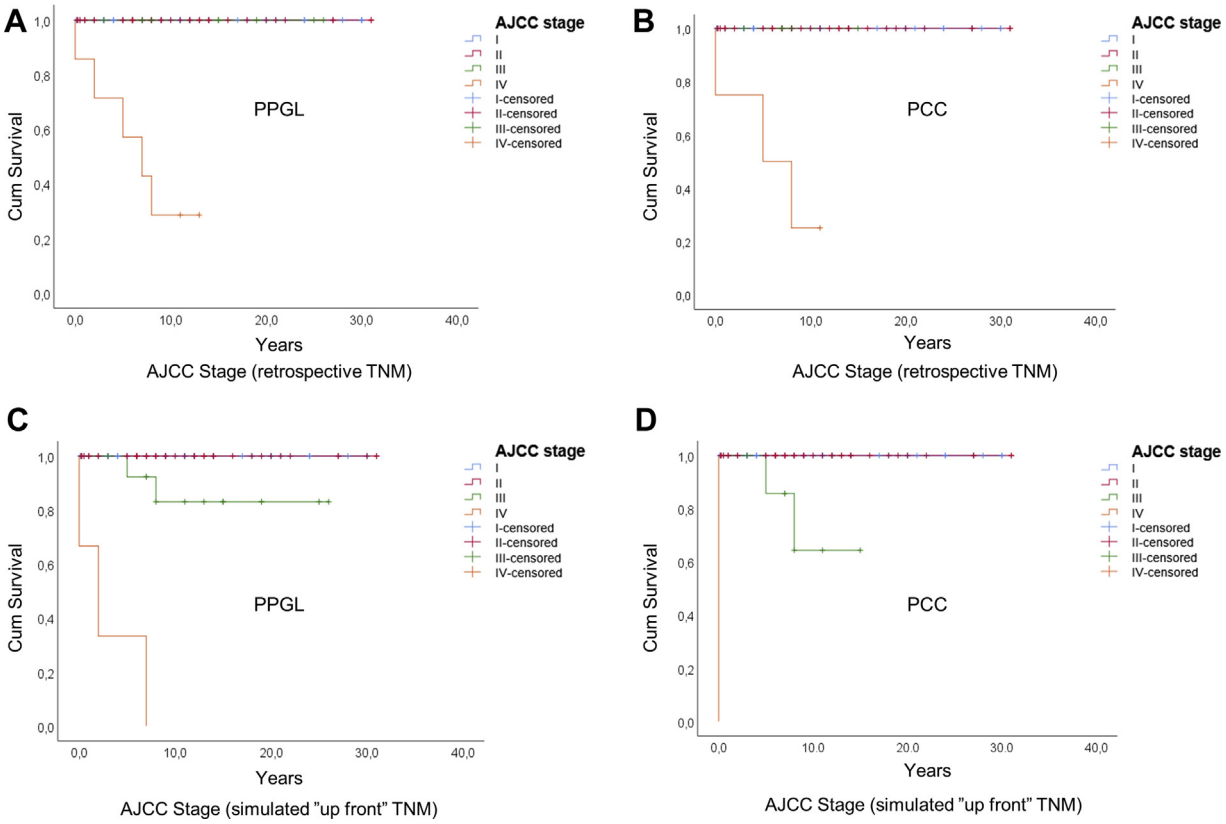

Fig 2. Kaplan-Meier analyses of PPGLs stratified by the AJCC stages. (*A*) Retrospective application of the TNM criteria revealing stage IV PPGLs displaying worse survival compared to all other stages (log-rank $P < .001$). (*B*) Same correlation, but only including PCCs (excluding PGLs). Stage IV PCCs exhibit worse survival compared to all other stages (log-rank $P < .001$). (*C*) Simulated up front application of TNM criteria (only allowing information about synchronous metastasis) indicating worse survival in stage III and IV PPGLs compared to stage I and II cases (log-rank $P < .001$). (*D*) Simulated up front application of TNM criteria (only allowing information about synchronous metastasis) on PCCs alone (excluding PGLs) showing worse survival in stage III and IV PCCs compared to stage I and II cases (log-rank $P < .001$). *PCC,* pheochromocytoma; *PPGL,* pheochromocytoma and abdominal paraganglioma; *AJCC,* American Joint Committee on Cancer; *TNM,* tumor-node-metastasis.

Discussion

Given the recent implementation of the TNM staging for PPGLs, there are no prospective data sets available to the scientific community in which the possible impact of the staging as well as the coupling with patient outcome is detailed. Given the rarity of PPGLs even in high-volume endocrine surgery centers, we will probably be dependent of national and international collaborations to collect statistically powerful number of cases for an extensive evaluation of staging and survival data, with the risk of mingling heterogeneous data stemming from various institutions with local differences in treatment protocols and follow-up regimes. To partially counter this, we applied the TNM staging retrospectively to a large cohort of PPGLs with long-term follow-up available. By doing so, we show that the current TNM classification algorithm identifies correctly the high-risk cases as stage III and IV tumors, as PPGLs with these stages were lethal and coupled to increased PASS on histologic examination as well as distinct molecular signatures usually overrepresented among metastatic PPGLs. These findings are expected given the coupling between stage IV and metastatic disease, but nevertheless, have not yet been proven, because the advent of the TNM classification model was introduced in 2017.

We also simulated an upfront setting in which a TNM was applied retrospectively with only synchronously available information. By doing so, most of our stage IV PPGLs were immediately down-staged to stage III. This difference reflects the clinical dilemma of PPGLs, in which distant metastases often are detected many years postoperatively, indicating that PPGLs with an initial stage IV will be encountered only rarely. Both the timing and the location of metastases have been considered as important determinants of prognosis, because patients with synchronous metastases to other organs than bone exhibit a worse outcome.[10,12] Stage III PPGLs are neoplasms with either regional lymph node metastases extra-adrenal invasion, or both. In our material, the acquisition of stage III was only due to extra-adrenal invasion (10 out of 10 cases) using the retrospective TNM approach, and in 12 out of 14 cases using the upfront TNM application. Not a single case displayed direct overgrowth into adjacent organs, but instead the extra-adrenal invasion was proven by the histologic manifestation of infiltration into periadrenal adipose tissue. Therefore, in our cohort, of the pT3 PPGLs with invasion of adipose tissue, 2 of the 14 patients would later develop distant metastases, indicating that patients with radically resected stage III tumors should be monitored closely in the clinical setting. This finding indicates further that the microscopic finding of extra-adrenal invasion is a central prognostic feature and signifies the importance of carefully conducted histopathology, and also indicates that elements from both the pathologic TNM (microscopic findings) and clinical TNM (clinical investigations) are needed to fully characterize these lesions from a staging viewpoint.

PPGLs are tumors known for their high proportion of heredity, and appraising malignant potential in these lesions is notoriously difficult. This difficulty is especially true, because hereditary cases might present with multifocal primary tumors, which might mimic histologic features of malignant behavior. In our study, the majority of malignant PPGLs were defined due to the occurrence of

distant metastases, and only a single case was listed as malignant due to grossly infiltrative, recurrent disease (Supplementary Table I). Therefore, we think that our cohort is well-characterized in terms of malignant properties, even though the number of malignant cases is small, which constitutes a natural consequence of the indolent nature of most PCCs. Albeit the number of patients who actually died of disease is low in our series, we were still able to detect statistically significant differences in overall survival in stage IV patients compared to other stages. Hypothetically, an even larger cohort might give us the opportunity to detect associations between outcomes among lower stage groups, not mirrored by the lack of obvious differences between AJCC stages I and II in terms of patient outcome, indicating that these stages should indicate a low-risk tumor. Even though allocating patients to either stage I or stage II seem to have little prognostic relevance based on our findings, larger studies conducted in the future might be able to discern an eventual difference in terms of patient outcome.

We found a specific expressional profile in tumors presenting with advanced AJCC stages, which indicates that one or several gene products within this cluster might serve as prognostic markers. The *CHGB* gene, which was identified recently as the most markedly altered gene associated with total PASS as well as the presence of distant metastases,[19] had the strongest correlation to AJCC stage in this study, with lesser expression in PPGLs with higher AJCC stages. In addition, previous analyses using data derived from the Cancer Genome Atlas database have also revealed *CHGB* as downregulated in relapsing PPGLs and PCCs.[19] In all, these findings validate the present stratification of the AJCC model, because molecular events coupled to metastatic potential in PPGLs also show a clinically important association to higher TNM stages. This in turn indicates that high-stage PPGLs display a distinct global gene expressional profile that sets them apart from stage I to II tumors, to some extent possibly reflecting the deregulation of molecular biologic processes coupled to tumor progression. Indeed, the observed downregulation of the cancer-associated genes *Proprotein Convertase Subtilisin/Kexin Type 2* (*PCSK2*) and *Mitogen-Activated Protein Kinase 13* (*MAPK13*) in stage III-IV PPGLs could merit further attention, given the association between *PCSK2* and pituitary adenomas as well as the coupling between MAPK13 and the microtubule regulator stathmin, the latter being a dysregulated protein in PPGLs.[20,21]

We conclude that the retrospective application of the newly proposed TNM classification identify correctly the poor-prognosis cases and validate the coupling between stage III and IV PPGLs and histologic and molecular risk signatures. Because very few PPGLs were metastatic at initial presentation, the up-staging of subsequent lethal tumors was dependent on the identification of invasion of periadrenal adipose tissue.

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Authors' contributions

Conception and design (AS, CCJ), acquisition of data (AS, CCJ), analysis and interpretation of data (AS, CCJ, JZ), drafting of manuscript (AS, CCJ) and critical revision of manuscript (JZ).

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies on animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Disclosure

The authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.04.030.

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