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Clinical Research Article

Surveillance Improves Outcomes for Carriers of *SDHB* Pathogenic Variants: A Multicenter Study

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Abstract

Context: Carriers of succinate dehydrogenase type B (SDHB) pathogenic variants (PVs) are at risk of pheochromocytoma and paraganglioma (PPGL) from a young age. It is widely recommended carriers enter a surveillance program to detect tumors, but there are limited studies addressing outcomes of surveillance protocols for *SDHB* PV carriers.

Objective: The purpose of this study was to describe surveillance-detected (s-d) tumors in *SDHB* PV carriers enrolled in a surveillance program and to compare their outcomes to probands.

Methods: This was a multicenter study of *SDHB* PV carriers with at least 1 surveillance episode (clinical, biochemical, imaging) in Australian genetics clinics. Data were collected by both retrospective and ongoing prospective follow-up. Median duration of follow-up was 6.0 years.

Results: 181 *SDHB* PV carriers (33 probands and 148 nonprobands) were assessed. Tumors were detected in 20% of nonprobands undergoing surveillance (age range 9-76 years). Estimated 10-year metastasis-free survival was 66% for probands and 84% for nonprobands with s-d tumors ($P = .027$). S-d tumors were smaller than those in probands (median 27 mm vs 45 mm respectively, $P = .001$). Tumor size ≥40 mm was associated with progression to metastatic disease (OR 16.9, 95% CI 2.3-187.9, $P = .001$). Patients with s-d tumors had lower mortality compared to probands: 10-year overall survival was 79% for probands and 100% for nonprobands ($P = .029$).

Conclusion: *SDHB* carriers with s-d tumors had smaller tumors, reduced risk of metastatic disease, and lower mortality than probands. Our results suggest that *SDHB* PV carriers should undertake surveillance to improve clinical outcomes.

Key Words: SDHB, succinate dehydrogenase, pheochromocytoma, paraganglioma

Abbreviations: ^{18}F-FDG-PET/CT, ^{18}F-fludeoxy glucose positron emission tomography computed tomography; APGL, abdominal paraganglioma; GIST, gastrointestinal stromal tumor; HNPGL, head and neck paraganglioma; MRI, magnetic resonance imaging; PC, pheochromocytoma; PoWH, Prince of Wales Hospital; PPGL, pheochromocytoma and paraganglioma; PV, pathogenic variant; RCC, renal cell carcinoma; RHH, Royal Hobart Hospital; s-d, surveillance-detected; RNSH, Royal North Shore Hospital; ROC, receiver operated curve; SDHB, succinate dehydrogenase type B; TPGL, thoracic paraganglioma.

Carriers of *succinate dehydrogenase type B* (*SDHB*) pathogenic variants (PVs) are at risk of pheochromocytoma and paraganglioma (PPGL), renal cell carcinomas (RCCs), and gastrointestinal stromal tumors (GISTs) from a young age (1). It is widely recommended carriers enter a surveillance program to detect tumors, as metastatic disease is associated with high mortality (2, 3). However, there are limited studies addressing outcomes of surveillance protocols for *SDHB* PV carriers.

A recent international Delphi consensus study recommended asymptomatic *SDHB* PV carriers commence surveillance for tumors from as young as age 6-10 years; baseline assessment should include clinical history for catecholaminergic symptoms, blood pressure, either plasma or urinary metanephrine and normetanephrine, and magnetic resonance imaging (MRI) of head and neck, thorax, abdomen, and pelvis and the option of functional imaging in adulthood (4). These guidelines recommended ongoing assessment, after a first negative initial surveillance, with annual clinical examination, biennial biochemical testing, and MRI every 2 to 3 years and/or functional imaging in adulthood (4).

The goal of surveillance is to detect *SDHB*-associated tumors early enough for curative surgical resection, since large

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tumor size is associated with metastatic progression (5-9). A multicenter European study of patients with metastatic PPGL reported primary tumor size was ≥5 cm in 76% of cases (5). Single-center studies from the United States have reported PPGL cut-offs of 4 cm (6), 4.5 cm (7), 5 cm (8), and 6.1 cm (9) are associated with metastatic disease in *SDHB* PV carriers. Tumor location also impacts on risk of metastatic disease. Head and neck paragangliomas (HNPGLs) tend to have a lower risk of metastatic progression than *SDHB*-associated abdominal or pelvic PPGLs (12% vs 33%) (10), and when metastases occur the disease course is often indolent (11).

The purpose of this study was to describe surveillance-detected (s-d) tumors in *SDHB* PV carriers undergoing surveillance compared with probands by (1) describing the nature of *SDHB*-associated tumors detected during surveillance; and (2) investigating case detection strategies that are helpful in detecting *SDHB*-related tumors and whether these translate into improved outcomes.

Materials and Methods

This was a multicenter observational cohort study of *SDHB* PV carriers with at least 1 surveillance episode (clinical, biochemical, imaging) in genetics clinics at Royal North Shore Hospital (RNSH), Prince of Wales Hospital (PoWH), and Royal Hobart Hospital (RHH) in Australia. Clinical data from medical records were collected by both retrospective and ongoing prospective follow-up using a bespoke data extraction form developed in Research Electronic Data Capture (REDCap) (12) software. Retrospective data were collected from July 2000 at RNSH, September 1994 at PoWH, and February 2002 at RHH up to September 29, 2019. Ongoing prospective data collection has been performed since September 30, 2019, with most recent data collection performed on August 10, 2021.

The data extraction form was tailored to the surveillance protocol at each site, but also had capacity to record types and frequencies of biochemical or imaging surveillance that differed to the standard protocol if relevant to that participant. Annual clinical assessment of symptoms, blood pressure, and biochemical measurements of plasma metanephrines or urinary catecholamines were included in surveillance protocols of all 3 centers. At RHH, biochemical assessment also included annual chromogranin A measurement, and imaging surveillance consisted of biennial MRI from base of skull to coccyx and, after age 18, of 4 yearly ^{18}F-fludeoxy glucose positron emission tomography computed tomography (FDG-PET/CT) alternating with 4 yearly neck and abdominal ultrasounds (13). RNSH and PoWH followed the Cancer Institute NSW guidelines for biennial MRI from base of skull to coccyx (14). After age 18, 5-yearly functional imaging with either ^{68}Ga-DOTATATE PET/CT or ^{18}F-FDG-PET/CT was included as clinically appropriate.

Probands were defined as the first individual in a family to be diagnosed with a *SDHB* PV after presenting with a tumor, and for this cohort were always the index case. S-d tumors were defined as tumors detected in nonprobands during surveillance. These were classified either as "clinical" s-d tumors if detected as part of familial surveillance prior to formal genetic diagnosis of *SDHB* PV, in other words before the advent of routine *SDHB* genetic testing, or "genetic" s-d tumors if diagnosed following predictive genetic diagnosis. Incidence density of s-d tumors was defined as the total number of new tumors over the person-time at risk contributed by each participant during the period of surveillance. Incidence was reported as number of tumors per 100 person-years. Genotypes were classified as loss of function (nonsense, splicing, deletion, or frameshift) or missense variants. Tumor diagnosis and size were obtained from histopathology reports, or from radiological appearance in combination with biochemistry if the tumor was not resected. "Classic" symptoms (ie, those typically associated with catecholamine excess) were defined as headaches, palpitations, or excessive sweating and were recorded systematically in the clinical records at each site: The majority of clinic visits recorded presence or absence of headaches, palpitations, or sweats and where absent were classified as not available. Poor adherence was defined as either attending only 1 follow-up visit or 2 or more years between surveillance episodes. Loss to follow-up was defined as 2 or more years since the last follow-up episode. Ethics approval was obtained from the Northern Sydney Local Health District Ethics Committee for RNSH and PoWH (ref. 2019/ETH09870) and from Tasmania Health and Medical Human Research Ethics Committee for RHH (ref. H0018520).

Statistical analysis was performed using GraphPad Prism version 7.03 and IBM SPSS version 26. Descriptive statistics were performed with numerical data presented as median and range. Groups were compared using the Mann–Whitney test for nonparametric data. Cumulative frequency analysis was conducted on s-d tumors to represent the timing of tumor diagnosis during surveillance. Sensitivity, specificity, positive predictive value, and negative predictive value of clinical, biochemical, and imaging methods of tumor detection were calculated using the Wilson–Brown method to compute 95% CI and Fisher's exact test to determine statistical significance. Predictors of disease diagnosis, metastatic disease, and mortality were assessed using a generalized linear model with binary logistic regression to perform a multivariate analysis. Explanatory variables included in this model were sex, genotype, history of smoking, classic symptoms, hypertension, age at first surveillance episode, tumor size, Ki-67, tumor location, tumor functional status (defined as production of catecholamines noradrenaline, adrenaline, dopamine or nonfunctioning), multifocality, and synchronous metastases. Significant predictors in the main effects model were then assessed for interaction. We estimated metastasis-free survival and overall survival of probands and nonprobands by Kaplan–Meier analysis in patients with any *SDHB*-associated tumors and in a subgroup of patients with thoraco-abdominal PPGLs. Receiver operated curve (ROC) analysis of tumor size for prediction of metastatic disease was presented as area under the curve with an area of 0.7 considered acceptable and a Youden's index determined based on the optimal value that maximized the sum of sensitivity and specificity. Cox proportional hazards regression was also performed to examine the impact of tumor size and risk of probands compared with nonprobands for metastatic progression and risk of a second primary tumor. $P \leq .05$ was considered to be statistically significant.

Results

Baseline Characteristics

This cohort includes 181 *SDHB* PV carriers from 59 families undergoing routine clinical surveillance (Table 1): 92 (51%)

from RHH, 50 (27%) from RNSH, and 39 (22%) from PoWH. There were 33 (18%) probands and 148 (82%) nonprobands. Median age at first surveillance for nonprobands was 33 years (range 1-81 years) and 84 (46%) were male. One proband and 3 nonprobands had poor adherence to surveillance. Median duration of follow-up was 6.0 years and was not different between probands and nonprobands. Nonprobands had 1059 person-years of follow-up. Of the total cohort, 110 (61%) had at least 5 years of follow-up, 54 (30%) had at least 10 years of follow-up, 24 (13%) had 15 years, and 5 (3%) had 20 years follow-up. Twenty (11%) carriers were lost to follow-up.

The Nature of *SDHB*-associated Tumors Detected During Surveillance

Surveillance-detected tumors

Tumors were detected in 29 (20%) of 148 nonprobands during surveillance (Table 2 and Fig. 1A). The incidence of s-d tumors was 1.3 cases per 100 person-years (95% CI 0.7-2.3 per 100 person-years). Twenty-two (15%) of 148 nonprobands had their first surveillance aged ≤10 years. The youngest age of first surveillance was at age 1 year. The youngest age of a s-d tumor was a bladder paraganglioma diagnosed at age 9 years. Seventeen (11%) of the 148 nonprobands had a final age of follow-up after 70 years of age, and 3 (2%) nonprobands had follow-up after age 80 years. The oldest age of a s-d tumor was an asymptomatic gastric GIST detected at age 76. The age of case detection of the 29 nonprobands with s-d tumors is represented in Fig. 2.

Clinical surveillance-detected tumors

Twelve (41%) of 29 nonprobands with disease had "clinical" s-d tumors, defined as tumor detected as part of familial surveillance but prior to formal predictive genetic diagnosis of an *SDHB* PV (Table 2). Four (33%) patients with clinical s-d tumors had tumors smaller than 40 mm and 1 (8%) had a tumor under 20 mm. Of the 8 nonprobands with clinical s-d tumors whose records on symptoms were available, 5 (63%) had classic symptoms consistent with elevated catecholamines, 2 had hearing loss in the context of HNPGL, and only 1 patient was asymptomatic.

Six (50%) of 12 patients with clinical s-d tumors had tumors resected and are in remission at most recent follow-up. One (8%) patient has a persistent localized HNPGL despite surgical excision. Four (33%) patients had metachronous tumors: 1 (8%) had a metachronous abdominal paraganglioma (APGL) resected and is in remission, 2 (17%) patients had an abdominal PGL resected but have persistent localized HNPGLs, and 1 (8%) patient has persistent localized HNPGLs. One (8%) patient developed recurrence of HNPGL and subsequently metastatic disease. One (8%) patient with clinical s-d tumor died from disease.

Genetic surveillance–detected tumors

Seventeen (57%) of 30 nonprobands with disease had "genetic" s-d tumors, defined as tumors diagnosed following predictive genetic diagnosis (Table 2 and Fig. 1B). Six patients had tumors diagnosed at the initial surveillance (35% of all genetic s-d tumors; Table 2). The remaining 11 (65%) patients with genetic s-d tumors had tumors detected at 3 to 152 months following the initial surveillance episode, of which 1 was a synchronous GIST and APGL. Notably 11 patients (65%) with genetic s-d tumors had tumors smaller than 40 mm and 7 (41%) patients had tumors smaller than 20 mm. Ten (59%) patients with genetic s-d tumors were asymptomatic. One patient had a 14 mm prolactinoma without suprasellar or cavernous sinus extension. Eleven patients (65%) with genetic s-d tumors had tumors resected and are in remission at most recent follow-up. Five (29%) have persistent localized disease (1 thoracic paraganglioma [TPGL], 1 pituitary adenoma, 2 HNPGL, 1 APGL) and 1 patient has metastatic disease. None of the patients with genetic s-d tumors experienced recurrence, a metachronous tumor, or death from disease at most recent follow-up.

Case Detection Strategies Helpful in Detecting *SDHB*-related Tumors and Translating Into Improved Clinical Outcomes

Method of detection of tumors and tumor size

To describe the methods by which tumors were detected, we then reviewed data on all 82 tumors detected in these 62 patients (33 probands and 29 nonprobands; Supplemental Table 1 (15)). Forty (65%) patients had 49 diagnoses of thoraco-abdominal PPGL (9 pheochromocytoma [PC], 4 TPGL, and 38 APGL). Data on tumor functional status were available for 38 thoraco-abdominal PPGLs. Twenty-nine (76%) secreted noradrenaline of whom 21 (72%) had classic symptoms. Three (8%) secreted adrenaline of whom 2 had classic symptoms and 6 (16%) were apparently nonfunctional of whom 1 reported classic symptoms. Of those whose tumor functional status were unavailable, 9 (18%) had unavailable data from the 1990s and 2 (4%) patients were probands who entered surveillance following surgery at another center where PPGL had not been suspected (of whom 1 survived an intraoperative hypertensive crisis). Median maximal tumor diameter was 40 mm (range 25-90 mm), 43 mm (range 35-75 mm), and 41 mm (range 8-190 mm) for PC, TPGL, and APGL respectively. Tumors were detected by functional imaging followed by directed anatomical imaging in 3 HNPGL, 2 PC, 1 TPGL, and 8 APGL (Supplemental Table 1 (15)). When we compared the size of tumors detected before and after the introduction of functional PET imaging, the difference was not significant albeit possibly limited by power (median 34 vs 23 mm, $P = .15$; Supplemental Table 2 (15)). The sensitivity and specificity of diagnostic modalities for detection of sympathetic PPGL are shown elsewhere (Supplemental Table 3 (15)).

Twenty (32%) patients had 23 diagnoses of HNPGL of whom 5 (25%) reported classic symptoms typically associated with catecholamine excess. Two (10%) patients with classic symptoms had concomitant APGL, but 3 (15%) curiously had classic symptoms of headaches, palpitations, or sweats despite absence of biochemical catecholamine excess. Median HNPGL tumor diameter was 23 mm (range 3-65 mm). Seven (35%) HNPGLs were detected smaller than 20 mm and imaging modalities of detection for these small tumors were 1 ultrasound, 5 MRI, and 4 ^{68}Ga-DOTATATE PET/CT scans. The sensitivity and specificity of diagnostic modalities in this cohort for detection of HNPGL are shown elsewhere (Supplemental Table 4 (15)).

Other *SDHB*-associated tumors are shown in Table 2. GIST tumor size was median 55 mm (range 36-60 mm). The imaging modalities for detection of GIST were 1 ultrasound, 2 CT, 2 MRI, and 2 ^{18}F-FDG-PET/CT scans. RCC tumor size was median 41 mm (range 25-167 mm) and CT-detected RCC in these cases. Finally, 1 pituitary adenoma was detected on MRI measuring 14 mm diameter.

Table 1. Baseline characteristics

	Complete cohort (n = 181)	Probands (n = 33)	Nonprobands (n = 148)	*P* value
Age at first surveillance, years; median (range)	33 (1-81)	35 (9-70)	33 (1-81)	.68
Male; n (%)	84 (46)	17 (52)	67 (45)	.50
Probands; n (%)	33 (18)	—	—	—
Genotype; n (%)				
Missense	57 (31)	9 (27)	48 (32)	.52
Nonsense	43 (24)	10 (30)	33 (22)	
Splicing	35 (19)	3 (9)	32 (22)	
Deletion	43 (24)	10 (30)	33 (22)	
Duplication	2 (1)	1 (3)	1 (1)	
Not available	1 (0.5)	0	1 (1)	
Country of birth; n (%)				
Australia	155 (86)	26 (79)	129 (87)	.86
UK	5 (3)	1 (3)	4 (3)	
Malaysia	1 (0.5)	1 (3)	0	
Philippines	2 (1)	2 (6)	0	
Brazil	2 (1)	0	2 (1)	
The Netherlands	2 (1)	1 (3)	1 (1)	
South Africa	1 (0.5)	0	1 (1)	
Not available	13 (7)	2 (6)	11 (7)	
Smoking status				
Nonsmoker; n (%)	95 (52)	19 (58)	76 (51)	.76
Current smoker; n (%)	29 (16)	4 (12)	25 (17)	
Past smoker	27 (15)	7 (21)	20 (14)	
Not available; n (%)	30 (17)	3 (9)	27 (18)	
Occupation; n (%)				
Student	49 (27)	3 (9)	46 (31)	.22
Professional	33 (18)	9 (27)	24 (16)	
Clerical, sales and service worker	12 (7)	2 (6)	10 (7)	
Laborer	11 (6)	3 (9)	8 (5)	
Manager	10 (5.5)	3 (9)	7 (5)	
Tradesperson	10 (5.5)	3 (9)	7 (5)	
Retired	7 (4)	0	7 (5)	
Full time parent	4 (2)	0	4 (3)	
Production and transport worker	2 (1)	0	2 (1)	
Disability support pension	1 (0.5)	1 (3)	0	
Not available	42 (23)	9 (27)	33 (22)	
Duration of ongoing follow-up, years; median (range)	6.0 (1 month-25.6 years)	8.1 (14 month-25.6 years)	5.9 (1 month-23.9 years)	.08

Predictors of disease diagnosis

Male gender, classic symptoms (headaches, palpitations, or sweats), absence of hypertension, and young age were associated with tumors on a generalized linear model with binary logistic regression (Table 3). However, there were multiple interactions in the model. Male gender was associated with absent symptoms ($P = .023$) and normal blood pressure ($P = .010$) while female gender was associated with younger age at first presentation ($P = .007$). There was no interaction between classic symptoms and hypertension ($P = .810$). Younger age was associated with normal blood pressure ($P = .003$), suggesting that young age rather than normal blood pressure was a predictor of disease. The age of disease diagnosis for females was median 34 years (range 9-72) and for males was median 41 years (range 9-76). Overall median age of diagnosis was 37 years (range 9-76). A generalized linear model with binary logistic regression for predictors of thoraco-abdominal PPGL was unable to be obtained due to sample size and therefore quasi-complete separation in the data. Probands had higher numbers of APGLs and overall *SDHB*-associated tumors than nonprobands with disease ($P = .002$ and $P = .03$ respectively, Table 2). Probands were more likely to develop multifocal disease over time than nonprobands (OR 3.28, 95% CI 1.02-9.74, $P = .046$) but were not more likely to have multifocal disease at baseline ($P = .68$). Cox proportional hazard assessment found the risk of a second tumor was not determined by primary tumor size 40 mm or larger (HR 2.61, 95% 0.69-9.87, $P = .157$). No other factors were able to predict

Table 2. *SDHB* PV carriers with disease diagnoses (n = 62): tumor types

	Probands (n = 33)	Nonprobands with s-d tumors (n = 29)	*P* value
HNPGL (n)	9	14	.16
PC (n)	7	2	.11
Thoracic PGL (n)	1	3	.25
Abdominal PGL (n)	27	11	.002[a]
RCC (n)	3	0	.21
GIST (n)	1	3	.25
Pituitary adenoma (n)	0	1	.29
Total tumors (n)	48	34	.03[b]

13 probands and 5 nonprobands had multifocal tumors. For probands, 1 patient had a synchronous APGL and GIST, 1 patient had synchronous APGL and PC followed by a metachronous APGL, 1 patient had synchronous bilateral RCC, 1 patient had synchronous bilateral APGL; 10 probands had metachronous tumors (31%). For nonprobands, 1 patient had synchronous APGL and GIST and 1 patient with synchronous HNPGL and APGL; 3 patients developed a metachronous tumor (2 HNPGL, 1 PC). Abbreviations: GIST, gastrointestinal stromal tumor; HNPGL, head and neck paraganglioma; PC, pheochromocytoma; PGL paraganglioma; RCC, renal cell carcinoma; s-d, surveillance-detected.
[a]$P < .01$.
[b]$P < .05$.

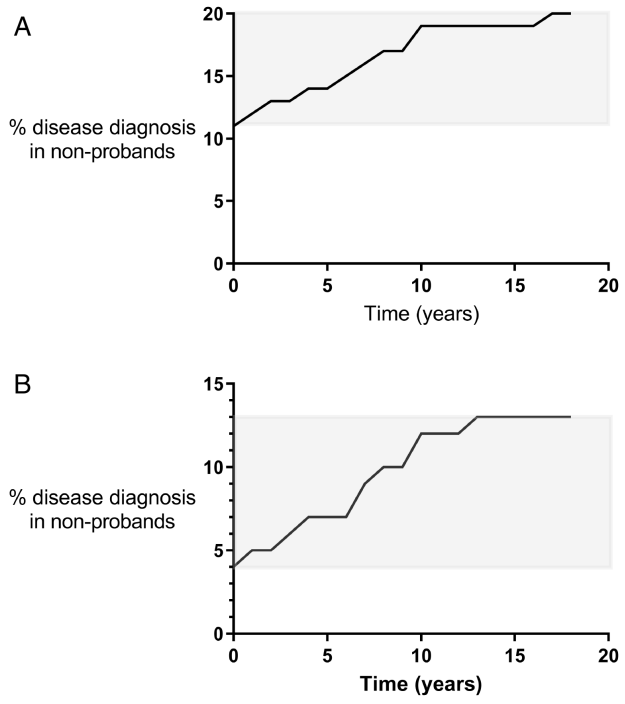

Figure 1. (A) Cumulative frequency of disease diagnosis in nonprobands. The prevalence of disease at the initial surveillance episode was 11% (n = 17) and 12 new cases were detected during surveillance. In total, 29 of 148 nonprobands were diagnosed with disease. The risk of disease in nonprobands was 20%. (B) Cumulative frequency of disease diagnosis made following predictive genetic diagnosis of *SDHB* PV. The prevalence of disease at the initial surveillance episode was 4% (n = 6) and 11 new cases were detected during surveillance. In total, 17 of 136 nonprobands were diagnosed with disease following the genetic diagnosis. The risk of disease in nonprobands following the genetic diagnosis was 13%.

recurrence or multifocal disease including gender, loss of function genotype, history of smoking, typical symptoms, hypertension, age, tumor size, and Ki-67.

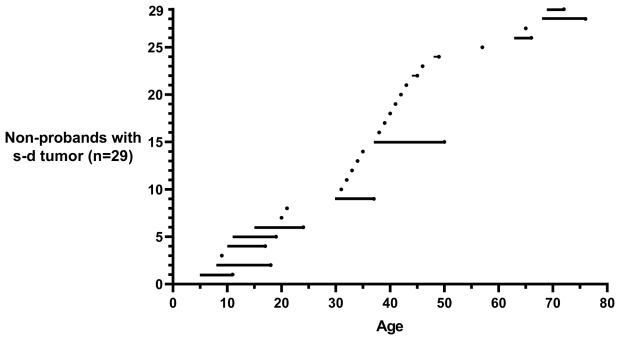

Figure 2. Nonprobands diagnosed with s-d tumors (n = 29). The age of case detection of each participant is represented by the black circle. Nonprobands who were not diagnosed with disease at the initial screen have a line to represent the age from the start of surveillance until case detection.

Metastatic disease

Patients with s-d tumors were less likely to be associated with metastatic than probands. Three (10%) of 29 patients with s-d tumors developed metastatic disease at most recent follow-up compared with 10 (31%) of 32 probands ($P = .04$). Overall, 13 (21%) of 62 patients with disease showed evidence of metastatic progression at a median of 66 months (range 0-127 months) with no difference in synchronous metastases between probands and nonprobands ($P = .061$). Two probands had synchronous metastases. Probands had increased risk of metastatic progression compared with nonprobands with s-d tumors (HR 4.13, 95% CI 1.15-14.9, $P = .03$). Estimated 5- and 10-year metastasis-free survival was 82% and 66% for probands and 100% and 84% for nonprobands ($P = .027$, Fig. 3A). Median time between initial diagnosis of any *SDHB*-associated tumor and diagnosis of metastatic disease was 68 months (range 0-193 months).

The risk of metastatic disease in HNPGL was 10% (2/20). In comparison, 10 (25%) of the 40 patients with thoraco-abdominal PPGL had evidence of metastatic progression at median 61 months (range 3-127 months) with higher risk of metastatic progression in probands than in nonprobands (OR 11.35, 95% CI 1.51-128.2, $P = .013$). One proband with thoraco-abdominal PPGL had synchronous metastases. Estimated 5- and 10-year metastasis-free survival for patients with thoraco-abdominal PPGL was 77% and 57% for probands and 100% and 91% for nonprobands ($P = .023$, Fig. 3B). Median time between initial diagnosis of thoraco-abdominal PPGL and diagnosis of metastatic disease was 60 months (range 3-127 months).

Tumor size was the only statistically significant predictor of metastatic disease on a multivariate generalized linear model with binary logistic regression (OR 1.08, 95% CI 1.03-1.14, $P = .004$, Table 3). S-d tumors were smaller than those in probands (median 27 mm (range 8-85 mm) vs 45 mm (range 13-190 mm) respectively, $P = .001$). Tumor size of 40 mm or higher was associated with progression to metastatic disease for all *SDHB*-associated tumors (OR 16.9, 95% CI 2.3-187.9, $P = .001$) and for patients with thoraco-abdominal PPGL (OR 11.5, 95% CI 1.57-133.1, $P = .02$). ROC curve analysis determined that size of the primary tumor >39 mm was the optimal cut-off value associated with increased risk of metastatic disease for all *SDHB*-associated tumors (area under the curve = 0.86, sensitivity = 58.5% [95% CI 42.1-73.7], specificity = 100% [95% CI 75.3-100], Youden's index = 0.59,

Table 3. Generalized linear model with binary logistic regression of predictors of disease diagnosis (n = 181), metastatic disease (n = 62), and death from disease (n = 62) for *SDHB* PV carriers

Predictors of disease diagnosis	***P* value**	**OR (95% CI)**
Male	.007[a]	3.05 (1.36-6.89)
Loss of function PV	.43	0.72 (0.32-1.62)
History of smoking	.33	1.75 (0.56-5.44)
Classic symptoms (headaches, palpitations or sweats)	.000[a]	4.90 (2.03-11.84)
Hypertension (BP ≥ 140/90)	.000[a]	0.10 (0.03-0.29)
Age at first surveillance episode	.003[a]	0.97 (0.94-0.99)
Test	***P* value**	**Σ^2**
Overall model likelihood ratio test (omnibus test)	.000[a]	38.79
Predictors of metastatic disease		
Tumor size	.004[a]	1.08 (1.03-1.14)
Male	.36	0.29 (0.02-4.19)
Loss of function PV	.39	0.29 (0.18-4.81)
History of smoking	.81	1.21 (0.25-5.91)
Classic symptoms (headaches, palpitations or sweats)	.48	3.35 (0.11-102.89)
Hypertension (BP ≥ 140/90)	.63	2.17 (0.09-50.49)
Age at first surveillance episode	.14	1.07 (0.98-1.16)
Multifocal tumors	.13	8.05 (0.55-117.43)
Tumor location	.09	5.99 (0.78-45.90)
Tumor functioning status	.47	2.09 (0.28-15.68)
Ki-67	.84	0.72 (0.02-8.44)
Test	***P* value**	**Σ^2**
Overall model likelihood ratio test (omnibus test)	.009[b]	29.41
Predictor of death from disease		
Tumor size	.09	0.97 (0.94-1.01)
Synchronous metastases	.99	No value[c]
Male	.38	0.28 (0.02-4.93)
Loss of function PV	.77	1.71 (0.05-59.16)
History of smoking	.20	6.58 (0.67-62.06)
Typical symptoms (headaches, palpitations or sweats)	.47	3.93 (0.10-157.93)
Hypertension (BP ≥ 140/90)	.63	1.97 (0.13-29.97)
Age at first surveillance episode	.74	0.98 (0.89-1.09)
Multifocal tumors	.33	3.79 (0.25-56.57)
Tumor location	.99	0.00 (no value)
Tumor functioning status	.99	0.00 (no value)
Ki-67	.99	0.00 (no value)
Test	***P* value**	**Σ^2**
Overall model likelihood ratio test (omnibus test)	.19	18.47

loss of function defined as nonsense, splicing, deletion, or frameshift PV.
Abbreviations: CI, confidence interval; PV, pathogenic variant.
[a]$P < .01$;
[b]$P < .05$.
[c]No value due to a quasi-complete separation in the data.

$P = .0001$, Fig. 4A) and for patients with thoraco-abdominal PPGL (area under the curve = 0.87, sensitivity = 56.0% [95% CI 34.9-75.6], specificity = 100% [95% CI 69.2-100], Youden's index = 0.56, $P = .0007$, Fig. 4B). Cox proportional hazards regression could not determine the hazard ratio of metastatic disease associated with tumors 40 mm or larger due to a quasi-separation in the data, whereby there were 0 cases of metastatic progression with tumor size below 40 mm. Similarly, a multivariate generalized linear model with binary logistic regression for predictors of metastatic disease in patients with thoraco-abdominal PPGL was unable to be obtained due to a quasi-complete separation in the data.

Mortality

Nine patients (14.5% of patients with disease) died in this cohort, 1 from a non-*SDHB*–related cause (metastatic colorectal cancer on a background of ulcerative colitis). One nonproband and 7 probands died from disease: 1 from bilateral RCC, 3 from APGLs, 1 from metachronous APGL (including 1 bladder PGL), 1 from metachronous APGL/PC, and 2 from metachronous APGL/HNPGL. Of patients who died of disease, primary tumor size was a median 68 mm (range 40-105 mm), age at initial disease diagnosis was median 38 years (range 27-60 years), and 2 patients had synchronous metastases at initial diagnosis. For the remaining patients who did not have synchronous metastases, time to metastatic disease following initial diagnosis was median 71 months (range 4-193 months). Duration of survival following the diagnosis of metastatic disease was median 61 months (range 27-311 months). The age at death was median 47 years (range 29-84 years).

Patients with s-d tumors had lower mortality than probands. Risk of death from disease was 21.9% for probands and 3.4% for nonprobands (OR 7.8, 95% CI 1.2-90.1, $P = .054$). Estimated 5- and 10-year overall survival was 89% and 79% for probands and 100% for nonprobands ($P = .029$, Fig. 3C). There was no difference in overall survival for patients with thoraco-abdominal PPGL between probands and nonprobands ($P = .179$, Fig. 3D).

In nonprobands diagnosed with disease, the risk of death was 8.3% and 0% for those with clinical and genetic s-d tumors respectively ($P = .433$). Results from the multivariate generalized linear model with binary logistic regression showed that no factors were able to predict death from disease (Table 3).

Discussion

Our study is 1 of the largest to report surveillance practice, and describe s-d tumors and disease-specific outcomes for *SDHB* PV carriers in a surveillance program. We found surveillance successfully detected *SDHB*-associated tumors prior to development of metastatic disease. We found that a tumor size of 40 mm or higher was associated with increased risk of metastatic progression. Ours is the first study to show surveillance is associated with lower mortality in an *SDHB*-specific population.

Median age of disease diagnosis in our cohort was 37 years in the 62 patients with disease diagnoses. Several studies have noted *SDHB* PV carriers are more likely to be diagnosed with disease at a young age (10, 16-19). Median age at diagnosis was younger for females than males (34 vs 41 years respectively) although male gender was associated with a higher risk of disease. Jochmanova et al found that the median age at diagnosis was younger for male *SDHB* PV carriers, but also observed a higher likelihood of disease in male than in

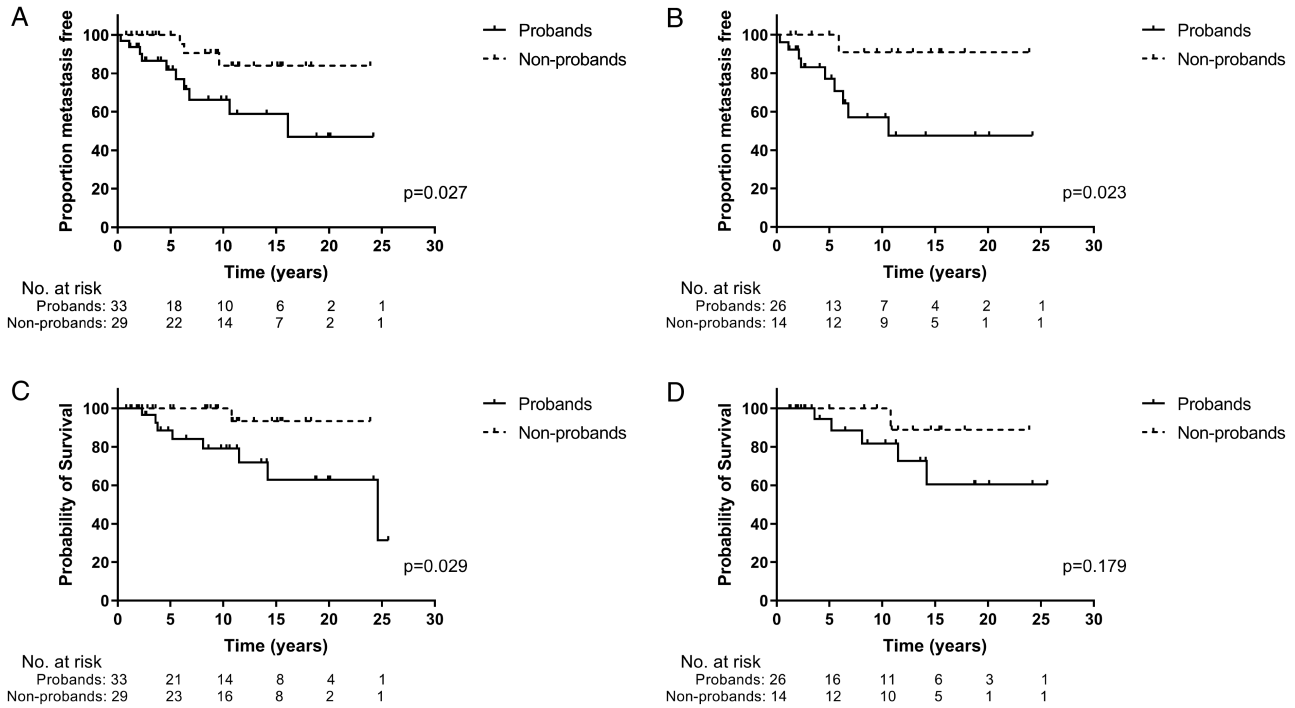

Figure 3. Kaplan–Meier curves of (A) metastasis-free survival for all patients with *SDHB*-associated tumors. (B) Metastasis-free survival for patients with thoraco-abdominal PPGL. (C) Overall survival for all patients with *SDHB*-associated tumors. (D) Overall survival for patients with thoraco-abdominal PPGL.

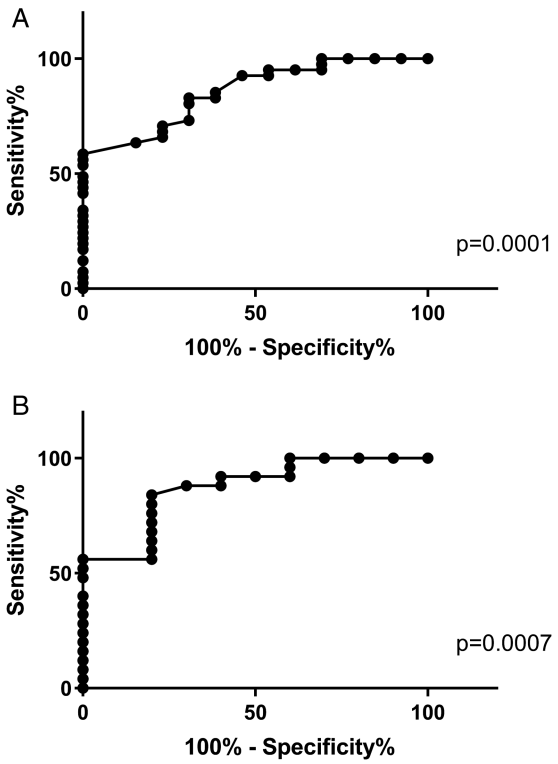

Figure 4. (A) ROC curve analysis of tumor size for prediction of metastatic disease in all patients with *SDHB*-associated tumors. (B) ROC curve analysis of tumor size for prediction of metastatic disease in patients with thoraco-abdominal PPGL.

female carriers (18). Andrews et al performed a retrospective multicenter study of 584 *SDHB* PV carriers with statistical adjustment for ascertainment bias, and similarly found a higher age-specific penetrance of HNPGL and PPGL in males (20).

The median age of first surveillance in nonprobands was 33 years (range 1-81 years). The youngest age of a s-d tumor (n = 29) was a bladder paraganglioma diagnosed at age 9 years; in the literature, APGL has been described in a proband as young as 6 years (21). The oldest age of a s-d tumor was an asymptomatic gastric GIST detected at age 76 years.

Blood pressure measurement is routinely recommended for asymptomatic *SDHB* carriers (4), but paradoxically in our cohort pretreatment hypertension was more prevalent in those without disease than those with disease. Our study may have found normotension was associated with disease due to interaction between young age and normotension, whereby young age was a risk factor for disease detection and essential hypertension is more common with advanced age (22).

Our study is the first to show the presence of "classic" symptoms of headaches, palpitations or sweats is associated with disease detection (OR 4.9), and highlights the importance of clinical history during surveillance of these patients. While association between classic symptoms and disease may have been due to ascertainment bias, we felt this was unlikely in this cohort where patients were routinely asked about symptoms at surveillance visits. Our observation that a subset of patients with apparently nonfunctioning tumors had symptoms has been noted by others (23). In a case series of 4 patients with biochemically silent *SDHB*-associated tumors, 1 patient reportedly presented with palpitations, headaches, and sweats (23). Absence of classic symptoms did not exclude disease, and indeed 10 of 29 (34%) s-d tumors were asymptomatic.

Regarding surveillance imaging modalities, MRI base of skull to coccyx formed the basis of surveillance in keeping with international guidelines (4). CT was used for anatomical imaging surveillance at all centers, but less commonly

than MRI, to minimize radiation exposure per international recommendations (4). For example, as shown in the supplemental tables, 33 CT head and neck/base of skull scans were performed on the entire cohort in comparison with 189 MRI head and neck/base of skull scans. International guidelines suggest functional imaging could be considered for surveillance in adults (4). In our cohort, adults at RNSH and PoWH undertook ^{68}Ga-DOTATATE PET/CT or ^{18}F-FDG-PET/CT 5-yearly and at RHH adults had ^{18}F-FDG-PET/CT 4 yearly. At RHH, functional imaging with ^{18}F-FDG-PET/CT was undertaken as a key component of imaging surveillance and was noted to have high sensitivity and specificity for the detection of sympathetic PPGL with the advantage of providing both anatomical and functional detail. Functional imaging with ^{68}Ga-DOTATATE PET/CT had high sensitivity and specificity for sympathetic PPGL and HNPGL. PET imaging was 4 to 5 yearly rather than biennially to reduce radiation exposure, despite being sensitive and specific. Ultrasound surveillance 4 yearly at RHH was also noted to have high specificity for the detection of sympathetic PPGL and HNPGL. ^{123}I-MIBG imaging was rarely utilized after the advent of PET imaging. Future research could assess cost-effectiveness of different imaging modalities for surveillance of *SDHB* PV carriers.

We observed that probands had higher numbers of APGLs and were more likely to have multifocal disease over time (OR 3.3). Given probands did not have a higher risk of multifocal disease at baseline, we speculate this finding is due to delayed diagnosis and therefore a longer period of "tumor incubation" in probands than in nonprobands. Tufton et al reported that 10 (11%) of *SDHB* PV carriers in their cohort had multifocal disease and all were index cases (3). Bausch et al found that of 6 of 25 (24%) probands with *SDHB* PV developed a second PPGL (24) and Daniel et al reported 2 of 9 (22%) probands developed a second tumor (25). More research is needed with longer follow-up to determine whether proband/index cases with *SDHB* PV have intrinsically increased risk of multiple tumors.

We found the risk of metastatic disease in *SDHB* carriers with s-d tumors was 10% and in the overall cohort (including probands) was 21%. A systematic review and meta-analysis found the risk of metastatic disease for *SDHB* PV carriers was 17% for a cohort including probands and asymptomatic carriers (26). A more recent review found overall risk of metastatic disease was 27.6% and like our study found the risk of metastatic disease was higher in thoraco-abdominal PPGLs than HNPGLs (10). Metastases were synchronous in 2 of 13 (15%) patients, which is slightly lower than reported rates in the literature ranging from 19% to 44% of *SDHB* PV carriers with metastatic disease (3, 7, 27-30). Schovanek et al noted synchronous metastases were associated with a median tumor size of 75 mm in *SDHB* PV carriers (7), whereas our patients with synchronous metastases had primary tumor sizes of 40 mm. In patients with disease (n = 63), median time to development of metastases was 68 months (5.7 years), which was comparable with the literature where median time to metastases was 4 to 5 years (8, 31, 32).

To our knowledge, ours is the first study to compare metastasis and overall 5- and 10- year survival of *SDHB* carriers between patients with s-d tumors and probands. In total, 14.5% of patients with disease died in this study. In other studies mortality of *SDHB* PV carriers with disease was between 2.1% and 13.0% (3, 8, 9, 28, 33-36). In studies that only examined patients with metastatic PPGL, mortality rates were understandably higher from 18.5% to 60.9% (2, 32, 37, 38).

Our study has implications for surveillance recommendations for *SDHB* PV carriers. Patients with s-d tumors of 40 mm or larger and those with abdominal or pelvic PPGLs should be followed more frequently to detect metastatic progression. Probands/index cases may also be at higher risk of metastatic progression and/or multiple tumors and surveillance should be increased accordingly. Given that the age of tumor detection is broad as shown in Fig. 2, we concur lifelong surveillance should start at a young age, in keeping with the current consensus guidelines (4). The value of surveillance programs has also been reported by others (3, 39-41). Buffet et al examined patients with PPGL who carried a germline PVs of whom 95 had a confirmed *SDHB* PV; they compared overall survival between those who received germline testing within 12 months after diagnosis of their first PPGL (the genetic group) and within 7 years of the PPGL (the historic group) (39). Overall survival was 100% in the genetic group and 50% in the historic group, and the authors postulated that patients with a knowledge of their genetic risk may have experienced a higher quality of surveillance (39). Greenberg et al described surveillance of 188 *SDHB* PV carriers and observed 15% developed tumors over mean follow-up duration 1.81 ± 2.75 years (40). A multicenter study of asymptomatic *SDHx* mutation carriers (n = 171 *SDHB* carriers) noted 22 of 171 (13%) asymptomatic *SDHB* carriers had a tumor detected during surveillance and 14 of 22 (64%) tumors were detected at the initial surveillance episode (41). Tufton et al reported that 10 of 15 (67%) tumors detected during surveillance were identified at the first surveillance episode (3) and we also noted that 59% (17/29) of all s-d tumors were detected at the initial surveillance episode. The optimal frequency of surveillance following an initial negative surveillance episode deserves further research.

There were several limitations to our study. Being a medical chart review, some historic data on primary tumor characteristics and initial presentation were not available. Similarly, we were only able to observe the data available and the form in which it was entered, which varied across the centers. Extraction of data by 1 researcher ensured consistency with respect to the interpretation of chart notation where required. Although the study was multicenter it was not a nationwide Australian cohort. The association of classic symptoms with disease may have been due to ascertainment bias. More studies are needed to further evaluate the sensitivity and specificity of diagnostic modalities for *SDHB*-associated tumors. However, strengths of this study were the long duration of follow-up, small rate of loss to follow-up (42), large patient numbers, and good adherence to standardized surveillance for *SDHB* PV carriers in our genetics clinics.

Conclusion

This is one of the largest studies to describe s-d tumors and outcomes for *SDHB* PV carriers in a surveillance program. Patients with s-d tumors had smaller tumors, reduced risk of metastatic disease and lower mortality than probands. Tumor size ≥40 mm was associated with increased risk of metastatic progression. Our results suggest that *SDHB* PV carriers should undertake surveillance to improve clinical outcomes.

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Author Contributions

D.F.D. designed the study, acquired the data, performed data analyses, and drafted/approved all versions of the manuscript. R.J.C.B. and R.D.A.L. designed the study, aided with interpretation of data, and edited/approved the manuscript. D.E.B., M.F., A.C., B.G.R, K.T., and J.R.B. aided with interpretation of data and edited/approved the manuscript.

Conflicts of Interest

The authors have nothing to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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