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ORIGINAL ARTICLE

Role of rapid sequence whole-body MRI screening in *SDH*-associated hereditary paraganglioma families

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Abstract Patients with germline mutations in one of the SDH genes are at substantially increased risk of developing paragangliomas, pheochromocytomas (pheos), and other tumors (all combined referred to as SDH-related tumors). However, limited data exist on screening in SDH mutation carriers and no studies have evaluated whole-body MRI as a screening tool in asymptomatic patients. This was a single-center observational study. We evaluated the results of screening in 37 SDH carriers who underwent 45 whole-body MRIs and 47 biochemical tests. Screening included annual biochemical testing (catecholamines, metanephrines and chromogranin A) and biennial or annual rapid sequence whole-body MRI from the base of the skull to the pelvis beginning at age 10 years old. Six tumors (paragangliomas of the organ of Zuckerkandl, the aortocaval/vas deferens, of the carotid body times three, and a renal cell carcinoma) were diagnosed in five patients. In total, 13.5 % of all patients screened were diagnosed with *SDH*-related tumors. Whole-body MRI missed one tumor, while biochemical testing was normal in five patients with SDH-related tumors. The sensitivity of whole-body MRI was 87.5 % and the specificity was 94.7 %, while the sensitivity of biochemical testing was 37.5 % and the specificity was 94.9 %. Whole-body MRI had a higher sensitivity for SDH-related tumors than biochemical testing in patients undergoing screening due to their *SDHB* or *SDHC* mutation status. Whole-body MRI reduces radiation exposure compared to computed tomography scan and time compared to dedicated MRI of the head/neck, thorax, and abdomen/pelvis.

Keywords SDHB · SDHC · Paraganglioma · Pheochromocytoma · Screening · MRI

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Introduction

Paragangliomas are rare tumors that can occur anywhere along the sympathetic or parasympathetic nervous system. According to the World Health Organization classification system, paragangliomas occurring in the adrenal medulla are called pheochromocytomas (pheos) [1]. Those occurring outside of the adrenal medulla are called paragangliomas or extra-adrenal paragangliomas (here on out referred to as paragangliomas) [1]. Germline mutations in the SDH (succinate dehydrogenase) genes (*SDH A*, *B, C, D* or *AF2*) predispose to paragangliomas, pheos, and/or other tumors such as gastrointestinal stromal tumors (GIST), renal tumors, and renal cancers [2]. Depending on the gene

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mutation, SDH mutation carriers have up to a 90 % risk by age 70 for tumors [3, 4].

Although most paragangliomas and pheos are benign, malignant transformation does occur and is more common in patients with SDH mutations than those with sporadic disease [5, 6]. This malignant transformation is especially true in the case of *SDHB* germline mutations, although mutations in any of the SDH genes may cause metastasis [4, 7]. The high rates of mortality and morbidity resulting from distant metastasis, complications (hypertensive crisis) and mass effect are of concern with SDH-related tumors [8]. Therefore early detection of SDH-related tumors is imperative to reduce morbidity and mortality [4].

In a large study of 216 patients with a suspected paraganglioma or pheo, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) out performed [^{123}I]-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy and computed tomography (CT)/magnetic resonance imaging (MRI) [6]. In addition, ^{18}F-FDG PET had a higher sensitivity for tumors in 47 SDH mutation carriers when compared to 23 non-SDH mutation carriers [6]. However, these patients already had suspected paragangliomas and/or pheos, and therefore this was not a screening study.

According to various publications, tumor screening in SDH mutation carriers is "reasonable" [9], "should be offered" [10], and "warranted" [11]. Peck et al. [12] even stated that SDH mutation carriers "deserve full-body screening" and Schiffman [13] indicated that "total-body MRI may ultimately be the safest imaging option for early cancer surveillance". However, no standard screening protocol has been endorsed for screening in these high risk patients. One study of asymptomatic *SDHB* and *SDHD* mutations carriers reported that an MRI scan was the gold standard for diagnosis of head and neck paragangliomas [14]. However, SDH mutation carriers are at increased risk of sympathetic paragangliomas, pheos, GISTs, and kidney cancers which will be missed by MRI of the head and neck alone. The only other screening study in SDH mutation carriers utilized an extensive screening protocol which may not be feasible in most clinical settings and may not be indicated given the concern for radiation exposure [15]. Here we described the first ever known study evaluating whole-body magnetic resonance imaging (MRI) as a screening tool in SDH mutation carriers. This novel screening approach is compared to biochemical testing.

Patients and methods

Study population

A clinical screening protocol was developed and offered to patients with a known SDH gene mutation (confirmed by molecular analysis or an obligate carrier) or suspected mutation (personal history of paraganglioma or pheo and a known mutation in the family). From November 2008 to March 2012 we followed 37 patients who were seen in the Family Cancer Assessment Clinic at Huntsman Cancer Institute and underwent rapid sequence MRI from the base of the skull to the pelvis (whole-body MRI). One of these 37 patients in our study underwent rapid sequence MRI, but only the base of the skull and neck were initially evaluated due to time constraints and the fact that a carotid body paraganglioma was detected during the first part of the MRI scan. All but one of the 37 patients also underwent biochemical screening (see screening protocol for additional details). In total, 45 rapid sequence MRIs and 47 biochemical tests were performed. The indication for screening in all patients was positive SDH mutation regardless of symptoms or known tumor diagnosis. Two patients already had known paragangliomas that had not been surgically removed at the time of initial screening. The whole-body MRI in these patients was performed to look for new tumors. This study was approved by the University of Utah's Institutional Review Board.

Screening protocol

Imaging biennially and biochemical screening annually were clinically recommended for all patients, however screening may have occurred at intervals that were more or less frequent than what was clinically recommended. MRI was performed using axial and coronal ultra-fast T2 half Fourier acquisition single shot fast spin echo "HASTE" technique using a sliding table platform with an integrated phased-array surface coil. The MRI examination included the base of skull to the pelvis (referred to as whole-body MRI). Each image was 5 mm in thickness and the entire procedure lasted <1 h.

Radiologists reviewed the initial images as part of routine clinical care during the procedure itself. Additional imaging and/or biochemical testing was recommended on a case by case basis when an uncharacterized or suspicious lesion was detected on whole-body MRI. The MRI was considered positive when a paraganglioma, pheo, and/or other SDH-related tumor (GIST, oncocytoma, or kidney cancer) was considered to be present by the radiologist. The MRI was also considered positive when the radiologist identified a lesion and recommended additional follow-up due to the possibility of an SDH-related tumor and subsequent follow-up confirmed an SDH-related tumor. The MRI was considered negative when the radiologist did not confirm a paraganglioma, pheo, and/or other SDH-related tumor. Incidental findings and uncharacterized lesions were not used to determine if an MRI was categorized as positive, but were recorded as part of our study.

Biochemical screening included plasma and/or urine catecholamines, fractionated metanephrines, and chromogranin A. Biochemical screening was considered positive when any one of the markers (chromogranin A, dopamine, norepinephrine, metanephrine, normetanephrine, and epinephrine) was at least double the upper limit of normal. Biochemical screening results greater than one but less than two times the upper limit of normal, were not considered suggestive of a paraganglioma or pheo. These results were categorized as normal in this study, though some patients chose to undergo repeat biochemical testing three to six months following these results because the laboratory values were slightly above the standardized normal level and of unclear clinical significance.

Data collection

Surgery and laboratory reports, clinic notes, histopathology records and family history were collected from the medical record (electronic and/or hard copies). Abstracted information included sex, genetic testing performed and result, age at first whole-body MRI, tumor diagnoses (location, type, and age of onset), presence/absence and type of symptoms prior to screening (symptoms were not evaluated for patients who were known to have a paraganglioma, pheo, or GIST at time of screening), screening performed and results, and family history.

Statistical analyses

We calculated descriptive statistics for the clinical and demographic variables of interest. We report means (range) and the proportion reporting each variable of interest as relevant. We determined the total number of SDH-related tumors detected by screening and the percent of patients with new tumors diagnosed. We also compared the proportion with new tumors diagnosed in patients with a past or current history of SDH-related tumor to those without a diagnosis of these tumors at the time of initial screening.

For each whole-body MRI performed, we determined true negative, true positive, false negative, and false positive results as defined in Table 1. From these results, we calculated the sensitivity and specificity. Only SDH-related tumors were included in these results. If a patient was found to have other findings such as kidney cysts, non-SDH-related tumor (e.g., hemangioma) these were considered incidental findings. We also determined the number and frequency of uncharacterized lesions detected by whole-body MRI. Uncharacterized lesions were those that needed additional follow-up to clarify the diagnosis.

For each biochemical test performed, we determined true negative, true positive, false negative, and false positive results as defined in Table 1. From these results, we calculated the sensitivity and specificity. Only SDH-related tumors were considered for these results. Results that were more than two times the upper limit of normal were called positive. Results between one and two times the upper limit of normal were categorized as negative. Although we categorized these as negative, we still determined the total number and percent of these results. Statistical analyses were performed in Stata 12.

Results

Patient characteristics

Characteristics of patients are presented in Table 2. The 37 patients screened in this study came from 10 distinct kindreds. There were 15 females (40.5 %) and 22 males (59.5 %), with an average age of 41.3 years (range 11–75) at the time of first whole-body MRI. There were 33 (89.2 %) *SDHB* mutation carriers and four (10.8 %) patients with mutations in *SDHC*. The majority (N = 28, 75.7 %) had never been previously diagnosed with a paraganglioma, pheo or GIST at the time of initial screening, while nine (24.3 %) had a past or current history. The majority (N = 34, 91.9 %) also had never been diagnosed with other cancers/tumors at the time of initial screening, whereas three (8.1 %) had a past or current history of non-SDH-related tumors/cancers. Past and current history of specific tumors and ages of onset are listed in Table 2.

MRI and biochemical testing results

Of the 37 patients who underwent a total of 45 whole-body MRIs, six SDH-related tumors were diagnosed, all in *SDHB* mutation carriers. The six tumors diagnosed in this study along with the size, age of onset, biochemical tests results, symptoms, and treatment are listed in Table 3. In addition, Table 3 includes the nine patients with 13 incidental findings that were discovered via MRI. Kidney cysts were detected in eight (21.6 %) patients. Four of the SDH-related tumors detected include a 3.3 cm carotid body paraganglioma, a 2.4 cm carotid body paraganglioma (Fig. 1a), a 7.1 cm renal cell carcinoma (Fig. 1b), and a 3 cm carotid body paraganglioma. One patient (51290) was found to have a 7.6 cm paraganglioma at the organ of Zuckerkandl (Fig. 1c) at age 34 and the following year was diagnosed with a paraganglioma of the aortacaval and vas deferens (the aortacaval and vas deferens tumor were considered one paraganglioma for the purpose of this study). It is not clear if the aortacaval/vas deferens paraganglioma was a new primary tumor or metastasis from the original organ

Table 1 True and false negative, true and false positive definitions

Whole-body MRI
True negative result: Radiologist did not report a lesion highly suspicious for an *SDH*-related tumor, and the patient did not have an *SDH*-related tumor at the time of screening.
False negative result: Radiologist did not report a lesion highly suspicious for an *SDH*-related tumor and the patient was either found to have or known to have an *SDH*-related tumor at the time of screening.
True positive result: Radiologist reported a lesion highly suspicious for an *SDH*-related tumor or recommended additional follow-up due to a suspicious lesion and the patient was found to have or known to have an *SDH*-related tumor at the time of screening.
False positive result: Radiologist reported a lesion highly suspicious for an *SDH*-related tumor and the patient did not have an *SDH* related tumor at the time of screening.
Biochemical testing
True negative result: All of the biochemical tests were normal or less than two times the upper limit of normal and the patient did not have an *SDH*-related tumor at the time of screening.
False negative result: All of the biochemical tests were normal or less than two times the upper limit of normal and the patient was either found to have or known to have an *SDH*-related tumor at the time of screening.
True positive result: At least one of the biochemical tests were more than two times the upper limit of normal and the patient was found to have or known to have an *SDH*-related tumor at the time of screening.
False positive result: At least one of the biochemical tests were more than two times the upper limit of normal and the patient did not have an *SDH*-related tumor at the time of screening.

Table 2 Patient demographics and clinical characteristics

Patients screened, n	37
Total kindreds, n	10
Sex, n (%)	
Female	15 (40.5)
Male	22 (59.5)
Age at first whole-body MRI, mean (range)	41.3 (11 - 75)
Genetic status	
SDHB, n (%)	33 (89.2)
SDHC, n (%)	4 (10.8)
History of *SDH*-related tumor[a]	
Never diagnosed, n (%)	28 (75.7)
Current or past history, n (%)	9 (24.3)
Glomus paraganglioma dx at 29	
Pheo dx at 17	
Malignant carotid body paraganglioma dx at 27	
Carotid body paraganglioma dx at 21	
Carotid body paraganglioma dx at 75	
Glomus paraganglioma dx at 28	
GIST dx at 11	
Glomus paraganglioma dx at 44	
Bilateral carotid body and glomus paragangliomas dx at 24	
History of cancer/tumor other than an *SDH*-related tumor[a]	
Never diagnosed, n (%)	34 (91.9)
Current or past history, n (%)	3 (8.1)
Non-melanoma skin cancers dx at ?	
Lung hamartoma dx at ?	
Spinal hemangioma dx at 32	

dx diagnosed, *GIST* gastrointestinal stromal tumor, *Pheo* pheochromocytoma, *MRI* magnetic resonance imaging, *?* age of onset unknown

[a] Paraganglioma, pheo, GIST, oncocytoma, or renal cancer

of Zuckerkandl paraganglioma. However, the radiologists believe these were truly independent tumors based on imaging and their anatomical location. In our analysis, we considered the Zuckerkandl paraganglioma to be a separate tumor from the aortacaval/vas deferens paraganglioma.

The proportion of SDH-related tumors detected was 13.3 % (6 tumors detected out of 45 MRIs performed). The percentage of patients with SDH-related tumors diagnosed in our cohort was 13.5 % (5 patients diagnosed with tumors out of 37 screened). None of the five patients in our own study diagnosed with an SDH-related tumor on screening had a past or current history of an *SDH*-related tumor. Out of the 28 patients without a past or current history of an *SDH*-related tumor, 5 (17.9 %) were diagnosed with an SDH-related tumor during screening. Out of the 9 patients with a past or current history of an SDH-related tumor, none (0 %) were found to have a new primary SDH-related tumor.

Of the six SDH-related tumors detected in this study by whole-body MRI, three of the corresponding biochemical tests had one or more markers that were at least double the upper limit of normal (see Table 3 for additional details). Out of the six biochemical markers evaluated (CA, D, NE, M, NM, and E), none of these three abnormal results had more than two markers elevated. The other three tumors detected had normal biochemical test results (false negative results) for all of the markers tested.

The total number of whole-body MRI and biochemical tests performed, in addition to their corresponding true negative, false negative, true positive, and false positive results are summarized in Table 4. The sensitivity and specificity of each screening method are also included. The result from one of the whole-body MRIs was read as positive for a carotid body paraganglioma that was later determined to not be a paraganglioma. This same MRI also was positive for a large renal lesion that was later determined to be a renal cell carcinoma. Therefore, this MRI had both a false positive and true positive result. Consequently, the total number of MRI results adds up to 46, even though only 45 MRIs were performed. Two patients had known paragangliomas that had not been surgically

Table 3 Tumor and incidental findings detected by whole body MRI

ID #	Gene (mutation)	Symptoms	Tumors and incidental lesions detected, (age years)	Biochemical results (CA, DA, NE, M, NM, and E performed)[a]	Treatment
56547	*SDHB* (Del exon 3)	Hypertension	Kidney cysts (51)	↑↑ (DA)	None
59753	*SDHB* (Del exon 3)	Lump in neck	3.3 cm carotid body paraganglioma (27)	↑↑ (DA); ↑↑(NE)	Surgically resected
73803	*SDHB* (P197R)	None	Kidney cysts (67)	Normal	None
48014	*SDHB* (P197R)	None	7.1 cm renal cell carcinoma (30)	Normal	Surgically resected
48103	*SDHB* (P197R)	None	Bilateral kidney cysts (51)	↑ (CA)	None
48104	*SDHB* (P197R)	None	Bilateral kidney cysts (35)	↑ (NE)	None
47941	*SDHB* (P197R)	None	2.4 cm carotid body paraganglioma (51)	Normal	Surgically resected
			Kidney cysts (51)		None
			Ovarian cyst (52)		None
			Spinal hemangioma (52)		None
56522	*SDHB* (R230L)	Headaches and dizziness	3.0 cm carotid body paraganglioma (58)	↑↑ (CA); ↑↑(NM)	Surgically resected
			Liver hemangioma or cyst (58)		None
			Kidney cysts (58)		None
51290	*SDHB* (R230L)	None	7.6 cm paraganglioma organ of Zuckerkandl (34)	↑↑ (DA)	Surgically resected
			1.8 cm aortocaval and 1.2 cm vas deferens paraganglioma (35)	Normal	Surgically resected
59781	*SDHB* (R230L)	None	3.7 cm kidney cyst (57)	Normal	None
49362	*SDHB* (R230L)	None	Liver cysts (32)	↑ (NE)	None
83832	*SDHC* (R15X)	Hypertension	Adrenal adenoma (59)	Normal	None
			Bilateral kidney cysts (59)		None

CA chromogranin A, *DA* dopamine, *E* epinephrine, *M* metanephrine, *MRI* magnetic resonance imaging, *NE* norepinephrine, *NM* normetanephrine, ↑↑ two or more times the upper limit of normal, ↑ one to two times the upper limit of normal

[a] Only elevated results listed, all other tests were normal

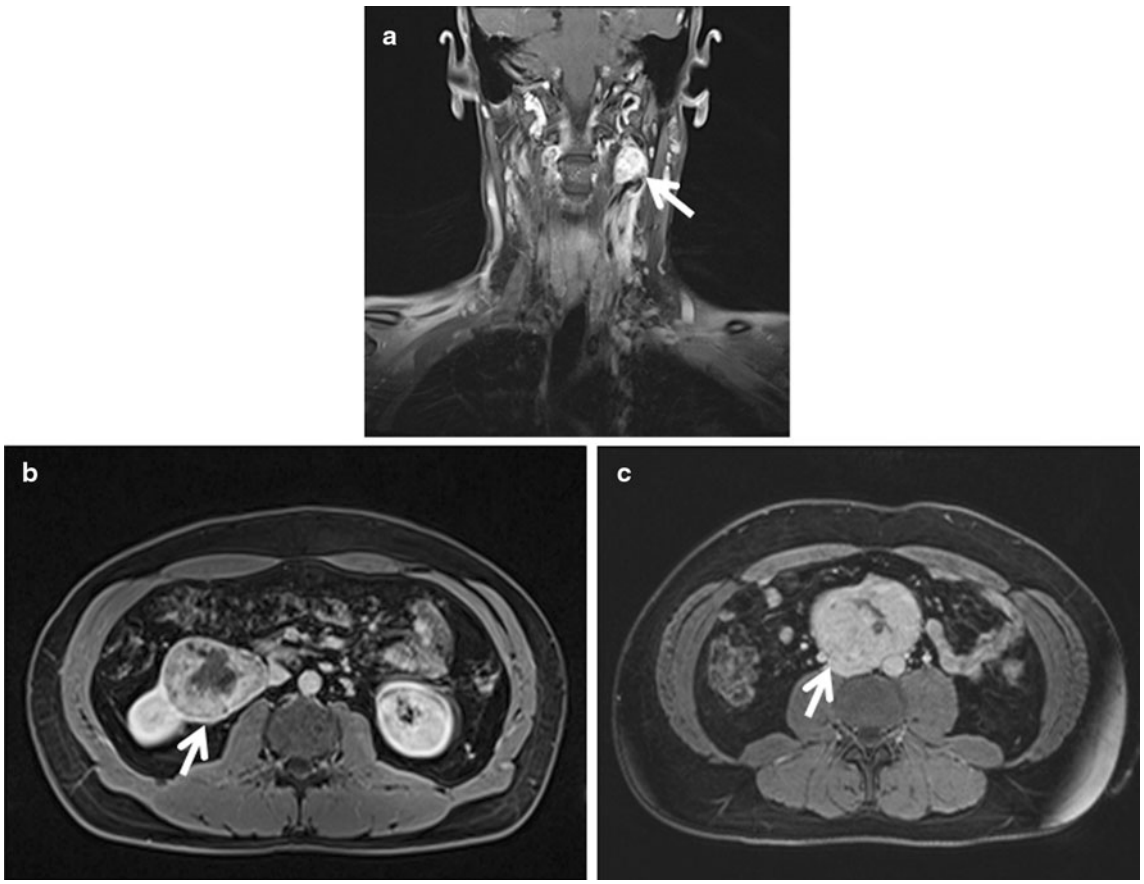

Fig. 1 Images from whole-body MRI, white arrow points toward tumor. **a** 2.4 cm carotid body paraganglioma. **b**. 7.1 cm renal cell carcinoma. **c** 7.6 × 6.2 cm paraganglioma at the organ of zuckerkandl

removed at the time of initial screening. One of these patients had a known 3.8 cm carotid body paraganglioma and the whole-body MRI was not read as positive and therefore this was considered a false negative result. This MRI was re-read and the carotid body paraganglioma was visualized, however, given it was not called as positive in the initial radiology report, it was still categorized as a false negative. Another patient had bilateral carotid body tumors and a right sided vagale paraganglioma (all at age 24). The carotid body parangliomas had been surgically removed, however the glomus tumor was still intact at time of initial screening. This paraganglioma was called positive on whole-body MRI and was categorized as a true positive result. This patient is not listed out in Table 3 since this was not a new diagnosis. Although not included in Table 4, 9 (19.1 %) of the biochemical tests were between one and two times the upper limit of normal.

Additional follow-up

Table 5 includes additional follow up performed and outcomes for three patients (3 out of 45 MRIs performed, 6.7 %) (69629, 49214, and 70875) with uncharacterized lesions on whole-body MRI, three patients (59782, 57355, and 56522) with elevated (at least two times the upper limit of normal) and/or slightly elevated (between one and two times the upper limit of normal) biochemical test results who proceeded with additional follow up, and two patients (48014 and 70611) with false positive whole-body MRIs.

Discussion

To the authors' knowledge, this is the first study evaluating whole-body MRI as a screening tool in patients with SDH mutations. This approach has been shown to be successful in Li-Fraumeni syndrome where the combined use of whole body MRI and biochemical screening led to 100 % 3-year overall survival in the screened group compared to 21 % survival (95 % CI 4–48 %) in patients who declined any screening ($p = 0.0{,}155$) [16]. Even though some patients in our study had nonspecific symptoms (hypertension, headaches, etc.) of paragangliomas and pheos, none of the patients were currently being worked-up for an

Table 4 Screening results

Patients screened, n	37
Whole-body MRIs performed, n (range)	45[a] (1–3)
True negative result, n (%)	36 (80.0)
False negative result, n (%)	1 (2.2)
True positive result, n (%)	7 (15.6)
False positive result, n (%)	2 (4.4)
Sensitivity, %	87.5
Specificity, %	94.7
Biochemical tests performed, n (range)	47 (0–3)
True negative result, n (%)	37 (78.7)
False negative result, n (%)	5 (10.6)
True positive result, n (%)	3 (6.4)
False positive result, n (%)	2 (4.3)
Sensitivity, (%)	37.5
Specificity, (%)	94.9

MRI magnetic resonance imaging

[a] One MRI resulted in both a false positive and true positive result therefore the total results for MRI adds up to 46 even though only 45 MRIs were performed

SDH-related tumor due to these symptoms. Therefore, these patients could still be considered as asymptomatic. Most importantly, the indication for MRI screening in all patients was their SDH mutation status and not symptoms or current tumor history.

The prevalence of SDH-related tumors diagnosed in our participants was 13.5 %. Furthermore, among patients without a past or current history of an SDH-related tumor nearly 18 % were found to have previously undiagnosed tumors. Hestermann et al. [14] recently found that 11.8 % of patients with *SDHB* mutations were found to have paragangliomas or pheos during screening. This is similar to out detection rate, which primarily consisted of patients with *SDHB* mutations. However, their screening protocol included only MRI of the head and neck, which will fail to detect most sympathetic paragangliomas, pheos, GISTs, and kidney cancers. Hestermann et al. [14] also screened with catecholamines and their 0-methylated metabolites. However, biochemical testing has already been previously shown to miss certain SDH-related tumors [17]. Hestermann et al. [14] also found that 28 of the 47 (59.6 %) patients with *SDHD* mutations had tumors, whereas no *SDHD* mutation carriers were included in our cohort.

Gimenez-Roqueplo et al. [15] found that in a cohort of *SDHD*, *SDHB*, or *SDHC* mutation carriers, 17.6 % of relatives were diagnosed with paragangliomas during screening. In their study, two radiological (head and neck

Table 5 Follow up performed for non-paraganglioma findings from whole-body MRI and biochemical testing

ID #	Reason for additional follow up	Additional follow up performed	Outcome
69629	Whole-body MRI revealed enlarged bilateral jugular nodes	Neck MRI	Normal nodes
59782	Biochemical testing revealed slightly elevated DA and CA	Biochemical testing repeated twice	Slightly elevated DA on first follow up and normal on second; No additional follow up recommended
48014	Whole-body MRI revealed 6 mm right carotid bifurcation mass called a paraganglioma	Whole-body MRI repeated	Follow up MRI revealed the mass was between the internal carotid artery and the internal Jugular vein, and not a paraganglioma
49214	Whole-body MRI revealed thyroid mass	Thyroid FNA and thyroid ultrasound	Normal, no additional follow up recommended
57355	Biochemical testing revealed slightly elevated DA and NE	Biochemical testing repeated	Normal, no additional follow up recommended
56522	Elevated CA and slightly elevated NE and NM	Whole-body 18F-FDG PET/CT scan plus a high resolution, magnified PET/CT of the head and neck with iodinated intravenous contrast	No evidence of recurrent, residual, or metastatic disease
		Biochemical testing repeated	Normal
70875	Whole-body MRI revealed a 4.0 × 3.0 cm mass in the liver	Abdominal MRI	Focal nodular hyperplasia, no additional follow up recommended
70611	A 1.7 × 0.9 cm lesion in the left paraspinous region at the level of T4, adjacent to the aortic arch, with markedly elevated T2-weighted signal, consistent with a paraganglioma	MRI chest-pelvis	Paraspinal cyst, no additional follow up recommended

18F-FDG PET/CT 18F-fluorodeoxyglucose positron emission tomography with computed tomography, *CA* chromagranin A, *DA* dopamine, *FNA* fine needle aspiration, *MRI* magnetic resonance imaging, *NE* norepeniphrine

magnetic resonance angiography and thoracic, abdominal, and pelvic CT scans) and two nuclear medicine ([^{123}I]metaiodobenzylguanidine scintigraphy and somatostatin receptor scintigraphy with ^{111}In-labeled pentetreotide scintigraphy) imaging techniques were evaluated [15]. The highest sensitivity was found (91.7 %) when both radiological tests were combined with somatostatin receptor scintigraphy [15]. However, the extensive nature (costs, time, etc.) of using these three separate tests is a limitation of their protocol, as is the concern of radiation exposure over a lifetime.

Whole-body MRI is a desirable alternative to various screening modalities such as ^{18}F-FDG PET imaging and CT scans, as there is no radiation exposure. Another advantage to this approach is that rapid sequence whole-body MRI evaluates the neck, thorax, abdomen, and pelvis at the same time. Therefore, patients do not have to set up separate MRIs to evaluate each of these body regions, which is often the case for region specific MRIs. The rapid sequence whole-body MRI takes substantially less time to complete than separate MRIs of the head, neck, thorax, abdomen, and pelvis, and can be completely within 1 h's time or less. At the conclusion of our SDH-related tumor screening study, we have since implemented a policy of re-evaluating any MRI finding suspicious of a paraganglioma or pheo with ^{18}F-FDG PET as this is the preferred method for tumor localization and to rule out metastases [18]. This approach also makes sense as SDH-related tumors are more likely to metastasize, thus the presence of one tumor warrants further evaluation for other occult tumors via PET scan. This is clinically important because if identified, the surgeon can remove all of the tumors during a single surgery.

Both biochemical testing and whole-body MRI missed tumors, five and one respectively. However the sensitivity of MRI (87.5 %) was higher than biochemical testing (37.5 %). It is not surprising that biochemical testing missed tumors since parasympathetic paragangliomas often do not secrete catecholamines or metanephrines. In addition, renal cancers (one was diagnosed in this study) and GISTs are not expected to secrete catecholamines or metanephrines, both of which are tumors associated with SDH mutations. Biochemical testing is also an enticing option due to the lower costs compared to various imaging modalities and also have been recommended by others as a sensitive method to detect secreting paragangliomas [17]. However, given the higher false negative rate than whole-body MRI in our study and since certain SDH-related tumors do not secrete catecholomines, metanephrines or chromogranin A, biochemical screening alone does not seem like the ideal candidate for early tumor detection.

The one tumor missed by whole-body MRI was actually seen on the images, but not until the MRI was read for a second time. We took a conservative approach and did not include this second read when determining the detection rate using whole-body MRI. However, if this second read was included, the sensitivity would have been 100 % for whole-body MRI. The sensitivity of whole-body MRI may improve with increased experience of the radiologists in interpreting images from these high risk patients. In addition, there were two whole-body MRI results in this cohort that were read out as paragangliomas, but later determined to not be paragangliomas. Both of these false positive results were easily clarified with one additional targeted MRI of the area in question. Three patients were also found to have an uncharacterized lesion by whole-body MRI and underwent additional imaging which revealed no SDH-related tumors or other cancers. Additionally, none of the patients in our study proceeded to surgical biopsy due to the false positive result. Although false positive and uncharacterized whole-body MRI results do occur, it is reassuring that this was not common in our study. Kidney cysts were found in 21.6 %, however it is not clear if this has any clinical relevance for these patients. The etiology of this high rate of renal cysts may be related to the inherited germline SDH mutations and needs to be investigated further.

There are several limitations of this study. Our sample size was relatively small. However, given the rarity of SDH mutation carriers, it is critical that results from even small screening cohorts are reported. Secondly, most of our cohort (89.2 %) had *SDHB* mutations. The mutations in the various genes in the SDH pathway are associated with different penetrance estimates and tumor distributions. Further studies will be needed to determine if our findings apply to patients at risk due to mutations in other SDH genes.

Also, additional imaging, such as ^{18}F-FDG PET, was not compared directly to whole-body MRI. However, given that we evaluated a clinical screening protocol, which requires patients to use their insurance for payment or pay out of pocket for the testing, additional imaging in our study could not be justified. In addition, radiation exposure from PET, CT, and ^{123}I-MIBG is a concern, especially given that SDH mutation carriers are already at high risk for tumors and it is unclear if radiation exposure over a long period of time will increase this risk. Lastly, the majority of patients underwent only one whole-body MRI and biochemical test and therefore follow up of these patients is limited at this time. It is quite possible that over a patient's lifetime that the ability of combined biochemical screening and whole-body MRI to detect early SDH-related tumors will be much higher than we report in our initial study.

Our findings demonstrate that tumor screening with rapid sequence, whole-body MRI is feasible for early

tumor surveillance and has a high sensitivity and specificity. Furthermore, whole-body MRI detected previously unknown SDH-related tumors in nearly one in five of our patients with no obvious symptoms. We recommend that patients with SDH mutations be offered whole body MRI as part of a tumor screening program, combined with traditional biochemical testing. Due to the high morbidity and tendency for malignant transformation of tumors in patients with SDH mutations, it is imperative to identify these tumors as earlier as possible. Rapid sequence, whole-body MRI provides clinicians with an important clinical tool to accomplish this. Additional studies are needed to compare the efficacy of screening using whole-body MRI with various modalities and in different cohorts. Longer term follow up in larger and different SDH mutation cohorts is also necessary and is ongoing.

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Conflict of interest None to declare.

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