1. Introduction

1.1 Purpose and objectives

Phaeochromocytomas are rare tumours in childhood. The rapid development of better and safer medical imaging techniques has resulted in a lack of data on the modern imaging characteristics of phaeochromocytomas in children. In addition, we correlated surgical, histological and imaging findings in order to try and determine what factors would affect the expected clinical outcome.

Our case series describes 15 children diagnosed with phaeochromocytomas at two tertiary level referral centres on two continents: Great Ormond Street Children's Hospital and The Johannesburg Academic Hospital Complex (Charlotte Maxeke Academic Hospital and Chris Hani Baragwanath Hospital).

1.1.1 Main objectives

i. to determine the imaging characteristics of phaeochromocytomas in children
ii. to correlate imaging, histological and surgical findings with clinical outcome

1.1.2 Secondary objectives

i. to document the demographic profile of children diagnosed with phaeochromocytomas as well as the clinical data at the time of presentation
ii. to correlate imaging features with the histological findings

1.2 Limitations

i. Retrospective data collection allows bias due to:
    a. Data deficiencies due to loss or incompletely recorded information
    b. Changes in diagnostic and surgical approaches
    c. Differences in data collection between different institutions involved in this study.

ii. Phaeochromocytomas are very rare in children, hence, the relatively small sample size (16 tumours in 15 children) and long period of data collection (21 years).

iii. Collecting the series from two national referral centres that serve populations from significantly different socioeconomic backgrounds on two continents may result in some bias mitigation.

iv. We note that there are significant differences in resource allocation between the South African and United Kingdom health care services.
    a. This difference is most evident at primary and secondary levels of health care, which are significantly underdeveloped in South Africa.
    b. This would conceivably result in a delay in the diagnosis and referral of children with phaeochromocytoma in South Africa as compared to the United Kingdom.

c. There is a significant possibility that many cases are going undetected in South Africa due to a large proportion of South Africans having poor access to health care.
d. Once children gained access to specialist care at the institutions we reviewed, we feel that both groups of children received comparable care with similar access to diagnostic tests and similar disease management.

In an attempt to limit bias, all the data was collected by the primary investigator (GS).

2. Literature review

A PubMed search was performed using the terms:

'phaeochromocytoma', 'pheochromocytoma' and 'paraganglioma'

The search was restricted to articles published in English and in study populations aged 0-18 years.

2.1 Definition

Phaeochromocytoma : from Greek phaios dusky, grey cell[1].

The WHO (World Health Organization) classifies phaeochromocytomas as intra-adrenal paragangliomas. Tumours related to the extra adrenal sympathetic and parasympathetic paraganglia are classified as paragangliomas [2]. In this report, we use the term 'phaeochromocytoma' to refer to both intra and extra adrenal paragangliomas. Malignant disease is defined as the presence of metastatic lesions outside of normal chromaffin cell containing sites.

2.2 Demographic and clinical

This rare childhood tumour with an estimated incidence of 8:1 000 000 [3] represents the most common paediatric endocrine tumour of which 80% arise from the adrenal medulla [4].

The formerly used 'Rule of 10's': 10% bilateral, 10% malignant, 10% extra adrenal, 10% in childhood, 10% familial, has been challenged [4].

Approximately 40% of phaeochromocytomas are associated with genetic mutations[5], 8-43% are extra-adrenal and 19-38% are bilateral [6].

The mean age of children diagnosed with phaeochromocytomas is 11 years with a male predominance (2:1). The clinical presentation of phaeochromocytomas is highly variable in childhood. Most symptoms are secondary to elevated levels of catecholamines or their metabolites. Children usually present with signs and symptoms related to elevated blood pressure. Sustained hypertension is found in 60-90% of childhood phaeochromocytomas, as compared to only 50% of adults. It is important to note that other causes of hypertension should be sought first as phaeochromocytomas are only present in 1% of paediatric hypertensives [6]. Normal blood pressure does not exclude a phaeochromocytoma and there is no clear correlation between catecholamine levels and symptoms[7,8].

Other described symptoms and signs of phaeochromocytomas in children include palpitations, headaches, excessive sweatiness, pallor, nausea, vomiting, weight loss, polyuria and visual disturbances. Phaeochromocytomas have been described in patients presenting with bouts of anxiety and even caused the misdiagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in children [4]. Symptom events can be triggered by physical activity; direct stimulation of the tumour (such as emptying of the bladder); food containing caffeine; medication such as: glucagon, tyramine, metoclopramide, tricyclic antidepressants and radiographic contrast agents [4].

Due to the high prevalence of a hereditary basis for phaeochromocytomas (approximately 40% [5]), genetic testing should be performed. Hereditary phaeochromocytoma syndromes include: Multiple Endocrine Neoplasia type 2 (MEN2), von Hippel-Lindau syndrome (VHL), Neurofibromatosis type 1 (NF1) and familial paraganglioma syndromes (succinate dehydrogenase gene mutations [4].

2.3 Biochemistry

Almost all phaeochromocytomas produce catecholamines or their metabolites and are generally found in the abdomen, pelvis and less frequently in the thorax.

Biochemical testing forms the first choice diagnostic investigation in children with symptoms and signs suggestive of phaeochromocytomas, an incidental adrenal mass and in children of parents with paraganglioma syndromes. Traditional biochemical testing includes measurement of 24 hour urinary and plasma catecholamines and their degradation product - urinary vanillymandelic acid (VMA). It has been shown though that metabolites (normetanephrine and metanephrine) are more accurate in the diagnosis of phaeochromocytomas in both adults and children [9]. It is important to note that some neuroblastomas may also secrete dopamine [10].

Invasive testing (including imaging studies using ionising radiation) to localize tumours should only be performed after biochemical confirmation of a catecholamine secreting tumour.

2.4 Imaging

2.4.1 Ultrasound

Ultrasound of the abdomen and pelvis is usually the initial investigation to locate phaeochromocytomas as they are usually located within the abdomen and 80% are situated within the adrenal medulla [4]. Although ultrasound is well known to have relatively low and user dependent sensitivity, it has no ionising radiation risk to the patient and is cost efficient and widely available.

2.4.2 Magnetic Resonance Imaging (MRI)

MRI of the abdomen and pelvis has become the cross sectional imaging modality of choice. MRI sensitivity ranges from 90-100% [11]. However its ability to specify a phaeochromocytoma from other pathology is low.

The imaging features of phaeochromocytomas on MRI is classically described as hypointense signal on T1 Weighted Imaging (T1WI) and hyperintense signal on T2 Weighted Imaging (T2WI). The high signal on T2WI is sometimes referred to as the “light bulb” sign[12]. If fat is present within the tumour, it would display a low signal on fat suppression sequences such as STIR (Short Tau Inversion Recovery) with the rest of the tumour hyperintense. Tumours usually enhance avidly post contrast.

It is important to note that MRI characteristics of these tumours vary widely with cystic changes and haemorrhages also adding to the diverse MRI findings[13].

2.4.3 Multidetector Computed Tomography (MDCT)

On Multidetector Computed Tomography (MDCT) studies, most phaeochromocytomas are solid with homogenous enhancement. Variants include cystic changes as well as heterogeneous appearance. Phaeochromocytomas do not necessarily obey the typical contrast washout characteristics of adrenal lesions. Low density on the pre-contrast scan and rapid washout of contrast in delayed phases is not reliable in excluding a phaeochromocytoma. The solid parts of these tumours usually enhance avidly on post contrast images, which reflects their capillary rich nature and this is the typical enhancement pattern of phaeochromocytomas.

2.4.4 Nuclear medicine

Due to the low specificity of MRI, ultrasound and Multidetector CT; functional imaging using I^{123} metaiodobenzylguanidine (MIBG) is utilized to confirm the diagnosis and direct the search for paragangliomas in other locations[14]. A prospective study by Wiseman et al demonstrated a sensitivity of 82%-88% and specificity of 82%-84% for I^{123} MIBG imaging of primary or metastatic phaeochromocytoma or paraganglioma[15].

Neuroblastomas may also take up MIBG and should feature in the differential diagnosis[16] of MIBG avid lesions. It has been reported that malignant paragangliomas lose the ability to concentrate MIBG thus reducing the detection rates of these lesions [17,18].

2.5 Histology

Phaeochromocytomas and paragangliomas usually have a characteristic histological appearance, being composed of a prominent nested pattern – “Zellballen”, with delicate spindle cell septae, the other major architectural pattern being prominent trabeculae. The tumour cells themselves usually appear similar to normal chromaffin cells with eosinophilic cytoplasm and prominent nucleoli.

There may be mild to moderate degrees of nuclear pleomorphism, but even a marked nuclear pleomorphism does not necessarily indicate malignant behaviour.
Areas of haemorrhage and haemosiderin deposition are common although mitoses are rare.

The definitive prediction of malignant behaviour in these tumours can only be made if metastatic disease is present. However, several histological features have been suggested as more common in phaeochromocytomas with malignant behaviour. These include the presence of capsular invasion, vascular invasion, extension into the surrounding soft tissues, necrosis and marked nuclear pleomorphism, particularly if associated with the presence of abnormal mitotic figures.

In addition, tumour size and weight are associated with malignant behaviour, larger tumours having an increased likelihood of malignant biology.

However, it should be made clear that no particular histological feature can unequivocally determine whether a given tumour will behave in a benign or malignant fashion.

Immunohistochemical staining confirms the diagnosis, phaeochromocytomas expressing Chromogranin A, with S100 staining highlighting the characteristic sustentacular spindle cells [19].

2.6 Management and follow up

Surgical excision is the mainstay of treatment. In 1951 peri-operative mortality for patients with Phaeochromocytomas was 45% and surgeons were taught to 'dissect the patient away from the phaeo' [20]. The latest peri-operative mortality figures for many centres is now 0%. This is mainly due to the aggressive management of blood pressure pre- and post-operatively as well as improvements in intensive post-operative care. Laparoscopic excision, previously thought to be too risky in the management of Phaeochromocytomas is now becoming much more common and is an accepted and increasingly popular approach[21]. Chemotherapy and radiotherapy are only useful in controlling the effects of excess catecholamines and do not achieve cure or remission [22].

Long-term follow up with regular blood pressure measurement is essential to detect local recurrence or metastases. This will also involve laboratory (urinary VMA) and radiological (usually ultrasound) investigations [22].

Paragangliomas have a higher rate of recurrence than Phaeochromocytomas [12]. Recurrence rates vary depending on length of follow-up however one series of 13 children had a recurrence rate of 30%, both locally and within the opposite adrenal[23].

Prognosis overall is excellent for benign Phaeochromocytomas.
In malignant phaeochromocytomas the overall survival ranges from 45%-55% 5 year survival rate [22].

3. Methods

The records of 15 children (<18 years of age at the time of diagnosis) with confirmed histological diagnosis of phaeochromocytomas were retrospectively reviewed. One child was excluded from the study as insufficient imaging and histological data was available. The series therefore consists of 16 children.

The records dated from 1990 to 2011 (21 years). The study was conducted in South Africa and the United Kingdom at two national referral centres: Great Ormond Street Hospital (GOSH) in London and the Johannesburg Academic Hospitals Complex (JAHC) (Chris Hani Baragwanath Academic Hospital and the Charlotte Maxeke Johannesburg Academic Hospital).

The choice of two sites in two countries was due to the primary investigator (GS) working at all of the institutions, which enabled the collection of this large series.

The review began in March 2006 and recruitment to the series ended in October 2011.

A retrospective review of available records in children with confirmed histological diagnosis of phaeochomocytoma was conducted. The children were all known to the endocrine or oncology clinics of the involved hospitals. National oncology data-bases were not consulted. 11 children were added to the study in this manner. 7 children were patients at GOSH and 4 children were from the JAHC.

5 children with phaeochromocytomas were added to the series after this study commenced. 1 from GOSH and 4 from the JAHC.
Therefore data was collected retrospectively and contemporaneously.

Ethical approval has been granted by the Ethics Committee of the Faculty of Health Sciences, University of the Witwatersrand. Reference M061014. *Appendix 2*

Ethical approval has been granted by the partner site – Great Ormond Street Hospital, Institute of Child Health, University College Hospital, London, UK. Reference 06RP14. *Appendix 3*.

All clinical records were reviewed by the primary investigator GS.

Histological diagnosis was obtained after surgical resection and by haematoxylin and eosin staining. Pathological assessments were performed by multiple pathologists, all of whom have specialist qualifications.

The actual images from the radiological investigations were not available for many of the patients and we have relied on the radiological reports from those studies. Where possible, original images were reviewed.

Follow up was conducted by recent clinic visits or telephonic correspondence. Patients were followed up until either contact was lost or they had died.

In 8 patients, follow up data was not available or the patients were lost to follow up.

One patient was very ill at the last visit and is presumed to have died after being followed up for 83 months.

Follow up time for the remaining 7 children as of October 2011 was between 1 month and 132 months (mean 43 months).

Data was recorded on the attached data sheet labelled *Appendix 4*. Columns indicate:

- Clinical data including: demographic data, clinical presentation and blood pressure at time of presentation.
- Blood and urine biochemistry - metabolic by-products of catecholamine breakdown.
- Imaging features on ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI).
- Nuclear radioisotope uptake and imaging.
- Surgical intra-operative findings.
- Histological findings.
- Follow up clinical data.

This data was further broken down to aid analysis in the tables attached to this report and labelled *Appendix 5*.

Determination of local spread was from the intra-operative surgical notes that described whether the tumour was fixed or encapsulated and whether it involved adjacent organs.

Metastatic spread is defined as tumour deposits in sites that are not normal locations of chromaffin containing cells.

Follow up was on the basis of clinical findings (especially blood pressure), biochemistry (urine catecholamine breakdown products) and by means of imaging if there was clinical concern about recurrence.

No statistical analysis software was used.

No intervention was made

No controls were used.

The project did not require any funds and the authors did not apply for or receive any remuneration.

4. Results

The results have been included at the end of this dissertation:

- The primary data collection sheet is marked *Appendix 3*.
- The results have been summarised and tabulated in *Appendix 4*.

Our series describes 16 phaeochromocytomas in 15 children collected from 1990-2011 (21 years). A metachronous tumour was found in a single patient. One patient had bilateral adrenal gland tumours at the time of presentation. The metachronous case has been counted as two tumour events, whereas the bilateral case has been counted as a single event.

4.1 Clinical and demographic data

The mean age of our study population is 11 years, age range 7-14 years (174 years divided by 16 tumour events).

Eight patients were collected from Great Ormond Street Children's Hospital (n=8) and 7 were collected from the Johannesburg Academic Hospital Health Complex (n=7).

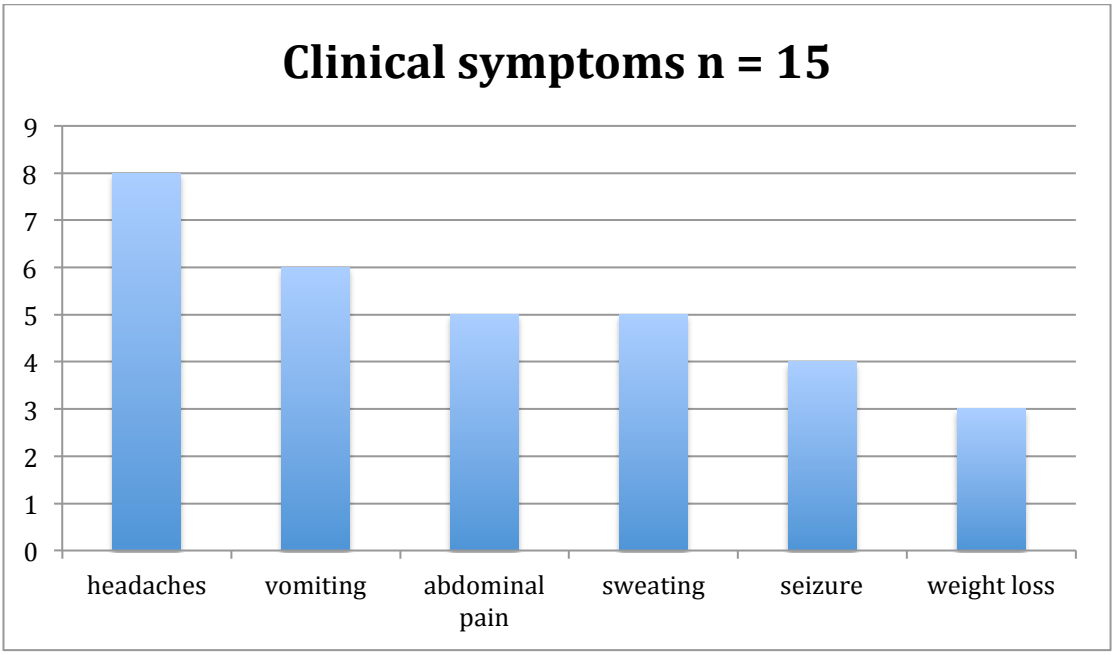
There was a male predominance (n=11) of 69%.

Blood pressure at presentation was recorded in 12 out of 16 tumour presentations.

Children were found to be hypertensive at the time of presentation in 10 out of 12 cases (83%).

Children presented with a variety of clinical symptoms and signs associated with metabolically active phaeochromocytomas. These have been tabulated per tumour presentation however in one patient, no clinical notes could be found (n=15).

Table 1



- Less frequent symptoms included dizziness, cold extremities, palpitations and eye pain.
- In one tumour presentation, the patient presented only with haematuria and no symptoms of catecholamine excess.
- In one tumour presentation, the child was asymptomatic but was found to be hypertensive on routine follow-up. The patient had previously had a phaeochromocytoma surgically removed.

4.2 Biochemistry

Biochemistry results were recorded in 13 out of 16 tumour presentations. Abnormal urine catecholamines or their metabolites were found in all recorded presentations 13 out of 13 (100%).

4.3 Location

Tumours were adrenal (n=11) and extra adrenal (n=5) in location.

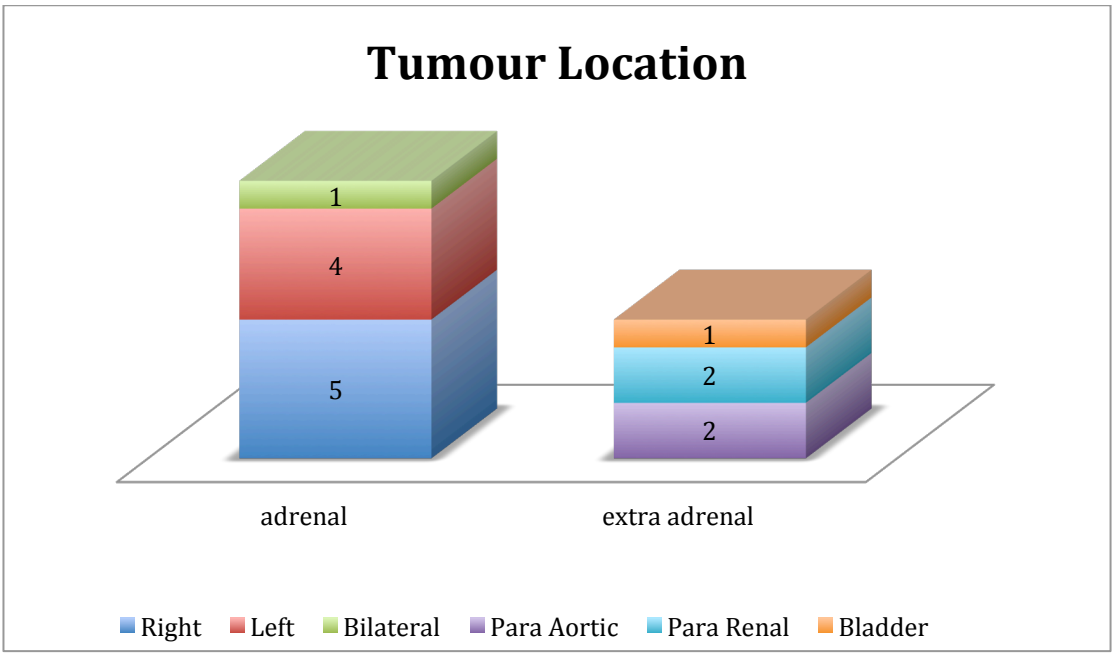
Of the adrenal based tumours (n=11):

- Left sided adrenal tumours (n=4)
- Right sided adrenal tumours (n=6)
- Bilateral at the time of presentation (n=1)
- One patient had metachronous adrenal tumours. A tumour was found in the opposite adrenal gland 3 years after the diagnosis of the first tumour.

Of the extra-adrenal tumours (n=5)

- 2 tumours were para-aortic.
- 2 tumours were described by the surgeon as being located in the renal hilum.
- In one case, the tumour was located in the urinary bladder wall.

Table 2


Tumour Location
1
4
5
1
2
2
adrenal
extra adrenal
Right
Left
Bilateral
Para Aortic
Para Renal
Bladder

4.4 Imaging findings

Imaging modalities that were used in our series were:

- Ultrasound
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Nuclear Medicine.

4.4.1 Ultrasound

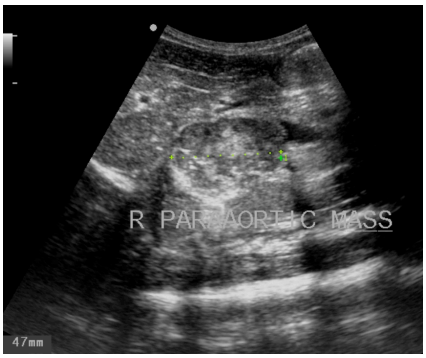
Ultrasound (sonar) was performed and the results recorded in 10 tumour presentations. Findings where of a soft tissue adrenal/suprarenal masses with varying vascularity and echogenicity (hyperechoic, hypoechoic and mixed echogenicity). *Figures 1.1 and 1.2.* Other sonographic findings included a thickened bladder wall, and a septated adrenal mass.

It is important to note the following shortcomings in the reviewed ultrasound reports. 4 out of 10 ultrasound reports contained a significant error.

i. Liver metastases were missed on the ultrasound examination.
ii. A para-aortic mass was identified and the adjacent adrenal gland was reported as normal. The surgeon found an adrenal mass with para-aortic extension.
iii. A renal hilum mass was missed on the original ultrasound; it was however discovered after review.
iv. An adrenal mass seen on sonar was found to be normal at surgery. It is important to note that in this case a CT scan was performed which does indeed show an enlarged left adrenal gland. *Figure 2.1*

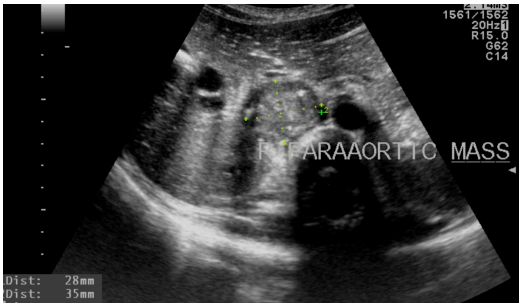
Figure 1

Figure 1.1



11 year old male. Ultrasound image of the right flank in the longitudinal plane shows a mixed echogenic mass adjacent to the aorta 47mm in diameter.

Figure 1.2



The same patient, as *Fig 1.1*. In this ultrasound image, the tumour seen above is in the transverse plane.

4.4.2 Multidetector Computed Tomography (MDCT)

MDCT data was available in 12 tumour presentations. The primary investigator (GS) was able to obtain and review the images of 6 of these presentations. In 6 presentations, the data recorded in the radiological report or in the patient's clinical notes was used in this study.

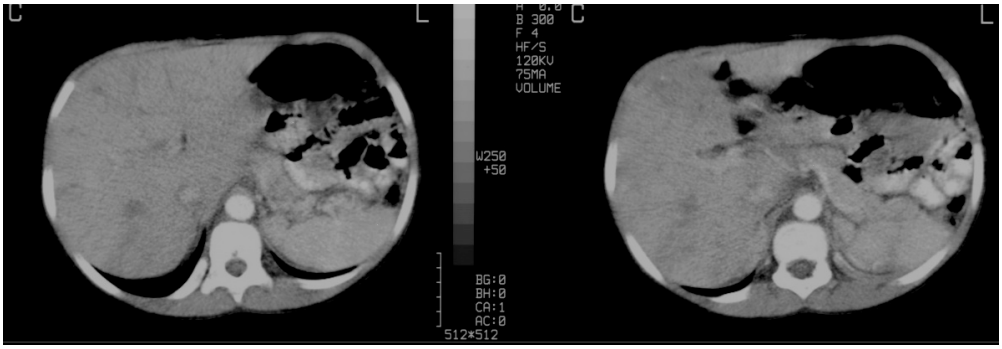
Soft tissue masses diagnosed as phaeochromocytomas had widely varying imaging characteristics. *Figures 2.1, 2.2, 3, 4.1 and 4.2*:
Homogenous enhancement; heterogeneous enhancement; central hypodensity possibly due to necrosis; peripheral enhancement; hyperdense mass on non contrast CT possibly due to haemorrhage. No distinct imaging characteristics could be identified that can be described as typical for a phaeochromocytoma.

In one case, an adrenal mass identified on sonar and MDCT was described as normal by the surgeon. *Figure 2.1*.

In another case a left adrenal mass later confirmed on histology was not identified in the CT scan (the CT was not available for review); however the adrenal mass was clearly visible on an MRI performed 3 weeks later *Figure 5* below.

Figure 2

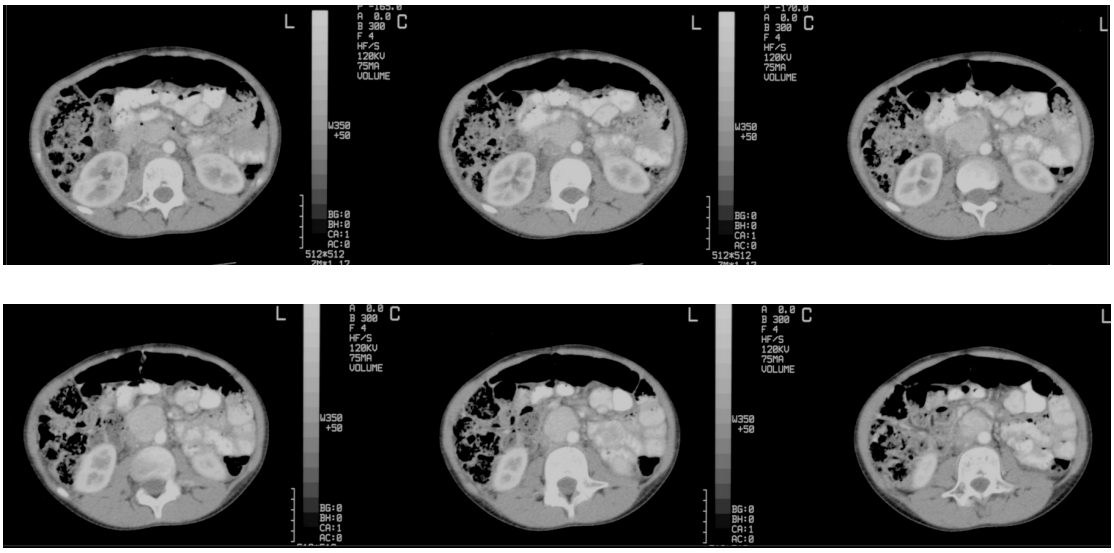
Figure 2.1



14 year old male. Post contrast MDCT shows a mass in the region of the left adrenal gland. The left adrenal gland was reported to be normal by the surgeon after laparotomy.

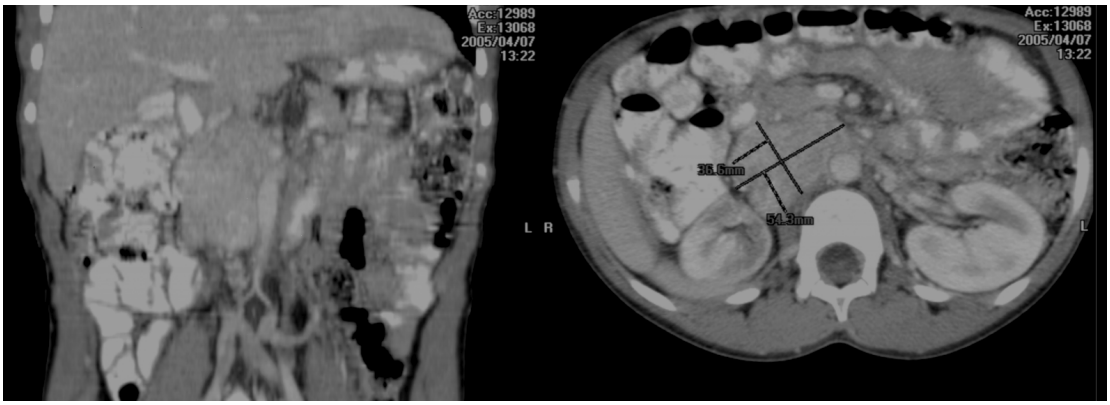
An ill defined mixed density lesion is noted involving segments 6 and 7 of the right lobe of the liver. This was confirmed to be a liver metastasis. The liver lesion was missed on ultrasound examination.

Figure 2.2



The same patient as 2.1 above. This contrasted MDCT shows the mid-abdominal para-aortic mass situated between the IVC and the aorta.

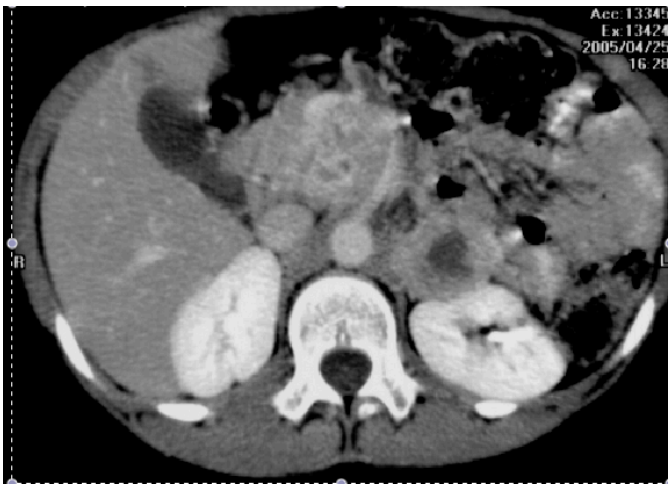
Figure 3



11 year old male. Post contrast MDCT of the abdomen shows a large right sided para-aortic mass involving the inferior vena cava (IVC). Note the delayed asymmetrical enhancement of the right kidney. The right renal vein was confirmed to be involved by tumour. Unresectable tumour inseparable from the IVC, aorta and right renal vein was surgically debulked. Histological diagnosis was an extra-adrenal paraganglioma.

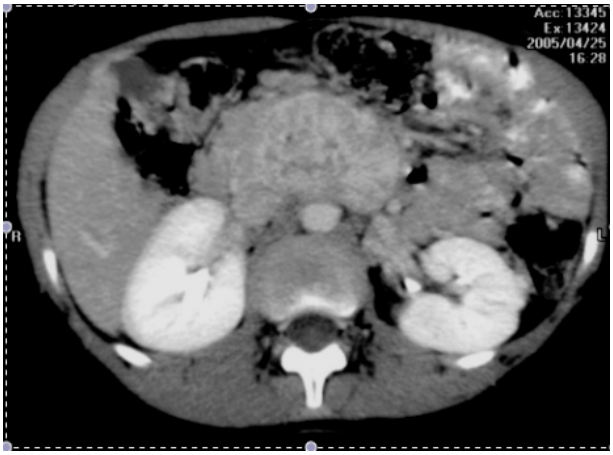
Figure 4

Figure 4.1



Post contrast MDCT of the abdomen in a 12 year old female. The patient was diagnosed with a right adrenal phaeochromocytoma 5 years previously for which she underwent an adrenalectomy. The patient was found to be hypertensive at routine follow up appointment which prompted a search for recurrence or a metachronous tumour. A left adrenal mass with central low density that is most likely due to necrosis. This lesion was missed on ultrasound of the abdomen

Figure 4.2



Post contrast MDCT of the abdomen. The same patient as *Figure 4.1* above. A large tumour is located anterior to the aorta and IVC and it is inseparable from the IVC. It has low density structures within it which on histological examination, was confirmed to be cystic degeneration and focal haemorrhage within the tumour.

4.4.3 Magnetic Resonance Imaging (MRI)

MRI findings were recorded in only 4 out of 16 disease presentations (25%). Please see *figure 5* for a phaeochromocytoma and *figures 6.1 and 6.2* for hypertensive changes in the brain of a child with hypertensive encephalopathy and subsequently confirmed phaeochromocytoma.

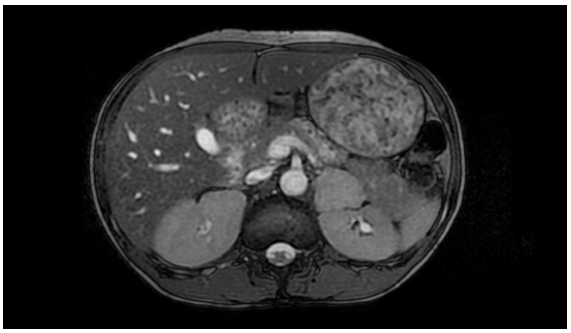
Table 3

MRI signal characteristics of phaeochromocytomas

	T1WI	**T2WI**	**STIR**	**Enhancement**
Bladder paraganglioma	Low	Intermediate to Low	Low	Minimal
Renal hilum	Low	High	High	Intense central with delayed peripheral enhancement
Adrenal*	-	Intermediate	-	-
Adrenal	Isointense	Foci of high signal	-	-

* In this case a limited MRI was performed of the renal arteries to exclude suspected renal artery stenosis as a cause for the patient's hypertension. A previously unidentified (missed) adrenal mass was seen on this investigation.

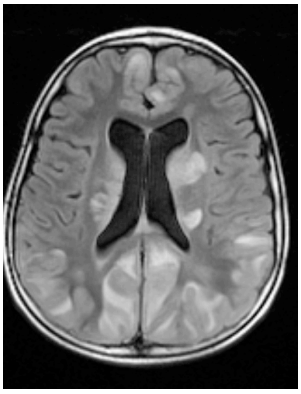
Figure 5

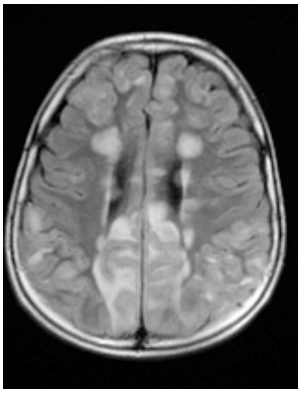


13 year old male. T2 WI with fat saturation shows a left adrenal mass with isointense signal compared to the adjacent kidney.

Figure 6

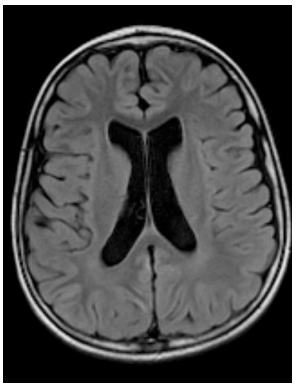
Figure 6.1

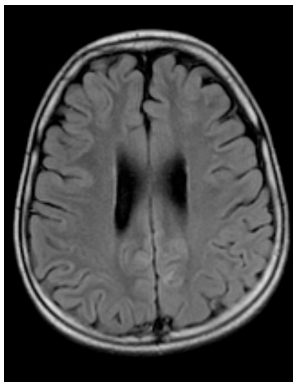




8 year old male. FLAIR (Fluid Attenuated Inversion Recovery) sequence. The patient presented in status epilepticus. The MRI shows symmetrical hyperintense signal affecting the deep white matter of the medial portions of the occipital lobes bilaterally and the subependymal white matter. The patient was subsequently found to be hypertensive.

Figure 6.2





Two months later and after antihypertensive treatment, the MRI was repeated. This study shows complete resolution of the abnormal high FLAIR signal. Confirming the diagnosis of hypertensive encephalopathy.

4.4.4 Nuclear medicine

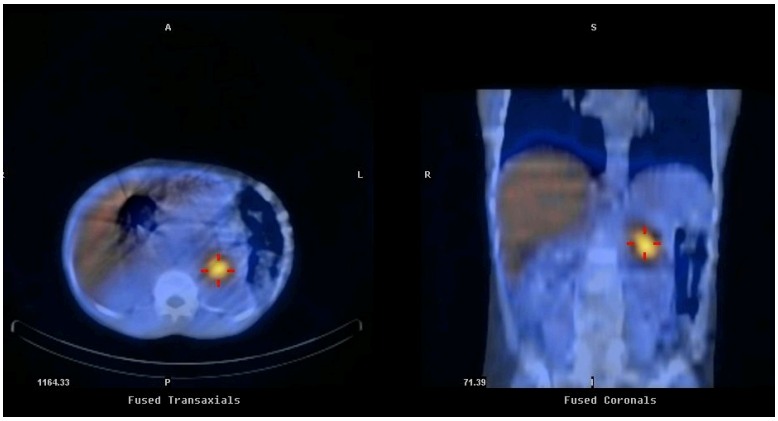
Traditionally, metaiodobenzylguanidine (MIBG) scintigraphy *(figure 7)* has been the radioisotope of choice to:

- determine the metabolic activity of phaeochromocytomas
- identify occult tumours or metastases
- treat unresectable tumours

MIBG scintigraphy was recorded in 11 tumour presentations. 10 of these cases had positive MIBG uptake.

One case (1:11) with a confirmed left adrenal phaeochromocytoma had no significant MIBG uptake (9.1%).

Figure 7



MIBG with fused SPECT/CT showing intense uptake in the left adrenal gland

Gallium 68 DOTA-D Phe^{1}-Tyr^{3}-Octreotide positron emission tomography (^{68}Ga-DOTATOC PET) has recently emerged as useful in imaging phaeochromocytomas. Studies have shown it to be comparable to MIBG if not superior [24]. This test was performed on the last patient in this series which showed avid uptake in the right adrenal gland.

4.5 Surgical findings

Surgical data was available in 13 out of 16 tumour presentations. Local invasion at surgery was found in 8 tumours out of the 13 available reports (62%) with tumours having been described as ‘stuck down’, ‘difficult resection’, ‘adherent’ or inseparable.

In 6 out of the 13 reported cases (46%) the tumour involved a vital structure or could not be completely removed with the operation being described as difficult.

4.6 Histo-pathological findings

Histology reports were available for the all 16 diagnosed tumours. Typical histological findings (Zellballen or nested cells) were found in all cases.

The size of the tumour was reported in all 16 cases:

Size greater than or equal to 5cm (n=7) 44%

Size less than 5cm (n=9) 56%

The tumour capsule is mentioned in all 16 cases

Capsular invasion (n=9) 56%

Capsule intact (n=7) 44%

Greatest cross sectional dimension on imaging (MDCT, MRI or Ultrasound)

Tumour diameter was only recorded in 8 out of 16 presentations.

Tumours greater than 5cm (n=4) 50%

Tumours less than 5cm (n=4) 50%

4.7 Outcome and follow up

Follow up data is available in 7 out of 15 children.

One patient with sustained hypertension did not return for follow up and is presumed deceased. This patient's total follow up time was 83 months (6 years and 11 months) until the patient was lost to follow up.

Two patients had incomplete resection and residual functioning tumours as was evident by persistent hypertension at the time of clinic visits. Follow up duration is 134 and 110 months each.

They are otherwise healthy children.

Four patients remained well not requiring any antihypertensive treatments. Follow up duration is 24, 22, 11 and 2 months respectively.

Total average duration of follow up was 55 months (4 years and 7 months).

5. Discussion

Our study contains one of the largest data sets of children with paragangliomas comparable to already published series [25,26,27].

We set out to:

i. Determine the imaging characteristics of phaeochromocytomas in children
ii. Correlate imaging, histological and surgical findings with clinical outcome
iii. Document the demographic profile of children diagnosed with phaeochromocytomas as well as the clinical data at the time of presentation
iv. Correlate imaging features with the histological findings

5.1 Imaging of phaeochromocytomas

Ultrasound is well known to be an operator dependent modality with widely varying sensitivity and specificity. In our series we found that in 4 out of 10 (40%) ultrasound reports, a significant finding was misreported:

1. A renal hilum mass was missed on the original ultrasound but it was discovered in a subsequent sonar examination after review.
2. An adrenal mass seen on sonar was found to be normal at surgery.
3. Liver metastases were missed on the ultrasound examination.

4. A para-aortic mass was identified and the adjacent adrenal gland was reported as normal. The surgeon found an adrenal mass with para-aortic extension.

MDCT was performed in 12 patients. We could find no MDCT imaging characteristic that we could declare as ‘typical’ for phaeochromocytomas. Our MDCT imaging findings varied from peripheral enhancement, central hypodensity, hyperdense or hypodense masses.

MDCT missed one adrenal mass (later histologically proven to be a phaeochromocytoma) that was later seen on MRI.

In one case an adrenal mass identified on MDCT was determined to be normal by the surgeon intraoperatively.

Therefore the sensitivity of MDCT in detecting phaeochromocytomas in our series was 10 out of 11 or 91%.

A false positive rate of 1 out of 12

A false negative rate of 1 out of 12.

MDCT has an advantage over MRI in the paediatric population due to speed of image acquisition. MRI may require a general anaesthetic (especially in the younger child) and has long sequence acquisition times resulting in movement artefact.

It is important to note that the use of intravenous iodinated contrast to perform contrasted MDCT carries a risk of anaphylactic reaction and renal function

compromise. None of the patients in our series suffered either of these complications. Prophylactic treatment for anaphylactic reactions was not given to any of the patients.

MRI was performed in only 4 out of 16 cases (25%) in our study. This may be due to the fact that abdominal MRI was not widely used at the time that many of these patients were diagnosed with phaeochromocytomas. No false positive or false negative results were obtained. Sensitivity was 100%. It is important to note that in all cases a phaeochromocytoma was highly suspected by clinicians due to strongly positive biochemical markers and/or positive MIBG scans. We suspect that a larger group of patients, in which phaeochromocytoma is not suspected, may have a very different sensitivity profile.

The classical imaging description of a “lightbulb” sign and avid enhancement of phaeochromocytomas was not observed in our series [12]. T1WI and T2WI intensities were variable as was tumour enhancement.

MIBG scintigraphy had a sensitivity of 91% (10 positive out of 11 tumours tested). This is in keeping with the study from Wiseman et al that showed a sensitivity of 82%-88% and specificity of 82%-84% for I^{123}MIBG imaging of pheochromacytomas[15] False negative findings on MIBG is thought to be due to malignant phaeochromocytomas being unable to concentrate MIBG due to the immaturity of the cells [17,18].

MIBG is also used in the treatment of metastatic or unresectable tumours. Multiple therapeutic doses are administered over time.

A single patient underwent Ga^{68} DOTATOC PET/CT which has recently emerged as a useful radioisotope in imaging phaeochromocytomas [24].

5.2 Correlating imaging, histological and surgical findings with clinical outcome

Pham et al[26] in their 2006 study of 30 children with phaeochromocytomas, found that larger tumours are more likely to be malignant than smaller tumours. The mean average size for malignant tumours in their series was 8.6 ± 1.3 cm versus benign tumours measuring 4.5 ± 0.4cm.

We could find no correlation between tumour size and the incidence of metastatic disease. In our series, 3 children with known metastases had primary tumour sizes of 3cm, 4cm and 5cm respectively which is not in keeping with the literature[26].

In our series, the presence or absence of local invasion was noted by the attending surgeon in 13 tumour presentations. In 8 of these cases cross sectional diameter measurement was available for imaging or histology. We found that where local invasion was thought to be present at the time of surgery, median tumour size was 5 ± 2cm. This suggests that larger tumours are more likely to be technically difficult to resect. We could not find any literature where tumour size was correlated with local invasion in children. This is therefore a novel finding.

Unfortunately we were unable to gain access to any of the follow up data of the Great Ormond Street Hospital patients. Due to administrative capacity limitations a moratorium had been imposed on requests for research data from that institution.

Children who attended the Johannesburg Academic Hospitals Complex (n=8) were followed up for between 2 to 134 months. Mean 4 years and 7 months.

One patient was very ill at the time of his last clinic appointment. By that time, he had been followed up for 83 months (6 years and 11 months). He was then lost to follow up. The clinic failed to contact him despite pursuing every means of contact. He is presumed to have died.

Two patients are still being treated for hypertension after surgery and MIBG therapy. Therefore 25% continue to harbour metabolically active cells despite surgery and nuclear therapy.

6 of the 8 patients that were followed-up, had capsular invasion on histological examination (75%) and two patients had metastatic disease at the time of presentation; yet, only one child is presumed to have died.

Therefore, despite the poor socioeconomic background of the South African group, and the presence of advanced disease in 75% of presentations, the mortality rate in almost 5 years of follow up was 13%.

5.3 Clinical symptomatology and demographic profile

The mean age of presentation was 11 years with male predominance of 11:4 (69%). This was comparable to most published case series[6].

The four most common presenting symptoms were headaches, vomiting and abdominal discomfort and sweating.

Hypertension at the time of clinical presentation was present in 83% of tumour presentations. This emphasizes the fact that these tumours secrete catecholamines intermittently and therefore a normal blood pressure reading does not exclude a phaeochromocytoma.

In children paragangliomas also tend to present as abdominal masses more than in adults, and this may be reason for the vomiting and abdominal discomfort found in our series[28].

Tumours were mostly adrenal in location (69%) with a small right sided predominance (55%).

A single child had bilateral adrenal tumours.

Extra-adrenal locations of tumours were para-aortic, para-renal hilum and on tumour was situated within the urinary bladder wall. These findings are supported by the more recent literature[6].

One child had metachronous adrenal tumours. A new adrenal tumour was diagnosed 3 years after surgical excision of a phaeochromocytoma in the opposite adrenal gland.

No child in our series was proven to suffer from a genetic syndrome that is known to be associated with phaeochromocytomas. Genetic testing for chromosomal anomalies associated with phaeochromocytoma was not performed on any of our patients.

The initial work-up for a suspected phaeochromocytoma consists of measuring plasma or urine catecholamines and their metabolic breakdown products. The measurement of 24-hour urine adrenaline and noradrenaline breakdown products is a non invasive way to confirm excessive catecholamine secretion and is highly sensitive and specific in the diagnosis of phaeochromocytomas in both adults and children [9]. In our series, we found that the measurement of urinary catecholamine breakdown products had a sensitivity and specificity of 100%.

5.4 Correlation of imaging features with the histological findings

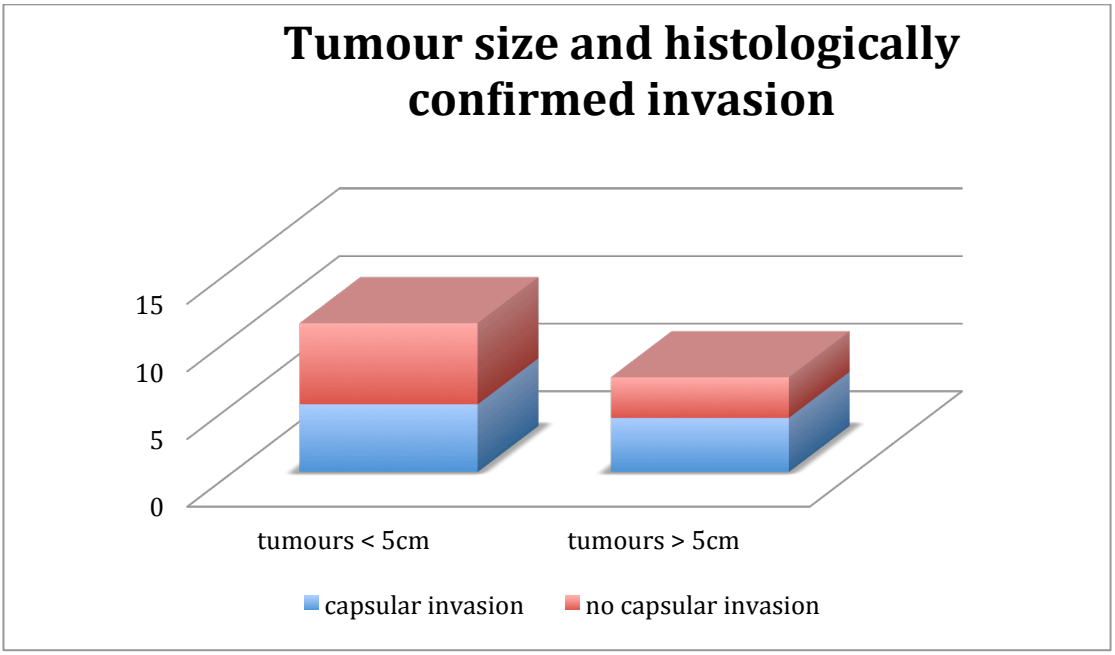
All of the resected tumours in our series (n=16) had histological features that are classically described as and consistent with being a phaeochromocytoma.

Local invasion was found in tumours sized 3, 4, 5.4, 5.6, 6 and 7cm. This meant that larger tumours were more likely to be technically difficult to resect.

Table 4

As stated in 5.2 above; we could find no correlation between tumour size in our series and the incidence of metastatic disease, which is not in keeping with the literature[26].

Table 4



6. Conclusion and recommendations

- Phaeochromocytomas are exceptionally rare in children. The old description of the '10% tumour' (10% extra adrenal, 10% familial, 10% bilateral and 10% malignant and 10% in children) no longer holds true.
- We have found that in children with hypertension, the presence of raised plasma and/or urine catecholamine levels will identify the presence of a phaeochromocytoma.
- We suggest that an MIBG nuclear medicine scan will identify the vast majority of phaeochromocytomas and assist in determining the focal point of cross sectional imaging.
- In our opinion MIBG should be the initial investigation of choice for patients with the appropriate clinical symptomatology and abnormal catecholamine biochemistry. MIBG that precedes cross sectional imaging will pick up tumours in occult locations that may not be covered on MDCT or MRI scanning such as the head and neck. Cross sectional imaging can be performed after MIBG to define anatomy and pick up the rare tumours that do not accumulate MIBG.
- We found an extremely high error rate in the sonographic detection of phaeochromocytomas in children (40%). Many authors point to the advantages of ultrasound (low cost, high availability and no ionizing radiation) and therefore tend to recommend it as a good baseline investigation [29, 30, 31,32].
- The very high rate of error (40%) of ultrasound can seriously mislead clinicians and therefore, in our opinion, ultrasound adds no benefit.

- We suggest that positive biochemical findings should be followed by either MIBG scintigraphy and MDCT or MRI.
- MRI has been put forward as the imaging technique of choice for the diagnosis of phaeochromocytoma due to its safety profile, multiplanar capability and high sensitivity [12]. MDCT may actually be better in defining these tumours due to the speed of image acquisition. Modern MDCT has multiplanar reconstruction capability, which along with multiphasic imaging, allows excellent preoperative surgical planning.
- The phaeochromocytomas in our study, showed a wide range of imaging characteristics on MDCT so that no specific imaging finding can be said to be typical of a phaeochromocytoma.
- MDCT and MIBG scintigraphy had sensitivities of 91%.
- MRI had a sensitivity of 100% in our group; however, this was in a very small subgroup of children with a high index of suspicion for phaeochromocytoma.
- We found that phaeochromocytomas had a wide range of imaging characteristics on MRI with no 'typical' imaging findings.
- We found no correlation between the size of the tumour and capsular invasion or the presence of metastatic disease. This is not in keeping with most of the literature.
- Children with phaeochromocytomas tend to have excellent long term clinical outcomes, even in cases with proven capsular invasion; incomplete resection; metastatic spread at the time of diagnosis and poor socioeconomic backgrounds.

Appendix 1

Approval of title - University of the Witwatersrand

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2075/6
011 717 7245
Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
03 December 2007
Person No: 0704343W
PAG

Dr G Sudwarts
P O Box 1899
HOUGHTON
2041
Johannesburg, South Africa

Dear Dr Sudwarts

Master of Medicine in the specialty of Diagnostic Radiology: Approval of Title

We have pleasure in advising that your proposal entitled "*Phaechromocytoma in childhood: Radiological-pathological correlation*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 2

Ethics clearance – University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Sudwarts

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M061014**
PROJECT	Phaeochromocytoma in Childhood: Radiological-Pathological Correlation
INVESTIGATORS	Dr G Sudwarts
DEPARTMENT	Dept Radiation Sciences
DATE CONSIDERED	06.10.27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.10.30 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr M Modi

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3

Ethics Clearance - Great Ormond Street Hospital

UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Trust

Joint Research and Development Office
Division of Research and Innovation

Dr Gary Sudwarts
Dr Derek Roebuck, Consultant Radiologist
Department of Radiology
Great Ormond Street Hospital
Great Ormond Street
London
WC1N 3JH

13th February 2012

RE: 06RP14- Phaeochromocytoma in Childhood: Radiological-Pathological Correlation

Dear Dr's Sudwarts and Roebuck,

Thank your recent correspondence regarding the subjected study registered with the R&D department.

After careful consideration and assessment of your original proposal I can confirm the study would fall under the remit of a clinical service evaluation, under the guidance provided by the National Research Ethics Service (NRES).

The study is a fully retrospective data analysis aiming to associate existing clinical data (histopathology and imaging) with existing clinical outcomes.

Under this categorization there is no requirement to seek formal ethics approval however you are reminded that Data Protection and NHS Code of Confidentiality rules apply. No participant/patient identifiable information should be shared with anyone external to the clinical care team or published legal consent.

If you require any additional information please do not hesitate to contact me.

Yours sincerely,

Subhir Bedi,
Senior Research Governance Manager

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