

Supplementary data – Clinical case descriptions of the patients that developed multiple tumours or malignant disease

Index cases

Patient 5 presented with a Horner's syndrome in 1975, aged 18 years, and was found to have a thoracic PGL on CT imaging, which was surgically resected, and he was subsequently discharged. Seven years later he presented with a mass in his neck and was found to have three metachronous neck PGLs. These were surgically resected and he went on to have two cycles of chemotherapy followed by a total dose of 1313MBq MIBG therapy between 1986 and 1998. Following this treatment he was reviewed annually for recurrence with urine metanephrines and clinical examination. An elevated noradrenaline level of 653nmol/day was noted on tests in 2007 and he went on to have a MRI that visualised a further 10mm thoracic PGL, which was confirmed on FDG PET and MIBG as avid disease. Genetic diagnosis of *SDHB* mutation confirmed in 2009. However as he was asymptomatic with normal blood pressure, the patient opted for conservative management and on repeat testing his biochemistry had normalised 6 months later and has remained normal. Therefore, due to the patient's wishes, this PGL has remained *in situ* and is stable in size following ten years of follow up, with continued normal metanephrines levels.

Patient 18 was diagnosed in 1982, aged 10 years, with a secretory thoracic PGL. She underwent surgical resection and was followed up annually for several years where she remained well. She remained well for 13 years, but was lost to follow up in her late teenage years. She presented in pregnancy aged 23 years with symptoms of catecholamine excess and hypertension and was found to have raised noradrenaline levels and a PGL recurrence in her mediastinum and a metastatic deposit in her left shoulder on MRI. She was commenced on Phenoxybenzamine 20mg three times per day and Bisoprolol 2.5mg twice per day. Post-partum these were confirmed to be MIBG avid and she underwent five cycles of MIBG therapy with good response and stabilisation of her disease. However, seven years later she was found to have MIBG-avid metastatic spinal disease and underwent a further four cycles of MIBG therapy and external beam radiotherapy. Regular surveillance imaging identified increasing size of her thoracic recurrence two years later and she underwent a surgical debulking. Four years following this she developed further spinal and thoracic disease requiring chemotherapy and further MIBG therapy. She subsequently died from disease burden aged 41 years.

Patient 20 was diagnosed in 1988, aged 10 years, with a secretory para-aortic PGL which was surgically resected. Sixteen years later, she developed papillary renal carcinoma ?type 1 or 2, path?? with lymph node involvement and underwent surgical resection and chemotherapy. During the course of this treatment she was found to harbour an *SDHB* mutation and joined the *SDH* surveillance programme. MRI surveillance imaging one year later revealed metastatic disease (biopsied and confirmed to be from RCC) and a metachronous 35mm abdominal PGL. Plasma catecholamine and urine metanephrines were negative and an MIBG scan showed no avid disease. She died aged 31 years of disease burden.

Asymptomatic carriers

Patient 6 was first reviewed aged 15 years, he is the son of the index case 5. He was asymptomatic, normotensive, had normal metanephrines and first surveillance MRI did not show any evidence of disease. He was then lost to follow up for four years, but was re-referred aged 19 years due to hypertension. He had normal metanephrines, but MRI identified a 10mm para-adrenal PGL. As this lesion was small and deemed to be in a difficult surgical position, he was monitored with annual MRI. Following five years of surveillance the lesion is now 14mm and his plasma metanephrines

became elevated (normetadrenaline 1310pmol/L) five years after original diagnosis. He is currently awaiting a surgical date.

Patient 19 attended her first surveillance review aged 18 years following identification as a *SDHB* mutation carrier. She had been clinically reviewed with metanephrine levels and abdominal ultrasound from eight years old with her twin sister, before genetic status was known. Her mother had died during surgery for a pheochromocytoma, aged 23 years, but genetic status was never determined. She was asymptomatic and had normal biochemistry. The MRI scan at age 18 years identified an 11mm abdominal PGL. As the lesion is too small for surgical resection, she is currently under active surveillance. Repeat scanning nine months later her showed the lesion to be stable in size, she remains asymptomatic and has normal metanephrines two years after the initial identification of this PGL.

Patient 27 was asymptomatic when he underwent genetic testing aged 15 yrs. He had a strong family history; his father was the index case and was diagnosed with a malignant paraganglioma and then found to carrier an *SDHB* mutation. On exploration of his family history it emerged that his great-grandfather died in his forties from an inoperable mass in his abdomen. As a result of cascade genetic testing the index case's two sons (patients 26 and 27) and father were found to carry the mutation. The index case's father was found to have an asymptomatic abdominal paraganglioma on first surveillance imaging. At his first surveillance review patient 26 had significantly raised urinary metanephrines (normetadrenaline 2863nmol/day (NR 0-4400nmol/day) and 3-methoxytyramine (3MT) 3287nmol/day (NR 0-2500nmol/day), but was asymptomatic and normotensive. Initial surveillance MRI demonstrated an abdominal retroperitoneal mass invading the great vessels. He underwent incomplete surgical resection, due to malignant spread to local lymph nodes and invasion of the vessels. His biochemistry normalised following surgery and he remained well for the next six years of follow up and then missed an appointment. The following year he presented with malignant hypertension and palpitations and had a raised 3MT (4688nmol/day) level. MRI confirmed a new 1.2cm aortocaval soft tissue mass, and bone metastases in vertebrae T9 and L4. He is now undergoing treatment with bisphosphonates and cold Octreotide.