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# Intraoperative near-infrared fluorescence imaging of a paraganglioma using methylene blue: A case report



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## ABSTRACT

**INTRODUCTION:** Intraoperative identification of tumors can be challenging. Near-infrared (NIR) fluorescence imaging is an innovative technique that can assist in intraoperative identification of tumors, which may otherwise be undetectable.

**PRESENTATION OF CASE:** A 19-year-old patient with symptoms, normetanephrine levels and radiological findings suspicious for a paraganglioma, a rare tumor arising from extra-adrenal chromaffin cells within the sympathetic nervous system, is presented. Intraoperative NIR fluorescence imaging using intravenous administration of methylene blue (MB) assisted in intraoperative detection of the tumor, and even identified a smaller second lesion, which was not identified during surgery by visual inspection. **DISCUSSION:** Although the exact mechanism of MB accumulation in neuroendocrine tumors is unclear, it is described in both preclinical and clinical studies.

**CONCLUSION:** In this report, we describe the first case of intraoperative NIR fluorescence imaging of a paraganglioma using MB, which identified an otherwise undetectable lesion.

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## 1. Introduction

Paragangliomas are rare tumors arising from extra-adrenal chromaffin cells within the sympathetic nervous system [1–3]. They can be found anywhere from the neck to the pelvis in the vicinity of sympathetic ganglions, and belong to the family of neuroendocrine tumors. An incidence rate of 2–8 cases per million is reported, and tumors can be either functional or non-functional. When functional there can be production of catecholamine, epinephrine, or norepinephrine.

The only curative treatment of paraganglioma is complete surgical resection. To help localize all sites of disease, preoperative identification can be performed using different anatomical and functional imaging modalities [4]. However, no specific imaging modalities are available for the intraoperative identification of these tumors.

Near-infrared (NIR) fluorescence imaging is a promising technique to assist in the intraoperative identification of sentinel lymph nodes, tumors, and vital structures [5]. Advantages of this optical imaging technique include real-time imaging, high sensitivity, and high resolution, with penetration depths several millimeters into tissue.

Methylene blue (MB) is a clinically available tracer, which can be used at low dosage as a fluorescent tracer during NIR fluorescence imaging. Winer et al. [6] describe the successful identification of insulinomas, a pancreatic neuroendocrine tumor in transgenic mice, and clinically, the intraoperative identification of parathyroid adenomas was described [7].

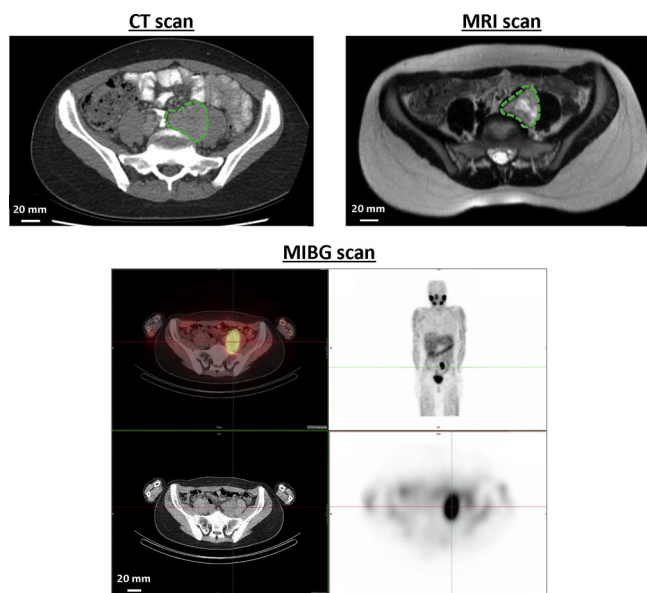
Based on these results, we explored the possibility to identify paragangliomas during surgery, using NIR fluorescence imaging and MB.

## 2. Presentation of case

A 19-year-old female patient presented with complaints of fainting, nausea, vomiting, headaches, excessive sweating, flushing attacks, hand tremors, and heart palpitations. She had a negative family history for endocrine diseases or paragangliomas. While volunteering to donate blood, her systolic blood pressure was found to be 180 mm Hg. After referral, physical examination revealed a blood pressure of 180/110 mm Hg on the left arm, 190/115 mm Hg on the right arm, but no other abnormalities. Laboratory evaluation showed a normetanephrine level of 3227 umol/mol creatinine (norm. value 64–260) in the urine.

CT scan showed a 46 × 38 mm retroperitoneal mass, just caudal to the aortic bifurcation (Fig. 1). Cranial to this, a smaller lesion of 6 mm was seen, which was characterized as a para-aortic lymph node. MRI scan confirmed the retroperitoneal mass just caudal to

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**Fig. 1.** Preoperative imaging of paraganglioma: Preoperative CT, T2 weighed MRI and MIBG scan of the paraganglioma (dashed circle), retroperitoneally located, just caudal to the aortic bifurcation.

the aortic bifurcation, with features suspicious for a paraganglioma. A slight encasement of the common iliac vein was seen. The cranially located smaller lesion was not clearly identified by MRI.

A  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) scan was performed to search for lesions located elsewhere in the body. Strong accumulation of the tracer was seen in the lesion just caudal to the aortic bifurcation, but no other uptake was seen (Fig. 1).

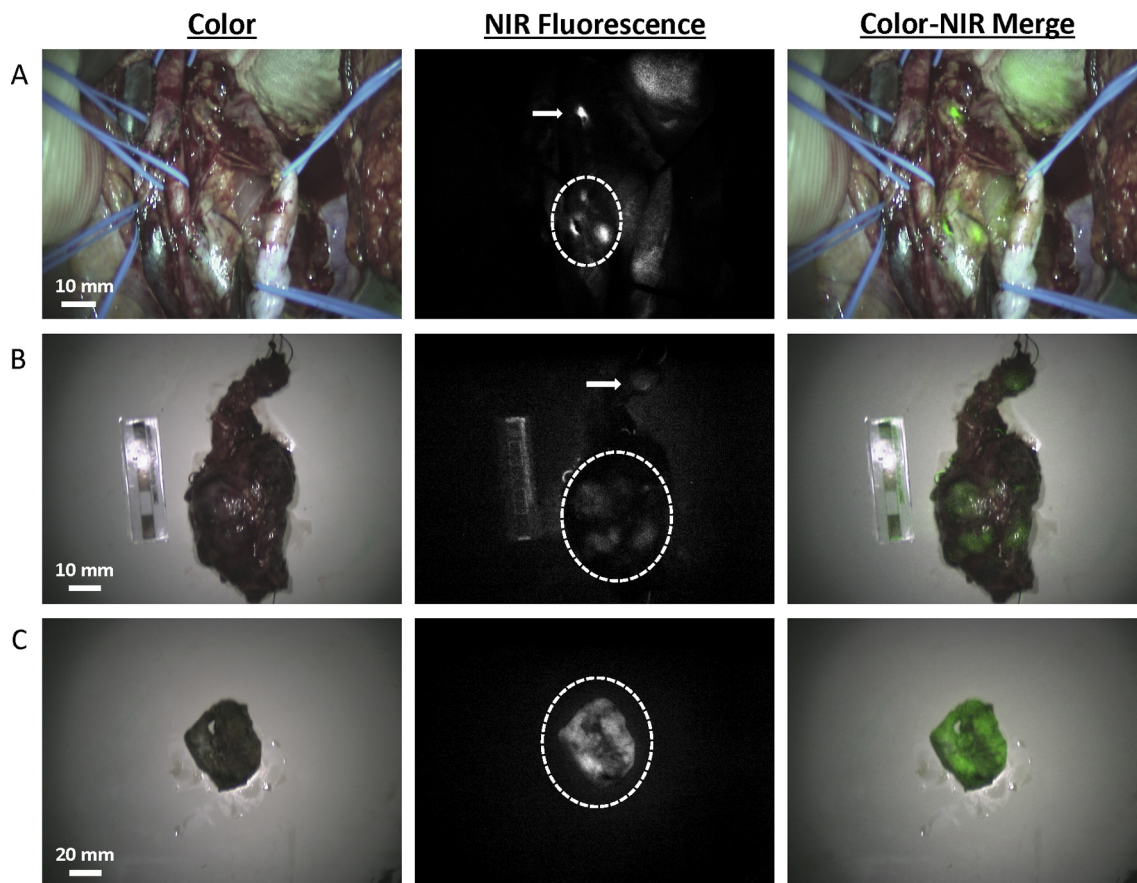
The patient was scheduled for resection. She was successfully pretreated with doxazosine, a selective alpha1-receptor blocking sympathetic drug, metoprolol, a beta-receptor blocking sympathetic drug, and nifedipine, a dihydropyridine, in order to prevent a hypertensive crisis during surgery.

### 2.1. Intraoperative NIR fluorescence imaging

The current study was approved by the Medical Ethics Committee of the Leiden University Medical Center and was performed in accordance with the clinical standards of the Helsinki Declaration of 1975. Written informed consent was obtained.

During surgery, and directly after exposure of the lesion distal to the aortic bifurcation, MB was administered intravenously (0.5 mg/kg; 33 mg in 3.3 mL of water; 10 mg/mL final stock solution concentration) over 5 min and NIR fluorescence imaging was performed using the Mini-FLARE image-guided surgery system as described previously [8]. Directly after infusion, imaging was performed at fixed time points (0, 1, 2, 3, 4, 5, 15, 30 and 45 min).

NIR fluorescence imaging showed a strong, but patchy, fluorescent signal corresponding to the suspected lesion (Fig. 2A, lesion indicated by dashed circle). Moreover, the additional small lesion that was only identified by CT but not by MRI or by visual inspection during surgery, was clearly identified using NIR fluorescence



**Fig. 2.** Intraoperative and ex vivo NIR fluorescence imaging of primary and metastatic paragangliomas: (A) Intraoperative NIR fluorescence imaging of the surgical field. A bright, patchy fluorescent signal was identified at the location of the tumor (dashed circle). A second, small, lesion located approximately 5 cm cranial to the main lesion, was also identified using NIR fluorescence imaging (arrow). (B) Ex vivo ( $T = 45$  min) imaging of the resection specimens. Fluorescent signal was seen in the large (dashed circle) and small lesion (arrow). A weaker fluorescent intensity was seen than *in vivo*, because fluorescent signal decreased over time during surgery. (C) Ex vivo imaging of the bisected main lesion. Bright fluorescent signal was seen throughout the paraganglioma (dashed circle).

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