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Invited commentary on: Can indocyanine green fluorescence aid operative decision making in neuroblastic tumor surgery? Early experience from a single centre

Irene Paraboschi [a, b], Gloria Pelizzo [a, b], Alida F.W. van der Steeg [c], Marc H.W.A. Wijnen [c], Stefano Giuliani [d, e, f, *]

[a] Department of Pediatric Surgery, "Vittore Buzzi" Children's Hospital, 20154 Milan, Italy
[b] Department of Biomedical and Clinical Science, University of Milano, 20157 Milan, Italy
[c] Princess Máxima Center, Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
[d] Great Ormond Street Institute of Child Health, University College London, London, United Kingdom
[e] Specialist Neonatal and Paediatric Surgery Department, Great Ormond Street Hospital, London, United Kingdom
[f] University College London Hawkes Institute for Interventional and Surgical Sciences, London, United Kingdom

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We read with great interest the report by Pachl et al. [1]. on the use of indocyanine green (ICG) near-infrared (NIR) fluorescence to support intraoperative decision-making during neuroblastic tumor biopsy and resection.

The authors should be commended for addressing a central dilemma in post-induction neuroblastoma surgery: neither preoperative imaging nor intraoperative assessment can reliably determine whether a residual mass contains viable tumour. This uncertainty becomes critical when residual disease encases major vessels or nerves, because attempting radical clearance may carry substantial morbidity yet may be unnecessary if the tissue is largely non-viable.

Their observation that hyperfluorescence correlated with poorly differentiated, viable neuroblastoma, whereas afluorescent lesions more often corresponded to mature or necrotic tissue, is clinically compelling. Of particular interest is the reported transition from hyperfluorescence at biopsy to afluorescence after chemotherapy, which suggests that ICG intensity may track biological activity rather than tumor bulk alone and therefore deserves careful prospective validation.

Several issues, however, warrant discussion before low or absent fluorescence is used to designate tissue as non-viable or to justify leaving residual tumour behind, as the current data do not establish the negative predictive value of ICG in chemotherapy-treated disease.

First, the frequent hypo/afluorescence of post-chemotherapy L2 and metastatic tumors raises a fundamental question: does lack of signal equate to lack of clinically meaningful disease? Neuroblastoma is biologically heterogeneous, and residual masses may contain small islands of viable primitive neuroblasts embedded within necrotic, fibrotic, or differentiating stroma. Because ICG is non-targeted and perfusion-dependent, afluorescence may reflect chemotherapy-induced vascular remodeling, reduced microvascular density, or fibrosis rather than true biological inactivity. This is precisely the situation in which surgeons may be tempted to spare tumour adherent to vital structures to minimize morbidity; yet the price of a false-negative intraoperative signal can be underresection. Importantly, persistence of viable, highly proliferative neuroblastic cells within the post-induction primary tumor has been associated with poorer outcomes, reinforcing that even limited residual viability may matter clinically [2]. Defining the negative predictive value of ICG in treated neuroblastoma should therefore be considered a priority before it is used to justify leaving tissue behind.

Second, ICG fluorescence intensity is driven by perfusion and vascular permeability, called enhanced permeability and retention (EPR) effect, all of which are profoundly altered by systemic therapy. Without robust analyses of sensitivity, specificity and negative predictive value in larger cohorts, it remains premature to

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* Corresponding author. Division of Specialist Neonatal and Paediatric Surgery (SNAPS), Great Ormond Street Hospital for Children NHS Foundation Trust, 5th Floor Paul O'Gorman Building Great Ormond Street, London WC1N 3JH, United Kingdom.
E-mail address: stefano.giuliani@gosh.nhs.uk (S. Giuliani).

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regard ICG signal as an intraoperative biomarker of viability. However, the interpretation of fluorescence as a surrogate of viability is currently supported by a limited number of cases with paired histology, and key parameters needed to estimate diagnostic performance are not consistently reported. In the reported series, only 3 patients with hyperfluorescent lesions had histologically confirmed viable NB, whereas 2 patients with afluorescent lesions (patients 10 and 12) were still reported to contain NB, but the proportion of viable tumour was not clearly quantified, limiting any inference about negative predictive value. Without such data, the negative predictive value of ICG remains uncertain. In this context, tumor-targeted anti-GD2 monoclonal antibodies conjugated to NIR fluorophores, currently in Phase I/II clinical evaluation in the Netherlands (NCT07399821), offer a credible pathway toward tumor-specific delineation that is less dependent on perfusion dynamics [3]. The clinical relevance of this distinction is clear: ICG primarily reports blood supply and EPR, whereas a targeted tracer aims to report tumor biology [4].

Third, technical factors likely contribute materially to the qualitative fluorescence grading reported. Currently, clinically used ICG-NIR-I (700–900 nm wavelength) is depth-limited, and detectability is influenced by camera sensitivity, exposure and gain settings, working distance, ambient light suppression, and post-processing, all of which vary between imaging systems and may vary between cases even within a single center [5]. To enable reproducibility and meaningful comparison across centers, future studies should incorporate standardized quantitative metrics with pre-specified thresholds, report device and acquisition parameters comprehensively, and correlate fluorescence with mapped histopathology, including differentiation, necrosis and proliferative activity, as well as long-term outcomes. Structured reporting standards such as REFLECT provide a practical framework to improve consistency and interpretability in this rapidly evolving field [6].

Finally, emerging optical technologies may further refine this paradigm. Multispectral NIR-I and NIR-II (900–1500 nm wavelength) detection has demonstrated improved tumor-to-background contrast and depth performance compared with NIR-I alone, which may be particularly advantageous to detect clusters of viable cells hidden in residual infiltrating high-risk anatomical areas [7]. Together, these considerations support a multimodal translational pathway in which ICG is evaluated with rigorous quantitative validation where appropriate, while tumor-targeted anti-GD2 fluorescence, potentially combined with NIR–II–capable detection systems, is accelerated through clinical translation to move from enhanced visualization toward biologically informed surgical decision-making in high-risk, chemotherapy-treated neuroblastoma.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Stefano Giuliani Associate Professor, Developmental Biology and Cancer, UCL Great Ormond Street Institute of Child Health 30 Guilford Street, London WC1N 1EH. Website: https://profiles.ucl.ac.uk/61400-stefano-giuliani. Clinical Co-Director at the UCL Hawkes Institute for Interventional and Surgical Sciences, London, United Kingdom.

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