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Intraoperative Indocyanine Green Fluorescence Imaging in Primary Breast Angiosarcoma: A Report of a Feasibility Case

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Abstract

Primary breast angiosarcoma (PBA) is a rare and aggressive malignancy for which no standardised intraoperative margin assessment tool currently exists, and complete surgical excision with negative margins represents the cornerstone of treatment. Near-infrared fluorescence imaging (NIR-FI) with indocyanine green (ICG) has emerged as a promising intraoperative tool for tumour visualisation and margin assessment in various solid tumours, but its application in PBA has not previously been described.

To our knowledge, we report the first use of ICG-FI for real-time surgical margin evaluation in PBA in a 42-year-old woman presenting with progressive right breast enlargement who was diagnosed with low-grade PBA following expert pathological review. After multidisciplinary discussion, radical mastectomy was performed; ICG (0.25 mg/kg) was administered intravenously at anaesthetic induction, and intraoperative ICG-FI was performed during flap dissection, after specimen removal, and following gross pathological sectioning. The tumour demonstrated clear and homogeneous fluorescence with a tumour-to-background ratio (TBR) of 3.7, enabling visual delineation from surrounding tissues. Final histopathological examination confirmed an 11-cm low-grade PBA completely excised with negative margins. The absence of residual fluorescence within the surgical bed and on the specimen margins correlated with histopathologically confirmed negative margins, and postoperative recovery was uneventful.

This case report demonstrates the technical feasibility of intraoperative ICG-FI in PBA, providing real-time visual confirmation of the surgical field, without identifying additional margins or altering the planned surgical strategy. Within the IDEAL framework for surgical innovation, this proof-of-concept report supports further prospective evaluation in collaborative registries to define the potential role of ICG-FI in improving local control in this rare and surgically challenging malignancy.

Categories: Pathology, Oncology, Healthcare Technology
Keywords: icg-fi, ideal framework, indocyanine green (icg), near-infrared fluorescence imaging, primary breast angiosarcoma, surgical margins

Introduction

Primary breast angiosarcoma (PBA) is an exceptionally rare malignancy, accounting for fewer than 0.05% of all breast malignancies, arising from breast vascular endothelial cells. It is characterised by rapid growth, infiltrative behaviour, high local recurrence rates, and early haematogenous dissemination, resulting in poor overall prognosis [1,2]. Diagnosis relies on histopathological and immunohistochemical confirmation, and complete surgical excision with negative margins (1-3 cm, a range reported in the literature) remains the cornerstone of treatment [1,2].

Negative margins are typically achieved by radical mastectomy with extended cutaneous resection, often necessitating complex reconstructive techniques including free flap mobilisation, whereas routine axillary dissection is generally not recommended [1,2]. Balancing adequate tissue resection with preservation of sufficient skin for closure remains a significant surgical challenge. There is currently no consensus regarding optimal margin width or intraoperative margin assessment in PBA, and existing breast cancer margin assessment techniques have not been validated in this rare entity. Conventional intraoperative margin assessment can be particularly challenging in angiosarcoma (PBA included) due to its extensive and infiltrative growth pattern, with neoplastic vascular channels extending beyond the macroscopically apparent tumour boundaries and potentially resulting in occult margin involvement detected only on final histopathology.

Near-infrared fluorescence imaging (NIR-FI) with indocyanine green (ICG), a fluorescent dye approved for several clinical indications, including tissue perfusion assessment and sentinel lymph node mapping, has recently been explored as an intraoperative tool for tumour visualisation and surgical margin

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assessment [3,4]. Following intravenous administration, tumour ICG fluorescence has been primarily attributed to the enhanced permeability and retention (EPR) effect, although vascular perfusion, permeability, delayed clearance, and nonspecific tissue retention may also contribute to the observed fluorescence, enabling real-time fluorescence-guided surgery [3,4]. Early studies in soft tissue sarcomas (STS) have demonstrated high tumour detection rates and improved identification of close or positive margins [5,6].

To our knowledge, ICG-FI in angiosarcoma has been reported in only four cases: one liver metastasis resection from a radiation-induced angiosarcoma [7] and three cutaneous angiosarcomas [8], all limited to qualitative fluorescence without quantitative signal analysis. Building on our institutional experience with ICG-FI for margin assessment in breast cancer [4,9], we report here the first use of intraoperative ICG-FI for surgical margin evaluation in PBA.

Case Presentation

We present the clinicopathological features, surgical technique, and ICG-FI technical aspects for intraoperative margin assessment in a case of PBA. In accordance with institutional policy, anonymised individual case reports do not require Institutional Review Board approval. Written informed consent was obtained from the patient for publication of her clinical information and accompanying images. This case report has been reported in line with the SCARE 2023 criteria [10].

Clinical presentation

A 42-year-old woman presented with progressive enlargement of the right breast over six months. She had no significant medical or family history and no history of prior radiation exposure, chronic lymphoedema, breast surgery, or vascular lesions in the affected breast. Physical examination revealed diffuse enlargement and induration of the entire right breast, with mobile overlying skin and chest wall.

Mammography demonstrated global asymmetry of the right breast, and ultrasound showed diffuse hyperechogenicity of the breast parenchyma with associated interlobular oedema (BI-RADS 4C). Breast MRI showed an extensive lesion occupying nearly the entire breast (90 × 71 × 98 mm), in contact with the pectoralis muscle, without imaging evidence of infiltration. Core needle biopsy initially suggested a lymphangiomatous lesion. Following expert review at our Pathology Department, histopathological examination revealed an infiltrative proliferation of irregular, anastomosing vascular channels lined by endothelial cells with mild nuclear atypia and no identifiable mitotic figures. Tumour cells showed strong CD31 positivity, highlighting the infiltrative growth pattern, while AE1/AE3 staining was negative, supporting the diagnosis of well-differentiated PBA. PET/CT showed no significant 18F-FDG uptake within the breast lesion and no evidence of distant metastatic disease. After multidisciplinary team (MDT) discussion, radical mastectomy was recommended. The patient's clinical course is summarised in Table *1*.

Date / Time Interval	Clinical Event
Six months before day 1	Symptom onset/self-detected breast mass
Day 1	Initial medical consultation
Day 6	Breast imaging (mammography, ultrasound)
Day 9	Core needle biopsy
Day 25	Histopathological diagnosis confirmed
Day 33	Breast imaging (MRI)
Day 37	Distant imaging (PET-CT)
Day 44	Multidisciplinary Team (MDT) discussion
Day 58	Preoperative hospital admission
Day 59	Surgical intervention (radical mastectomy + ICG-FI)
Day 66 (postoperative day 7)	Final histopathological examination results
Day 67 (postoperative day 8)	Second surgical intervention - wound closure (abdominal wall advancement flap)
Day 68 (postoperative day 9)	Postoperative Multidisciplinary Team (MDT) discussion
Day 125 (postoperative day 66)	Last follow-up assessment - disease-free

TABLE 1: Timeline of clinical events.

MDT: multidisciplinary team; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; ICG-FI: indocyanine green fluorescence imaging

Surgical technique and ICG-FI protocol

ICG (0.25 mg/kg; Verdye®, Diagnostic Green) was administered intravenously at anaesthetic induction [4]. The patient was positioned supine with the ipsilateral arm abducted at 90°. Incision lines were delineated maintaining an approximately 2-3 cm macroscopic safety margin from the palpable tumour extent (Figure *1A*). Mastectomy flaps were circumferentially dissected in the conventional superficial fascial plane and carried down to the deep muscular fascia (Figures *1B*-*1D*).

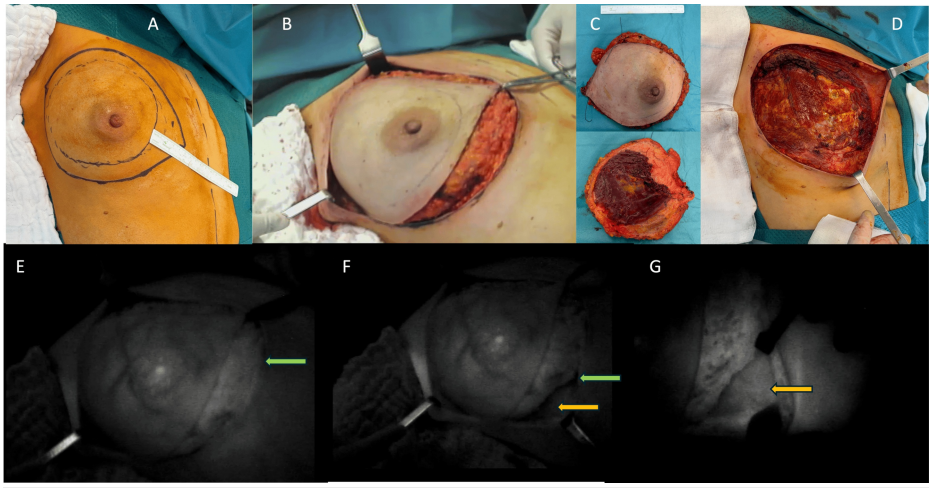


FIGURE 1: Intraoperative mastectomy procedure and real-time in vivo assessment of surgical margins using indocyanine green fluorescence imaging.

Intraoperative views showing skin incision markings positioned at a distance from the palpable tumour (A), the surgical specimen in situ before removal (B), the completely excised specimen ex vivo (C), and the residual surgical defect after resection (D). In vivo ICG-FI was performed to assess the resection margins (E, F) and tumour bed (F, G). Both the skin incision margins (green arrow) and the deeper surgical margins of the cavity (orange arrow) were examined for residual fluorescence potentially suggestive of remaining tumour tissue.

ICG-FI: indocyanine green fluorescence imaging

Following flap dissection, 72 min after ICG administration, the operating room lights were turned off, and the resection margins were systematically assessed using two dedicated fluorescence imaging systems (Novadaq SPY-PHI system, Stryker, Kalamazoo, MI, USA; and PDE-neo®, Hamamatsu Photonics K.K., Hamamatsu, Japan) (Figures *1E*-*1G*). Dissection was extended posteriorly to allow en bloc resection of the entire mammary gland with the pectoralis muscle and the superficial fascia of the serratus anterior. In keeping with sarcoma surgical principles (wide excision, en bloc removal, and inclusion of the underlying muscle and fascia as the deep barrier to tumour spread), this ensured an adequate posterior oncological margin despite the tumour's mobility over the chest wall (Figures *1C*-*1D*).

After specimen removal, both the resection cavity and the surgical specimen were re-evaluated using ICG-FI at 95 min after intravenous ICG administration to assess for residual fluorescence. The breast surgical specimen was subsequently serially sectioned into sub-centimetre (7-8 mm) slices, in accordance with standard macroscopic evaluation and preparation procedures, and immediately examined ex vivo using ICG-FI on fresh tissue, prior to fixation, for rapid qualitative assessment of the resection margins (Figures *2*-*3*).

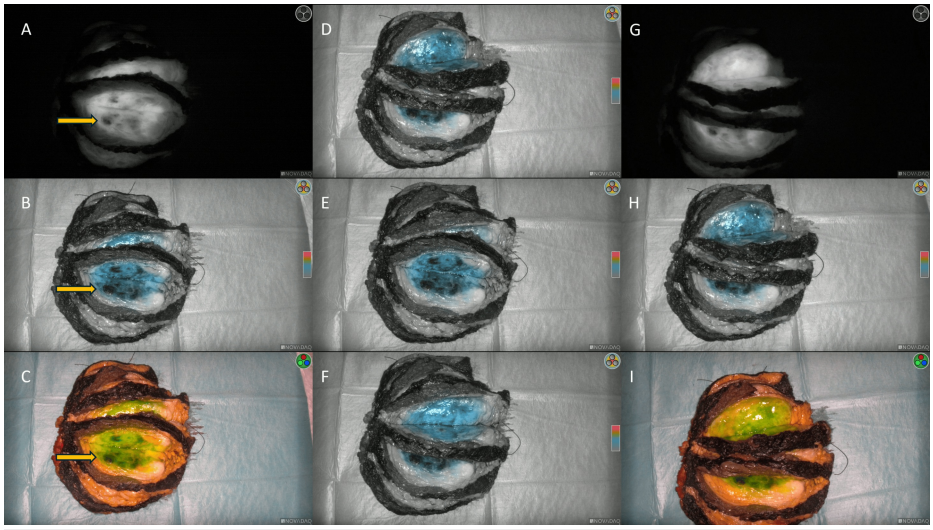


FIGURE 2: Ex vivo indocyanine green fluorescence imaging (ICG-FI) of the surgical breast specimen using the Novadaq SPY-PHI system (Stryker, Kalamazoo, MI, USA).

The tumour (arrow) is clearly delineated from adjacent normal breast tissue across all imaging modes. (A, G) White-light (grayscale) mode. (B, D, E, F, H) Overlay mode, in which the NIR fluorescence signal is superimposed on the white-light image in blue pseudocolor, enabling simultaneous visualisation of tissue anatomy and ICG fluorescence distribution. (C, I) SPY CSF mode, displaying the fluorescence signal as a green pseudocolour heat map encoding ICG signal intensity. Images D-F represent sequential cross-sections at progressively deeper levels, allowing evaluation of tumour extent and proximity to the surgical resection margins.

ICG: indocyanine green; NIR: near-infrared; CSF: colour-segmented fluorescence

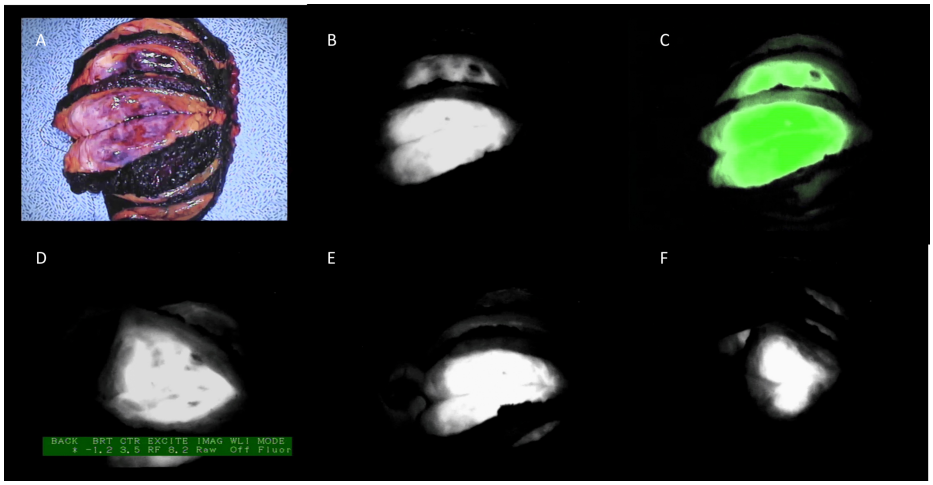


FIGURE 3: Ex vivo assessment of the breast surgical specimen using ICG-FI with the PDE-neo system (Hamamatsu Photonics K.K., Hamamatsu, Japan).

After gross sectioning into thin serial slices (A), the specimen was immediately examined by ICG-FI. The tumour is clearly demarcated from the adjacent normal breast tissue (arrow), appearing as a hyperfluorescent area on near-infrared grayscale images (B, D, E, F) and as a green-highlighted lesion on the pseudocolour image (C), in which digital subtraction enhances contrast between ICG-retaining and non-fluorescent tissue. Detailed examination of each macroscopic slice (D-F) enabled qualitative visual assessment of fluorescence relative to the resection margins throughout the surgical specimen.

ICG-FI: indocyanine green fluorescence imaging

Axillary lymph node exploration was omitted given the absence of clinical or radiological nodal involvement and the low propensity of PBA for lymphatic spread. Skin flaps were elevated superiorly to the clavicle,

medially to the sternal midline, and inferiorly to the inframammary fold. A closed-suction drain was placed, and the wound was closed in three layers. Owing to insufficient tissue for complete primary closure and pending final pathology, the central portion of the surgical wound was left open and managed with negative-pressure wound therapy (VAC).

Outcome

Both camera systems showed clear, homogeneous tumour fluorescence on ex vivo FI, performed approximately 95 minutes after intravenous ICG administration (Figures *2*-*3*). The tumour-to-background ratio (TBR) was 3.7, allowing clear delineation of the tumour from the surrounding normal breast tissue. TBR was defined as the ratio between tumour fluorescence intensity and that of the surrounding normal breast tissue, and was determined on PDE-neo ICG-FI using IC-Calc® software, version 2.0 (Pulsion Medical Systems, Feldkirchen, Germany) [4]. Measurements were performed on three tumour slices, with tumour intensity averaged over three locations per slice and compared with adjacent normal tissue. The reported value represents the mean of the three slice-specific ratios (mean tumour intensity 5.2 a.u.; mean normal tissue intensity 1.4 a.u.). The absence of residual fluorescence within the surgical bed and on the specimen margins correlated with histopathologically confirmed negative margins.

Final histopathological examination confirmed an 11-cm low-grade, well-differentiated PBA, characterised by a diffuse infiltrative proliferation of dilated vascular channels dissecting the breast parenchyma and lined by mildly atypical spindle cells, with no identifiable mitoses. Tumour cells were positive for ERG and CD34 (Figure *4*). Complete excision was achieved, with the nipple and all surgical margins microscopically tumour-free and no histological involvement of the pectoral muscle; the closest (posterior) margin measured >10 mm.

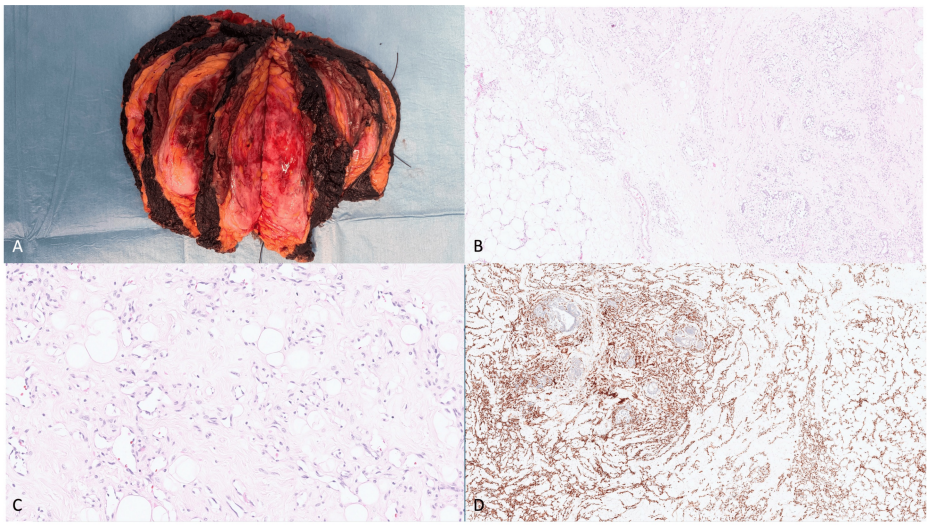


FIGURE 4: Morphological and immunohistochemical features of well-differentiated breast angiosarcoma.

Breast surgical specimen after gross slicing, demonstrating the large tumour and the surrounding normal breast tissue (A). Low-power view (H&E, x5) showing irregular, anastomosing vascular channels infiltrating the breast stroma and dissecting the surrounding adipose tissue (B). At higher magnification (H&E, x20), the vascular channels are lined by relatively bland endothelial cells with minimal cytological atypia (C). ERG immunohistochemistry (ERG, x2) shows strong nuclear expression in the neoplastic endothelial cells, highlighting the infiltrative vascular network (D).

Following confirmation of negative margins, delayed wound closure was performed one week later as planned, using an abdominal wall advancement flap. Negative-pressure wound therapy (VAC) was discontinued after a further week, with good wound healing already evident. No postoperative complications (e.g., infection, flap necrosis, seroma, or wound dehiscence) were observed. After MDT discussion within both the sarcoma and breast cancer tumour boards, and expert consultation with a European reference centre, adjuvant radiotherapy was recommended and subsequently administered. A dose of 48 Gy in 15 fractions was delivered to the chest wall using 6 MV photons, with treatment delivered in deep inspiration breath-hold to better spare the heart. No acute adverse events were recorded. At the most recent short-term follow-up, 16 weeks after surgery, the patient had no clinical or radiological evidence of recurrence on breast MRI and thoracic CT, with satisfactory shoulder mobility and ongoing physiotherapy.

Discussion

To the best of our knowledge, this is the first reported case of intraoperative ICG-FI for real-time surgical margin assessment in PBA. While ICG-FI-guided surgery has been increasingly investigated in breast cancer and STS [4-6,9], its application in PBA has not previously been described. To our knowledge, ICG-FI in angiosarcoma has been reported in only four cases: one liver metastasis from a radiation-induced angiosarcoma [7] and three cutaneous angiosarcomas [8], all limited to qualitative fluorescence without quantitative signal analysis.

In our case, low-dose ICG (0.25 mg/kg) administered at anaesthetic induction produced clear and homogeneous fluorescence with a TBR of 3.7, consistent with previously reported values in breast cancer and STS (range 2.0-3.7) [4,5,9]. Despite the lower dose and shorter interval between injection and imaging compared with previously reported sarcoma protocols, the high TBR achieved suggests that the richly vascular nature of angiosarcoma may favour rapid ICG accumulation and effective fluorescence-guided imaging [5-8].

The absence of residual fluorescence within the surgical bed and on the specimen margins was concordant with the histopathologically confirmed negative margins in this case, in line with previous reports in breast cancer and sarcoma exploring the potential of ICG-FI for intraoperative margin assessment [4,5,7-9]. Although ICG-FI did not alter the planned surgical procedure, it provided real-time visual information on the resection margins, with no residual fluorescence observed and negative margins confirmed on final histology. This concordance does not, however, establish that fluorescence can exclude microscopic residual disease. Furthermore, it may be hypothesised that, by enabling real-time delineation of tumour extent, ICG-FI could allow more precise definition of resection boundaries in future applications, potentially limiting surgical excision and facilitating less morbid reconstructive solutions. This hypothesis was not demonstrated in the present case, which required extensive resection and complex reconstruction, and warrants prospective evaluation. Additionally, ICG-FI was used only for real-time visual assessment of the margins and not to measure margin distances, as this case report primarily aimed to demonstrate feasibility; however, Figures *2*-*3* suggest that the fluorescence signal may allow qualitative margin estimation, warranting further investigation in future PBA studies.

This report is limited by its single-case nature and short follow-up, precluding conclusions on diagnostic accuracy or clinical effectiveness. Fluorescence intensity may also vary according to tumour biology, vascularity, timing of ICG administration, and the imaging system used. Near-infrared fluorescence has limited tissue penetration depth, so absence of surface fluorescence cannot exclude deeper or microscopic residual tumour. False-positive signals may also arise from normal vascular tissue, inflammation, haemorrhage, surgical trauma, or nonspecific ICG retention. Therefore, our findings should be interpreted as proof of technical feasibility rather than evidence supporting routine clinical implementation. Moreover, this report aligns with the IDEAL framework for surgical innovation, corresponding to IDEAL Stage 1, as it represents the first-in-indication application of ICG-FI in a single patient with PBA, reported as a proof-of-concept case report [11], providing a basis for future prospective evaluation. Given the rarity of PBA, registry-based data collection remains the most feasible study design for further assessment of ICG-FI in this disease.

Conclusions

To our knowledge, this case report describes the first use of intraoperative ICG-FI as a visual adjunct in the surgical management of PBA. The technique appears technically feasible, providing complementary real-time visual information that was concordant with the subsequently confirmed negative histological margins, although it did not alter the planned surgical strategy or identify additional margins in this case. Although limited to a single patient, these findings suggest that ICG fluorescence imaging may warrant further exploration as a complementary intraoperative tool in the resection of this rare and challenging malignancy. Within the IDEAL framework, this proof-of-concept report supports further evaluation in larger collaborative registries to establish diagnostic accuracy and effects on surgical management and re-excision, as prerequisites before any impact on local recurrence can be assessed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: C. Florin Pop, Gabriel Liberale

Acquisition, analysis, or interpretation of data: C. Florin Pop, Jenna Hannuille, Nejla Gumus, Christiane Jungels

Drafting of the manuscript: C. Florin Pop, Gabriel Liberale

Critical review of the manuscript for important intellectual content: C. Florin Pop, Jenna Hannuille,

Nejla Gumus, Christiane Jungels, Gabriel Liberale

Supervision: Christiane Jungels, Gabriel Liberale

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** C. Florin Pop declare(s) a grant from Diagnostic Green GmbH. A grant of IMP indocyanine green supplies from Diagnostic Green GmbH for work outside the submitted manuscript. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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