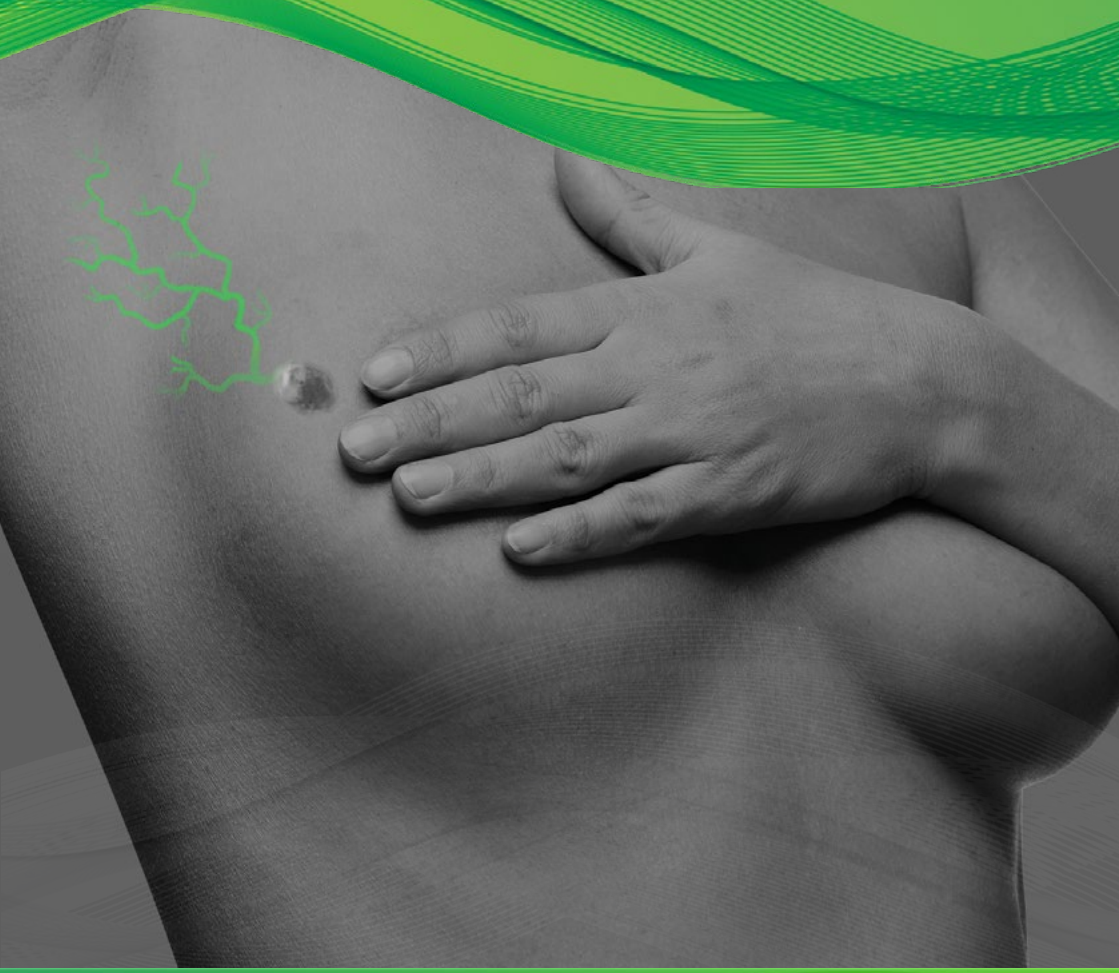
Diagnostic Green

Verdye (Indocyanine Green)

Use of ICG in Breast SLN



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Diagnostic Green

Intraoperative identification of sentinel lymph nodes and visualisation of lymphatic pathways in breast cancer

The presence of lymphatic metastases is an important prognostic factor for the survival of breast cancer patients and their identification has a bearing on further treatment.[1] Sentinel lymph node biopsy (SLNB) remains a cornerstone in the management of early breast cancer and is the current standard of care for clinically and radiologically node-negative patients.[2] Importantly, SLNB enhances patient's quality of life without compromising diagnostic accuracy or prognostic information for node-negative patients.[3]

Until recently, the gold standard for SLNB in patients with breast cancer is radio-guided surgery with radioisotope technetium-99m (99mTc) which has a reported sentinel lymph node (SLN) detection rate of 86.4%.[4] Some clinicians combine 99mTc with blue dyes such as Methylene Blue dye, increasing the detection rate to 96%-99.8%.[4] However, both 99mTc and blue dyes have many associated adverse effects.[5,6] In particular, Methylene Blue dye is associated with many devastating effects including soft tissue necrosis, (permanent) skin tattooing at the injection site, metabolic and hematologic side effects making it infrequently utilised for routine surgical care.[7] Further, Patent Blue and Isosulphan Blue are associated with increased rates of adverse reactions (0.7% - 1.1% of cases) in comparison to Methylene Blue.[8,9] Also, the use of 99mTc imposes a significant burden on patients and hospitals, including the logistical challenges associated with pre-operative administration, risk of exposure to ionising radiation for healthcare professionals, and adherence to regulatory requirements for handling and storage of radio-pharmaceuticals.

INDOCYANINE GREEN (ICG) APPROVED FOR BREAST SLN DETECTION

A recently approved method for detecting sentinel lymph nodes (SLNs) in breast cancer utilises Indocyanine Green (ICG).[10] Diagnostic Green's Verdye, is now approved for intraoperative identification of SLN and visualisation of lymphatic pathways in breast cancer.

Preparation and administration of ICG for SLNB

Immediately prior to surgery, a 25 mg vial of ICG is prepared with 10 ml of sterile water. Once the patient is anaesthetised, ICG (2 ml) is injected intradermal, subcutaneous or peritumoural in the lateral areolar region.

PROCEDURE

Holding the near infra-red (NIR) camera system above the injected tissue, lymphatic vessels containing ICG are visible transcutaneously (up to a depth of 2 cm) and can be mapped to the axilla **(Fig 1)**. Additionally, mapping of the fluorescent lymphatic vessels help to identify the approximate location of the SLNs in the axillary region **(Fig 2)**.

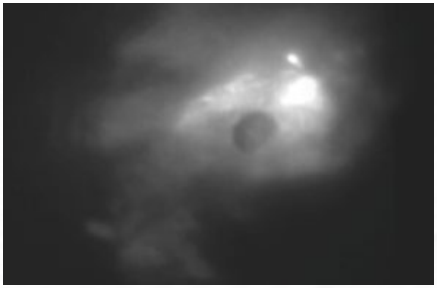

Fig 1. Fluorescence begins to spread

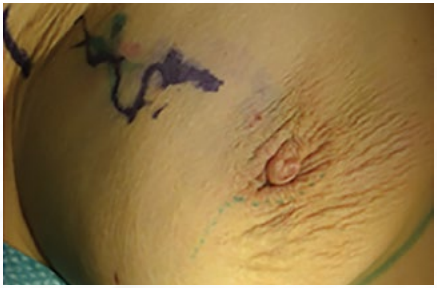

Fig 2. Mapping of fluorescent lymphatics

After the axilla is incised, the tissue is dissected until the axillary fascia is exposed. Using the NIR camera, the axilla is examined for tissue fluorescence **(Fig 3)** and the SLN can be identified **(Fig 4)**.

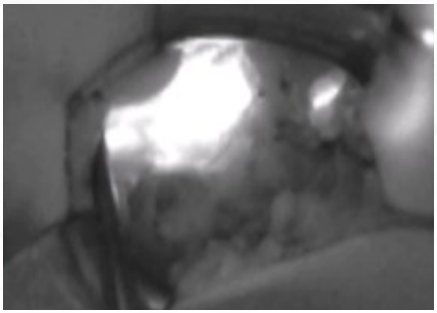

Fig 3. Tissue dissection reveals fluorescent tissue

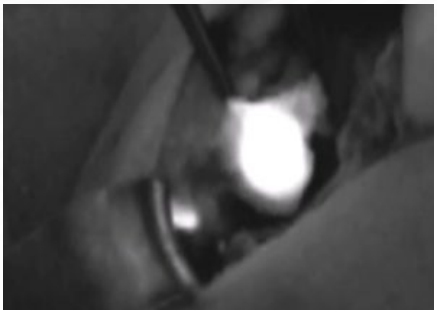

Fig 4. Fluorescent SLN identified

SIGNIFICANT BENEFITS OF USING ICG

- **Real-time Imaging:** ICG provides real-time visualisation, allowing surgeons to precisely identify and remove SLNs during surgery.
- **Accuracy:** ICG-based SLN detection has been shown to be highly accurate in identifying lymph nodes.[11] Requires a small injection only which can be administered whilst patient is anaesthetised, thus minimising patient discomfort.
- **Excellent Safety Profile:** ICG has a significantly safer profile to blue dyes.*
- **Minimal Skin Irritation:** Little or no skin tattooing associated with ICG use, compared to blue dyes.[6]
- **No Preoperative Procedure Required:** The use of RIs creates logistical challenges for hospitals, legislative requirements, and a risk of radiation exposure for healthcare professionals.

Results from eight meta-analyses: 2016-2021 [11]

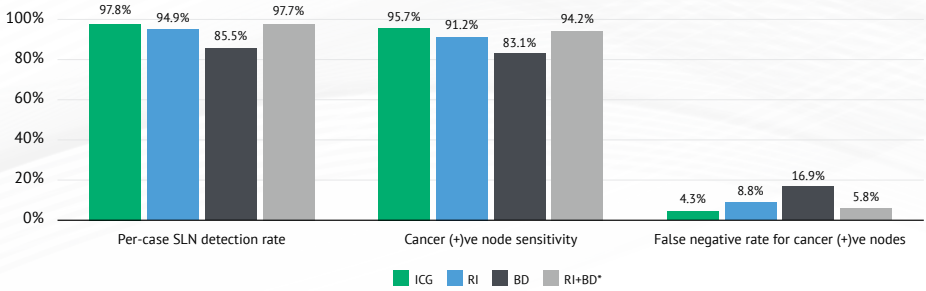

Fig 5. Meta-analyses

SUMMARY

In summary, ICG-based SLN detection offers several advantages to surgeons, including improved accuracy **(Fig 5)**, reduced invasiveness, enhanced patient comfort, reduced cost and safer alternatives to traditional radioactive tracers.[11] These benefits contribute to better surgical outcomes and a higher quality of care for breast cancer patients. Studies have shown that ICG has high sensitivity and specificity in SLN detection, meaning it accurately identifies the SLN while reducing the chances of false-positive or false-negative results. This reliability is crucial for making informed decisions about treatment and staging of breast cancer disease.

**Based on Diagnostic Green Pharmacovigilance data, a single adverse reaction was identified in 22,248 patients.*

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VERDYE PRESCRIBING INFORMATION – SPAIN

Name of the Medicinal Product
Verdye 5 mg/ml Injection
25 mg / 50 mg, powder for solution for injection

Pharmaceutical Form
Powder for solution for injection
Dark-green powder

Clinical Particulars
Therapeutic indications
This medicinal product is for diagnostic use only.

Diagnostic indications

Cardiac, circulatory and micro-circulatory diagnostics:
- measurement of cardiac output and stroke volume
- measurement of circulating blood volumes
- measurement of cerebral perfusion

Liver function diagnostics:
- measurement of liver blood flow
- measurement of excretory function of the liver

Ophthalmic angiography diagnostics:
- measurement of perfusion of the choroid

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Posology and method of administration

Method of administration
Before administration the powder must be reconstituted with water for injection.

Shelf life
5 years. After reconstitution, the solution should be used immediately, protected from light.

Instructions for use and handling
This medicinal product should be reconstituted immediately prior to use. This medicinal product is reconstituted by addition of 5 ml water for injections to the vial containing 25 mg of active substance or 10 ml water for injections to the vial containing 50 mg of active substance, respectively, giving in both cases a dark-green solution for injection with a concentration of 5 mg/ml (0.5 % w/v). Visually inspect the reconstituted solution. If an incompatibility is noted in the form of an unclear solution, the reconstituted solution should be discarded. Only use clear solutions free from visible particles.

This medicinal product is for single use only.

The reconstituted solution is clear and free from visible particles.

Diagnostic procedures with Verdye should be performed under the supervision of a physician. Verdye is administered by intravenous, intradermal, subcutaneous or peritumoral injection.

The administration and site of Verdye are of critical importance for the quality of the measurements. In principle, for obtaining optimal quality first pass indicator dilution curves, the injection should be as close as possible to the vascular bed, organ or tissue of interest.

On peripheral injection the injection should be made immediately after application of tourniquet and the arm should be raised after release of tourniquet. This ensures rapid transport of the dye from the site of injection and peripheral injection is then practically equivalent to central venous injection.

For the identification of sentinel lymph nodes and visualisation of lymphatic pathways in breast cancer, Verdye is injected into a region that is upstream of the particular lymph nodes that are of interest and that is drained by these. The injection can be intradermal, subcutaneous (interstitial) or also peritumoral. It is possible to accelerate the transport of indocyanine green into the sentinel lymph nodes through a breast massage.

Dosage
Single dose per measurement in adults, elderly, children:
Cardiac, circulatory, micro-circulatory and tissue perfusion diagnostics as well as cerebral blood flow: 0.1 to 0.3 mg/kg body weight as bolus injection
Liver function diagnostics: 0.25 – 0.5 mg/kg body weight as bolus injection
Ophthalmic angiography: 0.1 to 0.3 mg/kg body weight as bolus injection
Total daily dose:
Identification of sentinel lymph nodes and visualisation of lymphatic pathways regardless of body weight: 1 to 10 mg per injection (intradermal, subcutaneous or peritumoral). The volume per injection should not exceed 2 ml.

Adults, elderly, adolescents 11-18 years:
The total daily dose of Verdye should be kept below 5 mg/kg body weight.
Children 2 – 11 years:
The total daily dose should be kept below 2.5 mg/kg body weight.
Children 0 - 2 years:
The total daily dose should be kept below 1.25 mg/kg body weight.
Adults, elderly:
For the identification of sentinel lymph nodes and visualisation of lymphatic pathways, the total daily dose of Verdye should not exceed 10 mg; the use in children and adolescents is not recommended due to insufficient data on safety and efficacy.

Contraindications
Verdye is contraindicated for safety reasons in:
- patients with hypersensitivity to indocyanine green or to sodium iodide unless special precautions are taken
- patients with hypersensitivity to iodine
- patients with hyper-thyroidism, patients with autonomic thyroid adenomas
- as in-vitro experiments have shown that indocyanine green displaces bilirubin from its protein binding, Verdye should not be used in premature infants or neonates in whom an exchange transfusion is indicated due to of hyperbilirubinemia
- if injection of Verdye was poorly tolerated in the past it must not be used again, since severe anaphylactic reactions might occur.

For full prescribing information go to www.diagnosticgreen.com

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