Patent Blue V

See & make the right choice

Guerbet
Contrast for Life
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Breast cancer epidemiology

- Second most common cancer in the world (1)
- Most frequent cancer in women: 1.67 million new cases diagnosed in 2012 (25% of all cancers) (1)
- 5th cause of death from cancer overall (522,000 deaths in 2012) (1)

Breast cancer staging

- Second most common cancer in the world
- Most frequent cancer in women
- 5th cause of death from cancer overall

Breast cancer staging

- Tumor and metastasis localization and size
- TNM Classification of breast cancer

Tumor and metastasis localization and size

- Tis: carcinoma in situ
- T1: < 0.5 cm
- T1a: < 0.5 cm
- T1b: 0.5 to 1 cm
- T1c: 1 to 2 cm
- T2: 2 to 5 cm
- T3: > 5 cm
- T4: extends to skin or chest wall whatever its size

TNM Classification of breast cancer

- The TNM System, developed by the American Joint Committee on Cancer (AJCC), is considered very precise and this system is widely used for classification of breast cancer.
- T: Primary Tumor
- N: Regional Lymph Nodes
- M: Distant Metastases

- Stage 0: Tis, N0, M0
- Stage I: T1, N0, M0
- Stage IA: T1a, N0, M0
- Stage IB: T1b, N0, M0
- Stage IIA: T2, N0, M0
- Stage IIB: T3, N0, M0
- Stage IIC: T4, N0, M0
- Stage IIIA: T1, N1, M0
- Stage IIIB: T2, N1, M0
- Stage IIIC: T3, N1, M0
- Stage IV: Any T, Any N, M1

STAGING – CRUCIAL TO DETERMINE APPROPRIATE TREATMENT
Patent Blue V indication in breast cancer

Marking sentinel nodes before biopsy in patients with operable breast cancer.

**Sentinel lymph node identification – SLNI:**
- Injection into the immediate area surrounding the tumor or into the tumor bed periareolar
- Subcutaneous but not intradermal injection
- Systematically breast massage

<table>
<thead>
<tr>
<th><strong>Patent Blue V injection</strong></th>
<th><strong>Massage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image 668x88 to 706x126]</td>
<td>[Image 668x156 to 706x194]</td>
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</tbody>
</table>

**Sentinel Lymph Node Biopsy (SLNB) international management guidelines**

SLNB: standard-of-care for axillary staging in early breast* cancer according to the clinical practice guidelines(4)

**Europe** | ESMO guidelines (European Society for Medical Oncology)(4)
- The choice of treatment strategy is based on biology/pathology including biomarkers, gene expression and tumor extent/location size and location of primary tumor, number of lesions, number and extent of lymph node involvement as well as on the age, body habitus and general health status of the patient and her/his preferences.
- SLNB rather than full nodal clearance is now accepted as the standard of care for axillary staging in early breast cancer. 
- Level of evidence & Grade of recommendation: SNB as the standard of care for axillary staging — [II, A], SLNB delivers less morbidity & allows for a reduced hospital stay— [I, A]

**America** | ASCO Guidelines (American Society of Clinical Oncology)
- Women with operable breast cancer and multicentric tumors, […] who received preoperative/neoadjuvant systemic therapy may be offered SNB.
- Evidence quality & Strength of recommendation: SNB for early-stage breast cancer — High & Strong

**Australia** | NBOCC guidelines (National Breast and Ovarian Cancer Centre)
- Patients with unifocal tumours equal to or less than three centimetres in diameter and clinically negative axillary nodes should be offered sentinel node biopsy as an alternative to axillary dissection. 
- Level of evidence: SNB for staging and management of the axilla— I

*early breast: breast cancer that has not spread beyond the breast or the axillary lymph nodes

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**PATENT BLUE V INDICATION TO FIGHT BREAST CANCER**
Efficacy & Accuracy
Van la Parra R.F.D et al. EJSO (2014)"}

Conclusion: « SLN biopsy in multicentric breast cancer seems feasible and accurate and should therefore be considered in patients with multicentric breast cancer and clinically negative axilla. »

Results: « The SLN was successfully identified in 30 of 30 patients (identification rate 100%). The incidence of axillary metastases was 66.7% (20/30). The false negative rate was 0% (0/20) and the sensitivity was 100% (20/20). The negative predictive value was 100% (10/10). »

Multicenter prospective trial: SMMaC trial
30 patients with multicentric breast cancer.
- Periareolar injection of radiotracer and Patent blue dye was administered
- SLN biopsy (SLNB) was validated by back-up completion axillary lymph node dissection

Endpoint: to assess SLNB feasibility and accuracy in multicentric breast cancer

<table>
<thead>
<tr>
<th>n</th>
<th>Tumor</th>
<th>Injection</th>
<th>Identification rate</th>
<th>FN rate %</th>
<th>Sens</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>MC</td>
<td>SA</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

MC = multicentric; SA = subareolar; FN = false negative rate; Sens = sensitivity; NPV = negative predictive value

PATENT BLUE V ENDOURED BY INTERNATIONAL GUIDELINES

Europe
- There are two current techniques used to identify the sentinel node(s): Radiopharmaceutical, technetium sulfur colloid, and isosulfan blue dye (used in the United States), Tc-99m-labeled albumin and Patent blue dye (used in Europe).»
- «Dyes cause the blue colouring as they pass slowly through the sentinel node. Iosulfan blue is of greater use in the United States, and Patent blue V in Europe.»

UK
- «Increasingly sentinel lymph node biopsy (SLNB) is the preferred method for staging the axilla in early breast cancer (NICE Guidelines 2009). In the UK, the SN is successfully localized in 99% of patients using a combined technique of radioactive Tc-99m labelled nanocolloid and 2 ml of diluted Patent blue V dye injected into the breast (NEW START Programme). SLNB using the dual localisation protocol is now being used for other tumours, notably melanoma, penile, testicular, cervical and head and neck cancers.»

France
- «Le traceur utilisé est un colorant, un radioisotope ou les 2. L'injection du colorant (bleu patenté, bleu isosulfan ou bleu de méthylène) est faite au bloc opératoire avant induction de l'anesthésie, une dizaine de minutes avant l'incision...»
- «The tracer is either a dye, a radiopharmaceutical or both. The dye (Patent Blue, isosulfan blue or methylene blue) is injected in an operating room under anesthesia, approximately ten minutes before incision.»

SLNB – ACCURATE FOR MULTICENTRIC BREAST CANCER

Monocenter prospective randomized trial: SNAC trial
1 088 patients
  • Preoperative lymphoscintigraphy (LSG) and gamma probe (GP) combined with peritumoral injection of Patent Blue V (BPV): 971 patients
  • BPV alone: 106 patients

Endpoint: Effect of clinical factors on sentinel node (SLN) identification in the sentinel node biopsy versus axillary clearance (SNAC) trial

Objective:
• To define the contribution of each detection technique on the identification of SLNs in women involved in the sentinel node biopsy versus axillary clearance (SNAC) trial who were randomized to either SLNB with axillary clearance only if the removed SLNs were positive (SLNBM group) or SLNB followed by immediate axillary clearance (AC)»

Results:
• Blue SLNs were removed in 890 of 1073 patients (82.9%)»
• The identification rate among patients who had BPV injection only as the identification technique was 85.8% (91 of 106 patients)»
• BPV detected the SLNs in 141 of 178 women with negative LSG mapping and in 44 of 79 women with no hot SLNs detected intraoperatively»

Conclusion:
• BPV had an important salvage role in the SNAC trial when SLN identification failed using the GP and LSG»
• The use of BPV is recommended in patients who have unsuccessful SLN detection utilizing the radioactive tracer in order to improve the detection rate»
• There is merit in the use of patent blue in a combined technique, which could outweigh concerns about allergic reactions»
• BPV enabled the detection of SLN when use of scintigraphy and GP failed and retention of its use in a combined technique is recommended»

PATENT BLUE V DETECTS SLN WHEN OTHER TECHNIQUE FAIL
**Efficacy & Accuracy**


**Conclusion:**
« This study strongly validates the PA injection technique given the high detection rate (99.1%) of SLN and the high concordance (95.6%) between blue dye and the radiotracer, as well as higher significant ex and in vivo counts, improving SLN probe detection. »

Fransenode trial
449 patients

- A prospective randomized multicentric study was initiated to compare the peritumoral (PT) injection site to the periareolar (PA) site in 449 patients.
- The peritumoral (PT) injection site: 222 patients; The periareolar (PA) site: 223 patients

**Endpoint:** To determine the optimal injection path for blue dye and radiocolloid for sentinel lymph node (SLN) biopsy in early breast cancer.

**Objective:**
- The primary objective of the study was to determine the axillary sentinel lymph node (SLN) identification rate and the secondary objectives were to determine locoregional recurrence, survival, and morbidity.

**Results:**
- Intraoperative detection rate by blue dye and/or gamma probe was similar (99.11%) in both groups.
- The rate of SLN detection was somewhat higher in the PA group than in the PT group: 95.6% versus 93.8% with blue dye (P = .24) and 98.2% versus 96.0% by probe (P = .16), respectively.

**Conclusion:**
This study strongly validates the PA injection technique given the high detection rate (99.1%) of SLN and the high concordance (95.6%) between blue dye and the radiotracer, as well as higher significant ex and in vivo counts, improving SLN probe detection.

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**Patent Blue V safety**


**Conclusion:**
« The allergic potential of patent blue V dye compares favourably with isosulfan blue. Severe anaphylaxis is rare… »

Review of adverse reactions of Patent Blue V in patients who participated to NEW START training programme and the ALMANAC trial
7 917 patients

- All patient underwent sentinel lymph node biopsy for breast carcinoma using Patent Blue V in combination with $^{99}$m Tc-albumin colloid

**Objective:**
- Patent blue V is used in the UK while its isomer isosulfan blue is used in the US. The allergic potential of isosulfan blue is well documented (1.4% adverse reactions) but that of patent blue V is less clearly defined.
- In this paper we review the adverse reactions of patent blue V…

**Results:**
- In total, 72 of 7 917 (0.9%) patients experienced adverse reactions...

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse reactions</th>
<th>Objective</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Urticaria, blue hives, pruritis</td>
<td>23 patients</td>
<td>0.7%–1.1%</td>
</tr>
<tr>
<td>Grade II</td>
<td>Transient hypotension/bronchospasm</td>
<td>16 patients</td>
<td>0.4%–2.4%</td>
</tr>
<tr>
<td>Grade III</td>
<td>Severe hypotension requiring vasoressor support and/or HDU/ITU admission</td>
<td>5 patients</td>
<td>0.6%–2.0%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Cardio-respiratory arrest and/or death</td>
<td>24 patients</td>
<td>0.9%–1.1%</td>
</tr>
<tr>
<td>Total allergic reactions</td>
<td>68</td>
<td>0.7%–1.1%</td>
<td></td>
</tr>
<tr>
<td>Total non-allergic reactions</td>
<td>72</td>
<td>0.4%–2.4%</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:**
- The allergic potential of patent blue V dye compares favourably with isosulfan blue. Severe anaphylaxis is rare...
**Conclusion:**

> Sentinel lymph node biopsy (SLNB) is associated with reduced arm morbidity and better quality of life than standard axillary treatment and should be the treatment of choice for patients who have early-stage breast cancer with clinically negative nodes.

**Objective:**

- Compare quality of life outcomes between patients with clinically node-negative invasive breast cancer who received sentinel lymph node biopsy and patients who received standard axillary treatment.

**Results:**

- **Lymphedema:** Moderate or severe lymphedema was reported more often by patients in the standard axillary treatment group than by patients in the sentinel lymph node biopsy group at 1, 3, 6, and 12 months after surgery (all P < .001).
- **Sensory deficit:** At all time points, statistically significantly more patients in the standard treatment group than in the sentinel biopsy groups reported sensory deficit (P <.001 for all).
- **Intercostobrachial nerve damage:** Was more extensive in the standard treatment group than in the sentinel lymph node biopsy group at 1, 3, 6, and 12 months after surgery (all P < .001).
- **Quality-of-Life Assessments:** TOI score (Trial Outcome Index): statistically significant differences in TOI scores between treatment groups favoring the sentinel lymph node biopsy group at all time points (P < .001, 1 month after surgery; P = .001, 3, 6, and 12 months after surgery).

**SLNB WITH PATENT BLUE V REDUCES MORBIDITY & IMPROVES QUALITY OF LIFE**

**SLN identification with Patent Blue V alone & biopsy procedure**

- **Patient Blue V injection**
- **Massage**
- **Patent Blue V diffusion**
- **Incision**
- **Spotting & withdrew**

**ANATOMO-PATHOLOGY EXAMINATION**

- **NO CANCERS CELLS**
- **REDUCED ARM MORBIDITY**
- **BETTER QUALITY OF LIFE**

**CANCERS CELLS**

Full axillary lymph nodes resection.
Patent Blue V use and mechanism of action

- **Volume preparation:** Identification of SLN consists to inject 2 ml of Patent Blue V.
- **Injection site:** Injection into the immediate area surrounding the tumor or into the tumor bed periareolar.
- **Injection path:** Subcutaneous but not intradermal injection.
- **After injection:** Systematically breast massage.
- After approximately 5 minutes’ delay, during which time the injection site was gently massaged, a 3- to 5-cm axillary incision was made in the standard location for ALND or the predetermined line for mastectomy.

Two blue (axillary) lymphatic trunks clearly visible after periareolar intradermal dye injection. The vessels pass over the breast tissue and join to drain into a single blue sentinel node (held in the forceps) in the lower axilla.

Identification with Patent Blue V and radioisotope & biopsy procedure

- **Patent Blue V injection**
- **Massage**
- ** PATENT BLUE V INJECTION **
- ** NO NEED FOR A AXILLARY LYMPH NODE RESECTION **
- ** REDUCED ARM MORBIDITY **
- ** BETTER QUALITY OF LIFE **
- ** CANCERS CELLS **
- ** ANATOMO-PATHOLOGY EXAMINATION **
- ** REDUCED MORBIDITY & IMPROVES QUALITY OF LIFE **

Sendinel node clearly visible 5 min. after injection
## Features & benefits of Patent Blue V

<table>
<thead>
<tr>
<th>Features</th>
<th>Benefits</th>
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| Visualizer | • Clear Identification & localization of Sentinel nodes 5 mins after injection\(^{17}\)  
              • High identification rate\(^{19}\)                                      |
| Improver   | • Participate to reduce morbidity \(^{10,12}\)                              
              • Improve quality of life \(^{13,15}\)                                   |
| User-friendly | • Subcutaneous injection \(^{16,17}\)                                       
              • No obligation to dilute \(^{16,17}\)                                 |

\(^{18}\)
(2) NATOMIMAGES - Callimedia
(4) Senkus E. et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, 2015, 26: v8–v30
(10) HAS, Note de cadre, Role de la technique du ganglion sentinelle dans la strategie diagnostique de l'envahissement ganglionnaire d'un cancer du sein au stade precoce, 2011, p. 21
(12) Elmadahm A. A. et al., Identification of the sentinel lymph node in the SNAC-1 trial, Royal Australasian College of Surgeons, ANZ J Surg., 2015, 85 38-63
PATENT BLUE V. Composition: PATENT BLUE V SODIUM 2.5 g per 100 ml of solution for injection. List of excipients: Sodium chloride, disodium phosphate, sodium carbonate, water for injection.

Indications (**): Diagnostic use only. Marking lymph vessels and internal regions. Marking sentinel nodes before biopsy in patients with operable breast cancer. Posology and method of administration (**): See table. Marking sentinel nodes: not more than 10 ml intrathecally, marking lymph vessels: 0.5 to 2 ml subcutaneously, marking the sentinel node 1 to 2 ml subcutaneously around the tumor or areola. Contraindications (**): Hypersensitivity to Patent Blue V, tryphenylmethane dyes or any of the excipients. Special warnings and special precautions for use (**): There is a risk of allergy reactions whatever the administration route or dose. Patent Blue V may cause minor or major immediate allergic reactions that may be life-threatening or even fatal (anaphylactic shock). They are often unpredictable but they occur more frequently in patients with a history of hypersensitivity reactions to Patent Blue V-related tryphenylmethane dyes contained in drugs, food and cosmetics. The indication should be very carefully assessed in these predispersed patients. Contraindications and/or type I allergy to Patent Blue V-related tryphenylmethane dyes may be indications of anaphylactic shock. They can also be a warning sign of anaphylactic shock. The risk of a major reaction implies that emergency measures must be immediately available especially in patients on beta blockers in whom adrenaline and vasodilator would be insufficiently effective. Therefore, Patent Blue V must only be administered in an establishment under the supervision of qualified personnel.

Other forms of interaction (**): Medicinal products
- Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists. These medicinal products reduce the efficacy of cardiovascular compensation mechanisms for haemodynamic disorders. The physician must be aware of this before injecting Patent Blue V and emergency measures must be available. Other forms of interaction:
- The value of partial oxygen pressure measured by spectrophotometry may show a transient false decrease of 5 to 10% below baseline values during water immersion, respiration, in patients on beta-blockers. It is advisable to check, by arterial blood gas analysis, the value of serum methaemoglobin measured by the same spectrophotometric method may be slightly increased. Fertility, pregnancy and lactation (**): Contraindicated. The use of this medicinal product is not recommended during pregnancy. Lactation. It is not known whether Patent Blue V is excreted in breast milk. Effects on ability to drive and use machines (**): Immediate hypersensitivity reactions may occur. The patient must be warned to avoid exposure to the dye until the reaction is over. The patient must be informed that they can show a warning sign of sharp shock and, in very rare instances, cause even fatal shock (anaphylactic shock). A careful checking of the preparations is observed after the injection, which disappears within 24 to 48 hours. In patients with lung and or pulmonary disorder, the coloration may last longer. Gemcitabine followed by Anthracyclines, or Fluoropyrimidines. Day for vessel marking, ASC: code: VX01. Pharmacokinetic properties (**): The dye is administrate i.v. at 24 to 48 hours, mainly in urine (which is highly colored) but also in bile. Nature and content of container: colorless type I glass ampoule containing 2 ml. Date of revision: September 2013.

For complete information please refer to the local Summary of Product Characteristics. **Indications may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your Health authorities or to our local Guerbet representative.

Indications and dosage may vary from country to country. Countries where indication, Sentinel Nodes Identification, before biopsy in patients with operable breast cancer is registered are: Belgium/Luxembourg, Canada, France, Germany, Hong Kong, Hungary, Israel, Mexico, The Netherlands [Netherlands], Philippines, Slovakia, Switzerland, Taiwan, Thailand.

For a copy of the SmPC, please contact a Guerbet representative.
Bleu Patente V
Sodique Guerbet 2,5%

Solution injectable en ampoule de 2 ml, boîte de 5 ampoules
Voir sous-cutanée et intraveineuse
Colorant pour repérage vasculaire
Solution for injection in ampoule of 2 ml, box of 5 ampoules
Subcutaneous and intravenous route
Dye for marking vessels

Guerbet
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