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► **To cite this version:**

V. White, J.R. Harvey, C.D.M. Griffith, M. Youssef, M. Carr. Sentinel Lymph Node Biopsy in Early Breast Cancer Surgery - working with the risks of vital blue dye to reap the benefits. *EJSO - European Journal of Surgical Oncology*, 2011, 37 (2), pp.101. 10.1016/j.ejso.2010.12.007 . hal-00663073

HAL Id: hal-00663073

<https://hal.science/hal-00663073>

Submitted on 26 Jan 2012

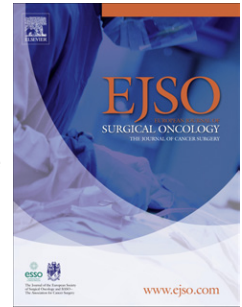
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Accepted Manuscript

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PII: S0748-7983(10)00606-2

DOI: [10.1016/j.ejso.2010.12.007](https://doi.org/10.1016/j.ejso.2010.12.007)

Reference: YEJSO 3086

To appear in: *European Journal of Surgical Oncology*

Received Date: 8 September 2010

Revised Date: 21 November 2010

Accepted Date: 6 December 2010

Please cite this article as: White V, Harvey JR, Griffith CDM, Youssef M, Carr M. Sentinel Lymph Node Biopsy in Early Breast Cancer Surgery – working with the risks of vital blue dye to reap the benefits, *European Journal of Surgical Oncology* (2010), doi: 10.1016/j.ejso.2010.12.007

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Sentinel Lymph Node Biopsy in Early Breast Cancer Surgery – working with the risks of vital blue dye to reap the benefits.

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Abstract

Aims

Sentinel lymph node biopsy (SLNB) is an important method of staging early breast cancer because of the inherent benefits it confers on patients in terms of arm function and quality of life. Its success depends on a high level of accuracy in detecting the sentinel node. This is achieved by a dual mapping technique that employs a radio-labelled nanocolloid and a vital blue dye. The vital dyes however carry the risk of anaphylaxis, and as more surgeons employ SLNB in their daily practice, a proportionate rise in the number of anaphylactic reactions can be expected. A comprehensive review of risks and benefits associated with using vital blues dyes has not been published and therefore a retrospective review was undertaken of the different levels of anaphylaxis associated with vital dyes, their benefit to SLNB and methods of reducing the risk.

Methods

An OVID MEDLINE search was performed of the English published literature using appropriate search terms to find published trial data and case series that focused on adverse reactions to vital blue dyes.

Results

The risk of severe anaphylaxis (grade 3) can be as low as 0.06%, and up to 0.4% for patients undergoing SLNB when data is analysed from large trials. Furthermore, adverse reactions associated with blue dyes are reversible with appropriate management.

Conclusions

Surgeons should continue to use vital dyes to ensure that SLNB remains highly sensitive procedure.

Introduction

A sentinel lymph node is defined as the first node that lymphatic fluid encounters as it drains from a primary tumour. First described in the 1960s and 1970s for parotid cancer¹ and penile cancer², the concept was applied as a method of staging cutaneous melanoma by Morton et al^{3,4}. They demonstrated that the status of sentinel nodes, with respect to the presence of metastases, accurately reflected the metastatic content of the local nodal basin⁵. Their work validated SLNB as a procedure of staging melanoma by a minimally invasive method. The principles of SLNB were subsequently applied to early breast cancer in the 1990s by pioneers who confirmed that focused histological analysis of sentinel lymph nodes accurately staged the disease^{6,7}. Further accumulation of evidence on the benefits of SLNB e.g. a lower incidence of pain, numbness, shoulder joint stiffness and long term lymphoedema compared with axillary dissection⁸⁻¹⁰, led the American Society of Clinical Oncology in 2005¹¹, and more recently the British Association of Surgical Oncology¹² to endorse SLNB as the recommended method of staging early breast cancer in clinically node negative patients. SLNB is not however without its controversies and complications, in particular the risk of anaphylaxis associated with the use of vital blue dyes. To obtain a comprehensive analysis of the risks and benefits of vital blue dyes in SLNB we undertook a detailed study of the literature which has been synthesised into the following review.

Literature Search

An OVID MEDLINE search was performed of the English published literature to find published studies and case reports that focused on adverse reactions to vital blue dyes. The following search terms were used; “sentinel lymph node”, “sentinel lymph node biopsy”, “Patent Blue dye(s)”, “isosulfan blue”, “methylene blue”, “anaphylaxis”, “allergic reaction”, “breast cancer”. The references in the identified publications were also reviewed to obtain additional articles that were not found during the electronic searches. 64 studies were identified. 50 were excluded either because they did not analyse their data with respect to adverse reactions, or because they did not use a vital dye. 14 studies were used in the analysis of adverse reactions to vital blue dyes, together with 9 case reports and 4 letters that focused on anaphylaxis.

Sentinel Node Methodology

Intra-operative detection of the sentinel lymph node is achieved with vital dyes or lymphoscintigraphy either alone, or by using a combination of both techniques. The methods depend on carriage of the vital dye (Patent Blue V, Isosulfan blue or Methylene blue) and/or a radioactive colloid (e.g. technetium-99m in nanocolloid [99m Tc nanocolloid]) in the breast and axillary lymphatics. The uptake kinetics of each mapping agent are different, but the function of both is to localise the sentinel node. It is thought that nanocolloids become entrapped within the sentinel lymph nodes either through a function of their particulate size^{13,14} (the larger hydrodynamic diameter of 50-100nm for colloid requires a transit time of usually more than 1 hour¹⁵) or because of phagocytosis by leukocytes which migrate to and are retained within the draining lymph nodes¹⁶. These entrapment processes are unlikely to be mutually exclusive, and other mechanisms may also exist, but the end result is localisation of the nanocolloid within the sentinel nodes rather than its diffuse spread

to secondary nodes. In contrast, patent blue dyes bind to interstitial albumin and are taken up by local lymphatic tissue¹⁷. The efficiency with which the lymphatics are converted to bright blue channels by the vital dyes reflects their smaller hydrodynamic diameter, their ability to disperse quickly and even their capacity to readily progress through and beyond the sentinel nodes^{15, 16, 18}. The different properties of the nanocolloids and the vital dyes act synergistically in SLNB; injection of the radio-isotope between 2 and 24 hours before surgery optimises its localisation in the sentinel nodes and intra-operative injection of the vital dye directs the surgeon to the lymphatics that track to the sentinel node.

The exact site of injection of the mapping agent varies between studies¹⁹⁻²⁵, but can be broadly divided into “superficial” or “deep”¹⁹. Radioactive colloid is injected pre-operatively, with the assistance of radiological imaging either around the tumour, or into the overlying skin. Vital dyes are injected intra-operatively either into or around the tumour, or superficially into the section of areolar tissue that correlates with the index quadrant. In the United Kingdom, the NEW START training programme recommends that patent blue dye is injected subdermally into the index quadrant of the periareolar tissues. Despite the different injection protocols, the precise position of the vital dye injection may be immaterial given the embryology of breast lymphatic tissue; studies have shown that the lymphatics of breast parenchyma and those of its overlying skin are connected by a common subareolar lymphatic plexus (Sappey’s complex)²⁶. The presence of this plexus supports the hypothesis that a mammary gland and its overlying skin share the same lymphatic channels to the draining sentinel node^{16, 27}.

The choice of vital dye varies between operating surgeons. In the United States, Isosulfan blue, as a 1% sterile solution is the vital dye approved for use in humans by the Food and Drug Administration. Isosulfan blue is a monosodium isomer of the 2,5 disulfonated triphenylmethanes which are also known as the patent blue dyes²⁸. One of these patent blue dyes, Patent Blue Violet (or Patent Blue V), is preferentially used in Australia and Europe²⁹. Another vital dye, Indocyanine green has been used in Japan²⁹. All the vital dyes are selectively absorbed into lymphatic tissue and therefore facilitate localisation of the lymphatic channels and nodes.

Level of Anaphylactic Risk

The use of vital dyes as mapping agents is associated with risk. Anaphylaxis from Patent Blue V and Isosulfan blue is an IgE mediated event³⁰, and in the UK, patients must give informed consent to their use¹². Many of the early studies on SLNB in breast cancer did not address the issue of adverse reactions to vital dyes presumably because their focus was on the primary outcomes that the trials were designed to measure^{6, 8, 31-37}. Other studies specifically considered adverse reactions to the blue dyes in later publications^{9, 38}. With respect to anaphylaxis, this complication has been documented since the 1960’s; in 1966 Kopp reported anaphylactic reactions in 2 patients who were injected with 0.25ml of an 11% solution of Patent Blue dye³⁹. In 2002, an editorial on the Consensus on Sentinel Node Biopsy, acknowledged that there had been at least 2 deaths caused by anaphylaxis from blue dye⁴⁰. These deaths were included in the outcome results from over 10 000 cases, and represented the extreme of a spectrum of adverse reactions. This spectrum of adverse reactions was clarified by Montgomery et al in 2005⁴¹, they noted that the severity of anaphylaxis

was not uniform, but could be subclassified into 3 grades (see Table 1); grade 1 reactions are limited to a cutaneous response, whereas grade 3 reactions equate to severe anaphylaxis. Their findings correlated with assertions that if the whole spectrum of adverse reactions is considered, the risk of any grade of anaphylaxis is approximately 1%, but that the risks are “rarely irreversible”⁴⁰.

That grade 3 anaphylaxis rarely occurs is supported by data published from the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial³⁸ which reported a 0.06% risk. Other large international trials also reported low risk rates such as the ACOSOG Z0010 trial which reported the risk rate of 0.1%⁴², and the NSABP-B32 trial which reported the incidence of grade 3 allergic reactions to Isosulfan blue as 0.2%⁴³. No deaths occurred. These and other studies which have addressed the issue of incidence of anaphylaxis with vital dyes^{10, 21, 38, 41-51} are summarised in table 2.

In studies that have published risks of greater than 1%, the rate is often a reference to all grades of anaphylaxis for example, Cox et al (2000) reported a 1% risk of adverse reaction⁴⁴. This 1% risk related to patients who had an allergic reaction “manifested by an initial wheal reaction at the injection site, followed by the development of blue hives scattered about the ipsilateral axilla, neck, groin and other intertriginous areas”⁴⁴. These reactions cleared quickly with intravenous antihistamine. Only 3 patients out of 1700 had a marked decrease in blood pressure which suggests that only 0.17% of patients had a grade 3 or higher reaction⁴⁴. A study by Thevarajah et al (2004) which estimated a 1% to 3% risk of anaphylaxis to Isosulfan blue⁵², was based on analysis of data from several published studies that combined all grades of hypersensitivity reaction. For studies that have quoted risks of greater than 1% specifically for a grade 3 reaction, the number of patients in the cohort have been much smaller than in the large trials^{45, 46}. In addition to trial data on hypersensitivity reactions, awareness of anaphylaxis has also been raised through case reports in the literature^{53 54, 17, 55, 56}. None of these cases reported long term sequelae or deaths.

Avoidance of risk by using radio-active colloid as a single agent

Avoidance of anaphylaxis in SLNB can be achieved by the use of radio-colloid as a single mapping agent. The risk of anaphylaxis from nanocolloids is extremely rare^{57, 58}. Several of the initial studies designed to validate SLNB used radioactive tracer alone^{7, 59}. Krag et al (1998) showed that the technique had a sensitivity of 88.6% for accurately locating a positive sentinel node with a false negative rate of 11%⁷. The lower success rate in identifying sentinel nodes in these early studies, compared with many of the later studies, probably reflects the relative inexperience of breast surgeons with the SLNB technique. It has subsequently been shown that surgeons who are experienced in SLNB can obtain a high intra-operative success rate of identifying sentinel nodes with lymphoscintigraphy without reliance on vital dyes⁶⁰. Furthermore, since publication of the initial validation studies, newer techniques have emerged such as superficial injection of the mapping agents. Studies focusing on the superficial injection of radioactive colloid have demonstrated sentinel node identification rates of up to 98%^{22, 61, 62}. These higher success rates for radioactive colloid may occur because the superficial injection obtains immediate access to the common lymphatic pathways that lead to the sentinel node. The superficial injection technique also is easier to learn^{22, 63} and it eliminates the “shine through” effect of

radioactivity from the primary tumour⁶³. The studies also used dual mapping techniques, which have been shown by previous studies³⁵⁻³⁷, and a recent meta-analysis, to improve sentinel lymph node localisation⁶⁴. However, a caveat to the conclusions of this meta-analysis is that it included many of the early validation studies that did not focus on the newer superficial injection techniques.

The same meta-analysis also looked at the false negative rate (FNR) of SLNB⁶⁴, which is determined by SLNB followed by conventional axillary dissection in the same axilla. The meta-analysis established that the FNR is variable (0-29.4% but averaging 7.3% overall) and is affected by the SLNB method used; 10.9% and 8.8%, respectively for vital blue dyes and radiocolloid used as single agents, and 7.0% when a combined mapping procedure is used⁶⁴. Subsequent studies which addressed both issues of FNR and anaphylaxis are recorded in table 2^{10, 38, 43, 44, 51, 65}. The FNRs of these “later” studies are consistent with the meta-analysis findings, but the precise contribution of Patent Blue V, Isosulfan Blue or Methylene blue in the studies cannot be accurately quantified.

Avoidance of risk by using Methylene Blue or Corticosteroid prophylaxis

Methylene blue has been used as an alternative to the other vital dyes. Its attraction as a mapping agent is its low risk profile. Methylene blue lacks the sulphur trioxide group (SO₃) that is used by the patent blue dyes to form sulphonamide complexes with proteins and antibodies⁶⁶. These sulphonamide complexes facilitate localisation of the patent blue dyes within the lymphatics and the sentinel lymph nodes⁶⁷, but they are also implicated in the type 1 hypersensitivity reactions. The inability Methylene blue to form these sulphonamide complexes contributes to its safety profile, but this vital dye is not without its side effects; intradermal and subdermal injections of Methylene blue can cause erythematous skin lesions, superficial ulceration and tissue necrosis^{16, 68, 69}. These side effects are thought to be caused by the oxidation of Methylene blue to substances such as formaldehyde which excites an intense inflammatory response hence the erythematous lesions and ulceration^{68, 70}. Methylene blue can also trigger localised vasospasm^{68, 71} which will contribute to skin necrosis. Proponents of Methylene blue as a mapping agent suggest these side effects can be avoided by “deeper non-dermal injection techniques”⁶⁸. However, this introduces another variable into the SLNB technique with the attendant problems of data interpretation. The small molecular weight of Methylene blue may also compromise its function as a mapping agent because of its capability for more rapid diffusion through the lymphatics which will limit the time it spends within the sentinel lymph nodes before moving on to higher level lymph nodes⁷². The capacity of Methylene blue to function as a mapping agent needs to be tested in large trials, but evidence from small studies suggests that Methylene blue is equivalent to the patent blue dyes, e.g. one study demonstrate an identification rate of 98.7% in 329 early breast cancer patients⁶⁵. Other studies have shown similar identification rates⁷³⁻⁷⁵. The other advantages of using Methylene blue include its lower cost⁷⁴ and wider availability.

The risk of anaphylaxis from patent blue dyes may also be reduced by pre-operative prophylaxis with corticosteroids, antihistamines and H₂-receptor antagonists. No significant difference has been shown between patients with and without such an intervention except a trend for increased wound complications (infection, dehiscence)⁷⁶.

Benefits of Vital Dyes

The advantage of vital dyes is their “real time” efficiency in guiding the gamma probe to the sentinel node. This reduces exploratory dissection and tissue plane disruption. Limited dissection is pertinent if the patient is to be spared the morbidity associated with conventional axillary dissection. Several randomised controlled trials using a patent blue dye alone or in combination with radioactive nanocolloid tracer have now unequivocally demonstrated that symptoms of lymphoedema, numbness, shoulder mobility, weakness and pain are lower in patients who have undergone SLNB compared with patients who had axillary clearance^{8-10, 43, 77}. These widely acknowledged benefits of SLNB should be weighed against the small risk of an adverse reaction to the dye. Blue dyes also contribute to increased sensitivity of the SLNB procedure when used in conjunction with radioactive colloids⁶⁴. Finally, as the clinical benefits of the SLNB technique has become established, its use in the management of other invasive carcinomas has expanded, and with this, the wider use of vital blue dyes. For example, in primary cervical cancer, it has been suggested that for carefully selected cases, SLNB may impact positively on younger women who do not want their fertility affected by extensive lymphadenectomy⁷⁸. In urinary tract cancers, vital dyes have shown potential in identifying the lymph nodes which drain the bladder¹⁵. Similarly, preliminary data in head and neck cancers, suggest that SLNB may limit the post operative morbidity associated with radical neck dissections⁷⁹. SLNB in lower gastrointestinal cancers may have a role in improving the staging of the disease through the identification of small volume nodal disease and hence identifying which patients should be up-staged^{80, 81}.

Discussion

Scrutiny of the evidence on anaphylactic reactions to patent blue dyes in early breast cancer has shown that although the risks are real, they are manageable. All grades of reaction are important, but it is the more severe reactions that generate greater concern. Review of the data suggests that the risk of severe anaphylaxis (grade 3) can be as low as 0.06%, and up to 0.4% for patients undergoing SLNB when data is analysed from large trials^{38, 41-43} or databases⁵⁰. Acceptance of this small degree of risk is arguably in the interests of the patient given the high level of evidence which demonstrates that SLNB is associated with low morbidity⁹. Therefore, a measured approach should persuade surgeons that the benefits of using vital blue dyes do exceed the risk, and that while vital dyes are not benign chemicals, there is good evidence that adverse reactions are reversible with the appropriate management³⁰. Furthermore, the long term morbidity or death after an adverse reaction is extremely rare⁴⁰. The risks associated with vital blue dyes may also be ameliorated by the use of a “best practice protocol” for all SLNB operations where anaesthetic and theatre staff are routinely informed of the risks and of the management plan to be implemented in the event of anaphylaxis.

There are circumstances where the use of blue dyes may become limited e.g. if data emerges to conclude that superficial injection of radioactive colloid, as a single agent, reliably reproduces a high success rate in identifying sentinel lymph nodes. Even with this progress, vital blue dyes would not be rendered redundant because of their

essential contribution to accurate lymphatic mapping in the absence of axillary “hot spots” or where only weak axillary hot spots are located on lymphoscintigraphy. Vital blue dyes will also facilitate surgeons less experienced in SLNB techniques, since using the dual mapping techniques does achieve high success rates in identifying the sentinel nodes^{51, 64}. Blue dye can also be used to demonstrate the principles of SLNB and functional anatomy of the breast lymphatics to medical students and trainees.

In the future, an accurate knowledge of the level of risk or predictors of risk may become available if there is central collation of pertinent data on all patients who have had a hypersensitivity reaction to patent blue dyes. Assessment of risk may also be facilitated by further research trials e.g. the use of Methylene blue or superficial injection of radioactive colloid, which may offer safer alternatives to patients who are at a higher risk of anaphylaxis. For now however, with the number of SLNB procedures increasing and the indications for the procedure widening^{9, 82}, a comprehensive understanding of the risks and benefits of using vital blue dyes in SLNB is essential.

Conflicts of interest: none declared.

Funding: None received.

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Table 1 Doc.

Sentinel Lymph Node Biopsy in Early Breast Cancer Surgery – working with the risks of vital blue dye to reap the benefits.

White, V.; Harvey, J.R.; Griffith, C.D.M.; Youssef, M.; Carr, M.

Grade of reaction	Clinical presentation
1	Urticaria, pruritis blue hives or a generalised rash.
2	Transient hypotension (systolic blood pressure >70mmHg) not requiring pressor support.
3	Hypotension (systolic blood pressure <70mmHg) requiring pressor support.

Table 1: Allergic reactions to vital blue dyes as defined by Montgomery et al⁴⁰

Table 2 Doc.

Sentinel Lymph Node Biopsy in Early Breast Cancer Surgery – working with the risks of vital blue dye to reap the benefits.
White, V.; Harvey, J.R.; Griffith, C.D.M.; Youssef, M.; Carr, M.

Authors	Cox et al ⁴⁴	Cimmino et al ⁴⁵	Albo et al ⁴⁶	Montgomery et al ⁴¹	King et al ⁴⁷	Komenka et al ⁴⁸	Wilke et al ⁴²
Publication	2000	2001	2001	2002	2004	2005	2006
Trial Design	Observational study	Observational study	Observational study	Retrospective study using MSKCC database	Prospective study from MSKCC	Retrospective review of data from C-P BC	ACOSOG Z0010 trial. Prospective multicenter trial
Number of patients	>1700 Completed analysis of 1356 patients	267 (included melanoma patients)	639	2392	1728	352	5527 (4978 had blue dye)
Primary outcome measures	Review of mapping techniques	Adverse reactions during SLNB	Adverse reactions during SLNB	Adverse reactions during SLNB	Impact of volume of vital dye on adverse reactions	To determine the incidence of adverse reactions	Prognostic significance of micrometastases
Vital dye	1% Isosulfan blue	1% Isosulfan blue (3 to 5ml)	1% Isosulfan blue (3 to 5ml)	1% Isosulfan blue (mean volume 3.9ml)	1% Isosulfan blue (variable volumes)	1% Isosulfan blue	1% Isosulfan or Methylene blue
Dual mapping (Radiocolloid)	Yes	Yes	Yes	Yes	Yes	Not specified	Yes
Identification rate	96%	N/A	N/A	N/A	99.1%	N/A	N/A
False negative rate	0.84%	N/A	N/A	N/A	N/A	N/A	N/A
Risk of anaphylaxis	0.17% incidence of a grade 3 reaction. 1% for all grades of reaction. No deaths.	1.1% incidence of grade 3 reactions. 2% for all grades of reaction. No deaths	1.1% incidence of a grade 3 reaction. No deaths.	0.37% incidence of a grade 3 reaction. 1.5% incidence for all adverse reactions. No deaths	0.1% incidence of a grade 3 reaction. 1.8% incidence for all adverse reactions. No deaths	0.0% incidence of a grade 3 reaction. 0.85% incidence for all adverse reactions. No deaths	0.1% incidence of anaphylaxis (grade1). 0.6% of mild or moderate allergy (grade 1-2). No deaths
Other risks	A, B	A, B	A, B	A, B	A, B	A, B	A, B

Table 2: Studies that analysed the risks of allergic reaction to vital blue dyes when used during sentinel lymph node biopsy (SLNB)

Allergic reactions to Isosulfan Blue (Defined by Montgomery et al 2002⁴¹)

Grade 1: urticaria, pruritis blue hives or a generalised rash

Grade 2: transient hypotension (systolic blood pressure >70mmHg) not requiring pressor support

Grade 3: Hypotension (systolic blood pressure <70mmHg) requiring pressor support.

MSKCC (Memorial Sloane-Kettering Cancer Centre), C-P BC (Columbia Presbyterian Breast Centre), ACOSOG (American College of Surgeons Oncology Group), USS (ultrasound scan), NSN (non-sentinel node), DFS (Disease free survival), OS (overall survival), NSABP (National Surgical Adjuvant Breast and Bowel Project), ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance), QOL (quality of life),

A; skin tattooing, B; interference with pulse oximetry measurements, C; erythematous skin lesions and ulceration, D; skin necrosis

Authors	Hsu et al ⁴⁹	Varghese et al ⁶⁵	Rodier et al ²¹	Kragg et al ⁴³	Grantley Gill ¹⁰	Hunting et al ⁵⁰	Barthelemes et al ³⁸
Publication	2006	2007	2007	2007	2009	2010	2010
Trial Design	Observational study	Retrospective study	Prospective randomised multicentre trial	NSABP B-32 trial Multicenter randomised trial	Multicenter, centrally randomised trial	Retrospective review of the Norwegian national registry for allergy during anaesthesia	ALMANAC trial. Multicenter randomised trial
Number of patients	509	329	449	5536	1083	1418	7917
Primary outcome measures	Intra-operative USS used to identify NSN metastases	Evaluation of safety & efficacy in SLNB	Optimal injection site: periareolar -v- peritumoral	Survival. Regional control. Morbidity.	Axillary & Arm morbidity. DFS. OS.	Clinical features of the adverse reactions	Arm & shoulder morbidity. QOL ⁹
Vital dye	Patent Blue V	Methylene blue	Patent blue V	Isosulfan blue (5ml undiluted)	Patent Blue V (up to 4 ml)	Patent blue V	Patent blue V (2ml diluted to 5ml)
Dual mapping (Radiocolloid)	No	Yes	Yes	Yes	Yes	Yes	Yes
Identification rate	98.8%	97.6%	99.1%	97.1%	94.5%	N/A	96.1% ⁵¹
False negative rate	N/A	3.9%	N/A	9.8%	5.5%	N/A	6.7% ⁵¹
Risk of anaphylaxis	0 Grade 3 reactions. 0.6% incidence of grade 1-2 reactions. No deaths	None	No anaphylaxis	0.2% incidence of a grade 3 reaction. No deaths	3 cases of “allergic reaction” i.e. 0.28% incidence for all adverse reactions No deaths.	0.4% incidence of a grade 3 reaction. 0.5% incidence for all adverse reactions. No deaths	0.06% incidence of a grade 3 reaction 0.3% & 0.2% incidence of grade 1 & grade 2 reactions respectively. No deaths
Other risks	A, B	A, B, C, D	A, B	A, B	A, B	A, B	A, B

Table 2 (continued): Studies that analysed the risks of allergic reaction to vital blue dyes when used during sentinel lymph node biopsy (SLNB)

Allergic reactions to Isosulfan Blue (Defined by Montgomery et al 2002⁴¹)

Grade 1: urticaria, pruritis blue hives or a generalised rash

Grade 2: transient hypotension (systolic blood pressure >70mmHg) not requiring pressor support

Grade 3: Hypotension (systolic blood pressure <70mmHg) requiring pressor support.

MSKCC (Memorial Sloan-Kettering Cancer Centre), C-P BC (Columbia Presbyterian Breast Centre), ACOSOG American College of Surgeons Oncology Group), USS (ultrasound scan), NSN (non-sentinel node), DFS (Disease free survival), OS (overall survival), NSABP (National Surgical Adjuvant Breast and Bowel Project), ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance), QOL (quality of life),

A; skin tattooing, B; interference with pulse oximetry measurements, C; erythematous skin lesions and ulceration, D; skin necrosis