The Role of Blue Dye in Sentinel Node Detection for Breast Cancer: A Retrospective Study of 203 Patients

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Keywords

Breast cancer · Sentinel lymph node · Surgery · Mapping · Blue dye · Radiolabeled colloid

Summary

Objective: We aimed at examining the potential benefits of blue dye in sentinel node biopsy (SNB) in comparison with its proven drawbacks. **Patients and Methods:** In 2007, 203 T1 primary breast carcinomas had been operated on in our institute. The patients had undergone a lumpectomy and SNB. Sentinel node (SN) detection was exclusively isotopic (ISO) in 77 patients and performed with blue dye combined with a radioactive isotope (COMBI) in 126 patients. We compared the number of SNs and the rate of SN positivity in both groups. **Results:** The detection rate was 99% in both groups: 76/77 in the ISO group and 125/126 in the COMBI group. The mean number of SNs was 2.14 and 1.91 in the ISO group and the COMBI group, respectively (difference not significant (NS)). SN positivity was found in 26.1% and 24.6% in the ISO group and the COMBI group, respectively (NS). Only 1 SN had been removed in 26% of the patients in the ISO group versus 45.2% of the patients in the COMBI group ($p = 0.004$). No significant differences were observed in the tumor characteristics. **Conclusion:** The systematic use of patient blue dye combined with isotopic detection does not appear to increase the overall performance of the SNB technique in this retrospective study.

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Introduction

The sentinel node biopsy (SNB) technique is now a standard technique for axillary nodal staging in primary N0 breast carcinomas measuring less than 30 mm [1, 2]. This technique allows better axillary staging than the classical lymphadenectomy and obviously fewer sequelae [1, 3, 4].

The international community of surgeons conducted a rigorous evaluation of this technique, and methodological standards were established [5]. However, many technical details were not validated by randomized studies but are based on the opinions of experts from renowned reference centers. Thus, many variations still exist for sentinel node (SN) detection: For example, the number of injection sites varies between 1 and 4, and the site can be periareolar or not.

Right from the outset, experts recommended the combined technique with blue dye and an isotope for lymphatic mapping. The reasons will be discussed later in the article. However, blue dye has some major disadvantages:

- Allergic reactions occur in 0.5–2.7% of cases, with a mean value of 0.71% [6–8], often with severe reactions and some very rare deaths.
- The blue dye can stain the injection site for months and sometimes indefinitely.
- A deeply located blue lymph vessel may be difficult to find, and its dissection requires substantial expertise.

In order to avoid these disadvantages, some well-known teams switched to isotope detection alone, but provided limited new data. A controversy then arose about the systematic use of both tracers.

In this retrospective study, we compared the feasibility and performance of isotope detection alone (ISO) versus the classical combined method (COMBI). With the ISO method, the isotopic marker is used alone and detection is verified by the surgeon with a probe in the operating room. Blue dye is injected only in the event of percutaneous isotope detection failure. COMBI is the standard method using both tracers.

Patients and Methods

We retrospectively analyzed 203 patients treated at the Gustave Roussy Cancer Campus between January 2007 and September 2007, for unifocal primary breast carcinoma (T1 N0) who had undergone a lumpectomy and SNB. Axillary clearance (AC) had been performed if the immediate histological analysis of the SN was positive or if the tumor size had attained 20 mm, according to our protocol at that time. All procedures had been performed by senior surgeons or senior assistants. The ISO technique had been used in 77 patients and COMBI in 126 patients. The choice between the 2 methods was mainly linked to the surgeon, as some surgeons prefer one technique over the other. There was no other selection criterion.

Four subcutaneous injections of 0.2 ml of rhenium colloidal sulfur (Nanocist*, CIS Bio International, Saclay, France) had been administered around the areola on the day before or on the day of the operation.

Most often, lymphoscintigraphy had not been performed, according to our protocol, to facilitate 1-day surgery. A CdTe probe (Gammed 2TM, Eurorad, Strasbourg, France) had been used for perioperative detection.

Firstly, detection had been carried out by the surgeon through intact skin, in the operating room just after the induction of anesthesia.

In the ISO group, if isotope detection had failed, 2 ml of patent blue dye (Lab. Gerbet, Paris, France) had been injected into 1 site subcutaneously. In the COMBI group, blue dye had been injected systematically. In both cases, the injection site was gently massaged over a few minutes. The axillary incision was made at least 10 min after the blue dye injection. The SN was defined as 'hot' when its isotopic activity was at least 3-fold the background noise. The SN was defined as 'blue' when at least part of its surface was blue or when it was connected to a blue lymphatic channel.

All hot or blue nodes had been removed and up to 4 of them had been sent for an immediate pathological examination. The probe and manual palpation were used systematically to verify the nodes. Any suspicious palpable nodes were removed, identified as 'non-sentinel' and also sent for immediate examination.

If the tumor size had attained 20 mm, AC had been systematically performed according to our protocol at that time. The SN was examined immediately by slide apposition and, eventually, by some limited frozen sections. Only the first 3 nodes were examined immediately.

The definitive pathological reports had been written following the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification. When macrometastasis was found in the SN, AC was performed systematically. If a micrometastasis or an isolated cell, i.e. pN1mi or pN0 i+, was found, inclusion in the randomized International Breast Cancer Study Group (IBCSG) trial B 23-01 comparing AC and follow-up was proposed to the patients. If the patient refused, AC was performed.

We compared the detection rate (DR) and histological results in both groups. The small population size and the short follow-up prohibited evaluation of the axillary recurrence rate and survival.

Results

The inclusion criteria for the SNB technique are described in table 1. In both groups the mean age was 58.8 ± 24 years, with a homogeneous distribution of the cancer at various ages (table 2).

The body mass index (BMI) was comparable between the 2 groups: mean 25.7 (range 16.3–46.7). The tumor characteristics are described in detail in table 3; there was no significant difference between the 2 groups.

Detection

The SN had been identified successfully in 76/77 cases in the ISO group and in 125/126 cases in the COMBI group. Thus, the DR was 99% in both groups. The 2 patients with a detection failure

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Invasive breast cancer	N1 or positive cytology
T1, unifocal tumor	T2, T3, T4
N0 or negative cytology in case of a detectable axillary node	multifocality
Absence of neoadjuvant treatment	pregnancy or breast-feeding
Absence of previous breast or axillary surgery	allergic history
	patient's refusal

Table 2. Patient characteristics

	ISO	COMBI
Mean age, years (range)	58.8 (34–81)	58.8 (32–86)
Patients, n (%)	77 (100)	126 (100)
≤ 45 years	9 (11)	19 (15)
46–55 years	24 (31)	30 (24)
56–65 years	22 (29)	42 (33)
> 65 years	22 (29)	35 (28)
BMI, kg/m ² (range)	25.7 (19.1–46.7)	25.7 (16.3–41.7)
Obese patients (BMI > 30), n (%)	8 (10)	21 (17)

ISO = Only isotope detection, COMBI = combined isotope and blue dye detection, BMI = body mass index.

Table 3. Breast tumor characteristics

	ISO	COMBI
Mean tumor size, mm	11 (5–20)	11 (4–20)
≤ 10 mm	29 (38%)	41 (33%)
11–15 mm	17 (22%)	28 (22%)
16–20 mm	6 (8%)	15 (12%)
Location		
External quadrants	48 (62%)	60 (48%)
Internal quadrants	17 (22%)	41 (32%)
Central quadrants	12 (16%)	25 (20%)
Histology		
Infiltrating ductal carcinoma	56 (73%)	80 (63%)
Infiltrating lobular carcinoma	6 (8%)	10 (8%)
DCIS microinfiltrating	14 (18%)	31 (25%)
Other types	1 (1%)	5 (4%)
EE histologic grade		
Grade I	26 (42%)	36 (39%)
Grade II	24 (39%)	41 (44%)
Grade III	12 (19%)	16 (17%)

ISO = Only isotope detection, COMBI = combined isotope and blue dye detection, DCIS = ductal carcinoma in situ, EE = Elston and Ellis.

had undergone AC. In the COMBI group, the patient was 61 years old, with a BMI of 26. The tumor was a 10-mm grade II infiltrating ductal carcinoma. There were 8/20 positive nodes at AC. In the ISO group, the patient was 51 years old with a BMI of 34. The tumor was a 14-mm grade III infiltrating ductal carcinoma. There

Table 4. Sentinel node detection

	ISO	COMBI	p
Detection rate, n (%)	76 (99)	125 (99)	NS
Mean number of SNs (range)	2.1 (1–5)	1.9 (1–7)	NS
Sentinel nodes, n (%)	76	125	
1	20 (26)	57 (46)	0.004
2	33 (43)	34 (27)	
≥ 3	23 (31)	34 (27)	

ISO = Only isotope detection, COMBI = combined isotope and blue dye detection, SN = sentinel node, NS = not significant.

Table 5. Sentinel node status

	ISO	COMBI	p
Patients, n (%)			
Negative SN	57 (74)	94 (75)	NS
Micrometastasis	10 (13)	17 (13)	NS
Macrometastasis	10 (13)	15 (12)	NS
Involved nodes (SN+), n (%)	43/165 (26)	58/241 (24)	NS
Preoperative SN+	12/165 (7)	20/241 (8)	NS
Definitive SN+	31/165 (19)	38/241 (16)	NS

ISO = Only isotope detection, COMBI = combined isotope and blue dye detection, SN = sentinel node, NS = not significant.

were no positive nodes among the 7 nodes examined at AC. In the ISO group, isotope detection had been unsuccessful in 11 patients (12.5%) and injection of the patent blue dye had been performed. During surgery, 10/11 patients had blue nodes and 5 of them were also hot. In this group of patients in whom isotope detection had failed, there were more obese women (BMI > 30): 36.4% versus 14% ($p = 0.06$), but not a greater number of elderly patients (> 60 years): 64% versus 60% (not significantly different (NS)).

Number of SNs

The mean number of SNs was identical in the 2 groups: 2.1 (1–5) for ISO and 1.9 (1–7) for COMBI. However, there were significantly more patients with only 1 SN removed in the COMBI group compared to the ISO group: 46% versus 26%, respectively ($p = 0.004$) (table 4).

Number of Non-Sentinel Nodes

Any suspicious palpable node was identified as ‘non-sentinel’ and removed: 6/77 patients (8%) for the ISO group and 12/126 (10%) for the COMBI group.

Histology

Immediate analysis of the SNs had unveiled metastases in 12/65 nodes (7.3%) and in 20/241 nodes (8.3%) in the ISO and COMBI group, respectively (NS). They were all macrometastases.

In the final analysis, the SN was positive in 26% and 25% of the patients in the ISO and COMBI group, respectively (NS). Micrometastasis had been found in 13% of the patients in both groups (table 5).

Table 6. Nodal status related to age and tumor size

	ISO	COMBI	p
Positive SN, n (%)			
≤ 45 years	2 (22)	5 (26)	NS
46–55 years	8 (33)	7 (22)	NS
56–65 years	3 (13)	10 (24)	NS
> 65 years	7 (32)	10 (28)	NS
Positive SN, n (%)			
T ≤ 10 mm	9 (27)	11 (22)	NS
11–15 mm	7 (35)	13 (39)	NS
16–20 mm	4 (50)	8 (44)	NS

ISO = Only isotope detection, COMBI = combined isotope and blue dye detection, SN = sentinel node, NS = not significant.

The levels of SN involvement according to clinical parameters (age, tumor size) are described in table 6. There was no significant difference.

When the SN was negative, none of the non-sentinel nodes was positive.

Discussion

The large studies conducted to validate the SN technique always used both tracers [1, 4]. But the performance of isotope detection alone is excellent. Gradually, because of the risks observed with blue dye, the use of isotope alone gained momentum. This retrospective study, with a literature review, aims at reviewing this debatable option.

Detection Rate

In our series, the DR was 99% in both groups, with only 1 failure in each group. These 2 failures were related to an extensive nodal involvement in the COMBI group and to obesity (BMI of 34) in the ISO group.

Some series indicate that each tracer alone yields a lower DR than the combined technique [4]. In the meta-analysis published by Kim et al. in 2005 [9], the mean DR was 83.1% with blue dye alone and 96.4% with both tracers. However, in the most recent series, the DR with the isotope alone or combined with blue dye was always excellent and very close, between 93.5% and 97.2% [4, 9–11]. The sole randomized trial comparing ISO and COMBI was published recently, with 667 patients [12]. This study failed to demonstrate any advantage with COMBI in the presence of a positive lymphoscintigram. So, given the published results, we can safely assume that there is no DR benefit with COMBI.

False-Negative Rate and Oncologic Safety

Until 2010, the false-negative (FN) rate was considered the main evaluation criterion for the routine use of the SNB technique. A meta-analysis of 69 trials showed a mean FN rate of 8.4% in 8,059 patients (5.5–16.7%), most often with combined tracers [9]. This rate was sufficiently satisfactory to allow the routine use of the

SNB technique, but clinicians remain dubious about the true consequences of this 8.4% FN rate. At that point in time, we could not exclude the risk of an increase in the FN rate with isotope detection alone. That is why all recommendations up to 2010 underlined the use of both tracers and were reluctant to dispense with the blue dye.

However, in many publications, the topographic concordance between the blue dye and the isotope was excellent [13], indicating that most often both tracers reach the same SN, which was found to be blue and hot.

In a large series, only 0.8% (4/496) of the patients who were SN positive had a blue-only node as their only positive node [2].

In 2010, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial comparing SNB to AC in 5,611 patients [4] indicated identical overall survival at 8 years: 90.3% and 91.8%, respectively (NS). The axillary recurrence rate was very low and also identical in the 2 arms: 0.7% and 0.4%, respectively (NS). This very low axillary recurrence rate is far lower than would be expected with an FN rate of 7–10%. This study therefore demonstrates that the clinical significance of the FN rate is really very low, with only 0.7% axillary recurrence at 8 years for 2,800 patients in the SNB arm. Thus, even if the ISO option could increase the FN rate (which is not proven), would this have any impact on the axillary recurrence rate? This impact is obviously nil or very low, but in the absence of a randomized comparison with systematic lymphadenectomy, it is not possible to come to a definitive conclusion.

Number of SNs Removed

The number of SNs removed is an important quality indicator of the technique [4, 10]. The FN rate decreases with the number of SN removed for up to 4 nodes [9]. The usual recommendation is to remove all blue and/or hot nodes, up to 4 [14].

However, the ideal mean number should be around 2 [15]. In our study, the mean number of nodes removed was similar and in accordance with the recommended standards, with 2.14 in the ISO group and 1.91 in the COMBI group (NS). Significantly more patients had only 1 SN removed in the COMBI group (46%) than in the ISO group (26%) ($p = 0.004$) (table 4). These results indicate that the ISO technique is not associated with a significant reduction in the number of SNs removed. The same results were found in the randomized trial [12].

The Non-Sentinel Nodes

Only highly suspicious palpable nodes were removed during the SNB procedure. The number of non-sentinel nodes was low and equivalent in both arms (8% and 10%). When the SN was negative, none of the non-sentinel nodes was positive. One could suppose that the surgeon would rather remove more nodes in the ISO group in order to improve the felt low DRs, but this was not the case.

Histological Nodal Status

The rate of SN invasion was similar in the 2 groups, ISO and COMBI, with 26.1% and 24.1%, respectively. This is in accordance with other larger series [4] and with the randomized trial [12].

Drawbacks of Blue Dye

The main drawback is the risk of allergic reactions, from a simple skin rash to an anaphylactic shock [6–8, 16], with a risk of death. This risk is unpredictable, and not related to atopic history [7, 17].

The second drawback is a persistent subcutaneous blue stain. This is observed in 70% of the patients at 3 months, and in 41% at 1 year with a subdermal injection [18]. In this study, all blue dye injections were made deeper in the subcutaneous plane and all blue staining of the skin had disappeared at 3 months.

Surgical Technique

There is a very significant technical point concerning SN dissection which is rarely discussed: At the beginning of surgery, each surgeon has to choose which tracer he wants to follow first, as the dissection technique is totally different. Later on, the surgeon will move frequently from one tracer to the other, but a choice has to be made at the beginning:

With the blue dye first, a large skin incision is required and a very accurate dissection is needed to find the blue channel without cutting it and then track the progression of the tracer up to the blue node. This can be more or less rapid. This procedure can lead to a wide dissection, which is associated with a higher risk of functional sequelae.

With isotope detection first, a real learning curve is needed for proper handling of the probe [19]. But thereafter, isotope detection would be easy and quick: The skin incision will be smaller, just in front of the detected signal, and the dissection will be minimal, following the probe. When the hot node is found, it is often blue with its blue channel, which is reassuring but finally of no use.

In our experience, dissection with isotope detection very rapidly became preponderant. When all hot SNs have been removed, the surgeon will be very reluctant to extend the surgical dissection in search of a hypothetical additional blue-only node. In the end, the blue dye injection has not helped improve this frequent situation.

Learning Curve

Conversely, during the learning curve, both tracers should be used systematically to improve the overall performance during this training period, and also to enable the surgeon to be at ease with the blue dye if isotope failure occurs.

Conclusion

In this study, systematic addition of the blue dye did not modify the overall performance of SNB, compared to isotopic detection alone in the presence of a positive percutaneous detection. This is in agreement with all published results [2, 12, 15].

So, to dispense with the blue dye in the presence of a positive lymphoscintigram or percutaneous detection is, for us, a valid option.

Disclosure Statement

The authors declare no conflicts of interest and no sponsorship.

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