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Original research

Limited effectiveness of patent blue dye in addition to isotope scanning for identification of sentinel lymph nodes: Cross-sectional real-life study in 1024 breast cancer patients

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HIGHLIGHTS

- Blue dye and radioisotope SLN mapping in 1024 BC pts.
- Limited blue dye effectiveness.
- Use of PBD should be avoided when a radioisotope mapping agent is available.

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ABSTRACT

Background: Although morbidity is reduced when sentinel lymph node (SLN) biopsy is performed with dual isotopic and blue dye identification, the effectiveness of adding blue dye to radioisotope remains debated because side effects including anaphylactic reactions.

Patients and Methods: Using data from a prospectively maintained database, 1884 lymph node-negative breast cancer patients who underwent partial mastectomy with SLN mapping by a dual-tracer using patent blue dye (PBD) and radioisotope were retrospectively studied between January 2000 and July 2013. Patients with tumors <3 cm and with >1 node detected by one of the two techniques (N = 1024) were included in this real-life cross-sectional study.

Results: Among the 1024 patients, 274 had positive SLN detected by isotopic and/or PBD staining. Only 4 patients having no detectable radioactivity in the axilla had SLN identified only by PBD staining (blue-only) while 26 patients had SLN only identified by isotopic detection (hot-only) illustrating failure rates of 9.5% (26/274) and 1.5% (4/274), respectively. Among these four patients, two had negative lympho-scintigraphy. Therefore, the contribution of PBD to metastatic nodes identification was relevant for only 2/274 patients (0.8%). Three patients (0.3%) had an allergic reaction with PBD, and anaphylactic shock occurred in two cases (0.2%).

Conclusions: The added-value of PBD to reduce the false-negative rate of SLN mapping is only limited to the rare cases in which no radioactivity is detectable in the axilla (<1%). When a radioisotope mapping agent is available, the use of PBD should be avoided, because it can induce anaphylaxis.

1. Introduction

Sentinel lymph node (SLN) mapping has become a standard for axillary staging in small clinically node-negative breast cancer [1–4], and multicenter studies suggest that dual mapping with blue

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dye and radioisotope significantly decreases false-negative rates. A recent meta-analysis [5] highlighted that (1) the use of blue dye is associated with the highest false-negative rate, (2) the false-negative rate can be lowered if the blue dye is combined with a radiotracer, and (3) no difference is observed between the dye and radiotracer versus the radiotracer alone. Further, neither the location [5] nor the mode of the injection, superficial or deep [6], had any influence on the false-negative rate, and blue dye has been reported to only contribute marginally [7–9] to the improvement of SLN mapping. In a recent study, it has been shown that the added value of blue dye was restricted to inexperienced surgeons during their learning phase and to patients with lymphoscintigraphic failure [9]. Additionally the belief that the use of blue dye, patent blue, isosulfan blue, and methylene blue has been associated with anaphylactic reactions and acute urticaria [9–14], as well as skin discoloration, these facts cause many surgeons to question its routine use in SLN mapping. Even if it has been considered as an alternative to patent blue and isosulfan blue [15], methylene blue has also been associated with some risk of severe anaphylactic shock [16]. The present paper evaluates retrospectively, in a real-life setting, the effectiveness of adding patent blue dye to radioisotope and its relative contribution to positive SLN identification in a total of 1024 women with tumors <3 cm undergoing partial mastectomy with SLN biopsy, who were prospectively followed in a single institution.

2. Patients and methods

2.1. Patient population

Using a prospectively maintained database, we analyzed 1884 consecutive lymph node-negative breast cancer patients who underwent a partial mastectomy with SLN mapping between January 2000 and July 2013. Among these patients, 1024 consecutive patients with tumors less than 3 cm underwent a partial mastectomy with SLN biopsies by a dual-tracer, patent blue dye (PBD), and radioisotope, using the same-site subareolar injection technique, according to the recommendations for clinical practice from Saint Paul de Vence [2]. Until the end of this study in 2013, no change in clinical practice of SLN mapping occurred in France.

Patients having at least one node identified by one of the two techniques were included in this cross-sectional study. Patients with bilateral surgery, tumors exceeding 3 cm or pure ductal *in situ* carcinoma were excluded; this was consistent with the clinicopathologic criteria at the time of the patient care. The median patient age was 60 years (range 28–86).

2.2. SLN mapping procedure

Consistent with the procedure used in many protocols including the ALMANAC trial [3], unfiltered technetium 99 m–labeled sulfur colloid (1 mCi, 37 MBq) was injected preoperatively and the day before surgery, and followed by lymphoscintigraphy 2–3 h later. The next day, after anesthetic induction in the operating room, the patients were injected with 2 mL of 1% PBD into the subareolar area. A lymph node was considered as an SLN when it was stained with PBD (either partial or complete), had a blue lymphatic afferent, or had increased radioactivity (until axillary counts were less than 10% of the hottest lymph node count). SLNs identified during these procedures were classified as containing both PBD and radiotracer ("blue-hot" nodes), radiotracer alone ("hot-only" nodes), or PBD alone ("blue-only" nodes). Cases were categorized and tabulated based on the presence or absence of these three types of SLNs.

Clinical and histopathologic data were entered prospectively in a database (Table 1), and a retrospective review was performed to evaluate the number of patients with positive SLNs, i.e. "blue-only", "hot-only," or "blue-hot." According to the sixth edition of the TNM [16], metastatic involvement of the SLN was considered to be positive when macrometastases (tumor deposit > 2 mm), micrometastases (0.2 mm < tumor deposit < 2 mm), and isolated tumor cells (tumor deposit < 0.2 mm) were histologically detected.

2.3. Statistical analysis

Assuming a proportion of 25% of positive SLN and significance level of the test set at 5%, a sample size of 1000 patients was required to achieve 80% power to detect an odds ratio of 1.5. The frequency of this factor was assumed to be equal to 50% in the negative SLN as the worst scenario for the power of the study.

Quantitative parameters were described with mean and standard deviation, and qualitative parameters were described with frequency and percentage.

Comparisons of SLNs identified per patient according to clinical characteristics (age<60 – corresponding to the median value, Body Mass Index (BMI) > 30, tumor size, localization, histology) were performed with a Student t-test or analysis of variance for qualitative parameters and with a Pearson correlation coefficient for quantitative parameters.

The relationship between clinical characteristics and SLN detection was assessed with univariate analyses (Chi-square test). A parsimonious multivariate model was identified by stepwise selection and the best-subset selection of all possible covariate combinations was identified to predict SLN detection. For building this model, the significance level for entering effects was set at 0.1. This level of 0.1 was preferred to the traditional levels such as 0.05 because it can fail in identifying variables known to be important [17,18]. Since the significance level for removing effects was set at 0.05, only the parameters with a p-value less than 0.05 were retained in the final parsimonious model.

The discriminant power of the model to predict SLN detection was quantified with the area under the curve (AUC). An AUC less than 0.8 corresponds to a low discriminant power.

All statistical analyses were performed using SAS version 9.3 (SAS, Cary, NC, USA). The significance level was set at 0.05.

3. Results

A total of 2198 SLNs were removed from the 1024 patients included in this study (Fig. 1). Mean (+/− SD) histologic tumor size was 13.2 ± 6.1 mm. The characteristics of the patient population are summarized in Table 1.

The mean number of SLNs identified per patient was 2.15 ± 1.28 (range 1–9), and was significantly higher in SLN-positive (2.29 ± 1.35, range 1–7) than SLN-negative patients (2.09 ± 1.25, range 1–9) ($P = 0.0374$).

In obese patients (Body Mass Index ≥ 30), no significant difference ($P = 0.0554$) was observed, but the number of identified SLNs tended to be lower than in patients with BMI ≥ 30 (1.95 ± 1.06 *vs.* 2.19 ± 1.32). The number of identified SLNs was significantly higher ($P = 0.0058$) in patients below 60 years old than in others (2.27 ± 1.37 *vs.* 2.02 ± 1.17, respectively). Tumor histology ($P = 0.1$) as well as tumor size ($P = 0.6$) did not influence the number of blue identified SLNs. The presence of ductal or lobular *in situ* carcinoma associated with the infiltrative contingent did not influence the number of detected blue or radioactive SLNs, nor did the tumor localization.

In the univariate analysis (Table 1), age<60 ($P = 0.0089$), tumor size ($P < 0.0001$), tumor grade ($P = 0.0436$), and blue SLNs ($P = 0.0109$) were significantly associated with node involvement (Table 1). In the multivariate analysis (Table 2), after adjusting for