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ORIGINAL REPORT

Extensive Nodal Disease May Impair Axillary Reverse Mapping in Patients With Breast Cancer

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ABSTRACT

Purpose
The aim of axillary reverse mapping (ARM) is to preserve arm lymphatics in patients with breast cancer who underwent surgical axillary staging.

Patients and Methods
From June 2007 to December 2008, 49 patients who required axillary dissection (AD) underwent ARM. One milliliter of patent blue dye was injected in the ipsilateral arm, and all blue nodes identified during AD were sent separately for pathologic examination. Main variables associated with the detection rates of blue lymphatics, the pathologic status of blue and nonblue nodes, and the complications of the procedure were analyzed.

Results
Identification rates of blue lymphatics and blue nodes were 73.5% and 55.1%, respectively. Blue node identification was influenced by the time elapsed between injection of blue dye and surgery ($P = .002$) but not by the learning curve of the procedure. Although the blue node was clear of metastases in 24 of 27 patients, three patients with extensive nodal metastatic involvement (ie, pN2a and pN3a) showed breast cancer metastatic cells in the blue nodes as well. The only adverse effect of the procedure was skin tattooing at the injection site, which disappeared within 4 months in almost 80% of the procedures.

Conclusion
In patients with clinically negative axillary nodes, additional study is warranted to assess whether ARM may be used to spare the lymphatics from the arm. In the presence of extensive nodal disease, this technique may identify metastatic blue nodes, which demonstrates that there is not reliable separation of arm and breast lymphatic pathways.

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INTRODUCTION

Axillary dissection (AD) represents the standard treatment for breast cancer patients with clinically or histologically involved axillary nodes. In 2007, two research groups in the United States and France[1,2] described the injection of blue dye into the arm to map and spare the lymphatic drainage of the arm in patients with breast cancer who underwent AD. They postulated that, because the lymphatic pathway from the arm (at least, until it enters the axillary nodal basin) cannot be involved by the metastatic process of the primary breast tumor, its preservation should not imply any risk of leaving undetected disease in the axilla. Conversely, the preservation of arm lymphatics should lead to a decrease of lymphedema, which is the most severe morbidity after AD.[3]

To confirm the feasibility of the technique and the proof of principle that arm lymphatics are never involved by the metastatic process, we started a pilot study at Institute for Cancer Research and Treatment of Candiolo (Turin, Italy). We also investigated the parameters associated with the success rate of the technique, which has not been proven optimal in previous studies.

PATIENTS AND METHODS

All patients submitted to AD by a single surgeon (R.P.) from June 2007 to December 2008 were entered on the study after giving their written consent according to the ethical rules of Institute for Cancer Research and Treatment of Candiolo. To identify the lymphatic pathway from the arm, 1 mL of patent blue dye (Guerbet, Roissy-Charles-de-Gaulle, France) was injected in the cranial

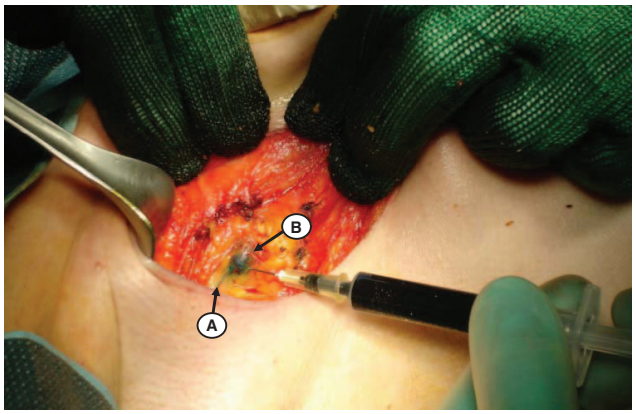

Fig 1. Injection of 0.1 mL of blue dye in the first blue node. (A) Blue lymphatic channel from the arm entering the first blue node. (B) First blue node.

third of the inner aspect of the arm with a 25-gauge needle. Mean elapsed time from injection and axillary surgery was 38 minutes. After a few occurrences, the subdermis was chosen as site of injection, because it is associated with less persistent skin tattooing than the dermis but allows good tracer migration. After the injection, the arm was elevated, and the site of injection was massaged centripetally for approximately 5 minutes to enhance tracer migration.

The classical surgical steps of AD have been modified slightly to preserve the lymphatics coming from the arm. Because the most critical part is the identification of the thin blue channels entering the axilla from its lateral aspect, a careful dissection is required at this stage. Blue lymphatics generally are located approximately 1 cm below the course of the axillary vein and 1 cm above the course of the second intercostalbrachial nerve; therefore, these two anatomic landmarks must be evidenced initially. The careful dissection of the fat pad between the structures just mentioned allows the identification of a variable number of blue channels leading medially to one or two blue nodes. These blue nodes are generally, but not exclusively, located in the angle delimitated cranially by the axillary vein, caudally by the second intercostalbrachial nerve and medially by the serratus muscle that covers the thoracic wall.

In this study, all blue nodes have been selectively excised and sent for pathologic examination separately from the other axillary nodes. In the more recent events, we reinjected the blue node before its excision with 0.1 mL of patent blue dye to identify the efferent lymphatics also (Fig 1). This has allowed the identification of both efferent lymphatics and additional echelon blue nodes located deeper in the axillary basin at the second and third levels, according to classification by Berg.[4]

A minority of the patients (20 of 49) initially underwent a sentinel lymph node biopsy (SLNB), which was negative at intraoperative evaluation performed by touch imprint cytology and which then required an AD because of the detection of micro- or macro-metastases at final histology. The remaining patients (29 of 49) underwent immediate AD because of the intraoperative detection of a metastatic sentinel node (six of 29 patients) or the preoperative clinical or cytologic diagnosis of nodal metastasis (23 of 29 patients). Slightly more than 15% of the patients underwent four cycles of preoperative polychemotherapy with a conventional schedule that contained anthracyclins and taxanes.

Mean tumor diameter was larger than 2 cm, and almost 95% of the lesions were larger than 1 cm. This finding, as well as the high prevalence of lesions characterized by high pathologic grade and peritumoral lymphovascular invasion, was expected in a group of patients selected for requiring AD. Nonetheless, a micro-metastatic sentinel node was the only sign of nodal involvement in greater than 30% of the lesions (ie, pN1mi), and an additional 35% of the patients carried less than three metastatic nodes (ie, pN1a). Therefore, only one fourth of all disease incidences were characterized by extensive nodal involvement (Table 1).

For the statistical analysis, lymphatic pathway identification rates, operating times, complications, and clinicopathologic characteristics were recorded. All these variables were compared by Pearson's χ^2 test and by Fisher's exact test, when required. *P* values less than .05 of the two-tailed test were considered significant. Statistical analysis was performed with Primer software version 4.02i for Windows (Statistica, Biomedica; Statsoft, Tulsa, OK).

Table 1. Correlation Between Clinicopathologic Variables and Blue Node Identification

Variable	Identification		Failed Identification		*P*
	No.	%	No.	%	
BMI, kg/m^2					
< 18.5	2	100	0	0	
18.5-24.9	17	60.7	11	39.3	NS
25-29.9	5	41.7	7	58.3	
> 30	3	42.9	4	57.1	
Age, years					
< 50	10	58.8	7	41.2	
50-70	13	59.1	9	40.9	NS
> 70	4	40.0	6	60.0	
Timing of injection, minutes*					
< 15	2	25.0	6	75.0	
15-30	16	80.0	4	20.0	.002†
30-60	10	58.8	7	41.2	
> 60	0	0	4	100	
Neoadiuvant chemotherapy					
Yes	4	50.0	4	50.0	NS
No	23	56.1	18	43.9	
Type of surgery					
MRM	11	57.9	8	42.1	NS
WLE + AD	16	53.3	14	46.7	
Previous SLNB					
Yes	11	55.0	9	45.0	NS
No	16	55.2	13	44.8	
Tumor size, cm					
< 2	9	40.9	13	59.1	NS
≥ 2	18	66.7	9	33.3	
No. of metastatic nodes					
0	1	33.3	2	66.7	
1-3	18	56.25	14	43.75	NS
3-10	6	60.0	4	40.0	
> 10	2	50.0	2	50.0	
Histotype					
Ductal	19	52.8	17	47.2	NS
Lobular	6	60.0	4	40.0	
Other	2	66.7	1	33.3	
Grade					
1	0	0.0	0	0.0	NS
2	7	53.8	6	46.2	
3	20	55.6	16	44.4	
Peritumoral lymphovascular invasion					
Yes	16	47.1	18	52.9	NS
No	7	77.8	2	22.2	
Not evaluated	4	66.7	2	33.3	

Abbreviations: BMI, body mass index; NS, not significant; MRM, modified radical mastectomy; WLE, wide local excision; AD, axillary dissection; SLNB, sentinel lymph node biopsy.

*Measured up to the beginning of surgery.

†*P* refers to the comparisons of < 15 and > 60 minutes with 15 to 60 minutes.

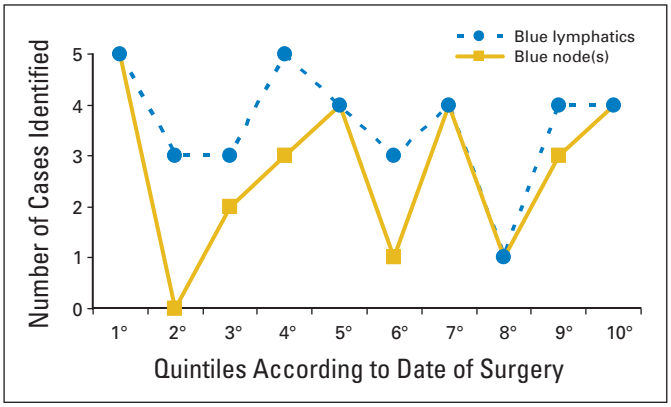

Fig 2. Learning curve for the identification of the arm lymphatic pathway.

Table 2. Adverse Effects of the ARM Procedure

Variable by Event Grade	Patients No.	Patients %
Pain at site of injection		
Mild	44	89.8
Moderate	5	10.2
Severe	0	0
Degree of skin tattooing*		
Mild	0	0
Moderate	47	95.9
Severe	2	4.1
Persistence of skin tattooing, months†‡		
≤ 1	19	42.2
≤ 4	16	35.6
≥ 6	10	22.2

Abbreviation: ARM, axillary reverse mapping.
*Degree of tattooing was evaluated in the immediate postoperative period.
†Four patients with persistent tattooing did not reach 6 months of follow-up.
‡Total number of patients evaluated for persistence was 45.

RESULTS

Identification of Arm Lymphatic Pathway

Overall, the identification of the lymphatic pathway (either blue lymphatics or blue nodes) was possible in 34 (73.5%) of 49 patients. A clearly blue node was detected in 27 (55.1%) of 49 patients. The identification of additional echelon nodes by injecting the first blue node was attempted in five patients and revealed a total of seven nodes, which all were negative for metastatic disease.

To assess the existence of a learning curve for the procedure, the whole series was subdivided in 10 quintiles according to the date of surgery (Fig 2). The identification rate of lymphatics stayed constant throughout all of the study period, whereas the identification rate of blue nodes was subjected to variations independent from the experience that accumulated with the procedure.

Variables Associated With Identification of Arm Lymphatic Pathway

In the literature, several clinical variables, such as body mass index (BMI) and patient age, are associated with sentinel node identification rates in patients with breast cancer; therefore, we assess their possible interactions with arm lymphatic identification in our series.

A trend toward lower identification of arm lymphatics with increasing BMI was found, but the difference did not reach statistical significance; however, the patient age had no apparent effect. Conversely, the time interval that elapsed from patent blue dye injection to start of surgery showed a significant association with the success of the procedure. Actually, an interval less than 15 minutes or greater than 60 minutes compromised the identification rate compared with the optimal interval of 15 to 60 minutes ($P = .002$). Neither preoperative chemotherapy nor an extensive nodal involvement or a previous SLNB significantly influenced the identification of arm lymphatic pathway, although numbers were small (Table 1).

Comparison of Pathologic Status of Arm Versus Breast Lymphatics

Blue nodes identified by ARM were negative for metastatic cells in 24 of 27 patients. All three incidences of a metastatic blue node were characterized by extensive nodal involvement; for each occurrence, there were 18 of 22, 18 of 24, and seven of 18 positive nodes at final pathologic examination.

Adverse Effects of the Procedure

No allergic/anaphylactic reactions were recorded. Most patients reported just mild pain at the site of injection. The degree of skin tattooing was defined as moderate by 95% of the patients, and tattooing completely disappeared within 4 months in the majority of the events (Table 2).

DISCUSSION

The ultimate aim of the ARM procedure is limitation of arm lymphedema, which represents the most invalidating complication of AD.[3] Thompson et al[1] reported a 61% success rate of the ARM procedure in 18 patients with breast cancer by injecting 2.5 to 5 mL of dermal blue dye in the medial aspect of the ipsilateral arm. Nevertheless, this figure refers to the identification of the blue lymphatics and/or the blue node, whereas the blue node itself was identified in 33.3% of the patients. The same group subsequently reported that, although initially thought to lie always just below the course of the axillary vein, the blue node actually could be located in several other anatomic sites within the axilla in up to one third of the occurrences.[5] The group also tested the procedure in a series of 46 patients undergoing both the ARM procedure and a conventional SLNB with radioactive tracer localization. The absence of concomitantly blue and hot nodes and the negativity for metastatic cells in all blue nodes convinced the authors that the ARM procedure actually identifies a different lymphatic pathway coming from the arm.[6] This hypothesis has been challenged recently by a Korean group that reported an experience of 96 successful ARM procedures, which showed a concordance rate of 18.9% between blue and hot nodes and the presence of metastasis in seven of such nodes.[7]

Nos et al[2] published a series of 21 patients who underwent the ARM procedure by using 1 to 4 mL of blue dye injected in the subdermis of the posterior aspect of the arm. Their first aim was to identify blue lymphatics and/or nodes, which they called lymphatic arm drainage (LAD). For their second aim, they verified whether the surgeon

could separate nodes that belonged to LAD from all the others (ie, LAD dissection rate); finally, they compared the pathologic status of LAD versus non-LAD nodes. The LAD identification rate was 71%; an improvement was noted between the first and the second half of the series (50% *v* 91%), which was attributed to a learning curve with the procedure. The LAD could be separated from the remaining nodes in 47% of the occurrences, and, contrary to what was reported in the American series,[1] the nodes were invariably located in the lateral aspect of the surgical field, just below the axillary vein. All blue nodes removed (in 10 patients) were pathologically negative for metastasis. In a subsequent publication, Nos et al[8] modified their surgical technique by using a double tracer injection (ie, blue dye and nanocolloidal tracer with technetium-99^{m}), which led to a considerable improvement of arm-specific node identification (ie, 21 [91%] of 23 patients).[8]

In our series, the detection rate of the blue node (55.1%) was slightly higher than that of the American series (33.3%)[1] and French (47.6%)[2] series by using blue dye as well as the overall detection rate of blue lymphatics and/or blue nodes (73.5% *v* 61% and 71%, respectively). Although our series was characterized by a larger sample size and by a single surgeon who performed all surgeries, we did not confirmed the existence of a learning curve for the detection of the blue lymphatic pathway, as reported by Nos et al.[1] Because the detection rate of the blue node varied markedly throughout the study period, we tried to find out whether the variables known to influence the detection of the sentinel node had the same effect on the ARM procedure. Apart from a possible negative correlation with BMI, the only significant finding pertained to the time interval elapsing from blue dye injection and start of surgery, with best results obtained for intervals between 15 and 60 minutes. Although we had the clinical impression that a previous SLNB did complicate ARM procedure by creating a scar of fibrous tissue that often appeared faintly blue, this association was not significant, possibly because of the small sample size.

The most important issue of the study concerned the pathologic status of the blue nodes in relation to the other axillary nodes. The absence of breast cancer metastases in almost 90% of blue nodes is in line with previous literature data and adds additional support to the hypothesis that the ARM procedure may identify a separated lymphatic pathway.

Nevertheless, our three incidents of metastatic involvement of the blue node suggest that the ARM procedure is not completely accurate in differentiating the arm and breast lymphatic pathways. It has to be underlined that these three patients were characterized by massive metastatic involvement with several involved nodes, extracapsular diffusion, and vascular neoplastic embolization. This finding also was confirmed by the latest publication of the French group, which included a larger proportion of patients with locally advanced disease, and which found three incidents of metastatic arm-specific nodes in patients with 10 or more metastatic axillary nodes.[8,9] Therefore, our two independent experiences suggest that extensive metastatic involvement may favor the occurrence of interconnections or reverse flow between the breast and arm lymphatic pathways, making actually impossible their anatomic and surgical subdivision.

The complications of the procedure were minimal and mainly pertained to the persistence of skin tattooing. A lower volume and a deeper placement of the injection may minimize, but not eliminate, this problem, whereas the adoption of a radioactive tracer injected in the ipsilateral hand appears a viable option and currently is being tested in the French SENTIBRAS multicenter trial.[8,9] With the radioguided approach, the issues of lack of visualization of the thin lymphatics leading to the hot node and of interference with the conventional SLNB will have to be addressed. The latter problem may be reduced by ultrasound-guided, preoperative, fine-needle cytology of all suspicious nodes, which allows SLNB to be skipped and allows direct procession to AD in a substantial proportion of macrometastatic nodes.[10] Furthermore, intraoperative evaluation has a limited sensitivity for micro-metastases,[11] and this explains why the minority of patients in this study underwent SLND and AD at the same procedure.

A crucial issue pertains to the identification of the arm lymphatic pathway departing from the first blue node (ie, efferent lymphatics) and located deeper in the axilla (ie, second and third level according to Berg[4]). This is essential, because only the preservation of the full pathway could allow the lymphatic flow from the arm and hopefully could avoid arm lymphedema.[12] Therefore, we and others[8] currently are injecting the first blue node with a small amount of patent blue dye to follow and separately excise the complete pathway (Fig 1). Another promising approach suggested by Casabona et al[13] is represented by the creation of microsurgical lymphatic-venous anastomoses by using the blue lymphatic collectors coming from the arm and one of the collateral branches of the axillary vein.

In conclusion, we believe that additional research on ARM is warranted, because arm lymphedema still represents a devastating complication for a large number of patients with breast cancer. To assess whether ARM can reduce the rate of lymphedema, studies characterized by the preservation of the identified blue nodes, a long follow-up, and a randomized comparison with a group of patients undergoing conventional AD will be required. In our series, greater than 80% of ADs after a positive SLNB revealed no other metastatic node, and greater than 70% of the patients had less than three metastatic nodes (ie, pN1a). This clearly is relevant, because the lower the number of involved nodes, the lower the risk of leaving them behind while trying to preserve the lymphatic pathway from the arm. Furthermore, when AD after a positive SLNB reveals no additional metastatic nodes, potential serious complications are introduced by a therapeutically useless surgery. Therefore, patients with a micro-metastatic sentinel node, who have the lowest risk of carrying other positive nonsentinel nodes, are specifically those who may derive most benefit from the ARM procedure. At the same time, we suggest that patients with suspected extensive nodal disease either at clinical examination, ultrasound scan of the axilla, or intraoperative pathologic assessment should not be candidates for ARM because of the significant chance of metastatic involvement of the blue nodes identified by the technique in this setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Administrative support: Riccardo Ponzone, Piero Sismondi
Provision of study materials or patients: Riccardo Ponzone, Elisa Cassina, Paola Mininanni, Nicoletta Biglia, Piero Sismondi
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Data analysis and interpretation: Riccardo Ponzone, Nicoletta Tomasi Cont, Furio Maggiorotto, Nicoletta Biglia, Piero Sismondi
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