Detection of the sentinel lymph node under local anaesthesia in early-stage breast cancer: Feasibility study in a series of 78 unselected patients

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Summary

Aims: To evaluate the feasibility of excision of the sentinel lymph node under local anaesthesia in early-stage breast cancer.

Methods: Sentinel lymph node detection under local anaesthesia was carried out on all patients presenting with breast cancer at Stage T0, T1 or T2 < 3 cm and N0, M0. The lymph node was mapped using a radioisotope and patent blue dye and lymphoscintigraphy was routinely performed. No premedication was given, and local anaesthesia was carried out with xylocaine. The patients underwent tumorectomy one week later under general anaesthesia, with or without complete axillary dissection, depending on the results of the definitive histopathological examination of the sentinel lymph node.

Results: 78 patients underwent this procedure over a period of 20 months. The procedure was successful in 76 out of the 78 patients, with one failure in mapping and one failure in detection (detection rate = 97.4%). The mean time to detection was 21 min (range: 6-45). It was unnecessary to interrupt the procedure due to patient discomfort in any of the cases. One allergic reaction to patent blue dye was noted and required corticosteroid therapy without interruption of the procedure.The time to detection was correlated with the experience of the surgeon carrying of the procedure, the patient's body mass index and the number of labelled lymph nodes found at lymphoscintigraphy.

Conclusion: We have shown that it is feasible to detect the sentinel lymph node under local anaesthesia in an unselected population. Using this procedure, patients can undergo surgery with the knowledge of their axillary lymph node status while at the same time avoiding the uncertainties of an intraoperative examination of the sentinel lymph node - a source of many false negatives, particularly in the event of micrometastases.

Key words: Sentinel lymph node; Breast cancer; Local anaesthesia.

Introduction

The idea of a sentinel lymph node (SLN) in breast cancer was first suggested by Giuliano *et al.* in 1994 [1]. Since then, numerous workers have confirmed the relevance of this technique and for many it has become the reference method for axillary evaluation [1, 2, 28] in the early stage of breast cancer. The classical technique consists of finding and excising the SLN(s) under general anaesthesia (GA) during tumorectomy. Intraoperative examination of the SLN serves as the basis in deciding whether or not complete axillary dissection is necessary.

Intraoperative examination of the SLN tends to give a high rate of false negatives which are later reversed when the final histopathological results are known. The false negative rate is variously quoted in the literature, ranging from less than 10% according to the most optimistic workers [2-5] to more than 40% according to the most pessimistic [6-9]. However, rates below 10% are obtained at the cost of very long response times [2, 3] or a few false positives [4, 5]. The false negative rate is due to the fact that lymph node micrometastases frequently go unrecognized during the intraoperative examination since the most sensitive methods for detecting micrometastases (immunohistochemistry and PCR) cannot be used intraoperatively. In this type of situation where a false negative has been obtained, patients have to be re-operated once the final histopathological examination results are available so that dissection can be carried out.

This procedure means that a large number of node-positive patients have to undergo two operations under general anaesthesia. Another problem with intraoperative analysis is that false positives are possible, according to reports by some workers [4, 5, 7], causing complete dissection to be wrongly carried out.

In order to circumvent the uncertainties attached to the intraoperative examination of SLNs and the risk of a second operation, we decided to do without it by carrying out SLN excision under local anaesthesia, as part of a pretreatment assessment of breast cancer, and subsequently to operate on patients when the definitive results from studying the SLN were known. In the present paper, we report on our preliminary experience of SLN detection under local anaesthesia. We thought to evaluate the feasibility of this procedure in a general population of patients with early-stage breast cancer, and to confirm that the detection of SLN under LA was equivalent in performance to that of detection under GA reported in the literature.

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Patients and Methods

Between July 2001 and March 2003, patients who consulted for breast cancer in our unit and satisfied the inclusion criteria (Table 1) were offered SLN detection under local anaesthesia (LA). We chose a combined method for mapping (patent blue dye and a radioisotope) and the systematic performance of lymphoscintigraphy (LS).

Table 1. — *Inclusion criteria.*

Patient recruited by a surgeon with experience in SLN detection (2 surgeons in our group).
Histologic diagnosis (by biopsy) of invasive or high grade intraductal breast carcinomas.
Unifocal tumour.
Tumour size < 3 cm, assessed clinically and from imaging data.
No palpable adenopathy in the axilla.
Understanding and acceptance of the protocol.
No known allergy to xylocaine or patent blue dye.

Each patient included in the protocol was hospitalized at the beginning of the afternoon on the day before the operation. Any patient with a T0 tumour initially went to the radiology unit to undergo skin marking vertically above the lesion in the dorsal decubitus position (ultrasound or radiological location). The patient was then transferred to the nuclear medicine unit (patients with palpable tumours went directly to this unit) and given a subcutaneous injection of colloidal rhenium sulphide (Nanocis, Cis Bio International) labelled with Technetium 99m. The doses injected in our series of patients ranged from 26 MBq to 37 MBq (i.e., 0.7 to 1 mCi) in a volume of 0.6 to 0.8 ml. The injections were made subcutaneously using 16 x 0.5 mm insulin syringes into the four cardinal points of the tumour. Scintigraphic images were obtained using a rectangular, wide field gamma camera equipped with a high resolution, low energy, parallel collimator. Static anterior and lateral scans centred on the breast (300 s, matrice 128*128) were made, five minutes apart, three hours after the injection (up to 14 hours if the result was negative). The first persistent hot focus was presumed to be the sentinel lymph node. The anterior and lateral position of SLN(s) were located using a Cobalt-57 pencil and marked on the skin of the patient in the operating position. A portable detection probe (Europrobe, Eurorad Strasbourg France) was used for the percutaneous verification of the location of the SLN. If labelling of the internal mammary nodes occurred, it was noted in the records but no attempt was made to excise such SLNs. On the day after the patient's hospitalization, one hour before the intervention, Emla® ointment (lignocaine + prilocaine) was applied vertically above the tumour and vertically above the lymph node labelling: no other premedication was administered. Then the patient was transferred to the operating room. The procedure began with a subcutaneous injection vertically above the tumour of 2 cc Patent blue® diluted 1:1 in normal saline. Massage was then applied for three minutes to improve diffusion of the dye. The site of the axillary lymph node labelling was checked before making the incision by transcutaneously determining the area of highest radioactivity using the portable detection probe. The operative field was prepared and 15 cc of xylocaine + adrenaline were injected subcutaneously at the point of lymph node mapping. An incision 2 to 4 cm long was then made vertically above the lymph node location. The search for the lymph node was guided by the probe and visualization of the blue lymphatic vessels or lymph nodes. If the patient felt any pain, repeat injections of xylocaine were made on demand into the site of the operation. Electrocoagulation was used to arrest bleeding, except if the lymph node was in contact with the nerve of the musculus latissimus dorsi, as happened on a few occasions. All radioactive and/or blue lymph nodes located were removed. The radioactivity of each removed lymph node was recorded ex vivo. Residual radioactivity in the dissected area was evaluated and, if positive, the search for lymph nodes was continued. A single layer was used for skin closure. The patient was discharged from hospital in the afternoon of the day of the operation. An intraoperative histopathological examination (IOE) was carried out if it did not compromise the quality of the definitive examination. In practice, if the lymph node was macroscopically suspicious or measured more than 8 mm, a single intraoperative section was made in the cryostat. IOE is carried out simply in order to evaluate its relevance *a posteriori*, but its result has no bearing on the conduct of treatment. The definitive examination included an initial stage of conventional histology: the SLN was macroscopically cut perpendicular to its major axis in 2 mm thick slices, totally embedded and stained in a standard manner using hematoxin-eosin (H-E). A single level was studied in each block. If the SLN was found to be positive with H-E, no additional study was made. If the SLN was found to be negative with H-E, the analysis was continued by carrying out an immunohistochemical (IHC) study on six serial sections 150 mm apart, using a KL1 anticytokeratin antibody on each block. Complete histological results – control of IOE, H-E and IHC – were obtained within one week of excision of the SLN. A treatment regimen was then proposed: for such small tumours, it always began with tumorectomy and complete axillary dissection if the SLN proved to be positive. Prognostic factors were determined once again based on the operative specimen: complete axillary dissection was carried out if the tumour exceeded 3 cm in size. The patients were seen again one week after detection of the SLN during their hospitalization to undergo tumorectomy. They were then systematically seen at D15 post-tumorectomy.

Data concerning each patient were recorded in computerized records and specially dedicated software (statview) was used to carry out a statistical analysis of the results. For relationships between continuous data, the Pearson correlation coefficient was calculated and its difference from zero assessed with the z-test. Bivariable comparisons were conduced using the chi-square test and Student's t-test for categorial and continuous variables, respectively.

Results

Seventy-eight patients were included in the study. In one case, no mapping was achieved with either the radioisotope or patent blue dye and we decided not to search for the SLN under LA. The patient underwent complete axillary dissection under GA during tumorectomy, and no metastatic lymph nodes were found. All the other patients had at least one radioisotope mapping depicted by LS (labelling rate 98.7%). Seventy-seven patients had at least one axillary mapping at level I (Berg classification). Ten patients (12.8%) also had internal mammary mapping, with none having solely internal mammary mapping. One patient had a single lymph node mapping at Berg level II. A search for the SLN was made under LA in all these patients. In one patient, in spite of Berg level I axillary lymph node mapping with the radioisotope, no hot or blue lymph node was found. In all other cases, at least one sentinel lymph node was removed (detection rate 97.4%). A mean of 1.28 lymph nodes were labelled by the radioisotope, a mean of 1.49 lymph nodes were harvested, and a mean of 1.59 lymph

nodes were found during the histopathological examination. The mean duration of removal (MDR) was 21.01 minutes (range 6-45). The MDR was significantly correlated with three parameters: (1) the surgeon (operations by one of two surgeons were significantly shorter: 19 versus 24.9; $p = 0.008$), (2) the BMI (the greater the BMI, the longer the operation, only for one surgeon $p < 0.014$), and (3) the number of lymph nodes depicted at LS: if a single lymph node was seen, the MDR was 19 minutes, if two lymph nodes were seen, the MDR increased to 25.7 minutes ($p = 0.004$).

Out of the 76 SLNs removed, 56 were negative at the intraoperative examination and negative at the definitive examination (73.7% of true negatives); eight were positive at the intraoperative examination with confirmation at the definitive examination (10.5% of true positives); 12 were negative at the intraoperative examination and positive at the definitive examination (15.8% of false negatives); no false positives were noted at the intraoperative examination. The sensitivity, specificity, negative predictive value (NPV) and positive predictive (PPV) value of the intraoperative examination were therefore calculated for our series of patients and found to be 40%, 100%, 82.4% and 100%, respectively. Of the 12 false negatives, six were positive at the definitive HES examination and six were only positive at the IHC examination.

All patients with involvement of at least one sentinel lymph node (even micrometastases) underwent complete axillary dissection during surgery under anaesthesia. We had no particular difficulties to carry out these dissections one week after the SLN removal. Two patients had a negative sentinel lymph node, but the tumour was found to be more than 3 cm in size at the histopathological examination of the tumorectomy specimen. We therefore performed a complete secondary axillary dissection in both patients (the two dissections proved to be negative). Thus, 22 patients underwent dissection, and a mean of 11.8 lymph nodes were removed per dissection. Finally, when a sentinel lymph node was involved (20 cases) no other lymph nodes were involved after complete axillary dissection in 15 patients.

All patients tolerated the procedure under LA, and no interruptions were necessary because of patient discomfort or pain. No known allergy to the patent blue dye was discovered in the population prior to the interventions. However, one allergic reaction was noted and required corticosteroid therapy but did not cause any interruption in the procedure.

Although the mean follow-up period for our series of patients is short (297 days), no axillary recurrence has been observed in patients subjected to SLN detection under LA.

Discussion

Few workers have reported on attempts made to excise sentinel lymph nodes under local anaesthesia. The feasibility of such a procedure was confirmed by three workers in a very short series of patients [10-12]. Luini *et al.* [13] and Van Berlo *et al.* [14] reported on larger series that are comparable with ours (Table 3).

There is no consensus so far as the method used for SLN mapping is concerned. However, data in the literature show that methods which combine labelling with a radioisotope and labelling with a dye give better results [9, 15, 16]. We decided to optimize our detection rates by using this combined method. We also decided to systematically perform lymphoscintigraphy, as suggested by some workers [17, 18] so as to facilitate and abbreviate as far as possible the search for the SLN and thereby improve patient comfort under LA.

The objective of this study was to evaluate the feasibility of the method and patient tolerance in searching for the SLN under LA. Study inclusion criteria are given in Table 1 and show that no consideration was given to age or morphology in the selection and exclusion of patients.

Table 2. — *Results from the literature concerning workers who used mapping with radiocolloids and blue dyes.*

Author (year)	n	Anaesthesia	Pathology	Detection rate	Mean number of SLNs	Single sentinel involvement
Albertini (1996) [15]	62	GA	HES	92%	2.2	67%
Barnwell (1998) [25]	42	GA	HES	90%	1	33%
O'Hea (1998) [26]	59	GA	HES	93%	2.2	41%
Cox (1998) [27]	466	GA	HES + IHC	94%	1.9	
Hill (1999) [28]	492	GA	HES + IHC	92%		
Manecksha (2001) [29]	73	GA	HES + IHC	96%		44%
Bobin (2000) [30]	75	GA	HES + IHC	98.75%	1.3	45%
Luini (2002) [13]	115	LA	HES + ICH	?	1.56	45%
Van Berlo (2003) [14]	162	LA	HES + ICH	100%	1.6	76.4%
Aubard (2003)	74	LA	HES + IHC	97.4%	1.59	75%

Table 3. — *Other data for the case series.*

Mean number of lymph nodes	Mean BMI	Clinical size of tumours	Histological size of tumours	Histologic forms	% Internal mammary labelling
Labelled at lymphoscintigraphy: 1.28	23.96	T0: 36	pT1a: 4	Ductal: 35	10/78
	(max	T1: 30	pT1b: 22	Lobular: 11	12.8%
Found by the surgeon: 1.49	32.9)	T2: 11	pT1c: 31	Duc. + lob.: 5	
			pT2: 20	Other: 6	
Found by the pathologist: 1.59			pT3: 1	Intraductal: 1	

Table 4. — *Comparison of our case series with others series of GS removal under LA.*

Author, year	n	Population	Local anaesthesia	Premedication	Method of mapping	Duration	Histopathology	Age	Tumour size	Lymph node metastases
Luini 2002	115	T1 and T2 < 2.5 cm	carbocaine	0.05 mg fentanyl 1 mg midozalam *	Colloid	20 min	HES and IHC	54 (27-77)	1.44 (0.2-4.5)	41.7% - 17.4% macro - 24.3% micro
Van Berlo	161	Most of all T1	prilocaïn 1%	none	Colloid plus patent blue	?	HES and IHC	?	?	33.9%
Aubard 2003	78	T0, T1 and T2 < 3 cm	xylocaine	Emla	Colloid plus patent blue	21.16 min	HES and IHC	61 (28-81)	1.59 (0.2-3.5)	26.3% - 13.15% macro - 13.15% micro

* in anxious patients.

Our results can therefore be applied to all patients with tumours less than 3 cm in size and N0.

Allergic reaction to patent blue dye has already been described by other workers [19, 20] and its incidence has been estimated at 2% [19, 20]. We obtained a similar figure in our series of patients (1/77 injected patients); such reactions are usually not serious and rapidly resolve. Nevertheless, this type of incident may raise the question as to whether a venous catheter should be set up for patients under local anaesthesia so as to be able to administer drugs quickly if required. However, we did not use a venous approach for the patients in our series. The advantage of local anaesthesia in this context is that the repercussions of an allergic reaction on the patient's general condition can be evaluated immediately – our patient reported pruritis before we noticed a rash.

None of the procedures had to be interrupted because of patient intolerance (pain, allergy or discomfort). No premedication was administered to the patients other than a topical application of Emla® ointment, unlike the study by Luini *et al.* [13]. We had one detection failure after 39 min of searching; the probe failed to detect any peak in radioactivity (in spite of labelling at LS) and no labelling with blue dye could be located in the operative field. Location of the single case of Berg level II SLN in our series did not constitute a handicap for detection under LA. The incision was not made vertically above the area of highest radioactivity as is our usual procedure (the area was underneath the clavicle at the level of the greater pectoral muscle), but at the outside edge of the upper portion of the greater pectoral muscle. We went around the muscle to reach the lymph node. This was not painful for the patient and detection took 17 minutes. The only local complications noted were ecchymoses of variable extent. One patient had a minor haematoma that did not require drainage.

Table 2 gives a comparison of our case series with extensive series reported in the literature. It can be seen that our detection rates are within the range of values achieved for the detection of the SLN under GA. In fact, they are even higher than those obtained in many of the series. This is probably due to the fact that we used the combined method in association with LS. This technique seems to give the best rates of detection. Be that as it may, carrying out SLN detection under LA did not produce a fall in the detection rate.

Patients were able to tolerate a MDR of 21 minutes. The mean consumption of local anaesthetics was less than 20 cc of xylocaine (maximum 40 cc). The BMI of patients was correlated with the Durakun of removal (DR) by one surgeon; however, no patient was excluded from detection under LA because of obesity; the maximum BMI in the case series was 32.9. The number of lymph nodes labelled at LS is also a factor that affects the DR. From this it may be deduced that it is wiser to avoid SLN detection under LA for obese patients with two distant labellings, even more so at LS. In any case, the decision must be taken with the concordance of the patient.

The DR also shows a correlation with the experience of the operator. Operators lacking in experience should avoid detection under LA until they have climbed the learning curve using detection under GA. At any rate, detection under LA should be carried out without undue hurry. The operator must also spend some time in explaining and commenting on his work to the patient, so that she is as relaxed as possible. He must also ask about any painful sensations felt by the patient so that further injections of anaesthetic can be made on demand. All of this takes a little more time compared with the procedure under GA.

Our false negative rate was high and hence the sensitivity of the IOE of our SLN was low, for the following two reasons: firstly, the aim of SLN detection under LA is to avoid IOE. We carried out these examinations only so as to record the false negatives since the result of the IOE had no effect on the operative approach. Therefore, the prime motivation of our pathologists during the intraoperative examination was to cause no damage to the SLNs so as not to compromise the results of the definitive analysis. With this in mind, they decided not to carry out an IOE on lymph nodes less than 8 mm and to prepare only one section for the others. Some workers prepare a greater number of intraoperative sections and examine the smallest lymph nodes: this makes the IOE more efficient, at the cost of having to wait much longer for the results (40 minutes according to Veronesi *et al.* [2]). Moreover, some workers do not use IHC during the definitive examination of the SLNs [5, 21-24], causing them to be unaware of some micrometastases and artificially increasing the sensitivity of the IOE.

Conclusion

This case series demonstrates that the detection of the SLN under LA in unselected patients with T0, T1 or T2 (< 3 cm) and N0, M0 breast cancer is perfectly feasible and well tolerated when performed by surgeons who have

already acquired good experience with detection under GA. Such an approach allows determination of the patient's lymph node status prior to the surgical intervention, avoiding the uncertainties of intraoperative examination of the SLN. We also think that not carrying out an IOE of the SLN improves the quality of the definitive examination since all of the lymph node can be prepared for the definitive analysis, which is more satisfactory.

Patient records, including the SLN results, are discussed at multidisciplinary oncology meetings. At this point, all the prognostic factors affecting the therapeutic decision are known: anatomicopathological tumour type, histologic grade, presence or absence of hormone receptors evaluated from the biopsy of the lesion, lymph node status evaluated by the SLN, and tumour size assessed by imaging. This makes it possible to plan therapy in the knowledge of most of the prognostic factors, and often allows a reduction in the number of interventions under general anaesthesia required for the treatment of the patient.

Moreover, detection of the SLN under LA, combined with radio-guided tumorectomy on a dedicated table under local anaesthesia, may make it possible to carry out surgery entirely under local anaesthesia on patients with tumours < 1 cm, as in the case of three patients in our series. Such management of small breasts tumours marks a step forward in the field of minimal invasive breast surgery.

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