An original approach in the diagnosis of early breast cancer: use of the same radiopharmaceutical for both non-palpable lesions and sentinel node localisation

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Received: 8 February 2001 / Accepted: 18 June 2001 / Published online: 12 September 2001

Abstract. A modern approach to the surgical treatment of early breast carcinoma requires intraoperative localisation of non-palpable lesions and assessment of the lymph node status. Localisation of breast lesions can be achieved by intratumoural injection of a small amount of radiotracer and intraoperative use of a gamma probe (i.e. radioguided occult lesion localisation, or ROLL). Assessment of the lymph node status is possible by means of the sentinel node approach. To date, two different radiopharmaceuticals have been used for localisation of tumour and sentinel node. We now propose the use of a single nanocolloidal tracer (Nanocoll, with a particle size of less than 80 nm) which is labelled with technetium-99m for simultaneous performance of ROLL and sentinel node identification. The aim of this study was to evaluate the feasibility of this approach, which should be easier and more practical than the dual-tracer injection method. We have employed this new technique in 73 patients with non-palpable, cytologically diagnosed breast cancer and non-palpable axillary lymph nodes. In all patients the radiocolloid, in a total volume of 0.3–0.4 cc, was injected under sonographic or stereotactic guidance. Half of the dose was injected intratumourally and half superficially, but very close to the tumour. Because of the slow lymphatic flow in the breast, Nanocoll must be injected some time before surgery in order to enable adequate migration to the axilla. We injected colloid in the afternoon before surgery (16–23 h before the start of the operation, with an average interval of 18 h). An average dose of 130 MBq (range 110–150) was injected in order to have about 10 MBq of radioactivity when surgery commenced. Lymphoscintigraphy was performed after 15–19 h, with an average interval of 17 h. The procedure was always successful in permitting the localisation of occult breast lesions. Lesions were always localised at the first attempt, and were always contained within the surgical margins. Histological examination revealed all 73 resected lesions to be malignant: there were 64 cases of infiltrating carcinoma and nine of intraductal carcinoma. All breast lesions were therefore confirmed to be early breast cancer. We achieved sentinel node localisation in 71 out of 73, either at scintigraphy or with the intraoperative probe; in two patients, radiopharmaceutical migration was absent. Lymphoscintigraphy showed only axillary drainage in 52 cases, only internal mammary chain (IMC) drainage in nine cases, and combined axillary and IMC drainage in eight cases. In two cases, lymphoscintigraphy suggested the sentinel node was located inside the same breast (intramammary lymph node). All the visualised sentinel nodes were biopsied except for four that were localised in the IMC. Histological examination of the nodes showed metastases in 20 cases: in 15 cases there were micrometastases, and in five, macrometastases. In conclusion, this study has demonstrated the feasibility of the proposed procedure. Simultaneous performance of ROLL and sentinel node localisation using a single tracer represents a useful and practicable choice in the management of early breast cancer.

Keywords: Early breast cancer – Sentinel node – Radioguided surgery

Eur J Nucl Med (2001) 28:1589–1596
DOI 10.1007/s002590100601

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Introduction

In the last few years, significant advances have led to modification of the surgical approach to breast cancer. On the one hand, improvement and extension of mammographic screening programmes has allowed the diagnosis of clinically occult breast lesions [1, 2]; on the other hand, sentinel node biopsy has become an accepted technique that enables avoidance of unnecessary axillary lymph node dissections [3, 4, 5, 6].

One of the keys to the successful management of non-palpable breast lesions is exact localisation, this being a prerequisite for correct surgical biopsy. Several techniques, such as guidewire localisation [7], have been proposed. Since 1999 we have been using a new technique, termed radioguided occult lesion localisation, or ROLL. This technique involves the intratumoural injection of a small volume of radiotracer which is able to remain at the site of injection for a long time. This allows for radiolabelling of the lesion, and localisation and excision are then performed with the aid of a gamma ray detection probe [8, 9, 10].

Sentinel node (SN) biopsy is a minimally invasive method for staging patients with early breast cancer. Our present management policy for non-palpable breast cancers provides for both ROLL and sentinel node biopsy. Up to now these procedures have been undertaken separately, or in a single intervention but using two different radiopharmaceuticals: one for the breast lesion and one to localise the SN [11].

In order to simplify and optimise this approach we now propose the use of a single tracer that is able not only to identify the SN but also to localise non-palpable breast lesions. The aim of this study was to evaluate the feasibility of this new approach, which should be easier and more practical than a dual-tracer injection method.

Materials and methods

Seventy-three patients (median age 60 years; range 46–80) with non-palpable lesions identified by screening mammography and/or ultrasound were investigated. All patients had clinically negative axillae. All the patients had positive needle cytology: 51 patients had a cytological report of C5 (malignancy), while 18 had C4 (probable malignancy) and four had C3 (lesion of uncertain nature; indication for surgical biopsy because of suspicious imaging findings) (Table 1) [12].

In this study a nanocolloidal tracer (Nanocoll, Nycomed Amersham Sorin, Saluggia, Italy) was used, with an average particle size of less than 80 mm. Nanocoll was labelled with a high technetium-99m activity and concentration (5,550 MBq/ml) [13]. We injected a dose of 130 MBq on average (range 110–150) in order to have about 10 MBq of radioactivity at the time of surgery. The injected volume was 0.3–0.4 cc. Administration of the tracer was performed under sonographic (US) or stereotactic guidance, the choice being made in accordance with the imaging features of the lesion. Half of the dose (0.2 ml maximum) was given intratumourally and half superficially, but very close to the tumour.

Table 1. Cytology, histology, pTNM classification and AJCC staging (73 lesions)

	No.	%
Fine-needle aspiration reports		
C5	51	69.9
C4	18	24.7
C3	4	5.5
Histological reports (primary lesions)		
Infiltrating ductal ca.	34	46.6
(+ intraductal component)	(20)	
Infiltrating lobular ca.	15	20.5
(+ intraductal component)	(9)	
Infiltrating lobular + tubular ca.	13	17.8
Infiltrating cribriform + tubular ca.	2	2.7
Intraductal ca.	9	12.3
pTNM		
Tis	9	12.3
T1a	6	8.2
T1b	15	20.5
T1c	41	56.2
T2	2	2.8
N0	53	72.6
N1	19	26.0
N3	1	1.4
M0	73	100
Staging (AJCC)		
0	8	11.0
I	45	61.6
IIA	18	24.7
IIB	1	1.4
IIIB	1	1.4

When the primary lesion had no mass but consisted only of microcalcifications, the entire dose was injected among these calcifications. Using the same needle, a radiographic contrast medium could be injected immediately after tracer injection, in order to confirm the positioning of the injectate by mammography (Fig. 1).

In the case of non-palpable breast lesions which appeared only as microcalcifications on mammography, we also inserted a hook wire while injecting radiopharmaceutical under radiological guidance. This was in order to help the pathologist to locate a lesion that could not easily be seen or felt.

If radiographic contrast medium had been injected, the patient underwent mammography. Then, a few minutes after radiopharmaceutical injection, scintigraphy was performed, which also provided information on injectate positioning. A breast massage by the patient was encouraged: no other preparation was required.

We performed scintigraphy on the morning of surgery, 15–19 h (average 17 h) after injection of colloid on the previous day. This timing maximises the likelihood that Nanocoll will identify the sentinel node (Fig. 2): in this way the use of the gamma camera is optimised with simple scintigraphic imaging. Anterior and lateral projections were performed using a large field of view gamma camera, Apex 409 GE or Vertex dual-head Adac (with gantries at 90°), equipped with high-resolution, low-energy parallel-hole collimators. Static scintigraphic images were obtained with an acquisition time of 300–600 s in a 256×256 matrix. A 15% window en-

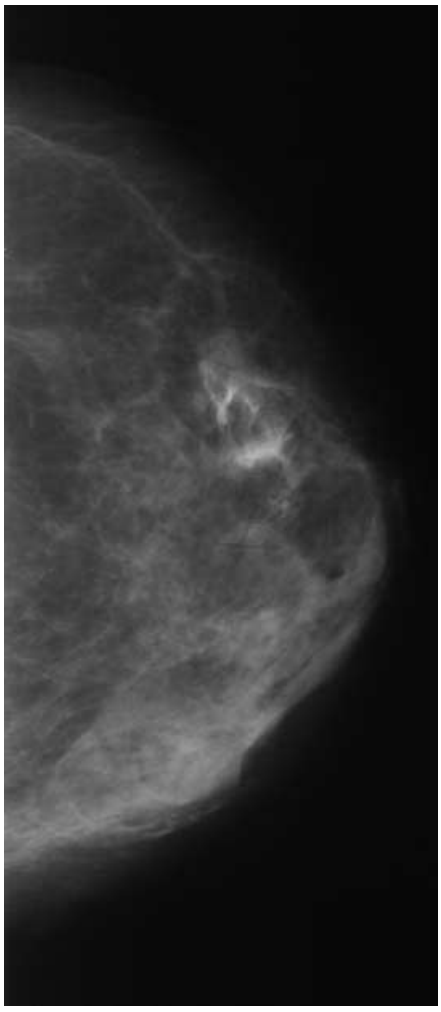

Fig. 1. Radiographic contrast medium can be injected soon after tracer injection, in order to verify the correct positioning of the injectate by mammography

ergy peak was used. The patient was positioned supine with the arm ipsilateral to the lesion in maximum abduction in order to achieve the shortest possible distance between the gantry and the thorax. At the end of this examination, the cutaneous projection of the SN was marked.

Every patient underwent conservative surgery with general anaesthesia. A gamma ray detection probe (Scintiprobe MR 100 or Neoprobe NEO 2000) was used to locate the lesion and to guide its surgical removal [14, 15]. First we located the cutaneous projection of the lesion in order to characterise the best surgical access area (independently from the position of the hook wire, if used). Then, we performed a radial cutaneous incision and a wide lesion excision – quadrantectomy. After specimen excision, we always verified the absence of high levels of radioactivity in the residual tissue, and the resected tissue was imaged by scintigraphy and mammography to verify the presence of the lesion in the specimen (Fig. 3).

Histological examination after embedding in paraffin was usually requested. Multilevel (100-µm interval) sectioning of the SN was performed, with haematoxylin and eosin staining and immunohistochemistry (anticytokeratin AE1, AE3, PCK26 antibodies) [16, 17].

The protocol is summarised in Table 2. This protocol was approved by the Ethics Committee of our hospital and every patient gave informed consent.

Results

The primary breast lesion was successfully localised in all cases. Breast lesions were always localised at the first attempt, and were always contained within the surgical margins. The average size of nodules was 12×7 mm (range 4×3–25×14 mm).

Because of the very high probability of malignancy, we performed quadrantectomies, with excision of the overlying skin and the underlying muscular fascia: this explains the apparently large specimen dimensions. Resected specimens had an average size of 11×8×3 cm, with the size of the cutaneous "lozenge" averaging 6.3×2.2 cm.

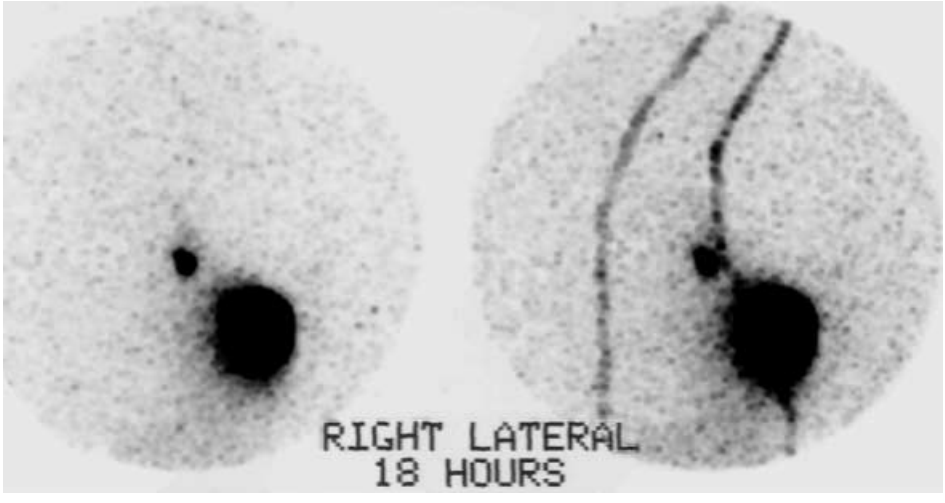

Fig. 2. Scintigraphy performed on the morning of surgery (18 h after tracer injection). Both the primary tumour site and the SN are evident. In the *right figure*, as in Fig. 5, the body outline is made evident by use of a radioactive-ink pen

Fig. 3. Scintigraphy of the resected specimen (to verify the presence of the lesion in the specimen). Two projections

Table 2. ROLL and SN detection: summary of the protocol for the single-tracer method

Time	Step
Before admission of patient to hospital	1. Patient selection: screening imaging, cytology, clinical criteria (non-palpable breast lesions, non-palpable axillary nodes) 2. Routine pre-operative assessment (ECG, chest X-ray, blood examination)
Admission early in the afternoon (surgical department)	3. Patient reception and procurement of informed consent 4. Patient goes to the mammography department, where injection of radiopharmaceutical by radiologist and nuclear medicine physician – US guidance (when possible) or stereotactic guidance – Nanocoll: ^{99m}Tc, 130 MBq in 0.35 ml – Half of the dose intratumourally, half superficially (very close to the tumour) 5. Injection of radiographic contrast medium (possible) 6. Hook wire insertion (possible; if X-ray shows only microcalcifications and there is no US evidence)
Few minutes after injection	7. Mammography (if radiographic contrast medium was injected; check on injectate positioning) Patient goes to nuclear medicine department 8. Scintigraphy (check on injectate positioning) Patient returns to surgical department
Morning of the day after admission	9. Patient goes to nuclear medicine department, where scintigraphy is performed (17 h after tracer injection on average): – SN site detection – Marking of cutaneous SN projection 10. Patient is sent to surgical theatre where surgery is performed: – Radioguided quadrantectomy – SN-selective biopsy 11. Resected specimen undergoes scintigraphy (nuclear medicine; correct excision check) 12. Resected specimen undergoes mammography (mammography department; correct excision check) 13. Resected specimen and SN are sent to pathologists Patient returns to surgical department
Afternoon after surgical operation (or the following morning)	14. Patient discharged

Table 3. Data on primary breast lesions

Results	No.	%
Localised lesions (scintigraphy and intraoperative probe)	73	100
Removed lesions	73	100
Surgery sufficiently radical	69	94.5
Surgery not sufficiently radical	4	5.5

Table 4. SN sites in the 73 patients

	No.	%
Non-visualised SNs	2	2.7
Visualised SNs	71	97.3
Axilla	52	71.2
Intramammary	2	2.7
IMC	9	12.3
Axilla + IMC	8	11

IMC, Internal mammary chain

Table 5. Axillary (n=60) and intramammary (n=2) SNs

	No.	%
Harvested SNs	62	100
SNs without metastatic involvement	43	69.4
Metastatic SNs	19	30.6
Micrometastases	14	22.6
Macrometastases	5	8.1

Table 6. Histology of the primary breast lesions in the 20 patients with metastases

	No.	%
Infiltrating ductal ca.	9	45
Infiltrating lobular ca.	6	30
Infiltrating lobular and tubular ca.	4	20
Intraductal ca.	1	5

See text for details

The shortest distance between tumour and surgical margins was generally sufficient (>10 mm), and lesions often appeared centred within the specimens. In four cases, however, the shortest distance was not adequate, being only 1, 1, 2.5 and 3 mm, respectively. In the first two patients (distance of 1 mm) we had to perform a wider excision successively, while in the other two patients we trusted in local radiotherapy. Our data on primary breast cancer are summarised in Table 3.

All the patients had a histological report of malignancy. There were 34 cases of infiltrating ductal carcinoma (with an intraductal component in 20), 15 cases of infiltrating lobular carcinoma (with an intraductal component in nine), 13 cases of infiltrating lobular and tubular carcinoma, two cases of infiltrating cribriform and tubular carcinoma, and nine cases of intraductal carcinoma (Table 1).

As regards identification of SN, our procedure permitted localisation with selective biopsy in all patients but two.

Lymphoscintigraphy showed the following lymphatic drainage patterns (Table 4):

- Axillary drainage only in 52 cases
- Internal mammary chain (IMC) drainage only in nine cases
- Axillary and IMC drainage in eight cases
- An intramammary lymph node (a node inside the same breast) in two cases

Localisation of the SN during surgery by means of the probe always confirmed the findings at lymphoscintigraphy. In two patients, however, the tracer seemed not to migrate from the injection site and the SN identification failed (pre-operative use of the probe also failed).

Histological findings in respect of the axillary SNs (n=60) and intramammary SNs (n=2) are summarised in Table 5. Figure 4 illustrates the appearance of a micrometastasis on histological evaluation. The histology of the primary breast lesions in patients with metastases is shown in Table 6.

Three patients with micrometastases rejected the proposal of further radical axillary lymph node dissection. One patient with macrometastasis has not yet undergone axillary dissection. Fifteen patients (11 with micrometastases and 4 with macrometastases) underwent axillary dissection: histological results are reported in Table 7.

In 17 cases SNs were localised in the IMC. The localisation of the primary breast tumours in these cases is summarised in Table 8.

Attempted surgical excision failed in four cases (the SNs were located under a rib) and in one case a minor pleural injury was also produced (this had no consequences and no particular care was required). Three of these patients showed axillary SNs too, which were harvested.

Histological findings in patients with IMC SNs are summarised in Table 9. The primary tumour in the single patient with a metastatic IMC SN was shown histologically to be an intraductal carcinoma without an infiltrating component (further evaluation confirmed this) (cf. Table 6). The presence of neoplastic cells in the IMC sentinel node was considered to be due to neoplastic epithelial displacement following needling trauma [18, 19].

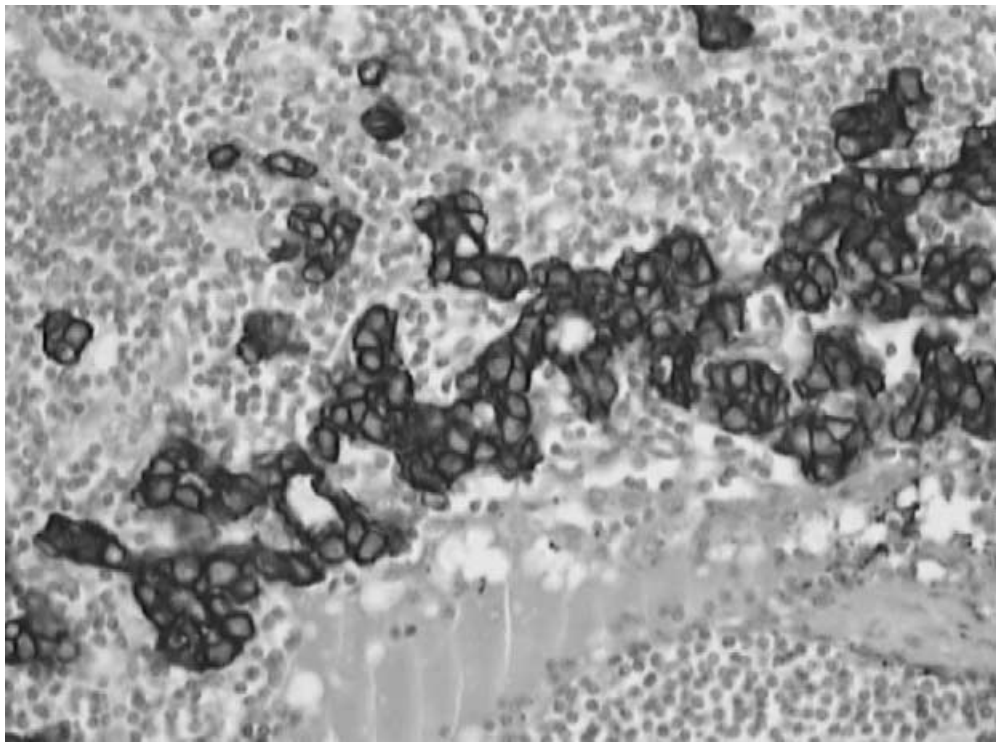

Fig. 4. Micrometastasis visualised by haematoxylin and eosin staining and immunocytochemical assay with anticytokeratin antibodies

Table 7. Results of further axillary lymphadenectomies in the 19 patients with axillary SNs with metastatic involvement

	No.	%
Further lymphadenectomies not performed	4	21.1
Metastases only in SN	13	68.4
Metastases in further axillary nodes too	2[a]	10.5

[a] Number of further metastatic nodes: 1 and 3

Table 8. Localisation of primary tumours in the 17 patients with IMC SNs

Breast quadrant	No.	%
Lower outer	8	47.1
Upper inner	4	23.5
Upper outer	3	17.6
Lower inner	2	11.8

Table 9. Histological findings in respect of the IMC SNs (*n*=17)

	No.	%
Harvested SNs	13	76.5
SNs without metastatic involvement	12	92.3
Metastatic SNs	1	7.7
Micrometastases	1[a]	7.7
Macrometastases	0	0

See text for details
[a] Primary tumour: intraductal ca.

Discussion

The advantages of ROLL (whether or not it is performed in association with SN biopsy) are:

- During surgery, ROLL always provides information on the location of the lesion so that the best route of surgical access can be selected. (By contrast, use of a hook wire forces the surgeon to follow the path of the wire, which is not always the shortest or the most practical route because hook wire insertion must be subject to radiological principles.)
- The possibility of verifying the absence of radioactivity by performing an intraoperative check on residual tissue increases the opportunity to achieve a radical excision immediately, thereby saving more breast tissue.
- When used without a hook wire, ROLL avoids some further hook wire-related disadvantages (local discomfort, displacements, migrations, accidental transections due to retained hook fragments) [20, 21, 22, 23, 24, 25].

Our current management strategy for early breast lesions always requires ROLL and SN biopsy. On the one hand, early breast lesions are small lesions which are not palpable and so a guide is needed to “hit the target” during surgery. On the other hand, small lesions have a low likelihood of being accompanied by nodal metastases (we found an incidence of 21.9% in one of our study samples [26]), and when this happens, often micrometastases are present. In these conditions, SN biopsy has

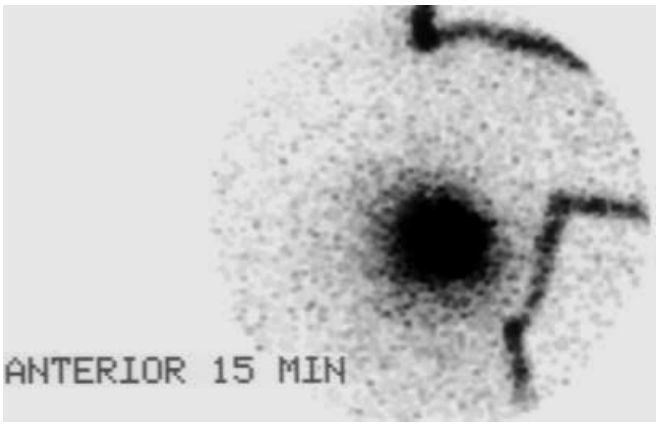

Fig. 5. Scintigraphy performed a few minutes after tracer injection provides information on positioning of the injectate. Here scintigraphy shows a concentrated and well-defined spot: this represents evidence of a correct injection

been becoming "the gold standard" [27, 28, 29, 30]. We have decided to apply a single tracer not only to identify SNs but also to simultaneously localise non-palpable breast lesions.

We emphasise that we prefer performing colloid injection under US guidance: it is more practical and cheaper, it does not entail any radiation dose to patients, and it allows visualisation of every moment of the needle insertion procedure. If no US evidence of the lesion is obtained, we resort to stereotactic guidance. We inject the colloid both intratumourally and very close to the tumour (50%/50%) in order to achieve both adequate localisation of the primary tumour and adequate migration to the SN. Giving all of the radiopharmaceutical intratumourally can prevent adequate migration within a reasonable time.

After injection we perform a scintigraphic control to verify colloid administration. If scintigraphy shows a concentrated and well-defined spot, this provides evidence of a correct injection (Fig. 5), while if scintigraphy shows multiple spots, or a single but large and poorly defined spot, something has probably gone wrong.

In this study of patients with early breast cancer, use of a hand-held gamma ray detection probe permitted exact localisation of lesions and thus enabled us to perform accurate, fast and often complete excisions. Frequently operations were radical at the first attempt (69 of 73 cases), rendering further wider excisions unnecessary. (The distances between tumour and surgical margins were oncologically adequate.)

This study demonstrates that colloid migration from the primary lesion to SN is not a problem for breast lesion localisation because the amount of the Nanocoll migrating to the lymph node is negligible in comparison with the amount persisting at the primary site (about 1:100).

As regards injection timing, tracer needs to be injected some time before surgery because of the slow lymphatic flow in the breast. Performing the injection on the afternoon before surgery gives the tracer more time to migrate and reduces waiting times on the morning of surgery. In fact, when we have injected on the morning of surgery, the interval between injection and surgery has varied between patients (from 20 min to 4 h) and so the gamma camera has been kept busy for an unforeseeable duration. This has caused problems in organising surgical sessions. In this study an interval between colloid injection and surgery of up to 24 h did not constitute a problem.

The single-tracer method allows complete treatment to be performed within a single operation. Radical operations on breast lesions can be performed immediately, while the SN often proves to be free of disease, rendering further surgery unnecessary. Histological evaluation during surgery by frozen sectioning in any case allows definition of nodal status by a single operation.

In our opinion, this management strategy offers great benefits from the economic point of view, with reduction of costs due to operations and hospital care. Furthermore, it is appreciated by patients, who witness the rapid surgical solution to their problem (with corresponding psychological benefit).

There are some aspects which must be considered when evaluating the method proposed here:

First, it is important to establish prior to surgery that there is a high probability that the lesion is malignant. In fact, one must be able to exclude with reasonable certainty the possibility of using this method on benign lesions. Accurate and reliable cytological evaluation assists in this. In our experience, there is a very high probability that a cytological report of malignancy will be confirmed by histology (about 98% for C5 and >90% for C4). Indeed, we would emphasise that in this study histological examination revealed malignancy in every resected lesion.

Second, when this procedure is used with histological examination after paraffin embedding, there is a risk of performing SN biopsy in patients with intraductal carcinomas (in situ carcinomas). However, a single node biopsy, even if unnecessary, does not represent significant damage for patients.

Frozen section examination during surgery can avoid the risk of unnecessary SN biopsies, but in other respects we prefer evaluation after embedding in paraffin. Nonpalpable carcinomas are often small lesions, and so frozen sectioning does not permit easy distinction between in situ and infiltrating forms; in addition, information about surgical margins is sometimes unclear [31, 32].

Conclusion

This study shows that our method works both in permitting the surgeon to localise the breast lesion and in identifying the SN. The use of only one tracer saves much time and money. Furthermore the injection procedure is easier and straightforward.

Even though further evaluation of the technique will be useful, we consider that ROLL and SN localisation using a single tracer offers advantages in the management of early breast cancer. Good co-ordination between the surgeon, radiologist [33] and nuclear medicine physician [34, 35] is needed: nowadays breast cancer care is the result of a team effort. Only then can best practice be achieved.

References

1. Tabar L, Fagerberg CJG, Gad A. Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985; 1:829–832.
2. McLelland R. Screening mammography. *Cancer* 1991; 67: 1129–1131.
3. Rodier JF, Routiot T, Mignotte H, Janser JC, Bremond A, David E, Barlier C, Ghnassia JP, Treilleux I, Chassagne C, Velten M. Lymphatic mapping and sentinel node biopsy of operable breast cancer. *World J Surg* 2000; 24:1220–1225.
4. Tafra L, Lannin DR, Swanson MS, Van Eyk JJ, Verbanac KM, Chua AN, Ng PC, Edwards MS, Halliday BE, Henry CA, Sommers LM, Carman CM, Molin MR, Yurko JE, Perry RR, Williams AR. Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. *Ann Surg* 2001; 233:51–59.
5. Motomura K, Inaji H, Komoike Y, Kasugai T, Nagumo S, Noguchi S, Koyama H. Sentinel node biopsy in breast cancer patients with clinically negative lymph nodes. *Breast Cancer* 1999; 6:259–262.
6. Krag D, Weaver D, Ashikagat T, Moffat F, Klimberg VS, Shriver C, Feldman S, Kusminsky R, Gadd M, Kuhn J, Harlow S, Beitsch P. The sentinel node in breast cancer – a multicenter validation study. *N Engl J Med* 1998; 339:941–946.
7. Frank HA, Hall FM, Steer FM, Steer ML. Preoperative localization of nonpalpable breast lesion demonstrated by mammography. *N Engl J Med* 1976; 295:259–260.
8. Luini A, Zurrida S, Galimberti V, Paganelli G. Radioguided surgery of occult breast lesions. *Eur J Cancer* 1998; 34:204–205.
9. Luini A, Zurrida S, Paganelli G, Galimberti V, Sacchini V, Monti S, Veronesi P, Viale G, Veronesi U. Comparison of radioguided excision with wire localization of occult breast lesions. *Br J Surg* 1999; 86:522–525.
10. Gennari R, Galimberti V, De Cicco C, Zurrida S, Zerwes F, Pigatto F, Luini A, Paganelli G, Veronesi U. Use of technetium-99m-labeled colloid albumin for preoperative and intraoperative localization of nonpalpable breast lesions. *J Am Coll Surg* 2000; 190:692–698; discussion 698–699.
11. Wilhelm AJ, Mijnhout GS, Franssen EJ. Radiopharmaceuticals in sentinel lymph-node detection – an overview. *Eur J Nucl Med* 1999; 26:S36–S42.
12. Wells CA, Ellis IO, Zakhour HD, Wilson AR. Guidelines for cytology procedures and reporting on fine needle aspirates of the breast. *Cytopathology* 1994; 5:316–334.
13. Gommans GM, Boer RO, Van Dongen A, Van Der Schors TG, De Waard JW. Optimisation of ^{99m}Tc-Nanocoll sentinel node localisation in carcinoma of the breast. *Eur J Nucl Med* 2000; 27:744.
14. Tiourina T, Arends B, Huysmans D, Rutten H, Lemaire B, Muller S. Evaluation of surgical gamma probes for radioguided sentinel node localisation. *Eur J Nucl Med* 1998; 25:1224–1231.
15. Hoffman EJ, Tornai MP, Janecek M, Patt BE, Iwanczyk JS. Intraoperative probes and imaging probes. *Eur J Nucl Med* 1999; 26:913–935.
16. Liu LH, Siziopikou KP, Gabram S, McClatchey KD. Evaluation of axillary sentinel node biopsy by immunohistochemistry and multilevel sectioning in patients with breast carcinoma. *Arch Pathol Lab Med* 2000; 124:1670–1673.
17. Van Diest PJ, Peterse HL, Borgstein PS, Hoekstra O, Meier CJ. Pathological investigation in sentinel lymph-node detection – an overview. *Eur J Nucl Med* 1999; 26:S43–S49.
18. Youngson BJ, Cranor M, Rosen PP. Epithelial displacement in surgical specimens following needling procedures. *Am J Surg Pathol* 1994; 18:896–903.
19. Rosen PP. *Breast pathology.* New York: Lippincott-Raven; 1997:818.
20. Owen AW, Kumar EN. Migration of localizing wires used in guided biopsy of the breast. *Clin Radiol* 1991; 43:251.
21. Tykka H, Roiha M, Sjoblom SM. Preoperative localization of breast tumor and pneumothorax. *Duodecim* 1993; 109:227–230.
22. Van Susante JL, Barendregt WB, Bruggink ED. Migration of the guide-wire into the pleural cavity after needle localization of breast lesions. *Eur J Surg Oncol* 1998; 24:446–448.
23. Davis PS, Wechsler RJ, Feig SA, March D. Migration of breast biopsy localisation wire. *Am J Radiol* 1988; 150: 787–788.
24. Bronstein AD, Kilcoyne RF, Moe RE. Complications of needle localization of foreign bodies and nonpalpable breast lesions. *Arch Surg* 1988; 123:775–779.
25. Homer MJ. Transection of the localisation hook wire during breast biopsy. *Am J Radiol* 1983; 141:929–930.
26. Querzoli P, Albonico G, Ferretti S, Rinaldi R, Beccati D, Corcione S, Indelli M, Nenci I. Modulation of biomarkers in minimal breast carcinoma. *Cancer* 1998; 83:89–97.
27. Carcoforo P, Feggi L, Sartori A, Navarra G, Pozza E, Donini I. Lymphatic mapping for the dissection of the sentinel node in the treatment of breast carcinoma. *Exp Clin Cancer Res* 1999; 22:478–482.
28. Anan K, Mitsuyama S, Tamae K, Nishihara K, Iwashita T, Abe Y, Ihara T, Toyoshima S. Axillary lymph node metastases in patients with small carcinomas of the breast: is accurate prediction possible? *Eur J Surg* 2000; 166:610–615.
29. Feggi LM, Querzoli P, Prandini N, Corcione S, Bergossi L, Basaglia E, Carcoforo P. Sentinel node study in early breast cancer. *Tumori* 2000; 86:314–316.
30. Keshtgar MR, Ell PJ. Sentinel lymph node detection and imaging. *Eur J Nucl Med* 1999; 26:57–67.
31. Naguchi M, Bando E, Tsugawa K, Miwa K, Yokoyama K, Nakajima K, Michigishi T, Tonami N, Minato H, Nonomura A. Staging efficacy of breast cancer with sentinel lymphadenectomy. *Breast Cancer Res Treat* 1999; 57:22–29.
32. Kelley SW, Komorowski RA, Dayer AM. Axillary sentinel lymph node examination in breast carcinoma. *Arch Pathol Lab Med* 1999; 123:533–535.
33. Schepps B, Scola FH. Contemporary diagnostic approaches for nonpalpable carcinoma of the breast: the role of the radiologist. *R I Med* 1995; 78:239–241.
34. Kotz D. Advancing medical care: the role of nuclear medicine in radioguided surgery. Part II. Sentinel node dissections. *J Nucl Med* 1998; 39:13N, 15N, 21N.
35. Paganelli G. Sentinel-node biopsy: role of nuclear medicine in conservative surgery of breast cancer. *Eur J Nucl Med* 1998; 25:99–100.