

Sentinel Node Detection and Imaging*

Introduction

The concept of the sentinel node represents a major new opportunity to stratify patients for appropriate surgery in cancer. Present enthusiasm is high judging by the many publications in the peer-reviewed literature, and significant attention is being paid to this subject by editorials in the major medical journals [1–3]. The reports are almost uniformly enthusiastic about the potential of this technique, and guidelines have been published for sentinel node detection in carcinoma of the breast. Patients have become aware of the potential of the technology, and it is not uncommon for patients to inform themselves and request the views of individuals or clinical groups on this new staging procedure. Despite all this enthusiasm, however, there are significant differences in practice relating to almost all aspects of the technology involved. Interestingly, in spite of these differences, in general terms groups are reporting encouraging results. It is therefore useful to review the subject of the detection of the sentinel node, introducing readers to the present areas of uncertainty and providing a critical analysis of the data as they have appeared in the literature.

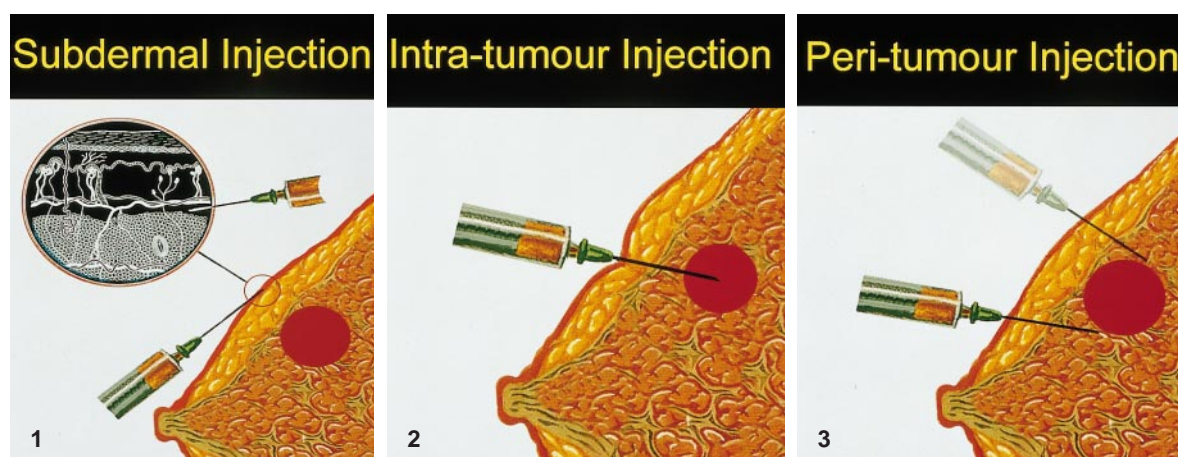
As can be seen from Table 1, many aspects are being investigated. Several instruments are available for detection of the sentinel node, several radiopharmaceuticals are available for injection, there is controversy as to the injection site, practice varies from single to multiple injections and between large and small volumes of injectate, and there is also considerable variation in the amount of radioactivity administered. With

regard to detection, there are groups which advocate external detection with probes and non-imaging, those which combine external detection using a probe with radionuclide gamma camera imaging, those which still advocate the use of blue dye alone or in combination with probe detection, those which have aimed at detection of the sentinel node alone, and those which have

Table 1. Technical issues in sentinel node detection and imaging

What probe?
What tracer?
What injection site?
Single or multiple injection sites?
Large or small volume of injectate?
Massage or no massage of injection site?
How many MBq's?
Which mode of detection is preferable?
– Probe detection only
– Probe detection and imaging
– Blue dye alone or in combination with probe detection
– Sentinel lymph node detection only
– Sentinel lymph node detection and lymphoscintigraphy (imaging)
Which form of imaging is best?
– Dynamic imaging
– Early imaging
– Early and late imaging
What is the most appropriate site of injection?
– Intratumoral
– Peritumoral
– Subdermal
– Subcutaneous
What pathological evidence is required?
– Fine-needle aspiration cytology
– Core cut biopsy
– Use of advanced breast biopsy instrumentation
– Excisional breast biopsy
– Imprint cytology
– Haematoxylin and eosin staining alone
– Cytokeratin immunohistochemistry (e.g. MNF 116)
– Polymerase chain reaction

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Figs. 1–3. Possible routes for administration of tracer for sentinel node detection. The lymphatic-rich area is seen in Fig. 1

attempted to combine detection of the sentinel node with detection of all lymph nodes in the appropriate lymph basin (lymphoscintigraphy). Furthermore there is significant controversy as to the minimum amount of histopathological evidence which needs to be obtained from the sentinel node.

It is astonishing that groups have used such varying techniques in terms of the delivery of an appropriate radiopharmaceutical to the area of interest (Figs. 1–3). It is well known from the literature that lymphatic tissue is most prevalent in the peripheral layer of the skin, such that a subdermal injection will deliver the tracer to an area rich in lymph vessels. It is also well known that subcutaneous tissue has fewer lymphatic vessels and that direct injection of the tracer into a tumour will consequently entail the administration of an indicator into a high-pressure system. By their nature, tumours have high interstitial and high intercellular pressures, and it is therefore possible that any attempt to administer a tracer directly into a tumour will only lead to leakage of the tracer from the tumour into the peritumoral tissue. There is debate as to the safety of puncturing a tumour directly since there is concern that this may lead to increased seeding of micrometastases from the needle track and puncture of the tumour. There is currently little evidence that this has any effect on the long-term evolution of the tumour and final outcome for a specific patient.

Nevertheless, it would seem appropriate only to perform a direct intratumoral injection if there are clear and overriding advantages – and there is scant evidence in the literature for such advantages.

It is also now clear from the literature that as the sophistication of the methods used to gather pathological evidence from sentinel nodes increases, so there is improved sensitivity of detection of micrometastases. What is not known is the extent to which an ever – increasing sensitivity leads to the detection of a few or even single micrometastases in a lymph node which will fail to develop clinical expression. This issue is raised by an editorial in the *Lancet* [2], where it is almost claimed that all the power of modern histopathological evidence gathering should be aimed not merely at the sentinel node but rather at all the nodes cleared during a surgical axillary lymph node clearance. That this is and probably will remain an entirely impractical proposition is also beyond doubt.

From a legal point of view, radiation protection legislation differs significantly from country to country but in general, a radiopharmaceutical needs to be licensed before it is made available for routine use. The tracers used in Europe for lymphoscintigraphy and sentinel node detection were mostly developed in the early 1970s and were aimed at the imaging of the reticuloendothelial system of the liver, spleen and bone marrow. The properties and overall characteristics of these tracers have therefore not been optimised, in general, for sentinel node detection. There is

Table 2. Inclusion and exclusion criteria employed in our ongoing trial of sentinel node imaging in patients with breast cancer

Eligibility criteria

- All patients with proven carcinoma of the breast on triple assessment (clinical examination, imaging and cytology/tissue diagnosis)
- Palpable and defined non-palpable breast cancer

Exclusion criteria

- Clinical involvement of the axilla
- Pregnancy/lactation
- Multifocal/multicentric carcinomas of the breast
- Previous breast surgery at the same sit

significant variability in the particle size of the tracers and ultimately, if this approach is to succeed, an appropriate licenced product will be required in Europe for lymphoscintigraphy in general, for the detection of the sentinel nodes in particular and possibly even for specific applications to specific cancer types.

It is to be emphasised that different results have been obtained with respect to sentinel node detection and imaging in specific patient groups. It is now evident from the literature that poorer results in the detection of the sentinel node in cases of breast cancer are obtained when all lesions are included, when inner quadrant or multicentric lesions are investigated, and when patients are investigated who have already undergone a surgical procedure. Refinement of the indications is in progress in the context of ongoing trials; our own ongoing trial in patients with breast cancer, mirroring that conducted by the Milan group [4], employs the inclusion and exclusion criteria defined in Table 2. In the case of melanoma patients, too, refinement of indications is required.

The Lymphatic System, Lymphoscintigraphy and Sentinel Node Detection

In the past 40 years, a significant body of knowledge has accumulated about the lymphatic system, its dynamics and circulation. Approximately 3 l of lymph flow into the circulation each day, equivalent to 120 ml of lymph flow per hour at rest. Lymphatic flow can increase with exercise by a factor of 10–30 and lymphatic channels are seen to contract and relax every 2–3 min. The lymphatic

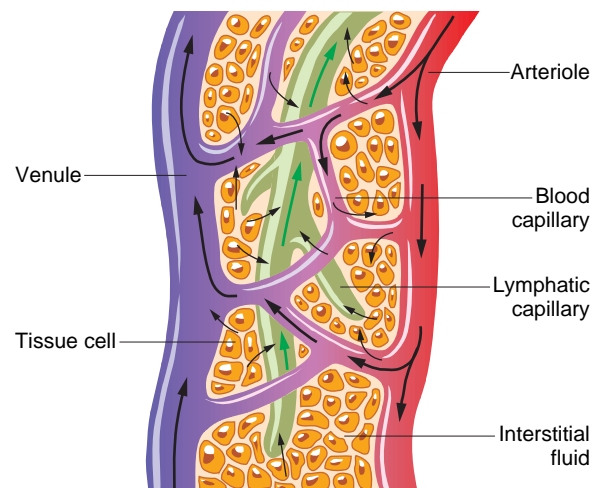


Fig. 4. A representation of lymphatic and blood vessels and the surrounding milieu. (Modified from [27])

system is hence an extremely dynamic and reactive system. Figures 4 and 5 show diagrammatic representations of a lymph vessel and its relationship with the surrounding milieu. It can be seen that lymph vessels are larger than the surrounding capillaries, and that they are end or terminal vessels with lymph flowing in a single direction determined by valves which ensure the unidirectionality of this flow. Individual lymphatic capillaries are anchored in the surrounding cells by so-called anchoring filaments, which will distend if the surrounding environment is distended (for

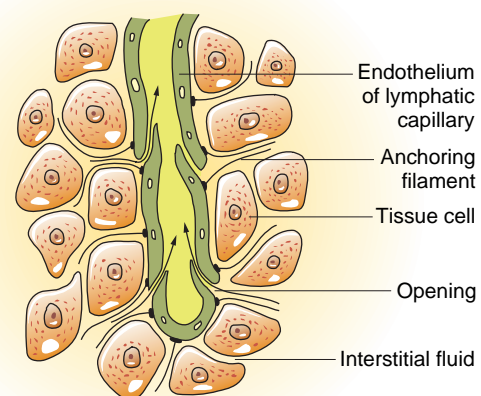


Fig. 5. A representation of a lymphatic capillary. (Modified from [27])

example by the administration of a certain volume of a substance). When particulate substances of an appropriate size are delivered to the interstitial fluid they can traverse the lymphatic capillary endothelium and hence be removed by the lymphatic system towards the first lymph draining nodes.

The first demonstration of lymphatics, by intra-lymphatic administration of Ethiodol, is accredited to Kinmonth, in 1952 [5]. The first lympho-autoradiographic study is attributed to Sherman and Ter-Pogossian [6], who in 1953 demonstrated the concentration of radioactive colloid gold following an interstitial injection in rabbits. At the Middlesex Hospital in 1954 Handley and Thackray, investigating the lymphatic spread of carcinoma of the breast, noted in a series of 150 patients that 10% were free of axillary disease. In the same year Turner-Warrick performed one of the first lymphoscintigraphic studies in conjunction with blue dye lymph drainage visualisation; his findings were subsequently published in the *Lancet* in 1955 [7].

One of the first lymphoscintigraphic studies in man, investigating the drainage of lymph from the breast to the supplying basins, was performed by Hultborn et al. in 1955, who showed that most of the breast lymph drained to the axilla in these patients [8]. Much more recently, in 1995, Uren et al. investigated the pattern of lymphatic drainage in a

group of 34 patients with breast cancer [9]. Drainage to exclusively the axillary node chain was found in 58% of all cases, to the axillary and internal mammary node chains in 19.4% of cases, to the axillary, internal mammary and subclavicular node chains in 13% of cases, to the axillary and infraclavicular node chains in 3.2% of cases and to the internal mammary node chain in 6.4% of cases [9]. It is important to underline that this study was carried out with an interstitial administration of antimony sulphide colloid with very small particle sizes ranging from 3 to 12 nm. A technique with multiple injections was used, surrounding the breast mass and not given subdermally. In this sense the technique was optimised for lymphoscintigraphy but clearly not optimised for the detection of the sentinel node.

Over the years almost every lymphatic basin and region has been demonstrated by lymphoscintigraphy employing a variety of injection techniques and tracers (Table 3), and much useful information has been recorded in the literature. It is evident that we must clearly distinguish between methodology appropriate for the demonstration of all lymph nodes in a particular lymph basin, which we will describe here as lymphoscintigraphy, and techniques suitable for localisation of the first draining lymph node, i.e. the sentinel node. For the former purpose, tracers with a

Table 3. Lymphatic regions demonstrated by lymphoscintigraphy (from Ege GN. Lymphoscintigraphy in oncology. In: Henkin et al., eds. *Nuclear Medicine*, vol II. St. Louis: Mosby; 1996: 1505–1523)

Injection site	Lymph node groups
Dorsum of the foot	Femoral, inguinal, external iliac, para-aortic
Dorsum of the hand	Epitrochlear, axillary, supraclavicular
Mammary, peri-areolar	Axillary, supraclavicular, upper parasternal
Chest wall subcutaneous, subperiosteal	Axillary, supraclavicular, upper parasternal
Subcostal posterior rectus sheath	Diaphragmatic, parasternal, internal mammary ± mediastinal
Buccal mucosa	Jugular
Orbit	Deep cervical
Larynx	Paralaryngeal, superior/inferior jugular
Hepatic capsule	Right parasternal, mediastinal
Splenic capsule	Splenic hilar
Lower oesophagus	Mid-mediastinal, coeliac, upper peri-aortic
Gastric cardia	Coeliac, upper peri-aortic
Peritoneal cavity	Anterior mediastinal
Vulva	Inguinal, external iliac
Rectal	Superior haemorrhoidal, inferior mesenteric, perirectal
Peri-anal, ischiorectal fossa	Internal iliac, presacral, obturator, common iliac, para-aortic
Intraprostatic	Periprostatic, internal iliac
Peritumoral, intracutaneous	Superficial lymphatics at risk

Table 4. Indications for lymphoscintigraphy

Tumour staging
Definition of radiotherapy fields
Evaluation of lymphoedema vs venous oedema
Evaluation of drainage patterns (leaks)
Lymphangiectasia
Chyle stasis

Table 5. Indications for sentinel node detection

Surgical management of:
– Melanoma
– Breast cancer
– Colorectal cancer
– Head and neck cancer
– Penile cancer
– Other

small particle size of less than 20 nm are preferable, whilst for the detection of the sentinel node colloids of larger particle size between 50 and 200 nm, are required. The clinical indications for the two techniques are also different (Tables 4, 5).

Technetium-99m Labelled Colloid Particles

With the report in 1965 by Garzom et al. of a first colloid labelled with the radionuclide technetium-99m [10] a new era began for lymphoscintigraphy. Rapidly, a very large variety of tracers appeared, all labelled with ^{99m}Tc . This radionuclide has ideal characteristics for detection and imaging, having a physical half-life of 6 h and an imaging energy of 140 keV, and in addition is universally available since it can be delivered on a daily basis from a generator. The low cost of ^{99m}Tc per MBq is a further reason why the initial labelling methodology was received with such enthusiasm.

A number of attempts were made to define the optimal characteristics for radiocolloid uptake in lymph nodes and a widely quoted study by Strand and Persson investigated these characteristics in a rabbit model where tracers were injected subcutaneously and bilaterally below the xiphoid process [11]. In general, it was found that the smaller the particle size, the higher was the colloid uptake in parasternal lymph nodes. The study was then extended by the same group, who concluded that the optimum particle size for interstitial lymphoscintigraphy is of the order of tens of nanometres [12]. In a study by Kaplan et al. [13], two ^{99m}Tc -labelled radiopharmaceuticals for lymphoscintigraphy were compared in man (stannous phytate and antimony sulphide). The authors concluded that antimony sulphide was to be preferred since it showed a greater number of internal mammary lymph nodes in patients with breast cancer. Again, in this study a subcostal injection of the radiocolloid was given below the xiphisternum. It is clear that in the 1970s and 1980s the aim of lymphoscintigraphy was to visualise the majority of lymph nodes in a particular lymph basin for staging purposes but also for delineation of lymph flow patterns and better definition of a radiotherapy field. In Table 6 data are compiled from the literature in respect of various radiocolloids and their uptake in parasternal lymph nodes. The data show the huge range of particle sizes and variation in percent uptake at 2 and 5 h following subcostal administration.

Recent *in vivo* comparisons in man tell a very different story and require reflection. Paganelli et al. investigated three different colloid sizes in a significant number of patients with carcinoma of the breast and determined the number of sentinel nodes detected [14]. The tracer was given subdermally and the methodology optimised for

Table 6. Properties of various radiocolloids, and their uptake in parasternal lymph nodes

Product	Proprietary name	Particle size (nm)	Stability	Uptake % (2 h)	Uptake % (5 h)
m μ AA	Microlite	10	Constant	1.5	1.5
μ AA	Albucoll	70	Constant	0.3	0.5
Sb ₂ S ₃	Labelaid	45	Constant	1.1	1.7
(Sn)S	Hepato	90	Constant	0.3	0.4
(Re)S		360, 60	Constant	0.3	1.3
μ AA	AlbuRES	250	Constant	0.6	0.7
Sulphur	In-house	600	Variable	0.2	–

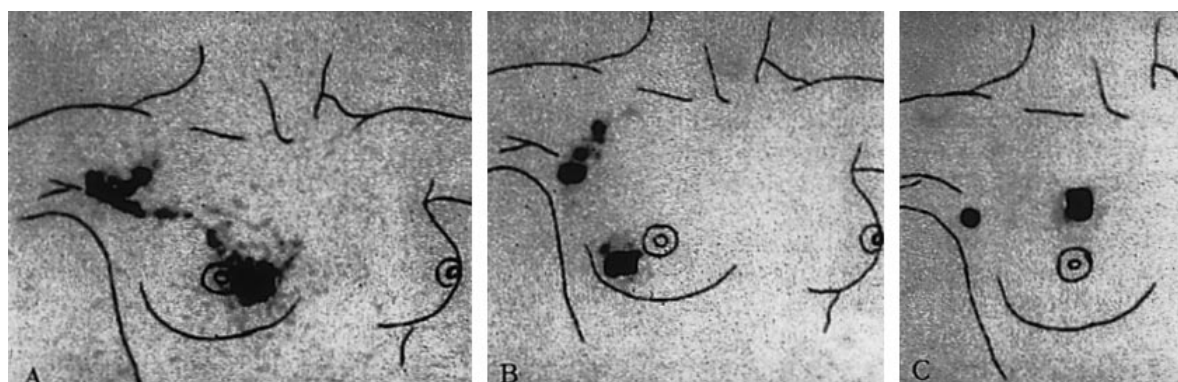


Fig. 6 and Table 7. The relationship between colloid particle size and number of sentinel nodes imaged. The smaller the particles, the greater the number of nodes imaged. (From Paganelli et al., *Q J Nucl Med* 1998; 42: 49–53)

sentinel node imaging and detection. Figure 6 and Table 7 summarise the main findings. From this it can be seen that the tracers with smaller particle sizes resulted in the visualisation of a greater number of lymph nodes, paradoxically rendering more difficult the imaging and external detection of the sentinel node. Best results were obtained with the larger particle size colloids.

In a study by Glass et al. published in 1998 the kinetics of three lymphoscintigraphic agents were investigated in patients with cutaneous melanoma [15]. Whilst all agents were passed through a similar sized filter (200 nm) it became clear that for sentinel node imaging, detection at 30 min is more appropriate than late imaging. Having passed the three agents through a similar sized filter, there were no significant differences in the quality of nodal visualisation or the half-times of tracer washout from these nodes.

Briefly summarising, then, it can be stated (Tables 8, 9) that there is a need to identify an ideal colloid for sentinel node visualisation, which will clearly be different from a particulate tracer optimised for the visualisation of all lymph nodes. It will be important that the exact range of particle sizes is known, that the product is stable on storage, that it is labelled with ^{99m}Tc and that it contains particles of an average size of the order of 80–200 nm. In fact the study by Paganelli et al. [14], where the authors quote a particle size range of 200–1000, is likely to have been conducted with a range of particles not exceeding 400 nm (personal observations).

Table 7

Size of Tracer (nm)	Positive Patients	No. of nodes
< 50	29/30	1–5
< 80	26/30	1–4
< 200 < 1000	155/155	1–2

Table 8. Characteristics of the ideal colloid

Licensed product
Narrow particle size range
^{99m}Tc label
Stable on storage
Lymph channel transport
Rapid transport
Retention in sentinel node
Stable in blood (no shrinkage or growth)

Table 9. Fate of colloids according to particle size

Particle size	Fate
Few nm	Exchange through blood capillaries
Tens of nm	Absorbed into lymph capillaries
Hundreds of nm	Trapped in interstitial space
Large particles	Do not migrate

Probe Selection

Once a radiopharmaceutical is administered, the passage of the tracer through the lymphatic system can be recorded fairly accurately. Imaging devices such as the conventional Anger gamma camera are ideally suited to record the early tracking of the tracer into the lymphatic vessels, given that they permit rapid imaging over short intervals of time. Early imaging, commencing immediately after

administration of the tracer, will give a prompt indication of the progress of the radiocolloid from the administered site. It will also provide an early warning, should the tracer fail to migrate. External probes are non-imaging detectors which can be optimised for intra-operative use. They hence allow a specific signal to be picked up from a focussed site within the body where the greatest concentration of tracer is encountered. With the renewed interest in sentinel node detection, probe technology has changed rapidly over the past few years, mainly in order to optimise portability, ease of use and signal detection.

In determining the most appropriate probe, consideration is usually given to sensitivity (number of counts detected per unit of time per area detector), resolution (the minimum distance between two signals which can be separated with sufficient statistical certainty), energy resolution (the ability of the probe to distinguish degraded from non-degraded radiation), collimation (the ability of the detector to pick up a signal from a circumscribed volume of tissue to be investigated), and other features such as the overall ergonomics and design of the probe, the ease of peri-operative use, facilities for use in a sterile environment and cost. Probe manufacturers are listed in Table 10.

A recent paper by Tiourina et al. [16] reviews the main characteristics of a number of probes available for sentinel lymph node detection. It is noteworthy that these characteristics vary significantly. Thus the resolution of probes may vary by a factor of 4, the transmission of signal through the shielding surrounding the detector may vary by a factor as great as 40 and the detection sensitivity of the probes in air or water may also vary by a factor of the order of 20! The reader is referred to the work of Tiourina et al. for a more detailed technical assessment.

Table 10. Examples of probe types and manufacturers

USSC Navigator
Neoprobe 1500, 2000
(C-Trak) Care Wise
Eurorad (Gammed)
ScintiProbe MR 100-Pol.hi.tech.

Carcinoma of the Breast

Breast cancer is a major disease. The 5-year survival rate is not much better than 85% for all stages. Localised disease has a 5-year survival rate of the order of 96%, dropping to 75% with regional spread and to 20% with distant spread. It is also known that axillary lymph node-positive patients are more likely to develop distant metastases, that axillary lymph node-positive patients die earlier and that postoperative adjuvant chemotherapy significantly reduces the risk of distant disease and dissemination. For all these reasons knowledge of the status of the sentinel lymph node chain is a most important prognostic factor and hence crucial for the appropriate management of these patients.

The theoretical basis for sentinel node detection in carcinoma of the breast is set out in Table 11. It is assumed that the first regional lymph node which drains lymph from a primary tumour is the first node to receive the seeding of lymph-borne metastatic cells. A survey of the literature does appear to indicate that tumour cells disseminate fairly sequentially and that so-called skip metastases are only rarely encountered.

There are two fundamental concepts which, however, are still the cause of much controversy. It has been stated (*Lancet* 1998) that the sentinel node concept is too Halstedian in nature. Tumours do not evolve and disseminate into local, regional and distant metastases in an orderly fashion (Figs. 7, 8). Indeed, most tumour biologists would lead us to believe that tumours have seeded distally at the time of clinical presentation or manifestation. This debate will continue in the literature but it is fair to state that advocates of sentinel node scintigraphy and detection

Table 11. Theoretical basis for sentinel node detection

Lymph flow is orderly and predictable
Tumour cells disseminate sequentially
The sentinel or “first” lymph node is the first node encountered by tumour cells
Sentinel node status predicts distant basin status
Patients present with earlier stage of disease
Basin involvement is less frequent
Surgery can be targeted to the appropriate population

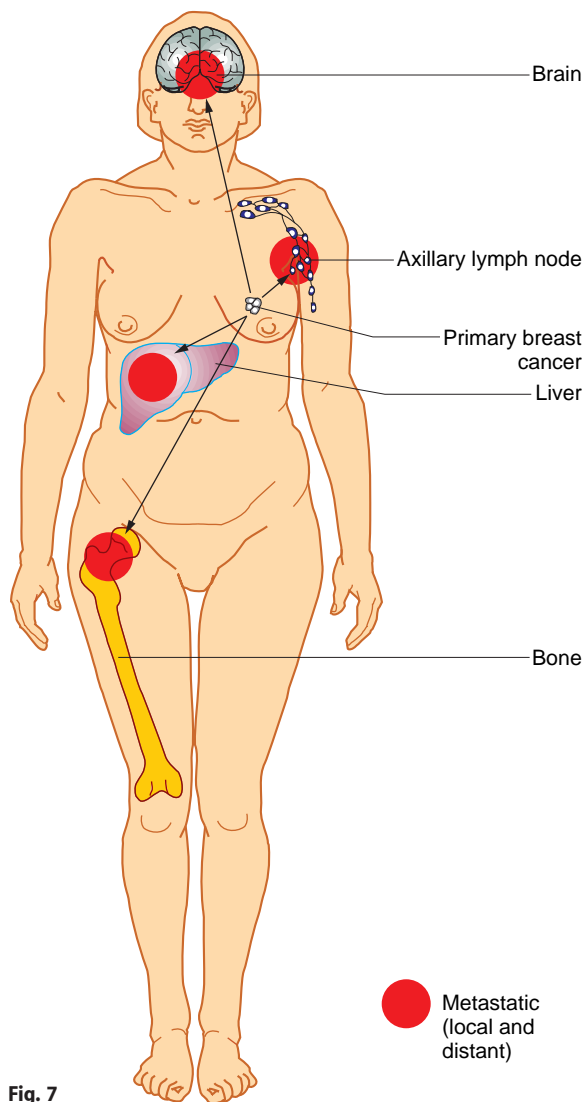


Fig. 7

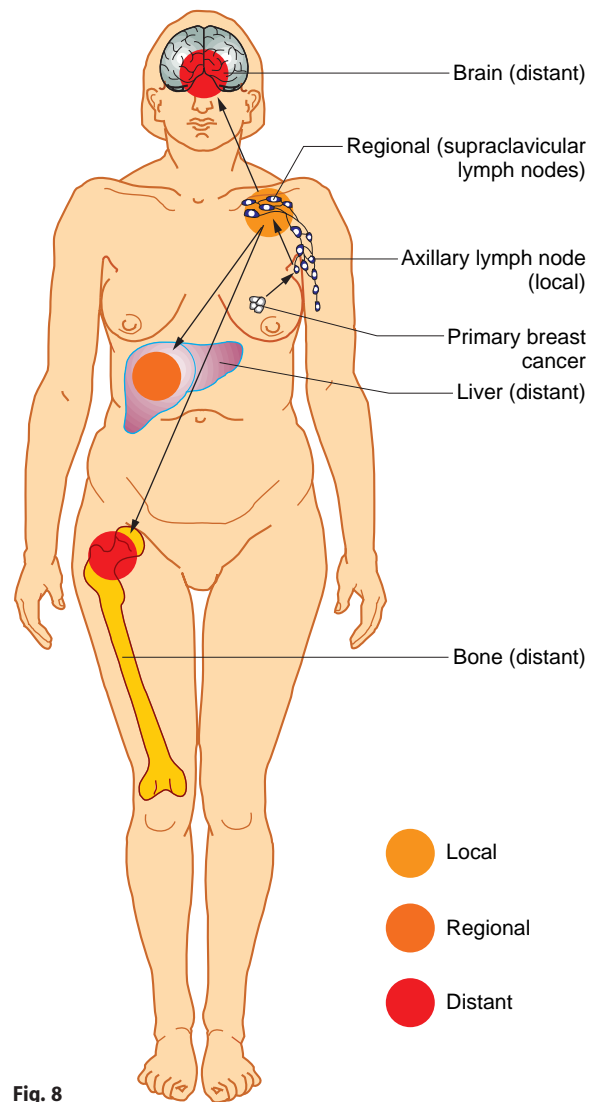


Fig. 8

Figs. 7 and 8. A representation of the metastatic spread of breast cancer: a random progression (17) or an orderly progression (18). (Modified from [28])

need to be aware of the possible pitfalls in this approach.

From a surgical management point of view, however, it is also clear that a significant number of patients who undergo axillary lymph node clearance do endure pain and significant side-effects, with no apparent benefit. Between 70 % and 80 % of breast cancer patients referred to a modern practice will have completely negative surgical axillary lymph node exploration, and 3 %–12 % of patients do develop limiting lymphoedema with

the associated morbidity. The additional costs of surgical exploration of the axilla must also be taken into account. On the other hand, an important study by Turner et al. (1997) provides ample evidence supporting the sentinel node hypothesis for breast carcinoma [17]. If H & E staining and immunohistochemistry indicate that the sentinel node is not involved, then the probability of non-sentinel node involvement is less than 0.1 % (the false-negative rate was 0.97 %, i.e. 1 patient in 103).

A thesis by B. A. E. Kapteijn on biopsy of the sentinel node in melanoma, penile carcinoma and breast carcinoma (submitted to the Netherlands Cancer Institute, 1997) documents that successful

Table 12. Results of sentinel node biopsy in breast carcinoma (data compiled by B.A.E. Kapteijn, The Netherlands Cancer Institute, 1997)

Author (year) in vivo/ ex vivo	No. of patients	Injection technique (peri/ intra)	PBD/ tracer	Size of primary tumour	Identifi- cation rate (%)	Metastases (%)	Remarks
Krag (1993), in vivo	22	Peri	Tracer	Not given	82	39	In 2 cases of posi- tive lymph nodes, no SN found
Giuliano (1994), in vivo	174	Intra	PBD	Tis: 15 mm T1: 104 mm >T2: 55 mm	66	32	FN = 5
Giuliano (1995), in vivo	134 ALND 162 SLND	Intra	PBD	Median: 1.5 cm	100	29 42	FN rate not given
Uren (1995), in vivo	34 (3: + ALND)	Peri	Tracer PBD (3)	Not given	100	67	FN rate = 0% LS performed
Schneebaum (1996), in vivo	15	Not given	Tracer + PBD	Not given	87	20	FN = 1 LS performed
Meijer (1996), in vivo	30	Peri	Tracer	18 < 2 cm	100	32	FN = 0 LS performed (2 cases; no SN)
Kapteijn (1996), ex vivo	30	Intra	PBD	Mean: 2.9 cm	87	38	FN = 0
Albertini (1996)	62	Peri	Tracer/ PBD	Mean: 2.2 cm	92	32	FN = 0 LS performed

SN, Sentinel node; PBD, blue dye; FN, false-negative; ALND, axillary lymphadenectomy; SLND, sentinel lymph node dissection; LS, lymphoscintigraphy.

localisation of the sentinel node in breast carcinoma has been possible since 1993. However, there has been significant variability in results and methodological practice, as shown by Table 12.

A recent meta-analysis of 821 patients with carcinoma of the breast reported an overall success rate of 93.5% for localisation of the sentinel node. This is very similar to the 92% rate reported by Albertini et al. in 1996 with reference to 62 patients [18]. Albertini et al. also documented an absence of skip metastases and the fact that in 67% of all patients with a positive sentinel node, this was the only site of disease. Veronesi et al., reporting in the *Lancet* in 1997, investigated 163 patients and reported 97.5% accuracy in the prediction of the lymph node status! In 95% of patients there was concordance between a negative sentinel node and negative status of the axillary nodes. Albertini et al. [18] stated that “the

beauty of lymphatic mapping is that it allows the surgeon to give the pathologist one or two sentinel nodes to perform a more detailed examination”. They also considered that the results suggest that sentinel node biopsy using a gamma probe can identify negative axillary nodes with high accuracy [4].

Borgstein, reporting in 1998 on 130 patients, demonstrated the sentinel node in 89% of cases; the failure rate was significant in patients submitted to previous excision biopsy (36%) and there was a small failure rate (4%) when the tumour was palpable in situ. Biopsy of the sentinel node was 98% accurate for the prediction of nodal metastases [3]. Also in 1998, Cox et al. showed successful identification of the sentinel node in 94% of 466 patients [19].

Clearly these data, derived from several studies with large samples, give credence to the sentinel

node concept and strongly point to the need for a large multicentre trial which would ultimately determine the appropriate clinical indications for this methodology and its impact on the surgical management of patients presenting with carcinoma of the breast.

Melanoma

Approximately 80 million cases of melanoma have been reported in Europe. The incidence appears to be increasing, with the 5-year survival heavily dependent on tumour thickness. For tumours of less than 1.5 mm thickness and without metastases, survival is greater than 90 %; for tumours greater than 4 mm thickness, survival drops to 50 %, and it falls even further, to 10 %, when patients present with distant metastases. Most melanomas (65 %) are of the superficial spreading type; nodular melanoma accounts for 25 % of cases, lentigo maligna melanoma for 5 % and acrolentiginous melanoma for 5 %.

Very significant experience has been obtained with regard to sentinel node detection in melanoma. Again from the data compiled by Kapteijn (Table 13) it can be seen that many studies have been carried out since the early investigations by Morton et al. in 1992 [20]. A review article by Singluff et al. in 1994 on the surgical management of regional lymph nodes in 4682 patients offers interesting background information [21]. Although in this particular analysis lymphoscintigraphy was performed only in a minority of patients, the authors concluded that lymphoscintigraphy is probably the best way to identify basins draining a specific area of the skin. It was also stated that the number of basins identified by this methodology may overestimate the number of basins in which nodal metastases acquire clinical relevance. Clearly the concept of the sentinel node was set to emerge. In the same year Reintgen et al. published an important study on the orderly progression of melanoma and nodal metastases (Figs. 9, 10). Forty-two patients were investigated, of whom 34 had histologically negative sentinel

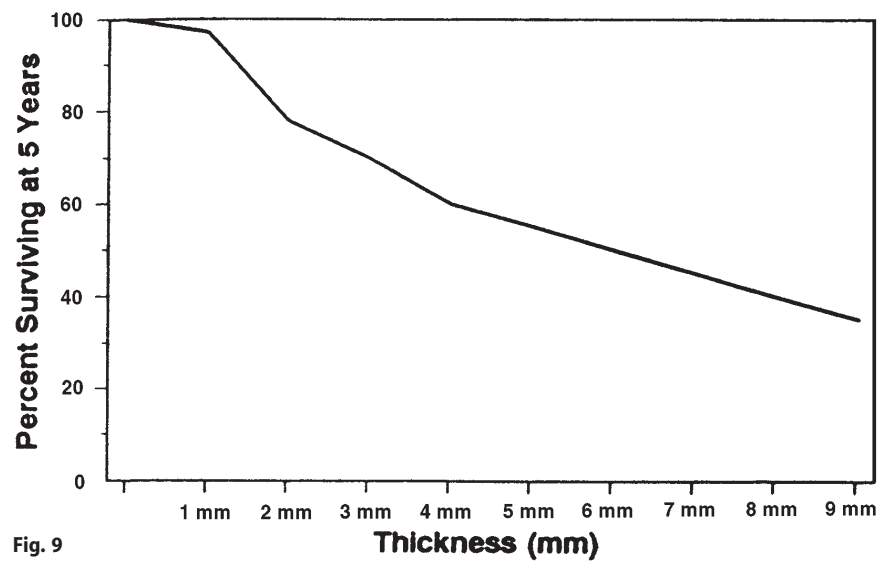
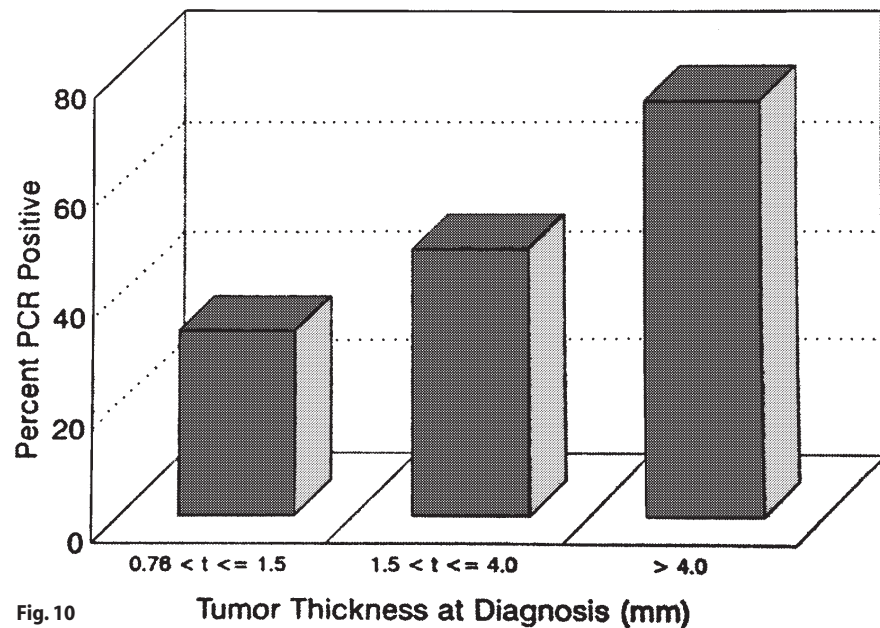
Table 13. Results of sentinel node biopsy in melanoma (data compiled by B.A.E. Kapteijn, The Netherlands Cancer Institute, 1997)

Author (year)	No. of patients	Breslow thickness	Identification of sentinel node (%)	Method (BD/GDP)	Metastases (% patients)	False-negative rate (%)
Morton (1992)	223	CS-I ^a	82	BD	21	1
Morton (1994)	72	68: > 0.65 mm 2: < 0.65 mm 2: unknown	90	BD	15	0
Lingham (1994)	15	Mean: 3.75 mm (range 1.5–8.1)	100	BD	27	0
Thompson (1995)	118	111: > 1.5 mm 7: < 1.5 mm	87	BD	23	0
Krag (1995)	121	109: > 0.75 < 4 mm 11: > 4 mm 1: unknown	98	GDP: 77 BD + GDP: 44	12	0
Abertini (1996)	106	Mean: 2.24 mm (> 0.75 mm)	96	GDP + BD	15	0
Mudun (1996)	25	3: < 1.5 mm 18: > 1.5 < 4 mm 4: > 4 mm	100	GDP	24	Not given
Karakousis (1995)	55	> 1 mm	93	BD	24	Not given
Kapteijn (1995)	110	> 1 mm	99.5	GDP+BD	23	2.7

^a Clinical stage I: clinically localised melanoma; no palpable lymph nodes.
BD, Blue dye; GDP, gamma detection probe.

Figs. 9 and 10.

The influence of Breslow thickness on survival and the relationship of the positivity of PCR with tumour thickness for melanoma at presentation. (From Reintgen et al., *Ann Surg* 1997; 225: 1–14)

**Fig. 9****Fig. 10**

nodes, with the remainder of the nodes in the basin also being negative. No skip metastases were documented. The authors concluded that nodal metastases from cutaneous melanoma are not random events. Sentinel nodes in the lymphatic basins could be mapped and identified individually, and these were shown to contain the first evidence of melanoma metastases. The authors concluded that this information could be used to revolutionise melanoma care [22].

In 1996 Albertini et al. reported on 106 consecutive patients, comparing the sentinel node detection technique with vital blue dye mapping. Whilst the blue dye staining identified 69.5% of sentinel nodes, radioisotope detection allowed for the identification of 83.5%. When combined, these techniques detected 96% of the sentinel nodes [23].

The following year Leong et al. reported their results obtained in 163 patients. The success rate

for detection of the sentinel node was 98%, the frequency of microscopic metastatic melanoma involving the sentinel node was 18.4%, and 27.3% of sentinel nodes were detected in the absence of blue dye! The authors concluded that gamma probe-guided resection would minimise the extent of lymph node dissection [24].

A study by Joseph et al. in 1998 looked at 83 melanoma patients with a positive sentinel node, among a total of 600 stage 1–2 patients. The sentinel node was positive in 30% of patients with a tumour thickness greater than 4 mm, 18% with a tumour thickness between 1.5 and 4 mm, 7% with a tumour thickness between 1.0 and 1.5 mm and 0% with a tumour thickness of less than 0.76 mm [25].

Cascinelli et al., publishing in the *Lancet* in 1998, confirmed that elective regional node dissection is not efficacious, that the dissection of clinically undetectable nodal metastases will lead to higher long-term survival, that the detection of the sentinel node will help the selection of patients with occult disease who will benefit from regional node dissection and that even Breslow thickness appears to be less important when adjusted by the status of regional lymph nodes [26].

Conclusion

A vast amount of literature has now been published relating to the detection of the sentinel node and its impact on the surgical management of cancer. Whilst most data have been collated from patients suffering from carcinoma of the breast or skin (melanoma), there is increasing interest in other areas such as head and neck cancer, colorectal cancer and penile cancer.

It does appear that the relatively new technique of detection of the sentinel node (as opposed to lymphoscintigraphy) is highly successful and accurate and that the correlation between histological involvement of this node and that of distant basins is very promising indeed. There is sufficient evidence in the literature to affirm that the time has come for a detailed cost-benefit analysis of these techniques in large multicentre trials, and there is hope that this methodology may become part of the routine surgical management of large numbers of patients. However, there is

evident scope for improvement of the technology involved and refinement of protocols.

Currently it can be stated that detection of the sentinel node is highly accurate at least in the context of carcinoma of the breast and melanoma, that there is a rapidly increasing database population, and that training programmes relevant to multi-disciplinary teams need to be developed for this methodology, with emphasis on standardisation of tracer and techniques, improved design of detector technology and patient education.

References

1. Dixon M. Sentinel node biopsy in breast cancer. *Br Med J* 1998; 317:295–296
2. della Rovere G, Bird PA. Sentinel-lymph-node in breast cancer. *Lancet* 1998; 352:421–422
3. Borgstein PJ. SLN biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg* 1998; 186:275–283
4. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrada ST, Bodeni N, Costa A, Chicco C, Geraghty JG, Luine A, Sacchini V, Veronesi P. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997; 349:1864–1867
5. Kinmonth JB. Lymphangiogram in man: method outlining lymphatic trunks and operation. *Clin Sci* 1952; 11:13–20
6. Sherman A, Ter-Pogossian M. Lymph node concentration of radioactive colloid gold following interstitial injection. *Cancer* 1953; 6:1238–1240
7. Turner-Warrick R. The demonstration of lymphatic vessels. *Lancet* 1955; 1:1371
8. Hultborn KA, Larsson LG, Ragnhult I. The lymph drainage from the breast to the axillary and parasternal lymph node: studied with the help of Au-198. *Acta Radiol* 1955; 43:52–64
9. Uren RF, Howman-Giles RB, Thompson JF, Malouf D, Ramsey-Stewart G, Niesche FW, Renwick SB. Mammary lymphoscintigraphy in breast cancer. *J Nucl Med* 1995; 36:1775–1780
10. Garzom OL, Palcos MC, Radicella R. Technetium-99m labelled colloid. *Int J Appl Radiat Isotopes* 1965; 16:613
11. Strand S-E, Persson DRR. Quantitative lymphoscintigraphy. I. Basic concepts for optimal uptake of radiocolloids in the parasternal lymph nodes of rabbits. *J Nucl Med* 1979; 1038–1046
12. Bergqvist L, Strand SE, Persson B, Hafstrom L, Jonsson PE. Dosimetry in lymphoscintigraphy of Tc-99m antimony sulfide colloid. *J Nucl Med* 1982; 23:698–705
13. Kaplan WD, Davies MA, Rose CHN. A comparison of two technetium-99m labelled radiopharmaceuticals for lymphoscintigraphy: concise communication. *J Nucl Med* 1979; 20:933–937
14. Paganelli G, Chicco C, Cremonesi M, Prisco G, Calza P, Luini A, Zucali P, Veronesi U. Optimised sentinel node scintigraphy in breast cancer. *Q J Nucl Med* 1998; 42:49–53

15. Glass EC, Essner R, Morton DL. Kinetics of three lymphoscintigraphic agents in patients with cutaneous melanoma. *J Nucl Med* 1998; 39:1185–1190
16. Tiourina T, Arends B, Huysmans D, Rutten H, Lemaire B, Muller S. Evaluation of surgical gamma probes for radio-guided sentinel node localisation. *Eur J Nucl Med* 1998; 25:1224–1231
17. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathological validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg* 1997; 226:271–278
18. Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, Shivers S, Berman C, Wells K, Rapaport D, Shons A, Horton J, Greenberg H, Nicosia S, Clark R, Cantor A, Reintgen DS. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *J Am Med Assoc* 1996; 276:1818–1822
19. Cox CE, Pendas S, Cox JM, Joseph E, Shons AR, Yeatman T, Ku NN, Lyman GH, Berman C, Haddad F, Reintgen DS. Guidelines for SN biopsy and lymphatic mapping of patients with breast cancer. *Ann Surg* 1998; 227:645–653
20. Morton DL, Wen D-R, Wong GH, et al. Technical details of intra-operative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127:392–399
21. Slingluff, CL Jr., Stidham KR, Ricci WM, Stanley WE, Seigler HF. Surgical management of regional lymph nodes in patients with melanoma. Experience with 4,682 patients. *Ann Surg* 1994; 219:120–130
22. Reintgen D, Cruse CW, Wells K, Berman C, Fenske N, Glass F, Schroer K, Heller R, Ross M, Lyman G, Cox C, Rapaport D, Seigler HF, Balch C. The orderly progression of melanoma nodal metastases. *Ann Surg* 1994; 220:759–767
23. Albertini JJ, Cruse CW, Rapaport D, Wells K, Ross M, DeConti R, Berman CG, Jared K, Messina J, Lyman G, Glass F, Fenske N, Reintgen DS. Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. *Ann Surg* 1996; 223:217–224
24. Leong SPL, Steinmetz I, Habib FA, McMillan A, Gans JZ, Allen RE Jr, Morita E, El-Kadi M, Epstein HD, Kashani-Sabet M, Sagebiel RW. Optimal selective sentinel lymph node dissection in primary malignant melanoma. *Arch Surg* 1998; 132:666–673
25. Joseph E, Brobeil A, Glass F, Glass J, Messina J, DeConti R, Cruse CW, Rapaport DP, Berman C, Fenske N, Reintgen DS. Results of complete lymph node dissection in 83 melanoma patients with positive SLN. *Ann Surg Oncol* 1998; 5:119–125
26. Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. *Lancet* 1998; 351:793–796
27. Tortora GJ, Reynold S, Grabowski S. *Principles of anatomy and physiology*, 8th edn. Addison Wesley Longman, 1996
28. Hayes DF. *Atlas of breast cancer*. Mosby, 1993

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