Methodology and implications of lymphatic mapping and sentinel lymphadenectomy

Tanis, P.J.

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CHAPTER SEVENTEEN

General Discussion and Conclusion
his thesis reflects The Netherlands Cancer Institute's efforts on lymphatic mapping and sentinel lymphadenectomy over almost a decade. Cooperation of radiologist, nuclear medicine physician, surgeon and pathologist is essential as is illustrated by the work on non-palpable breast cancer (chapter 8). A lesson we learned from the statistical analysis of the learning phase described in chapter fourteen is that continuous monitoring and evaluation of clinical practice is necessary to assure quality and safety of the procedure. This process should extend beyond the learning phase. Monitoring also provides feedback from attempts to further improve the technique as described in chapters six and seven. Literature review and clinical studies to understand (patho-) physiological mechanisms may help to elucidate the reasons for technical failure and lead to solutions for these problems (chapters three, four, five and seven).

Application in various tumour types

In recent years, lymphatic mapping with sentinel node biopsy has been applied in several other malignancies in addition to melanoma and breast cancer. In this thesis, the value of sentinel node biopsy in squamous cell carcinoma of the penis is described (chapters eleven and twelve). Initial experience with lymphoscintigraphy and laparoscopic sentinel node biopsy in testicular cancer has been obtained (chapter thirteen). Other urological cancers may be suitable as well. Extensive expertise in sentinel node biopsy for vulvar carcinoma exists, an indication which shares certain characteristics with penile cancer. The same is true for head and neck squamous cell carcinomas although published series still concern small numbers of patients.

In the late 1990s, sentinel node biopsy was introduced for gastro-intestinal malignancies, starting with colon cancer. In contrast to unsatisfactory results from Dutch investigators with blue dye only, American studies reported a high reliability of this relatively simple technique in colorectal cancer. Blue dye mapping of the colon can be performed in vivo as well as ex vivo. Less experience has been obtained with the use of radiolabelled colloids in this tumour type. Lymphatic mapping in colorectal cancer will primarily affect staging, although the extend of resection may be influenced by an aberrant drainage pattern in a small percentage of patients. This staging information can be used to help select patients for adjuvant chemotherapy. Japanese studies showed that sentinel lymphadenectomy is also feasible in the upper intestinal tract, using endoscopic submucosal administration of radiopharmaceutical or vital dye. The role of sentinel node biopsy in carcinomas of the stomach and oesophagus seems to be confined to better identification of metastasising routes from the primary tumour which may define the extent of lymphadenectomy.

Limited experience has been gained in sentinel node biopsy for other tumour types like cervical and uterine carcinoma, thyroid carcinoma and lung cancer. Application of lymphatic mapping in rare malignancies such as Merkel cell carcinoma, cutaneous lymphoma and anal carcinoma has been described.
Unresolved issues

It is generally known that answering certain questions will raise just as many new questions. Sentinel node biopsy as an answer to the question of how to prevent unnecessary morbidity in node-negative breast cancer patients has resulted in several new points of discussion. The technique of lymphatic mapping confronts us with the intricate lymphatic system of the breast by visualisation of several non-axillary drainage routes. We know from the past that the tumour-status of internal mammary nodes has prognostic value and, consequently, biopsy of sentinel nodes in the internal mammary chain will have implications for staging and treatment (chapters ten and sixteen). Randomised trials are needed to prove that pursuing these nodes impacts on survival of breast cancer patients. Several technical issues discussed in chapter four are still unresolved at the time this thesis was written. One of the most intriguing topics concerns the injection site. As we learned from anatomical studies and clinical practice, injection of tracers in or just beneath the skin overlying the breast will almost exclusively visualise lymph nodes in the axilla. Our concern about the reliability of such a superficial injection to identify the axillary sentinel node draining an intraparenchymally located tumour has been partially taken away by recent reports of favourable false-negative rates with intradermal injection although these studies do not furnish the ultimate proof.38,39

Another unresolved issue is the suitability of sentinel node biopsy for certain subgroups of patients. Recent studies disprove the fear that lymphatic mapping would be less reliable in larger breast carcinomas.40,41 Multifocal invasive breast cancer is still a contraindication for sentinel node biopsy in most institutions, but some authors have reported a satisfying reliability of the technique in such patients.42,43 Conflicting results have been described for sentinel lymphadenectomy after neo-adjuvant chemotherapy.44-47 It is our policy to perform sentinel node biopsy without surgical treatment of the primary tumour before neo-adjuvant chemotherapy in order to determine the need for axillary clearance later on. Bringing the procedure from the operating room to an outpatient setting using local anaesthesia would make this approach more attractive.48 The use of sentinel node biopsy in ductal carcinoma in situ (DCIS) can identify a small subgroup with lymph node metastasis.49 However, DCIS experts like Lagios and Silverstein, disagree with this indication.50 They stress the importance of adequate resection of DCIS followed by thorough pathologic evaluation to exclude the presence of an invasive component and question the significance of a micrometastasis in the sentinel node from a ‘true’ DCIS.

Some investigators have tried to define the appropriate indication for lymphatic mapping in melanoma based on parameters like Breslow thickness, presence of ulceration and Clark level.51,52 Recent studies have revealed unfavourable new information that questions the wisdom of this trend. Three studies published in 2001 with a combined total of 1851 patients show a disturbing lack of ability to identify tumour-positive lymph node basins. The false negative rates were 16%, 19% and 25%.53-55 The ultimate purpose of lymphatic mapping is to provide sentinel node
positive melanoma patients with early therapeutic measures, such as regional node dissection and adjuvant systemic treatment. However, there is currently no evidence that such approaches result in improved regional control and survival. It is unclear whether additional surgery should be performed when the sentinel node contains metastatic disease or how extensive such a lymph basin dissection should be. Another unnerving finding is the 13% to 19% incidence of in-transit metastases in patients with a tumour-positive sentinel node that was reported by three groups.\textsuperscript{53,56,57} The Multicenter Selective Lymphadenectomy Trial will provide more insight in these problems within several years.

**Completion lymphadenectomy**

The sentinel node is the only tumour-positive lymph node in about 40% to 65% of breast cancer patients, depending on the extent of the pathological examination of the axillary lymph nodes.\textsuperscript{58-62} The indication for axillary lymph node dissection can be restricted further if the presence of non-sentinel node metastases can be predicted. Patients with a micrometastasis in the sentinel node have a significant lower risk of non-sentinel node metastasis than patients with macrometastasis, but this former risk was not considered to be negligible (table 1).\textsuperscript{60-66}

**Table 1. Incidence of non-sentinel node metastases in breast cancer patients with mirometastatic involvement of the sentinel node.**

<table>
<thead>
<tr>
<th>First author</th>
<th>Definition SN micrometastasis</th>
<th>Evaluation non-SN</th>
<th>Non-SN metastasis</th>
</tr>
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<tbody>
<tr>
<td>Scemi\textsuperscript{66}</td>
<td>$&lt; 1.4\text{mm}, \text{H&amp;E and IHC}$</td>
<td>-</td>
<td>3/14 (21%)</td>
</tr>
<tr>
<td>Dauway\textsuperscript{63}</td>
<td>$&lt; 2\text{mm}, \text{H&amp;E}$ only IHC</td>
<td>-</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Reynolds\textsuperscript{64}</td>
<td>$\leq 2\text{mm}, \text{H&amp;E}$ only IHC</td>
<td>H&amp;E and IHC\textsuperscript{*}</td>
<td>6/27 (22%)</td>
</tr>
<tr>
<td>Wong\textsuperscript{65}</td>
<td>$\leq 2\text{mm}, \text{H&amp;E}$ only IHC</td>
<td>H&amp;E</td>
<td>3/28 (11%)</td>
</tr>
<tr>
<td>Mazzarol\textsuperscript{66}</td>
<td>$\leq 2\text{mm}, \text{H&amp;E}$ 3 levels, H&amp;E</td>
<td>-</td>
<td>9/49 (18%)</td>
</tr>
<tr>
<td>Rahusen\textsuperscript{67}</td>
<td>$&lt; 1\text{mm}^2, \text{H&amp;E and IHC}$ 1 level, H&amp;E</td>
<td>4/30 (13%)</td>
<td></td>
</tr>
<tr>
<td>Turner \textsuperscript{65}</td>
<td>$&lt; 2\text{mm}, \text{H&amp;E}$ only IHC 4 levels, H&amp;E and IHC</td>
<td>-</td>
<td>8/30 (27%)</td>
</tr>
</tbody>
</table>

SN=sentinel node; H&E=hematoxylin and eosin; IHC=immunohistochemistry; * =immunohistochemistry used in 18 of 27 cases

Other factors associated with a decreased risk of non-sentinel node involvement in case of a tumour-positive sentinel node are: small tumour size, absence of peritumoural lymphatic vascular invasion, limited number of tumour-positive sentinel nodes, absence of extranodal hilar tissue invasion, decreasing proximity to capsule and location of metastasis in lymph node sinusoids (as compared to parenchymal location).\textsuperscript{60-62,65,66} Some investigators have tried to identify sentinel
node-positive patients with a very low-risk of non-sentinel node metastasis in whom completion axillary clearance can be avoided by combining clinico-pathological factors (table 2).\textsuperscript{61,65} In melanoma, the sentinel node is the only tumour-positive lymph node in about 80% of the patients, although this percentage is smaller when molecular techniques are used by the pathologist.\textsuperscript{67} Similar attempts to predict non-sentinel node involvement have been made in melanoma.\textsuperscript{68,69}

Table 2. Sentinel node-positive patients with the lowest risk of non-sentinel node metastasis.

<table>
<thead>
<tr>
<th>First author</th>
<th>Clinicopathologic characteristics</th>
<th>Non-SN metastasis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>H&amp;E</td>
<td>IHC</td>
</tr>
<tr>
<td>Reynolds\textsuperscript{61}</td>
<td>SN metastasis ≤ 2 mm, T1 primary tumour</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>Turner\textsuperscript{65}</td>
<td>SN metastasis ≤ 2 mm, only 1 SN metastasis, T1 or T2 primary tumour, no peritumoral lymphatic vascular invasion, no extranodal hilar tissue invasion</td>
<td>1/58 (2%)</td>
</tr>
</tbody>
</table>

SN=sentinel node; H&E=hematoxylin and eosin; IHC=immunohistochemistry

Going one step further, one may question if axillary clearance in sentinel node-positive breast cancer patients will be of any benefit at all. Complete abolition of axillary lymph node dissection is the subject of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial.\textsuperscript{70} This trial randomises sentinel node-positive patients between axillary lymph node dissection and observation of the axilla. The rationale of the Z0011 trial is the controversial role of locoregional control for survival and the therapeutic effect of adjuvant chemotherapy and radiotherapy in conjunction with breast conserving surgery on residual tumour in the axilla. An ongoing European trial called AMAROS (After Mapping of the Axilla, Radiotherapy Or Surgery) is designed to determine the effectiveness and morbidity of axillary radiation therapy in comparison to axillary lymph node dissection if the sentinel node is tumour-positive.

Micrometastasis

The preceding discussion is closely related to the controversial issue of how the pathologist should assess the sentinel node. The use of step-sectioning, immunohistochemical staining and reverse transcription polymerase chain reaction (RT-PCR) results in the detection of small metastases, even submicroscopic tumour burden.\textsuperscript{71} But how much effort should we invest in scrutinising the sentinel node in the light of the uncertain significance of micrometastases? Dowlatshahi and co-workers have reported a conversion rate of 26% by intensifying the pathological examination of the sentinel node in 200 breast cancer patients from sections at 2-3mm intervals stained with hematoxylin and eosin (H&E) to sections at 0.25mm intervals stained with cytokeratin.\textsuperscript{72} It was the same group from the Luke's Medical Center in Chicago that reviewed the dilemma arising from minimal amounts of tumour which were detected in many retrospective studies by multiple sectioning
and additional staining of lymph nodes that were tumour-negative by routine pathological assessment.\textsuperscript{73} The impact of occult lymph node metastases on the prognosis remains controversial, because other prognosticators related to the primary tumour have also gained significance. The initial report of the International (Ludwig) Breast Cancer Study Group showed that the presence of occult lymph node metastases identified in H&E stained serial sections was an independent prognostic factor in 921 patients, thereby supporting the performance of thorough pathological investigation of sentinel nodes.\textsuperscript{74} In a recent analysis of the same patient population, Cote and associates found that immunohistochemically detected occult lymph node metastases adversely affected both disease-free and overall survival in postmenopausal patients, but not in premenopausal women.\textsuperscript{75} Confronted with the controversial data derived from retrospective studies, we look forward to the valuable outcome of prospective trials. Evaluation of the role of cytokeratin-positive breast cancer cells in bone marrow and lymph nodes will be part of the ACOSOG Z0010 and Z0011 trials.\textsuperscript{70}

What is the role of RT-PCR-detected micrometastases? This technique can identify one tumour cell in $10^6$ normal cells. Conversion rates of histologically negative lymph nodes can be up to 65\% using this technique, but the probability of false-positive results should be considered.\textsuperscript{76-78} Some authors have shown correlation of RT-PCR findings with clinico-pathological parameters in melanoma and breast cancer, thereby underlining the usefulness of molecular staging.\textsuperscript{79-83} Comparable results have been obtained with RT-PCR analysis of sentinel nodes in colon cancer.\textsuperscript{24} Ongoing studies like the Sun Belt Melanoma Trial will further establish the importance of molecular staging for prognosis and decision-making on adjuvant therapy.

**New developments**

The currently used tracers all have their disadvantages. The ideal tracer is rapidly and completely cleared from the injection site and retained in the sentinel node(s) without migration to higher-echelon lymph nodes.\textsuperscript{84} Investigators from the Texas Health Science Center tried to solve the problem of the passage of blue dye through the sentinel node, which restricts the window of opportunity for surgical exploration.\textsuperscript{85} Liposomes can encapsulate hydrophilic agents such as blue dye within their aqueous interior and, thereby, function as intermediates to enable retention of the dye by lymph nodes. Liposomes are coated with the high-affinity ligand biotin to increase lymph node extraction. Subcutaneous injection of the biotin-liposomes is then followed by injection of another ligand, avidin, which causes aggregation and entrapment of the liposomes in the first encountered lymph node. The blue-biotin-liposome particle can be labelled with $^{99m}$Tc and has shown to be an effective tracer in a rabbit model. Other investigators have developed a $^{99m}$Tc-labelled receptor-binding radiopharmaceutical with a small molecular diameter.\textsuperscript{86} The synthetic macromolecule diethylenetriaminepentaaceticacid (DTPA)-mannosyl-dextran with a diameter of 7.1nm ($\pm$ 0.9nm) exhibits faster injection site clearance and lower distal
lymph node accumulation than does filtered $^{99m}$Tc-sulfur colloid in rabbits. These properties based on receptor specificity and affinity make it a promising agent in a new class of tracers. The problem related to the small percentage of macromolecules that is cleared from the injection site forms a challenge for further improvement.

A better sentinel node imaging technique can also contribute to advance in the field of lymphatic mapping. Lymphoscintigraphy provides little anatomical detail and is limited by its poor discriminating power. In addition to injection of the radiolabelled colloid for sentinel node identification, administration of bone-seeking $^{99m}$Tc-methylene diphosphonate or $^{99m}$Tc-pertechnetate has been used for outlining the body contour in the head and neck region. Excellent images of the anatomy with high spatial resolution can be obtained with the use of Magnetic Resonance (MR) lymphangiography with injection of a MR contrast agent called USPIO (Ultra-Small Particles of Iron Oxide) as shown in pigs. This may be a valuable technique to solve problems related to tumours with a complex lymphatic drainage and a short distance to the primary draining lymph nodes.

The mechanisms underlying lodging of a micrometastasis in a sentinel node is a new unexplored field of research. Investigators from the John Wayne Cancer Institute studied the distribution and functioning of paracortical interdigitating dendritic cells in sentinel nodes. They suggest that immunosuppressive factors from a primary melanoma induce a localized and specific paralysis of the immunologic response to melanoma antigens in the primary draining lymph node. Gaining more insight in the failure of the immune surveillance mechanisms probably enables the development of effective cytokine therapy.

**Concluding remarks**

Selective lymphadenectomy has been a hot topic in surgical oncology and related disciplines during the last decade. Although we are still waiting for the results of large randomised phase III trials, the technique of lymphatic mapping with sentinel node biopsy has gained a place as staging procedure in melanoma and breast cancer and will probably do so in several other malignancies in the near future. In contrast to the situation in melanoma, there is not yet a standard technique that can be advocated to achieve more uniformity in performing the procedure in breast cancer. Major technical advances have to come from the development of new tracers with properties of complete and rapid clearance from the injection site and high selective affinity for the sentinel node. Sentinel node biopsy has re-opened discussions about the role of lymphatic tumour dissemination and regional lymph node dissection. Improvement in staging accuracy, in which the pathologist has an important task, helps medical oncologists and radiotherapists in selecting suitable candidates for adjuvant treatment. Future studies should focus on technical improvement and defining of the clinical consequences of lymphatic mapping with sentinel lymphadenectomy.
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