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REVIEW

Mapping lymph nodes in cancer management – role of ^{99m}Tc-tilmanocept injection

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Christoph Tausch
Astrid Baege
Christoph Rageth

Brust-Zentrum, Zürich, Switzerland

Abstract: Two decades ago, lymphatic mapping of sentinel lymph nodes (SLN) was introduced into surgical cancer management and was termed sentinel node navigated surgery. Although this technique is now routinely performed in the management of breast cancer and malignant melanoma, it is still under investigation for use in other cancers. The radioisotope technetium (^{99m}Tc) and vital blue dyes are among the most widely used enhancers for SLN mapping, although near-infrared fluorescence imaging of indocyanine green is also becoming more commonly used. ^{99m}Tc-tilmanocept is a new synthetic radioisotope with a relatively small molecular size that was specifically developed for lymphatic mapping. Because of its small size, ^{99m}Tc-tilmanocept quickly migrates from its site of injection and rapidly accumulates in the SLN. The mannose moieties of ^{99m}Tc-tilmanosept facilitate its binding to mannose receptors (CD206) expressed in reticuloendothelial cells of the SLN. This binding prevents transit to second-echelon lymph nodes. In Phase III trials of breast cancer and malignant melanoma, and Phase II trials of other malignancies, ^{99m}Tc-tilmanocept had superior identification rates and sensitivity compared with blue dye. Trials comparing ^{99m}Tc-tilmanocept with other ^{99m}Tc-based agents are required before it can be routinely used in clinical settings.

Keywords: lymphatic mapping, sentinel lymph node, new tracer

The role of lymph node mapping in cancer management

The sentinel node concept is based on the orderly spreading of tumor cells from a primary tumor to a defined lymph node in the relevant nodal basin. Therefore, this concept only applies to tumors in which these cells are spread via the lymphatic system. Lymphatic mapping has two major objectives: to reduce morbidity associated with lymph node assessment and to improve the accuracy of nodal assessment.[1]

Lymph node mapping of the sentinel lymph node (SLN) by radiologic lymphography was first introduced for penile carcinoma by Cabanas in 1977.[2] It was not until the early 1990s that this concept was applied for malignant melanoma. In 1992, Morton et al described the use of lymphatic mapping with a vital dye for early stage melanoma in 194 patients.[3] One year later, Krag et al reported for the first time the feasibility of radioguided lymphatic mapping with ^{99m}technetium (^{99m}Tc)-sulfur colloid in 22 breast cancer patients.[4] In 1994, Giuliano et al reported blue dye-based mapping for SLN biopsy (SLNB) in a cohort of 174 patients with early breast cancer.[5]

Many clinical investigators worldwide have evaluated this new concept in patients with breast cancer, in single-center and multicenter studies.[6–11] In these studies, the identification rate ranged from 85% to 97% while sensitivity ranged from 90% to 100%

Correspondence: Christoph Tausch
Brust-Zentrum, Seefeldstrasse 214, Zürich, Switzerland
Tel +41 44 380 76 60
Fax +41 44 380 76 61
Email c.tausch@brust-zentrum.ch

when SLNB was followed by axillary lymph node dissection (ALND). Sophisticated pathologic examination of the SLN has also improved the staging of axillary nodal disease.[12]

Ultrastaging enables pathologists to identify much smaller metastatic deposits in lymph nodes with improved sensitivity. Isolated tumor cells and micrometastases are now coded according to the American Joint Committee on Cancer staging systems as substages of N0 according to the tumor-node-metastasis staging for breast and colon cancer. Ultrastaging uses combinations of three complementary techniques: serial sectioning; immunohistochemistry; and reverse-transcriptase polymerase chain reaction.[13]

The sentinel technique was established shortly thereafter and SLNB has become the gold standard for axillary staging of early breast cancer (unifocal, T1–T2, clinically node-negative).[14,15] Several recent large-scale multicenter trials have confirmed that SLNB is equivalent to ALND in terms of correct staging but is associated with less-extensive morbidity than ALND.[16–18]

Some clinicians have extended the use of SLNB to a variety of specific situations. Lymphatic mapping is also safe in patients with multicentric disease when administering the agent via periareolar injection.[19] Combining SLNB with preoperative chemotherapy has also been a focus of intensive research. Although SLNB can be safely performed before preoperative chemotherapy, it requires an additional operation and patients with initial node-positive disease cannot benefit from downstaging by preoperative chemotherapy.[20–22] However, SLNB performed after preoperative chemotherapy is associated with higher false-negative rates, especially in patients with originally node-positive cancer.[23–25]

In 40% of cases, the SLN is the only involved axillary node.[26] Therefore, it is unclear whether ALND is necessary for all node-positive breast cancers. Several retrospective studies where ALND was omitted after detecting micro- or macrometastases in the SLN showed very low rates of axillary recurrence.[27–29] Two prospective randomized trials confirmed these results for micrometastases and up to two macrometastases. However, no difference was found in terms of the locoregional disease and survival rates.[30–32]

It is now possible to omit ALND in patients with clinically node-negative breast cancer if one or two SLNs are histologically positive and if the patient receives breast-conserving therapy and radiotherapy.

SLNB is increasingly being applied to malignant melanoma in clinical practice. For melanomas of the trunk, lymphatic mapping can reveal which regions are drained by the tumor.

SLNB is also recommended for intermediate melanomas with a Breslow thickness of 1–4 mm. In routine use, SLNB can provide accurate staging in this population, with high identification rates and sensitivity. Although relatively few studies have focused on patients with thick melanomas (T4; Breslow thickness $>$4 mm), SLNB may also be recommended for staging purposes and to facilitate regional disease control in this population. However, there is insufficient evidence to support routine SLNB for patients with thin melanomas (T1; Breslow thickness $<$1 mm).[33]

The 10-year results of the Multicenter Selective Lymphadenectomy Trial confirmed that disease-free survival was significantly longer if SLNB was followed by lymphadenectomy for nodal involvement compared with nodal observation and lymphadenectomy on demand. A significant improvement in melanoma-specific overall survival was additionally observed for intermediate-thickness melanomas (1.20–3.50 mm thick).[34,35] By contrast, the effects of SLNB on survival in patients with nonmelanoma skin cancer are still controversial.[36]

The SLN concept has also been applied to colorectal cancer in the last 2 decades. In colorectal cancer, sentinel node navigated surgery (SNNS) is not intended to reduce the surgical extension. However, it should detect additional lymph nodes located beyond the regional lymph nodes that are targeted for resection. Intensive work-up of the identified SLN improves the accuracy of staging of nodal disease,[37] which is important because node-positive patients with colorectal cancer require adjuvant chemotherapy. In 22% of cases, SLNB could change the extent of resection.[38] In a recent meta-analysis conducted by van der Zaag et al, the pooled identification rate was 90% and the pooled sensitivity was 70%.[39] Of note, the identification rate increased if $>$100 patients were investigated, if the lymphatic mapping was performed ex vivo, and if the patients' body mass index was low.[40] The sensitivity increased if more than four SLNs were removed, if the tumors were small (T1 or T2 versus T3 or T4), and in colon cancers relative to rectal cancers. The large number of false-negative results was due to aberrant drainage sites and skip lesions caused by obstruction of the lymphatic system.[41] The extent of the pathological work-up is another crucial factor in predicting the outcome of SLNB.[42] Because of these limitations, SLNB is not yet routinely applied to colorectal cancer.

Although data are limited, lymphatic mapping and SLNB of squamous cell carcinoma of the anus had high identification rates (47%–100%) and low false-negative rates (0%–14%) for the majority of patients.[43] Therefore, SLNB can be recommended for patients with squamous cell carcinoma of the anus.

The SLN concept has also been evaluated in several trials of esophageal cancer. The identification rates and the sensitivity were promising in patients with T1 or T2 tumors without clinical lymph node involvement.[44,45] Further prospective trials with larger numbers of patients are required to confirm these findings.

In gastric cancer, SLNB had identification rates of 80%–100% and accuracy of 90%–100%.[46] However, in the multicenter Japan Clinical Oncology Group study 0302, one serious limitation was the high false-negative rate of 46% for intraoperative frozen-section analyses of the SLN.[47] Therefore, lymphatic mapping may be unsuitable for gastric cancer.

Although SNNS is a controversial procedure in patients with cervical cancer and ovarian cancer, it has been extensively applied to squamous cell carcinoma of the vulva.[48] In this setting, the identification rate ranged from 92% to 96% and the sensitivity ranged from 90% to 95%.[49] In addition, the false-negative rate was $<2\%$ for tumors of ≤ 4 cm in diameter.[50] These results suggest that lymphatic mapping is suitable for midline tumors with clinically negative inguinal lymph nodes.

Table 1 Lymphatic mapping in cancer management

Type of cancer	Evidence	Clinical use	Features
Breast cancer	High	Gold standard	
Skin malignancies			
Melanoma	High	Gold standard	Addition look for lymph basin
Nonmelanoma skin cancer	Poor	Experimental	
Gastrointestinal malignancies			
Esophageal cancer	Poor	Experimental	
Gastric cancer	Poor	Experimental	Low sensitivity/ frozen section
Colorectal cancer	Good	Experimental	Aberrant lymph drainage
Anal cancer	Good	Established	
Head and neck malignancies	Poor	Experimental	
Squamous cell cancer	Good	Established	
Thyroid cancer	Poor	Experimental	
Parathyroid cancer	Poor	Experimental	
Gynecological cancers			
Vulva cancer	Good	Established	
Other gynecological cancers	Poor	Experimental	
Urological cancers			
Prostate cancer	Good	Experimental	
Penile cancer	Good	Established	
Other urological cancers	Poor	Experimental	
Lung cancer	Poor	Experimental	

Regarding urologic tumors, perhaps the most experience of SNNS has been gained for penile carcinoma, for which the pooled identification rate was 88% and the pooled sensitivity was 88%.[51] These values were increased by using blue dye in combination with a radiotracer.[51]

There are several reports of lymphatic mapping in patients with early head and neck squamous cell carcinoma, for which the identification rate was 95%, but the sensitivity was relatively poor at 86%.[52]

SNNS is now under investigation for application to other malignancies, including non-small-cell lung cancer and prostate cancer (Table 1).[53,54]

Lymph node mapping techniques

Several substances that are transported by lymph vessels have been developed for use in lymphatic mapping.

There is abundant evidence supporting the use of radioisotopes containing ^{99m}Tc. For example, the common use of filtered or unfiltered ^{99m}Tc-sulfur colloid in the United States of America, albumin-based colloids in Europe, and ^{99m}Tc antimony trisulfide colloid in Australia. The identification rate for ^{99m}Tc radioisotopes ranges from 86% to 99%.[55,56] The use of radioisotopes requires a nearby nuclear medicine unit for the preoperative injection, which is given 2–14 hours before imaging, and a γ detector in the operating room. Preoperative scintigraphy may be helpful but is not essential.

The injection of blue dyes, such as isosulfan blue or patent blue, can identify the sentinel node in 68%–86% of cases.[10,55,57] Blue dyes are used worldwide for lymphatic mapping in surgical cancer management. The blue dye is injected in the operation room about 10–15 minutes before the biopsy. Allergic reactions, one of the main adverse events associated with blue dye injection, occur in $<1\%$ of cases.[58]

Because injection of a radioisotope in combination with a blue dye can achieve high identification rates of 89%–97%, this combination is widely used.[11,57,58] The false-negative rate of this combination ranges from 6% to 10%, which is similar to the rate obtained with radioguided SLNB alone. However, the false-negative rate is higher if blue dye is used alone.[59]

The subareolar technique has equivalent value to peritumoral injection for lymphatic mapping in breast cancer.[60] Subareolar injection is preferred in the majority of institutions for several practical reasons, which include the need for single injection for multicentric disease and because radiologically guided injection (stereotactic- or ultrasonographic-guided) is not necessary for nonpalpable tumors.

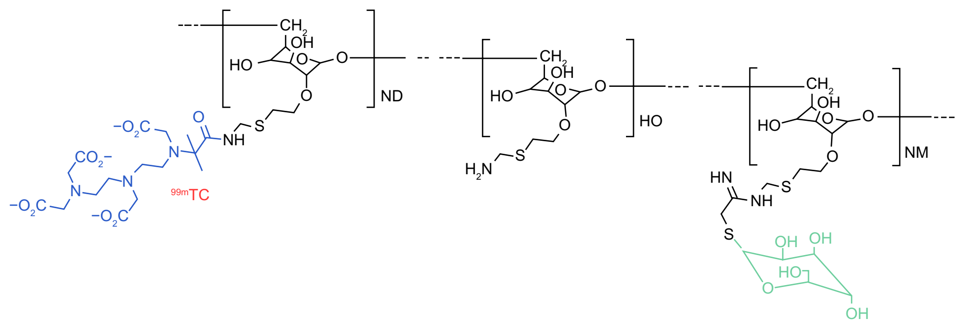

Figure 1 ^{99m}Tc-tilmanocept molecule.
Abbreviation: ^{99m}Tc, ^{99m}technetium.

Since 1999, when Motomura et al first described lymphatic mapping with fluorescent indocyanine green dye and visualization using a near-infrared camera, this technique has become widely used, especially in Eastern Asia.[61] Indocyanine green has similar identification rates and sensitivity to those of radioguided or blue-dye-based mapping. The main advantage of indocyanine green is that it allows percutaneous visualization of the afferent lymph vessels and lymph nodes. However, the operating room must be equipped with an infrared camera to enable this procedure.[62–65]

SentiMag® (Endomagnetics, Cambridge, UK) is a new radiation-free technique that was recently introduced. It consists of a magnetometer and a magnetic tracer, which can be visualized through the skin by its brown color. This system showed similar identification rates to radioisotopes and blue dye.[66]

Mechanism of action of ^{99m}Tc-tilmanocept in lymph node mapping

^{99m}Tc-tilmanocept (Lymphoseek®; Navidea Biopharmaceuticals, Dublin, OH, USA) is a synthetic radioisotope that was designed for use in SNNS. ^{99m}Tc-tilmanocept consists of multiple diethylenetriaminepentaacetic acid (DTPA) and mannose residues linked to a dextran frame. ^{99m}Tc is attached to DTPA while the mannose residues bind in a multivalent manner to mannose receptors (CD206) expressed on the surface of reticuloendothelial cells in lymph nodes (Figure 1).[67] Because of its small molecular size (molecular weight: 16.7 kDa) and its small diameter (7.1 nm), ^{99m}Tc-tilmanocept is quickly transported through the afferent lymph vessels. The mannose residues bind to the reticuloendothelial cells in the SLN with a residence time of about 30 hours. Several Phase I and Phase II trials have confirmed that ^{99m}Tc-tilmanocept does not escape from the SLN to the second echelon lymph nodes.[68–70]

Safety and effectiveness of ^{99m}Tc-tilmanocept

The first report describing the use of ^{99m}Tc-tilmanocept in SNNS was published in 2001.[71] Animal models confirmed that ^{99m}Tc-tilmanocept was rapidly cleared from the subcutaneous injection site and that it accumulated in the proximal lymph node, but not in distal lymph nodes. Similar data were also obtained in a pig model of the stomach and colon, in comparison with blue dye.[72,73] The first Phase I trial of 12 breast cancer patients showed that ^{99m}Tc-tilmanocept was cleared from the injection site more quickly than ^{99m}Tc-sulfur colloid by peritumoral injection, but the accumulation of both compounds in the axillary lymph nodes was equal. The median number of hot lymph nodes was lower for ^{99m}Tc-tilmanocept.[67] Similar results were obtained in the first Phase I trial of 24 melanoma patients.[69] The rapid clearance of ^{99m}Tc-tilmanocept from its injection site was also observed following intradermal injection in 12 patients with breast cancer.[70]

In a multicenter Phase II trial, 78 patients (47 with melanoma and 31 with breast cancer) were injected with 50 µg of ^{99m}Tc-tilmanocept.[68] Lymphatic mapping was possible in 52/55 patients (94.5%) who underwent lymphoscintigraphy. During surgery, the identification rate was 96%. Metastatic disease was found in 13.7% of patients.[68]

A multicenter Phase III trial compared ^{99m}Tc-tilmanocept and blue dye in 148 patients with breast cancer.[74] ^{99m}Tc-tilmanocept detected 207/209 nodes that were detected by blue dye, resulting in a concordance rate of 99%. However, ^{99m}Tc-tilmanocept detected the SLN in significantly more patients than did the blue dye (146 versus 131; $P<0.0001$). In 129/131 patients, all of the blue-stained nodes were hot. ^{99m}Tc-tilmanocept identified 31/33 positive nodes, whereas blue dye only detected 25/33 positive nodes ($P=0.0312$).[74]

Similar data were reported for malignant melanoma in a multicenter Phase III trial involving 154 patients.[75] The concordance rate was 98.7% (232/235 blue nodes were detected by ^{99m}Tc-tilmanocept). ^{99m}Tc-tilmanocept also identified at least one SLN in 150 patients compared with 138 patients with the blue dye (P=0.002). Overall, 4/34 node-positive patients were diagnosed by ^{99m}Tc-tilmanocept alone.[75]

In both trials, patients were injected with 50 μg of ^{99m}Tc-tilmanocept. Patients who were scheduled for surgery on the same day received around 0.5 mCi of ^{99m}Tc-tilmanocept. Patients scheduled for a 2-day procedure received 1.0–2.0 mCi of ^{99m}Tc-tilmanocept. ^{99m}Tc-tilmanocept was only injected intradermally for patients with melanoma, while in patients with breast cancer, the injection site (intradermal, subareolar, or peritumoral) was at the surgeon's preference.

There were no allergic reactions described for ^{99m}Tc-tilmanocept in either trial. Furthermore, there were no serious adverse events that were considered clinically relevant to the administration of ^{99m}Tc-tilmanocept.

There is currently only one indirect comparison between ^{99m}Tc-tilmanocept and the ^{99m}Tc-nanocolloid albumin (Nanocoll®; Nycomed Amersham Sorin SRL, VC, Italy).[76] In that study, the authors compared data from the results of Phase III trials of ^{99m}Tctilmanocept with historical data from ^{99m}Tc-nanocolloid-albumin-based protocols. It was postulated that the localization rate relative to the study population was 99.99% for ^{99m}Tc-tilmanocept compared with 95.91% for ^{99m}Tc-nanocolloid albumin ($P<0.0001$). In addition, the localization of SLN was significantly superior for ^{99m}Tc-tilmanocept compared with ^{99m}Tc-nanocolloid albumin.[76]

A small Phase III trial involving 20 patients with oral cavity squamous cell carcinoma was recently reported. In that study, ^{99m}Tc-tilmanocept combined with single-photon emission computed tomography/computed tomography achieved a sensitivity of 100% in 12 node-positive patients.[77]

Based on the results of these trials, ^{99m}Tc-tilmanocept was approved for SNNS by the United States Food and Drug Administration in March 2013.

Conclusion

Because of its small diameter, ^{99m}Tc-tilmanocept is cleared from the injection site much quicker than other radioisotopes or blue dye. The mannose residues of ^{99m}Tc-tilmanocept bind to mannose receptors (CD206) expressed on reticuloendothelial cells in lymph nodes. Therefore, the tracer remains in the SLN without migrating to the second echelon lymph nodes. The use of ^{99m}Tc-tilmanocept in patients with early cancer might avoid unnecessary resection of additional second echelon nodes and, thus, avoid the morbidity associated with this procedure. However, the comparative Phase III trials of breast cancer and malignant melanoma demonstrated that this approach was only suitable for early breast cancer.[74,75] Only 18% (27/148) of patients with breast cancer and 22% (34/154) of patients with melanoma presented with nodal involvement. The rate of nodal involvement in that study was low compared with the rate in other breast cancer trials (18% versus 26%–34%).[9,11,57,78] Therefore, it is still unclear whether these data can be applied to a higher-risk population with higher rates of nodal involvement where the likelihood of false-negative results decreases when second echelon lymph nodes are removed together with the SLN.[57] Since the clinical implementation of the data from the American College of Surgeons Oncology Group Z0011 trial, surgeons now prefer to resect more than one node in patients with nodal involvement in order to achieve more oncological safety when omitting full axillary clearance.[30,31,79] When SLNB is performed after neoadjuvant chemotherapy, especially in patients where lymph node involvement is found initially, a larger number of sentinel nodes should be resected to decrease the false-negative rate.[26]

The clinical value of ^{99m}Tc-tilmanocept in SNNS will be more clearly demonstrated in comparative studies using other ^{99m}Tc radiotracers than in studies using blue dye, which was used in the previous multicenter Phase III trials.[74,75] The results of such studies might support the use of ^{99m}Tc-tilmanocept instead of other radioisotopes used in combination with blue dye or used alone.

Disclosure

The authors report no conflicts of interest in this work.

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