In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma

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CHAPTER 18

Visualization of tumour-blockage and rerouting of lymphatic drainage in penile cancer patients using SPECT/CT

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Abstract

Introduction: The reliability of sentinel node biopsy is dependent on the accurate visualization and identification of the sentinel node(s). It has been suggested, that extensive metastatic involvement of a sentinel node can lead to blocked inflow and rerouting of lymph fluid to a ‘neo’-sentinel node that may not yet contain tumour, causing a false-negative procedure. There is, however, little evidence to support this hypothesis. Recently introduced hybrid single photon emission computed tomography and computed tomography (SPECT/CT) scanners provide both tomographic lymphoscintigraphy and anatomic detail. This device enabled the present study of the concept of tumour-blockage and rerouting in patients with palpable groin metastases.

Methods: Seventeen patients with unilaterally palpable and cytologically proven metastasis in the groin underwent bilateral conventional lymphoscintigraphy and SPECT/CT imaging prior to sentinel node biopsy of the contralateral groin. The pattern of lymphatic drainage in the 17 palpable metastatic groins was evaluated for signs of tumour-blockage and rerouting.

Results: On the CT-images, the palpable metastatic node could be identified in all 17 groins. Four of the 17 palpable metastatic nodes (24%) showed uptake of radioactivity on the SPECT/CT images. In ten groins, rerouting of lymphatic drainage to a neo-sentinel node was seen, of which one was located in the contralateral groin. Complete absence of lymphatic drainage was seen in the three remaining groins.

Conclusion: The assumed concept of tumour-blockage and rerouting was visualized in 76% of the groins with palpable metastases. Conscientious physical examination and preoperative ultrasound with fine-needle aspiration cytology may identify nodes with considerable tumour invasion at an earlier stage and thereby reduce the incidence of false-negative procedures.
Introduction

Sentinel node biopsy is used in a variety of malignancies with a lymphogenic dissemination pattern to assess the tumour-status of the regional lymph nodes.\textsuperscript{1-3} This procedure selects patients who may benefit from an early regional lymph node dissection and identifies others who can be spared such dissection in case of absence of metastasis in the sentinel node. Unfortunately, the sentinel node procedure is not 100% accurate and lymph node metastases have been reported after a negative sentinel node procedure.\textsuperscript{4} Such false-negative cases have a potential impact on survival.\textsuperscript{5,6} Several hypotheses have been postulated as to why a tumour-positive sentinel node might be overlooked.\textsuperscript{4} One of the proposed causes is the alteration of lymphatic drainage by a phenomenon called ‘tumour-blockage’.\textsuperscript{5} In case of tumour-blockage, massive tumour invasion of the sentinel node completely obstructs the lymph flow, preventing the tracers from accumulating in the sentinel node and thus preventing its identification. The tracers can be rerouted through other lymphatics to a so-called ‘neo’-sentinel node that may not yet be involved. In this scenario, the original sentinel node harbouring the tumour-cells is overlooked and may become apparent later on when the disease progresses and the node becomes palpable. Although the concept of tumour-blockage and rerouting is widely accepted, there is little reported evidence to support this hypothesis. Hybrid single photon emission computed tomography and computed tomography (SPECT/CT) scanners combine the physiological information provided by lymphoscintigraphy with the anatomical landmarks provided by CT. This technique creates the opportunity to demonstrate the process of tumour-blockage and rerouting in vivo.

At The Netherlands Cancer Institute, sentinel node biopsy is performed in penile carcinoma to assess the tumour status of clinically node-negative groins. More than 95% of penile malignancies are squamous cell carcinomas which typically metastasize to the inguinal lymph nodes.\textsuperscript{7-9} The present study concerns 17 patients with unilateral palpable and cytologically confirmed inguinal metastasis, who were scheduled for sentinel node biopsy of the contralateral clinically node-negative groin. The palpable metastatic groins were evaluated for signs of tumour-blockage and rerouting using SPECT/CT.

Materials and methods

Since August 2006, all penile carcinoma patients scheduled for sentinel node biopsy undergo preoperative SPECT/CT in addition to the conventional conventional scintigraphic images. Between August 2006 and September 2008, 105 consecutive patients with a $\geq$T1G2 penile tumour underwent hybrid SPECT/CT prior to sentinel
node biopsy.\textsuperscript{10,11} Included in this study were all 17 patients with a unilateral palpable node in the groin that was confirmed to contain metastatic disease using fine-needle aspiration cytology. Median age of the patients was 67 years (range 48-87). Six patients had a T1 tumour, nine patients a T2 tumour, and two a T3 tumour. Tumour differentiation was intermediate in 12 patients, poor in one patient and unavailable in four patients.

Conventional lymphoscintigraphic images were obtained from all patients one day before sentinel node surgery, after intradermal, peritumoural injection of the technetium-99m nanocolloid (Nanocoll\textsuperscript{®}, GE Healthcare, Eindhoven, the Netherlands). The tracer was administered at three or four sites around the tumour with a total volume of 0.3 ml to 0.4 ml in an average dosage of 70 MBq. SPECT/CT images were made immediately after the two-hour conventional images. The SPECT/CT system (Symbia T, Siemens, Erlangen, Germany) consisted of a dual-head variable-angle gamma camera equipped with low-energy high-resolution collimators and a spiral CT optimized for rapid rotation. SPECT acquisition (matrix 128x128, 60 frames in a 25sec/frame) was performed using six-degree-angle steps. The CT settings were 130 KV, 17 mAs, B60s kernel. After reconstruction, SPECT images were corrected for attenuation and scatter. Both SPECT and CT axial five millimetre slices were generated using an Esoft 2000 application package (Siemens, Erlangen, Germany). These were transferred to picture archiving after generation of Dicom files. Fusion of images was performed using an Osirix Dicom viewer in a Unix-based operating system (MAC OS X, MacPRO, Apple Inc., Cupertino, CA, U.S.A.).

All scans were evaluated by two experienced nuclear medicine physicians. First, the CT-images were separately analyzed in order to identify the palpable metastatic inguinal lymph node. The largest diameter of the node was measured. Subsequently, the fused images were analyzed for uptake of radioactivity in this node and to identify the radioactive sentinel nodes and higher-tier nodes. A sentinel node was defined a lymph node on a direct drainage pathway from the tumour.\textsuperscript{12} To facilitate the analysis of the lymphatic drainage patterns, the fused images were studied after orthogonal reslicing when needed.

All patients underwent an inguinal lymph node dissection of the palpable metastatic groin and sentinel node biopsy was performed in the contralateral clinically node-negative side.
Figure 1: A 74-year old penile cancer patient with palpable lymph nodes in the right groin and a clinically node-negative left groin. On the anterior conventional image (A) lymphatic drainage to both groins is observed. Fused axial SPECT/CT (C) shows an enlarged lymph node in the right groin without radioactive uptake (solid arrow) and a sentinel node on the left groin (dotted arrow). Fused axial 2D SPECT/CT with maximum intensity projection (B) and 3D SPECT/CT displayed with volume rendering (D) demonstrate lymphatic drainage (small arrows) bypassing the metastatic inguinal lymph node (large arrow). Note also uptake of the tracer in other inguinal and iliac lymph nodes.

Results

The palpable metastatic nodes were identified on the CT-images in all 17 groins and had a median size of 29mm (range 19-90mm). Four of the 17 (24%) palpable metastatic nodes showed uptake of radioactivity on the SPECT/CT images. In ten groins (59%) there was no uptake in the metastatic node and rerouting of the lymph to a neo-sentinel node was observed (figure 1). Nine of these neo-sentinel nodes were in the ipsilateral groin, while in the remaining case a neo-sentinel node was located in the contralateral groin (figure 2). Complete absence of lymphatic drainage to the clinically node-positive groin was observed in remaining three patients (18%) (figure 3). All patients underwent an inguinal lymph node dissection of the groin containing the palpable metastatic node. The dissection specimens contained a median of two tumour-positive lymph nodes (range 1-7 nodes). The median size of the metastatic nodes was 25 mm. Extracapsular growth was present in five of the 17 specimens. Five of the 17 contralateral clinically node-negative groins contained a tumour-positive sentinel node.
Figure 2: A 84-year old penile cancer patient with a palpable lymph node in the right groin and a clinically node-negative left groin. Both early (A) and delayed (B) conventional anterior images show a lymph vessel draining to the right groin (large horizontal arrow). On the delayed image, lymphatic crossing-over (small vertical arrows) to the left groin is visualized and a neo-sentinel node is observed here (dotted horizontal arrow). Note that the tracer accumulation in the right groin is not related to a lymph node, but to tracer stasis in the lymphatic vessel as seen (short vertical arrows) on fused SPECT/CT (C) and CT (D) in which no lymph node is visible at the location of the hotspot. This abnormal lymphatic drainage of the right groin is caused by an enlarged lymph node (solid oblique arrow) as seen on axial fused SPECT-CT (E). The neo-sentinel node in the left groin is displayed on fused SPECT-CT in colour (dotted arrow).

Discussion

The sentinel node procedure is based on the hypothesis that a lymph node on a direct drainage pathway from the primary tumour is the first to be involved in case of dissemination. This study proves that massive tumour invasion of this sentinel node can prevent the uptake of the injected tracers and hinder its identification by the nuclear medicine physician and surgeon. In addition, the obstructed sentinel node can cause diversion of the lymph flow to a neo-sentinel node that may not yet be involved. The presumption of this node being the only sentinel node while overlooking the original one can result in a false-negative procedure. In the present study, total absence of lymphatic drainage to the palpable metastatic groin was seen in 18% of the patients and in 59% rerouting to a ‘neo-sentinel node’ was observed. Tracer uptake was noted in only 24% of the grossly metastatic lymph nodes.
Figure 3: A 71-year old patient with palpable lymph nodes in the left groin and a clinically node-negative right groin. No lymphatic drainage to the left groin is observed on early (A) and delayed (B) conventional anterior images. This blockage is caused by a enlarged lymph node in the left groin (solid arrows) as observed on both 2D axial (C) and 3D volume rendered (D) fused SPECT/CT. Two sentinel nodes with radioactivity uptake are seen in the right groin (dotted arrows).

Two studies have examined the reliability of sentinel node biopsy in penile carcinoma patients with clinically palpable inguinal nodes, with the rationale that metastasis are found in only 50% of palpable nodes, while the rest are caused by an inflammatory reaction.\textsuperscript{13-15} Disappointing false-negative rates of 60\% and 75\% were found in both studies and it was concluded that sentinel node biopsy is unreliable in clinically node-positive groins. These results are in concordance with our current findings and emphasize the importance of accurately selecting only clinically node-negative patients for sentinel node biopsy.

In this study, the phenomenon of lymphatic blockage and rerouting was demonstrated in clinically palpable metastatic nodes. It seems plausible that this observation can, at least in part, be extrapolated to non-palpable metastatic lymph nodes. Such nodes cannot be detected by physical examination either because of their limited size or in case of an obese patient. We speculate that especially the latter scenario could lead to a false-negative sentinel node procedure. Although, there are no data available regarding the size of metastasis in relation to the uptake of radioactivity, it seems likely that a lymph node accumulates less radioactivity with an increasing tumour-load. An enlarged lymph node (potentially not accumulating tracers) is more challenging to
detect in obese patients, thus increasing the likelihood of a false-negative sentinel node procedure.

To assure the optimal selection of patients suitable for sentinel node biopsy, pre-operative staging of the lymph nodes is essential. Probably the most important and easy tool is precise physical examination to select only patients who have no palpable suspicious lymph nodes. An additional tool is pre-operative ultrasound with fine-needle aspiration cytology. Ultrasound may be able to diminish the risk of tumour-blockage by detecting sizeable metastatic nodes that are not yet palpable. Another measure to reduce the chance of a false-negative procedure is intraoperative palpation of the wound to identify unstained and non-radioactive that are suspicious because of their consistency but were not found during physical examination and ultrasound. The false-negative rates for sentinel node biopsy vary between different malignancies.

In a comprehensive review of 26 published series on sentinel node biopsy in breast cancer, followed by routine axillary node dissection, a wide variety of false-negative rates was seen ranging from 0% to 40% with a median of 7%. In a recent study at our institute regarding breast cancer patients, the false-negative rate without confirmatory node dissection was 1.2%. The recent favourable false-negative rates may be due to the adjuvant therapy that the majority of breast cancer patients receive. Postoperative radiotherapy is often given to the breast and is likely to clean up some of the tumour-positive nodes that surgeons may overlook and leave behind in the adjacent axilla. The same can be said for the adjuvant systemic treatment that many of these patients receive.

Contemporary false-negative rates in melanoma are around 10%. The lack of standard adjuvant therapy for this disease could explain the difference compared to the procedure in breast cancer. Reported false-negative rates in penile cancer vary from 4.8% to 29%. At our own institute, we saw a decrease in false-negative rate from 22% to 4.8% after introduction of a number of measures including pre-operative ultrasound and improved histopathological analysis of the harvested sentinel node. This study shows that tumour blockage and rerouting is a real scenario in lymphatic drainage. Accurate patient selection with conscientious physical examination and preoperative ultrasound might reduce the risk of a false-negative sentinel node procedure.
References


