Innovating image-guided surgery: Introducing multimodal approaches for sentinel node detection

Brouwer, O.R.

Citation for published version (APA):
APPENDIX

Clinical application of SPECT/CT and intraoperative radioguided sentinel node biopsy in cancers of the male reproductive system


Oscar R. Brouwer, Willem Meinhardt, Simon Horenblas, Renato A. Valdés Olmos
INTRODUCTION

This chapter describes the principles of lymphatic mapping and sentinel node (SN) biopsy for cancers of the male reproductive system, which includes penile, prostate, and testicular cancer.

Penile cancer is a relatively rare disease in the western world, with an incidence of approximately 1 per 100,000.1 Nearly all penile tumors are squamous cell carcinomas. The presence of lymph node involvement is the single most important prognostic factor for cancer-specific death.2 Since the introduction of the concept in penile carcinoma by Cabañas et al. in 1977, the SN procedure has evolved into a reliable staging technique, with a low complication rate compared to (prophylactic) inguinal lymphadenectomy.3

Prostate cancer

In prostate cancer, lymph node staging may be important for both prognosis and therapeutic management. The presence of lymph node metastases may lead to avoidance of local therapy with curative intents, such as radiotherapy or radical (salvage) prostatectomy, and influences the duration of androgen-deprivation therapy.4 To date, none of the available noninvasive diagnostic imaging modalities provide a reliable assessment of lymph node (micro)metastases. Therefore, surgical staging by extended pelvic lymphadenectomy (EPL) is still the current standard of care. However, SNB is emerging as an alternative staging method, with a lower incidence of complications and with the potential to identify relevant lymph nodes outside the standard EPL field.5

Testicular cancer

Testicular cancer is the most frequent malignancy in young men, and the incidence has risen by almost 100% in the last 20 years. At the time of diagnosis, approximately two-thirds of patients have clinical stage I disease.6 The optimal management of regional lymph nodes in stage I testicular cancer remains controversial. A surveillance policy requires intensive, frequent follow-up visits, with costly examinations, and defers detection and treatment of lymph node metastases to a later stage. There is a need for diagnostic techniques that enable patients with lymph node metastasis to be treated at an early stage, while preventing unnecessary treatment for those patients without metastasis. In this respect, the SN procedure is potentially highly valuable.7,8

THE CLINICAL PROBLEM

Penile cancer

There is no consensus on the management of patients with clinically node-negative (cN0) penile carcinoma, in whom radical inguinal lymph node dissection (ILND) is routine.9 However, only 20–25% of these patients harbor occult nodal metastasis. This means that, although prophylactic inguinal lymphadenectomy offers the best
chance of cure, it is unnecessary in approximately 75–80% of patients. In addition, this procedure is associated with substantial morbidity, such as lymphedema and infections. As currently available non-invasive staging techniques lack sufficient accuracy, mini-mally invasive staging remains necessary for the time being. However, since its clinical introduction in 1994, there have been reservations about the use of SNB for penile cancer, because of the supposedly long learning curve associated with the procedure and the possibility of false-negative cases (reported in up to 21% of the procedures). After analysis of false-negative cases, several modifications were made to the dynamic SN biopsy (DSNB) procedure, to increase its sensitivity.

**Prostate cancer**

Although EPL is the gold standard for the identification of lymph node metastasis in patients with prostate cancer, the incidence of postoperative complications increases with the number of excised lymph nodes, ranging from 10.5% for 1–5 lymph nodes to 24.3% when dissection includes more than 20 lymph nodes. The advantages of the SN node dissection are a lower incidence of complications and the possibility of identifying tumor-draining lymph nodes outside the field of an EPL. However, accurate laparoscopic localization of SNs in the pelvis can be challenging, especially when SNs are located near the prostatic injection site (because of the high radioactive background signal), or in the case of aberrantly located SNs (e.g. para-aortic).

**Testicular cancer**

To date, large-scale randomized clinical studies to validate and assess the added benefit of SNB for testicular cancer are still lacking. This may be partially due to the fact that patients are usually referred to tertiary, specialized centers only after orchiectomy has already been performed, thus after removal of the potential injection site. Furthermore, although lymphatic drainage of the testis is mainly directed towards the areas along the aorta and vena cava, aberrant drainage has also been observed. The identification of these SNs in relation to the anatomical structures can be difficult using two-dimensional (2D) lymphoscintigraphy alone.

**INDICATIONS AND CONTRAINDICATIONS FOR SENTINEL NODE BIOPSY**

**Penile cancer**

Patients with >T1G2 tumors and cN0 groins defined by ultrasound-guided fine needle cytology are eligible for SNB. Repeat SNB after tumor recurrence is also a validated procedure. If the SN is tumor positive, completion ipsilateral lymphadenectomy is performed. Groins with tumor-free lymph nodes are managed with close surveillance, thereby avoiding the morbidity associated with lymphadenectomy.
Prostate cancer
The chances of having lymph node metastasis from prostate cancer increase with the serum level of prostate-specific antigen (PSA), the biopsy grade (Gleason score), and clinical T stage. SNB is generally reserved for patients in the intermediate-risk group (clinical stage >T2b/T3, PSA >10 ng/l, or Gleason >6). Nevertheless, SNB has been able to identify metastases in as many as 6.8% to 10.7% of patients with favorable risk factors.14 In the intermediate-risk group, a tumor-bearing SN may influence the boundaries of the radiotherapy field and duration of hormonal (androgen-deprivation) therapy. Another possible indication is to select patients who are eligible for salvage treatment of the prostate, as the usual parameters to stratify patients in risk groups do not apply to patients with intraprostatic recurrence.4 Since salvage treatment of the prostate may result in serious complications, it should be considered when the prostate is actually the only tumor-bearing site.

Testicular cancer
SNB was introduced for patients with stage I disease. Clinical stage I seminoma and non-seminoma are defined by a negative computed tomography (CT) scan of the chest, abdomen, and pelvis, plus normal or normalized serum values of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH). In the case of mixed seminomatous/non-seminomatous tumors, treatment decisions are based on the factor with the highest malignant potential, which is the non-seminoma component. Generally, the absence of lymph nodes larger than 1 cm results in assignment of clinical stage I.

Radiocolloid and Modalities of Injection
Penile cancer
The tracer (technetium-99 [99mTc]-nanocolloid in most European countries) is injected intradermally. In fact, subcutaneous administration is easier to accomplish, but may not accurately identify the route of drainage from an overlying cutaneous site. Furthermore, lymphatic drainage from the dermis is much faster than drainage from subcutaneous tissue. Application of a spray containing xylocaine 10%, 30 minutes before tracer administration, is recommended. As an alternative, a lidocaine/prilocaine-based crème can be used. This local anesthesia ensures that the radiocolloid injections are well tolerated and relatively easy to perform. A volume of 0.3 ml containing 74 MBq divided into three depots (0.1 ml each) is subsequently administered intradermally around the tumor. Each depot is injected raising a bleb. The radiocolloid is injected proximally from the tumor. For large tumors not restricted to the glans, the radiocolloid can be injected in the prepuce. Injection margins within 1 cm from the primary tumor are recommended. A reproducibility rate of 100% for penile lymphoscintigraphy has been reported with an injection distance of 5 mm.15 In patients with a previous excision biopsy scar, injections may also be administered using similar margins.
Prostate cancer

Most of the experience in the SN procedure for prostate cancer has been acquired in European countries and the most frequently used radiopharmaceutical has been $^{99m}$Tc-nanocolloid. Transrectal intraprostatic injection is guided by (transrectal) ultrasound, injecting the radiocolloid under continuous monitoring using a needle of $0.5 \times 150$ mm (Fig. 1). Prostate cancer may be multifocal; therefore injections are performed in both lobes. An activity of about 240 MBq in $0.4$ ml is recommended. The lymph node visualization rate tends to be less optimal when lower activities are used. The particle concentration also appears to be important, and the use of a reduced labeling dilution volume ($0.4$ ml $^{99m}$Tc per $0.2$ mg nanocolloid) yields more visualized SNs with higher radioactivity count rates. The radiocolloid is divided into 2–4 injections, depending on the prostate volume. A three-way system is recommended, and after each depot saline is used for flushing the residual radioactivity in the needle.

Testicular cancer

The route of administration of $^{99m}$Tc-nanocolloid was evaluated in a feasibility study in stage I testicular cancer. While funicular administration showed only lymph node uptake in the inguinal region (which does not reflect the actual testicular tumor drainage pattern), intratesticular administration resulted in visualization of retroperitoneal SN(s), in accordance with known drainage patterns. No side effects were observed using the latter method, which proved to be easy to perform and was well tolerated under local anesthesia (funicular block using lidocaine 2%, performed by the urologist in the outpatient clinic). Generally, a single aliquot of radioactivity (approximately 100 MBq) in a volume of $0.2$ ml is injected into the testicular parenchyma with a fine needle.

**PREOPERATIVE IMAGING OF SENTINEL NODES AND LYMPHOSCINTIGRAPHY INTERPRETATION**

Based on lymphoscintigraphy, the main criteria to identify lymph nodes as SNs are the visualization of lymphatic ducts, the time of appearance, the lymph node basin, and the intensity of lymph node uptake. Following these criteria visualized radioactive lymph nodes may be classified as:

1) Definitely SNs: this category includes all lymph nodes draining from the site of the primary tumour through an own lymphatic vessel, or a single radioactive lymph node in a lymph node basin.

2) Highly probable SNs: this category includes lymph nodes appearing between the injection site and a first draining node, or nodes with increasing uptake appearing in other lymph node stations.

3) Less probable SNs: all higher echelon nodes (in trunk and extremities) or lower
echelon nodes (head and neck) may be included in this category.

Early planar images are essential to identify first draining lymph nodes as SNs by visualization of their lymphatic ducts. These nodes (category 1) can be distinguished from secondary lymph nodes (category 3) mostly appearing on delayed planar images. In other cases a single lymph node is seen on early and/or delayed images. This node is also considered as a definite SN (category 1). In some cases SPECT/CT can detect additional lymph nodes in other basins. This may occur for instance in the pelvis when two basins are located at the same level and there is superposition of the radioactive nodes on planar images. These nodes can be considered as definite (category 1) or highly probable SNs (category 2). Less frequently a radioactive lymph node may appear between the injection site and a first draining node; its increasing uptake can confirm this node as a highly probable SN (category 2) and it helps to differentiate this node from prolonged valve activity in a lymphatic duct, which mostly decreases in intensity on delayed images.

**Penile cancer**

As aforementioned, lymphoscintigraphy after radiocolloid injection consists of two phases: (a) dynamic scintigraphy, performed during the first 10 minutes after radiocolloid injection, preferably in both the anterior and lateral views. The dynamic study is helpful to identify lymphatic ducts and the first directly draining lymph nodes; (b) static planar imaging at 20–30 minutes and at 2 hours. The early planar images visualize the first draining lymph nodes in about 85% of cases. Additional images at 4 hours, or radiocolloid reinjection are recommended when no SNs are visualized. Generally, the lymph nodes draining directly from the injection site are classified as SNs. In the case of multiple visible nodes without visible afferent vessels, the first node appearing in a basin is considered to be the SN.

**Prostate cancer**

In the pelvis, lymphatic ducts are seldom visualized and the relatively slower deep lymphatic drainage renders dynamic lymphoscintigraphy less useful. Early planar images of lymphoscintigraphy acquired 15 minutes after radiocolloid administration can visualize the first draining lymph nodes in almost 88% of cases. Delayed imaging may be performed 2–4 hours after injection. On delayed imaging, the lymph node visualization rate increases to more than 95%. Comparing the early and delayed images enables differentiation of second-echelon lymph nodes from the first draining nodes. This discrimination is based on the anatomical lymph node basins of the pelvis. As a rule, late-appearing lymph nodes located higher in the same basin are considered as second-echelon lymph nodes. Late-appearing lymph nodes in distal or more ventral and dorsal basins suggest direct draining from the prostate. These lymph nodes may also be considered as SNs. If no single photon emission computed tomography (SPECT)/CT is available, lateral planar images can differentiate between dorsal and more ventrally located SNs.
Testicular cancer
The fast lymphatic drainage from the testicle requires dynamic gamma camera acquisition to facilitate differentiation between first- and second-echelon lymph nodes in the retroperitoneum. Immediately following radiocolloid injection, anterior and lateral dynamic images are obtained with a dual-head gamma camera over 10 minutes, and the lymphatic flow and early-draining lymph nodes are visualized in almost all cases. Static images are obtained 5 minutes after the dynamic study. Late static images are obtained 2–4 hours after injection and are required to differentiate first-echelon nodes from higher-echelon nodes (if there is no visualization of SNs on the early dynamic and static images), and to identify unexpected drainage patterns.

Lymphatic drainage
Penile cancer
The most frequently visualized lymphatic drainage pattern is bilateral drainage to both groins (80%). This pattern is, however, asynchronous in two-thirds of cases, and visualization of the contralateral lymph nodes is often only possible on delayed imaging. Drainage from the injection site mostly occurs through one or two visualized afferent lymphatic ducts leading to one or two SNs in each groin. In some cases, a cluster of inguinal lymph nodes is observed.

Prostate cancer
The main lymph node basins where the prostate drains generally follow the iliac vessels. The common iliac lymph nodes are located caudally of the aortic bifurcation and are subdivided into a lateral, medial, and middle group. This latter basin is located in the lumbosacral fossa and is demarcated by the promontorium, the psoas muscle, and the common iliac vessels. The external iliac lymph nodes are located caudally to the bifurcation of the common iliac vessels and cranially to the inguinal ligament; they are also subdivided into lateral, middle, and medial groups. The lateral (lateral of the artery) and middle (between the artery and the vein) lymph nodes are located more in the proximity of the anterior abdominal wall, while the medial nodes are located along the cranial segment of the external iliac artery. Although the object of some debate, the obturator lymph nodes are generally considered to be part of the medial subgroup. The internal iliac lymph nodes are located more posteriorly in the pelvis and include the lateral sacral nodes (adjacent to the paired lateral sacral arteries), the presacral nodes (anterior to the sacrum and posterior to the mesorectal fascia), and the anterior nodes (at the origin of the proximal branches of the anterior division of the internal iliac artery; this subgroup includes the hypogastric nodes).
Testicular cancer

Lymphatics from the right testis drain primarily to regions lateral, anterior, and medial to the vena cava and anterior to the aorta (Fig. 2). Lymphatic drainage from the left testis is primarily directed towards areas lateral, anterior, and medial to the aorta. SNs may therefore be preoperatively detected at interaortocaval, para-aortic, or pre-aortic locations.

INTRAOPERATIVE DETECTION OF SENTINEL NODES

Penile cancer

As is customary for SNB in melanoma and breast cancer, intraoperative SN detection is guided by a gamma-ray detection probe and blue dye. After excision of all pre-operatively defined SNs, it is important to carefully search for any residual radioactivity using the probe, to ensure that no remaining/additional SNs are left behind. Furthermore, intraoperative palpation of the wound should take place, to identify suspicious lymph nodes that failed to pick up any radiocolloid.

Prostate cancer

Initial validation of the SNB in prostate cancer was based on open surgery and the use of a gamma-ray detection probe to guide detection of the radioactive SNs. More recently, laparoscopic SNB has been validated, and the feasibility of robot-assisted SNB has been demonstrated. In either approach, SN localization is guided by a laparoscopic gamma probe. Deeply located SNs can be difficult to localize using a gamma-ray detection probe, because of tissue attenuation and because the large amount of radioactivity at the injection site may cause SNs located nearby to be missed.

Testicular cancer

SNB in testicular cancer was introduced in a laparoscopic setting. As such, intraoperative SN localization is also guided by the acoustic signals originated by a laparoscopic gamma-ray detection probe.

IMPLEMENTATION AND CONTRIBUTION OF SPECT/CT

SPECT/CT has successfully been incorporated in the SN procedure. SPECT/CT does not replace lymphoscintigraphy. The principal aim of SPECT/CT is to anatomically localize SNs already visualized on planar images. However, SPECT/CT can also detect additional SNs.

Technical aspects of SPECT/CT for SN imaging

Protocols for SPECT/CT are determined by the objectives of the SN procedure. SPECT/CT is essentially oriented to the anatomical localisation of SNs. This explains why SPECT/CT is acquired using a low dose CT. Acquisition of a diagnostic high dose CT, with or without intravenous contrast, is not really necessary because
the SN procedure primarily aims to identify subclinical metastases in lymph nodes that are not enlarged. However, for SN localisation the CT component of SPECT/CT must be of sufficient quality to provide optimal anatomical information. The second generation of SPECT/CT cameras enables the evaluation of the lymph nodes corresponding with the radioactive nodes on fused SPECT/CT images by acquiring a low dose (40 mAs) CT. In superficial areas such as the groin, 5 mm slides may provide adequate anatomical details. For more complex anatomical areas (pelvis, abdomen) 2 mm slides may be necessary. With this approach SPECT/CT can accurately localize SNs in relation to the vascular structures in deep anatomical areas. The CT component is also used to correct the SPECT signal for tissue attenuation and scattering. After these corrections SPECT can be fused with CT. A grey scale is used to display the morphology in the background image (CT) whereas a colour scale is used to display the SN in the foreground image (SPECT).

To read images SPECT/CT is mostly displayed in a similar manner as that of conventional tomography. Multiplanar reconstruction (MPR) enables two-dimensional display of fused images in relation to CT and SPECT. The use of cross-reference lines allows for the navigation between axial, coronal and sagittal views. At the same time this tool leads to correlate radioactive SNs seen on fused SPECT/CT with lymph nodes seen on CT. Most frequently, a radioactive SN corresponds with a single lymph node on CT but in some cases it correlates with a cluster of lymph nodes. This information may be helpful for the intraoperative procedure and the post-excision control using portable gamma cameras or probes as more radioactive SNs may be harvested at the same location.

Fused SPECT/CT images can also be three-dimensionally displayed using volume-rendering. In this modality different colours are assigned to anatomical structures such as vessels, muscle, bone and skin. This results in better anatomical reference points and incorporate an additional dimension in the recognition of SNs, for instance in relation to the vasculature or muscles.

**Penile cancer**

SPECT/CT images are usually acquired after the 2-hour planar images, and contribute to better understanding of the location of the SNs in penile carcinoma (Fig. 3). SPECT/CT enables anatomical localization of the SNs that were previously identified by lymphoscintigraphy. For instance, the modality can differentiate inguinal from iliac (most frequently second-echelon) lymph nodes. Moreover, SPECT/CT enables visualization of the SNs in the so-called Daseler’s superior and central inguinal zones, which are superior and directly overlying to the saphenofemoral junction, respectively (Fig. 3). SPECT/CT has confirmed that in the majority of patients, SNs are found in the superior medial (73%), superior lateral (9%), and central quadrants (18%). Lymphatic drainage to the inferior quadrants is rare. Finally, SPECT/CT is able to identify contamination of the skin with the radiocolloid, an occurrence that can sometimes be erroneously interpreted on planar lymphoscintigrams as lymph nodes.
Prostate cancer

Hybrid imaging with SPECT/CT enables anatomical localization of SNs. A 98% SN visualization rate has been reported for SPECT/CT (versus 91% for planar imaging). Moreover, in 96% of cases SNs are localized inside the area of EPL; nevertheless, there is a considerable number of SNs in regions not routinely excised when performing an EPL.22 SPECT/CT is mostly performed after the delayed planar imaging, and must be interpreted in combination with lymphoscintigraphy. Sequential planar images are able to identify the lymph nodes draining directly from the tumor site, but give only limited information about their anatomical location. With SPECT/CT, it is possible to better localize SNs both inside and outside the pelvis. In many cases, early-appearing lymph nodes seen as a single hot spot on planar imaging are displayed as separate lymph nodes in different basins by SPECT/CT, and all of them must be considered as SNs. In other cases, intense lymph node uptake seen on fused images may correspond to a cluster of SNs as depicted on the CT component of the SPECT/CT acquisition. As such, SPECT/CT provides valuable information for the urologist, which may lead to a significant shortening of the operation time, as less-extensive exploration might be required. Furthermore, SPECT/CT may also provide important information for planning radiotherapy, concerning especially treatment volume and optimization of irradiation fields in the pelvis.

Testicular cancer

In the initial feasibility study, preoperative lymphatic mapping was performed using planar lymphoscintigraphy only.7 However, this technique can only provide 2D information, and exact preoperative anatomical SN localization is not possible. Not only does SPECT/CT provide useful anatomic information about the location of SNs, but its improved sensitivity and the added third dimension may also lead to the detection of additional SNs (Fig. 2). Sequential planar imaging will remain important for the preoperative identification of early-appearing lymph nodes as SNs. To date, one study evaluating the use of SPECT/CT for preoperative SN localization in testicular cancer has been published.8 SPECT/CT enabled accurate localization of the SNs and provided anatomical reference points to plan their laparoscopic retrieval.

INTRAOPERATIVE IMAGING

Penile cancer

Accurate staging with SNB can only be achieved if all nodes on a direct drainage pathway from the tumor are harvested. If SNs are left behind, this constitutes one of the potential causes for false-negative results. The integration of a portable gamma camera in the intraoperative procedure may increase the detection sensitivity, as it provides an intraoperative overview image of the radioactive SNs and enables post-excision confirmation of complete removal of the SNs in the operating room. For optical visualization of the SN, vital blue dyes are traditionally used. However, SNs do not always stain blue. Recently, a hybrid tracer comprising the fluorescent
dye indocyanine green (ICG) and $^{99m}$Tc-nanocolloid has been developed. $^{23}$ Adding the fluorescent moieties does not alter the biological properties of the parental radiocolloid, and it enables near-infrared fluorescence imaging of all preoperatively identified radioactive SNs. $^{24}$ These developments may help to further refine intraoperative retrieval of SNs.

**Laparoscopic Surgery: Prostate cancer and testicular cancer**

Since the (retroperitoneal) lymphatic drainage of the prostate and testes is directed to areas deep within the abdomen that can often be complex, preoperative anatomical information about the location of the SNs is important for planning the surgical procedure. For this reason, the SPECT/CT images should be displayed in the operating room. Urological surgery has shifted from the open approach toward less-invasive laparoscopic and robot-assisted techniques. During laparoscopic surgery, the urologist localizes a SN under guidance by the sound pitch originated by the laparoscopic gamma probe. However, intraoperative spatial orientation using this device can sometimes be difficult, as a laparoscopic probe does not provide visual information. The use of a portable gamma camera helps to intraoperatively guide laparoscopic SN localization. Current portable gamma cameras are capable of detecting two different signals: the signal of $^{99m}$Tc-nanocolloid for the visualization of SNs, plus the signal of an iodine-125 ($^{125}$I) seed pointer placed on the tip of the laparoscopic gamma-ray detection probe. $^{25}$ The “hot” tip of the probe can be moved to the hot node, guided by the image of the portable camera. This approach helps navigate towards the location of the SNs. After removal of all SNs, the portable gamma camera can show whether there are any remaining SNs that have to be removed, or a second-echelon node that can confidently be left in place (Fig. 4). This approach provides certainty about the completeness of the surgical procedure and complements the laparoscopic probe. Currently, intraoperative navigation approaches that are based on the preoperative (SPECT/CT) images are being developed. $^{26}$ In prostate cancer, SNs may be located in close proximity to the primary injection site (the prostate), where the high radioactive background signal may hinder radioguidance with the gamma probe. By injecting the aforementioned hybrid radioactive and fluorescent tracer ICG-$^{99m}$Tc-nanocolloid, the high resolution of near-infrared fluorescence imaging (enabled by a fluorescence endoscope) may facilitate intraoperative visualization of the SNs that were preoperatively identified by SPECT/CT (Fig. 5). $^{27}$
COMMON AND RARE VARIANTS

Penile cancer

One of the advantages of lymphatic mapping is its ability to identify SNs outside the usual nodal basins. In penile cancer, direct drainage to prepubic SNs has been described.28 In particular, dynamic lymphoscintigraphy often shows one or two lymphatic vessels leading to the SN(s). Such vessels have also been observed to directly lead to deep inguinal and even to iliac SNs. Blockage of the lymph flow by tumor metastasis in the lymph node may cause nonvisualization and lymph rerouting, and even retrograde flow of the 99mTc-nano-colloid containing lymphatic flow. This occurrence has been visualized by SPECT/CT imaging.20

Prostate cancer

In prostate cancer, lymphoscintigraphy and SPECT/CT may identify SNs outside the extended dissection in 31% of cases.5 These aberrantly located SNs can be located proximal to the most distal part of the aorta, in the vicinity of the common iliac artery above the crossing of the ureter, around the inferior mesenteric vessels, in the perivesical area, and near the umbilical ligament.29,30

Testicular cancer

Although drainage from the testes is usually directed to paracaval, interaortocaval, and para-aortic SNs, in some patients SNs may also be seen along the testicular vessels.8

TECHNICAL PITFALLS

Penile cancer

The most frequent pitfall is skin contamination. The high pressure of the intradermal bleb can result in leakage during injection or after removal of the needle. The use of (surgical) lights to adequately visualize the site of injection, and of a fenestrated drape to cover the area, may help to avoid skin contamination. Furthermore, voiding of radioactive urine between the early and delayed scintigraphic imaging may also cause skin contamination. The hot spots due to contamination may be confused with SNs, thus leading to an unnecessary intraoperative pursuit. In these cases, skin decontamination is mandatory. Complementary SPECT/CT may also be helpful in detecting these artifacts. Another possible pitfall is accidental injection into the corpus cavernosum, an occurrence that will cause no visualization of lymphatic flow. Furthermore, in some cases the injection site (penis) may obscure visualization of the more inferiorly located SNs on anterior planar imaging.

Prostate cancer

The relatively complicated radiocolloid injection procedure for prostate cancer is probably the most frequent cause of pitfalls. Care must be taken to avoid tracer
leakage during injection, possibly resulting in subsequent contamination of the floor or of the ultrasound probe. It is therefore recommended to check for contamination of the room after injection, using a Geiger counter. During injection, incorrect needle placement may result in passage of the radiocolloid directly to the bladder or bloodstream, which in turn may cause nonvisualization during scintigraphy. By monitoring the injection procedure with a portable gamma camera, it is possible to ensure adequate radiocolloid retention in the prostate. As the injection is performed transrectally, a possible pitfall is visualization of lymphatic drainage from the rectum, leading, for example, to visualization of inguinal lymph nodes on SPECT/CT imaging. Furthermore, accidental funicular administration can also occur, possibly leading to retrograde drainage towards the scrotum.

Testicular cancer
The route of administration of $^{99m}$Tc-nanocolloid may cause pitfalls. For instance, funicular administration may result in lymph node uptake in the inguinal region, which does not reflect testicular tumor drainage. Intratesticular administration in the parenchyma results in retroperitoneal SN visualization, in accordance with known drainage patterns.

Accuracy of sentinel node biopsy
Penile cancer
Initially, the most significant drawback of SNB for penile cancer was found to be a relatively high false-negative rate (22%). After analysis of the false-negative cases, several modifications were made to the procedure to decrease the false-negative rate and thus increase sensitivity. Histopathologic analysis was expanded with serial sectioning of the harvested SNs. Furthermore, preoperative ultrasonography of cN0 groins with fine needle aspiration cytology (FNAC) of suspicious lymph nodes was added, as well as exploration of the groin in the case of nonvisualization during scintigraphy, and intraoperative palpation of the wound to identify suspicious lymph nodes that failed to pick up any radiocolloid. Thanks to these modifications, the procedure has evolved into a reliable minimally invasive staging technique, with an associated sensitivity of 93–95% and low morbidity in experienced centers. However, a recent multicenter meta-analysis reported pooled sensitivity rates of 88%. One explanation for this lower sensitivity may be represented by differences in protocols (that is screening with ultrasound and FNAC to detect lymph node metastases that fail to pick up radioactivity), and/or by possibly different phases of the learning curve.

Prostate cancer
Original validation of SNB for prostate cancer was based on open surgery and on the use of a gamma probe to guide detection of the radioactive SNs. Out of more than 2000 evaluated patients, only 11 false-negative cases (5.5%) were reported.
More recently, SNB has been validated using a laparoscopic gamma probe during minimally invasive surgery. A recent meta-analysis reported a pooled detection rate of 94% (89–96.6%) and a pooled sensitivity rate of 95% (92–97%).

Testicular cancer
To date, no studies have been published other than the aforementioned feasibility studies limited by small size of the study populations (<25 patients per study), which therefore lacked the statistical power and follow-up data to assess sensitivity/false-negative rates. Although refinement of the SN procedure may enable better selection of patients who would benefit from adjuvant treatment after orchidectomy, further studies are required to substantiate the clinical value of the SN procedure in this disease.
Figure 1. Preoperative SN mapping in prostate cancer. A) Tracer administration with transrectal ultrasound guidance using a long needle and a three-way system. B) The radioactive dose is divided in 2–4 injections. The procedure is monitored using a portable gamma camera to verify adequate tracer retention within the prostate. C) Early planar lymphoscintigram showing two SNs with direct drainage from the prostate (arrows). D) The delayed lymphoscintigram enables differentiation of the SNs and a higher-echelon lymph node (arrow). E-F) Three-dimensional (3D) volume-rendered SPECT/CT image displaying the location of the SNs in more detail (arrow). G) Axial fused SPECT/CT image showing the SN on the right side along the external iliac veins, and h) the SN on the left side in the obturator fossa.
Figure 2. Intratesticular injection of hybrid ICG–99mTc-nanocolloid in a 52-year-old male patient with a seminoma in his left testicle, followed by lymphoscintigraphy and SPECT/CT.

A) Early planar anterior image showing drainage from the left testicle towards an abdominal SN (arrow). B) The delayed lymphoscintigram reveals an additional sentinel node just below the SN that was visualized on the early image (upper arrow), a second echelon node to the right, and an additional hotspot located more caudally (lower arrow), which was therefore also defined as a SN. C) Fused SPECT/CT image displayed with 3D volume rendering, showing the cranial two SNs alongside the aorta, the interaortocaval second echelon node, and the more caudal SN (arrow) next to the funiculus. D) Axial fused SPECT/CT image depicting the caudal SN along the external iliac vessels next to the funiculus. All SNs were excised during laparoscopy guided by a laparoscopic gamma probe and fluorescence endoscope. E) Ex-vivo fluorescence image of a para-aortic SN, revealing the location of the node within the excised tissue specimen.
Figure 3. Lymphatic drainage in penile cancer and the five inguinal zones of Daseler: in the majority of patients, SNs are seen in the superior medial quadrant (73%), superior lateral (9%), and central (18%). Drainage to the inferior quadrants is rare (4%). Lymphoscintigraphy shows drainage to a SN in both groins (arrows) and bilateral higher-elevation drainage. C) 3D volume-rendered image revealing that both SNs are located in the central zone of Daseler. D-E) Axial fused SPECT/CT images depicting both radioactive SNs, with the corresponding lymph nodes on CT (arrows).
Figure 4. A) Early lymphoscintigraphy after transrectal intraprostatic visualization of bilateral lymphatic drainage with an early-appearing SN along the great abdominal vessels (arrow). B) Axial SPECT/CT image showing the exact location of this SN next to the common iliac artery (arrow). C) 3D volume-rendered SPECT/CT image providing an overview of all SNs: the upper SN next to the common iliac artery (upper arrow), two along the external iliac vessels on the left side, one along the external iliac artery on the right side, but also an additional SN located more medially (lower arrow). D) The axial image shows that this SN is located paravesically. E) All SNs were harvested laparoscopically, aided by a portable gamma camera (arrow) and a laparoscopic gamma probe. F) Intraoperative visualization of a SN(s) (arrow) using a portable gamma camera, allowing post-excision confirmation that the SN has been removed completely. After excision (right screen), no significant remaining activity is seen.

Figure 5. Aberrant drainage after transrectal intraprostatic injection of hybrid radioactive and fluorescent ICG–99mTc-nanocolloid in a 59-year-old male patient with intermediate-risk prostate cancer. A) Delayed planar lymphoscintigram showing retrograde drainage towards the scrotum on the right side, due to partial funicular tracer administration as well as drainage to sentinel nodes on both sides (obturator fossa) and a sentinel node located more caudally on the left side (arrow). B–C) The 3D volume-rendered and axial SPECT/CT images reveal that the most caudal sentinel node on the left side reflects aberrant drainage ventrally against the abdominal wall (arrow). The sentinel nodes were harvested during robot-assisted laparoscopy guided by a laparoscopic gamma probe and fluorescence endoscope. D) Fluorescence endoscope image showing the sentinel node against the abdominal wall along the umbilical ligament (green). This sentinel node (and an iliac sentinel node on the right side) contained metastases at histopathology.
REFERENCES


