Innovating image-guided surgery: Introducing multimodal approaches for sentinel node detection
Brouwer, O.R.

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Purpose: The purpose of this study was to evaluate the utility of SPECT/CT and real-time intraoperative imaging with a portable gamma camera for laparoscopic sentinel node localisation in stage I testicular cancer.

Methods: Ten patients with clinical stage I testicular cancer were studied between November 2006 and November 2010. Their mean age was 37 years (range 25-50). The primary tumors were situated on the right side in 5 patients and on the left side in 5. Following a funicular block with lidocaine 2% an average dose of 80 MBq (range 59-98 MBq) $^{99m}$Tc-nanocolloid in a volume of 0.2 ml was injected into the testicular parenchyma. Shortly after injection, a 10 minute dynamic study was performed followed by static planar images at 15 minutes and 2 hours. SPECT/CT was performed at 2 hours. After image fusion SNs were visualized and their exact anatomic location was determined. The SPECT/CT images were displayed in the operation room to guide SN detection using a laparoscopic gamma ray probe and a portable gamma camera.

Results: Lymphatic drainage to the retroperitoneum was seen in all patients. SPECT/CT identified inter-aortocaval or paracaval SNs in the 5 patients with right-sided tumors, in one patient with an additional SN adjacent to the testicular vessels. In all 5 patients with left-sided tumors para-aortic SNs were visualized and a node along the testicular vessels in 2 patients. A total of 26 SNs were laparoscopically removed (range 1-4 per patient). A SN contained metastases in one case. No recurrences developed in the 9 patients with a tumor-free SN during a median follow-up of 21 months (range 2-50 months).

Conclusion: SPECT/CT enables accurate anatomical localization of retroperitoneal SNs in patients with testicular cancer facilitating their laparoscopic retrieval. Real-time image guidance by a portable gamma camera improves intraoperative SN detection and appears to identify (20%) additional SNs.
INTRODUCTION

The optimal management of regional lymph nodes in stage I testicular cancer remains controversial. A surveillance policy requires an intensive, frequent follow-up with costly examinations, and defers detection and treatment of lymph node metastases to a later stage. The established treatment options for non-seminomatous germ cell tumors consist of surveillance, retroperitoneal lymphadenectomy or chemotherapy, resulting in overtreatment in 65%–75% of the patients.\(^1\)\(^2\) Treatment options for seminomatous germ cell tumors at this stage are surveillance, radiotherapy or chemotherapy. Here, overtreatment is even more frequent, because occult metastases are present in less than 20% of patients.\(^2\)\(^-\)\(^5\) There is a need for diagnostic techniques that enable patients with lymph node dissemination to be treated at an early stage while preventing unnecessary treatment of those without dissemination. To this end, the sentinel node (SN) biopsy was introduced for patients with stage I testicular cancer using intratesticular radiocolloid administration.\(^6\) In this study, preoperative lymphatic mapping was performed using planar lymphoscintigraphy only. However, this technique solely provides two-dimensional information and exact preoperative anatomical SN localization was not possible. The introduction of hybrid SPECT/CT imaging appears to solve this limitation. With the new generation of large field gamma cameras the functional information of SPECT can be combined with the morphological one of CT by acquiring images in one session. This innovative approach enables accurate localisation of retroperitoneal SNs.\(^7\)

Intraoperatively, the urologist localizes a SN guided by acoustic signals from the laparoscopic gamma ray detection probe. However, intraoperative spatial orientation using this device can be difficult, as a laparoscopic probe does not provide visual information. Recently, our initial experience with the use of a portable gamma camera to provide real-time intraoperative visual guidance for laparoscopic SN localization in several urological malignancies was reported.\(^8\) In the present study, our experience with SPECT/CT for preoperative SN localization combined with the use of a portable gamma camera for image guided laparoscopic SN biopsy in stage I testicular cancer patients is evaluated.

METHODS

Patients

The study involved ten patients with clinical stage I testicular cancer referred to The Netherlands Cancer Institute between November 2006 and November 2010 with a mean age of 37 years (range 25-50). All patients had a testicular germ cell tumor, situated on the right side in 5 and on the left side in 5 of them (table 1). Three patients had a past history of stage I testicular cancer on the contralateral side for which they had undergone orchidectomy without SN procedure or lymphadenectomy. Two of them (seminoma) had also received adjuvant radiotherapy, and a third patient (nonseminoma) had been treated with standard platinum-based chemo-
therapy because of elevated serum tumor markers during follow-up. The study protocol was approved by the Medical Ethical Committee and all patients were included after giving informed consent.

**Preoperative procedure**

Local anesthesia was obtained with a funicular block using lidocaine 2%, performed by the urologist in the out-patient clinic approximately 30 minutes before tracer administration. In the nuclear medicine department, an average dose of 80 MBq (range 59-98 MBq) $^{99m}$Tc-nanocolloid (GE-Healthcare, Eindhoven, the Netherlands) in a volume of 0.2 ml with approximately 0.1 ml of air behind the solution to flush any remaining radioactivity in the syringe, was injected with a fine needle (25G) into the affected testicular parenchyma guided by palpation. Immediately after injection, anterior and lateral dynamic images were obtained with a dual-head gamma camera over 10 minutes to visualize the lymphatic flow and to identify early draining lymph nodes. Subsequently, static planar images were acquired. Two hours after injection of the tracer, delayed planar images were obtained to differentiate first-echelon nodes from higher-echelon nodes and to identify unexpected drainage patterns. In the same session, SPECT/CT was performed using a hybrid camera (Symbia T, Siemens, Erlangen, Germany). After correction for attenuation and scatter, the SPECT was fused with CT and analyzed using two-dimensional orthogonal reslicing. The first node in each nodal basin appearing on early planar imaging were considered to be the SN. Nodes appearing later in the same basin were considered to be higher-echelon nodes. The level of a SN was marked on the skin to provide an external centering spot for the laser pointer of the portable gamma camera during the operation.

**Intraoperative procedure**

All patients underwent SN excision and orchidectomy within 6 hours after injection of the tracer. The SPECT/CT images were displayed in the operation room to guide the laparoscopic detection with a laparoscopic gamma ray probe (Europrobe, Euro Medical Instruments, London, UK). In addition, SNs were intraoperatively identified using a portable gamma camera (Sentinella, Oncovision, Valencia, Spain) in 9 patients. In the remaining patient, the portable gamma camera was not yet available. SN localization with the portable gamma camera was facilitated using a radioactive $^{125}$I seed set on the tip of the laparoscopic probe as previously described. A radioactive $^{125}$I seed is used as a pointer, being displayed separately (as a yellow circle) on the screen of the portable gamma camera. The camera could thus visualize the proximity of the probe to the $^{99m}$Tc-signal and thereby provide visual guidance to the SN. Post-excision images were obtained with the portable gamma camera to provide certainty about the completeness of the surgical procedure. A hot node remaining after excision of a SN at the same location was considered part of a cluster SNs and was also removed. All removed SNs were formalin-fixated,
bisected, paraffin-embedded, and cut at a minimum of 6 levels at 50 to 150 μm intervals. Pathological examination included haematoxilin and eosin staining as well as immunohistochemistry staining.

RESULTS

Intratesticular administration of $^{99m}$Tc-nanocolloid under local anesthesia proved to be easy to perform and was well tolerated. No side effects were observed. Lymphoscintigraphy in combination with SPECT/CT showed lymphatic drainage in all ten patients (100%) and a total of 21 SNs were preoperatively identified. SPECT/CT enabled accurate localization of the SNs and provided anatomical reference points to plan the laparoscopy in all patients. The five patients with right-sided tumors had SNs at inter-aortocaval or paracaval locations (figures 1-2). One of them also had a SN adjacent to the testicular vessels. All 5 patients with left-sided tumors had drainage to para-aortic SNs and two of them had an additional SN along the testicular vessels as well (figure 3).

All preoperatively identified SNs were localized and excised (table 1). Higher-echelon nodes were left in place. The portable gamma camera enabled real-time SN visualization in all 9 patients in whom the device was used (100%). Moreover, intraoperative images after excision of a SN showed unexpected significant residual radioactivity at the same location in 3 of these patients, resulting in identification and removal of 5 additional SNs (20%). In total, 26 SNs were laparoscopically removed (range 1-4 per patient).

Histopathological examination revealed metastases in 1 excised SN alongside the testicular vessels. This patient was treated with 4 cycles of carboplatin, etoposide, and bleomycin chemotherapy. All other patients were observed in a surveillance program. No recurrences developed in the 9 patients with a negative SN during a median follow-up of 21 months (range 2-50 months).

DISCUSSION

This study demonstrates the ability of SPECT/CT to provide preoperative anatomical localization of retroperitoneal SNs in patients with stage I testicular cancer. Furthermore, it demonstrates the feasibility and additional value of the use of a portable gamma camera for real-time intraoperative SN visualisation. The route of administration of $^{99m}$Tc-nanocolloid has previously been studied. Intratesticular administration showed only lymph node uptake in the inguinal region, which does not reflect testicular tumor drainage. Intratesticular administration resulted in retroperitoneal SN visualization, in accordance with known drainage patterns. In the above-mentioned study, preoperative lymphatic mapping was performed using planar lymphoscintigraphy only. Planar lymphoscintigraphy images are not able to visualize SNs in relation to the surrounding anatomical structures. This aspect remains crucial when laparoscopy is used to remove SNs located in retroperitoneal areas. In the current study, SPECT/CT visualized SNs in their anatomic habitat in
paracaval, inter-aortocaval, and para-aortic regions in all patients. Moreover, retroperitoneal SNs along the testicular vessels were found in 3 patients, an uncommon area of lymphatic drainage in testicular cancer. Their position was accurately indicated by preoperative SPECT/CT, but not by conventional lymphoscintigraphy (figure 2). In one of these nodes micrometastases were found. Previous reports on the use of SPECT/CT in SN detection also showed favorable results using this modality in other malignancies. Sequential planar images remain essential to distinguish between first- and second-echelon nodes.

Accurate staging with SN biopsy can be achieved only if all nodes on a direct drainage pathway from the tumor are identified and harvested. The procedure in the operating room is facilitated by the anatomical information preoperatively given by SPECT/CT. A portable gamma camera was introduced and evaluated as an additional tool to improve intraoperative SN retrieval in laparoscopic procedures for urological malignancies. An iodine-125 seed pointer was introduced to further facilitate intraoperative SN localization. The use of this device enables real-time display and combination of the visual and acoustic signals to find the site of the SN. This protocol provides good results in terms of laparoscopic SN detection rates (100%). The portable gamma camera can detect residual radioactivity caused by other SNs after removal of the initial SN at the same site. Such adjacent additional SNs are not depicted separately on the SPECT/CT images. This feature resulted in the removal of 20% additional SNs in these series. The intraoperative camera increased the certainty about the completeness of the surgical procedure and complements the laparoscopic gamma probe. The latter does not always detect remaining nodes located deeply in the retroperitoneum because it is difficult to position the tip at the correct angle. We expect that with increasing experience, these aspects will shorten the procedure and increase its reliability.

The refinement of the SN procedure may enable better selection of patients who would benefit from adjuvant treatment after orchidectomy, avoiding costly surveillance and decreases the risk of finding lymph node metastases at a later stage. Further study is required to substantiate the clinical value of the SN procedure in this disease.

**CONCLUSION**

SPECT/CT enables anatomical localization of retroperitoneal SNs in patients with testicular cancer. In addition, real-time image guidance using a portable gamma camera together with a laparoscopic gamma ray detection probe improves intraoperative SN detection and appears to identify 20% additional SNs.

**ACKNOWLEDGEMENTS**

We would like to thank the urologists, surgical assistants, and the technicians of the nuclear medicine department for their contribution.
Figure 1. A) Planar anterior image showing drainage of 99mTc-nanocolloid from the injection site in the right testicle to 2 abdominal lymph nodes as well as radioactivity along the lymphatic channel which decreased in time; indicating lymphatic tract visualization B) Coronal SPECT/CT fusion showing both sentinel lymph nodes (displayed in yellow) alongside the inferior vena cava. C) Laparoscopic SN procedure using a portable gamma camera and a laparoscopic gamma ray detection probe D) Pre-excision image acquired with the portable gamma camera showing both SNs on the left on screen in the operation room. After excision no significant remaining activity is seen on the right.

Figure 2. A) Planar anterior image showing drainage from the right testicle to 2 adjacent lymph nodes in the medial area of the abdomen. Some uptake is also seen in a more lateral located lymph node (arrow) B) Coronal fused SPECT/CT showing both medial lymph nodes between aorta and vena cava, and the lateral one in the trajectory of the right testicular vessels C-D) Transverse SPECT/CT showing 2 SNs displayed in yellow C). The CT image D) shows that the medial SN corresponds with a small lymph node ventral from the area between aorta and cava whereas the lateral one is seen in the ventral area of the psoas muscle (circles). In this funicular SN micrometastases were found at histopathology.
Figure 3. A) Planar anterior image showing drainage from the injection site in the left testicle to 2 abdominal lymph nodes (arrows) and radioactivity along the lymphatic channel indicating lymphatic tract visualization. B) Fused SPECT/CT displayed with 3D volume rendering showing the cranial lymph node alongside the aorta and the caudal one in the retroperitoneal trajectory of the left testicular vessels (arrows). Some remaining activity is seen in the lymphatic channels. C-D) Transversal fused SPECT/CT showing the caudal SN (displayed in yellow) and CT showing the corresponding lymph node ventral from the left psoas muscle (within circle). E-F) The para-aortic SN is displayed in both fused SPECT/CT (yellow on E) and CT (within circle on F).
### Table 1. Patient characteristics and SN results

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<th>Patient</th>
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<th>SPECT/CT findings</th>
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REFERENCES


