Sentinel nodes in complex areas: innovating radioguided surgery
Vermeeren, L.

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Chapter 7

Intra-operative radioguidance with a portable gamma camera; a novel technique for laparoscopic sentinel node localisation in urological malignancies

L. Vermeeren
R.A. Valdés Olmos
W. Meinhardt
A. Bex
H.G. van der Poel
W.V. Vogel
F. Sivro
C.A. Hoefnagel
S. Horenblas

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ABSTRACT

Purpose: To assess the feasibility of intra-operative radioguidance with a portable gamma camera during laparoscopic sentinel node procedures in urological malignancies.

Methods: We evaluated the use of the intra-operative portable gamma camera in twenty patients; sixteen patients with prostate carcinoma, two patients with renal cell carcinoma and two patients with testicular cancer. Intra/peri-tumoural injection of 99mTechnetium-nanocolloid (99mTc) was followed by planar lymphoscintigraphy, SPECT/CT and marking of sentinel node levels. Before laparoscopy a 125 Iodine (125I) seed was fixed on the laparoscopic gamma probe as a pointer of sentinel node seeking. The portable gamma camera was set to display the 99mTc signal for sentinel node localisation and the 125I signal for sentinel node seeking. Matching of these signals on screen indicated exact sentinel node localisation, and consequently this sentinel node was removed.

Results: Mean injected dose was 218 MBq in prostate cancer, 228 MBq in renal cell carcinoma and 88 MBq in testicular cancer. Pelvic sentinel nodes were visualised in all patients with prostate cancer, with uncommonly located sentinel nodes in seven patients. Sentinel node metastases were found in seven patients (one in a uncommonly located sentinel node). Both patients with renal cell carcinoma and patients with testicular cancer had para-aortic sentinel nodes, which were all tumour-free. A total of 59 sentinel nodes was removed. The portable gamma camera enabled real time sentinel node display / identification in eighteen patients (90%).

Conclusion: The use of a portable gamma camera in combination with a laparoscopic gamma probe incorporates intra-operative real-time imaging with improved sentinel node identification in urological malignancies. This procedure might also be useful for sentinel node identification of other deep draining malignancies.
INTRODUCTION

Lymph node staging in urological malignancies is a relevant issue, for the assessment of prognosis and the determination of adequate treatment policy. Unfortunately, conventional imaging techniques are not able to detect very small lymph node metastases. Therefore, operative dissection of the lymph nodes can be used as a staging procedure. However, extended pelvic lymphadenectomy in prostate cancer causes significant morbidity.\textsuperscript{1,2} Clearing of the obturator fossa only, is considered insufficient.\textsuperscript{3-7} To spare patients the morbidity following extensive invasive staging procedures, sentinel node procedures have been introduced. Sentinel node lymphadenectomy through open surgery appeared to be as accurate as staging through extended pelvic lymphadenectomy in a large cohort of prostate cancer patients studied by Weckermann et al.\textsuperscript{3} More recently, laparoscopic sentinel node lymphadenectomy has been introduced to accurately stage prostate cancer.\textsuperscript{4} Following our experience with a laparoscopic gamma probe,\textsuperscript{1,8} we introduced the use of a portable gamma camera to guide laparoscopic localisation of sentinel nodes in urological malignancies.

With the use of a laparoscopic gamma probe only, no visual information is provided, making spatial orientation difficult. Furthermore, discrimination between sentinel node and secondary echelon nodes with a gamma probe often is problematic. The portable gamma camera is capable of detecting two different signals: the signal of 99mTechnetium-nanocolloid (99mTc) for the visualisation of sentinel nodes, plus the signal of a 125 Iodine (125I) seed pointer (which is placed on the laparoscopic gamma probe) as a seeker of the sentinel node localisation. This not only provides exact localisation information, but also helps to quantify the amount of radioactive nodes and the extent of radioactivity within the nodes, making discrimination between sentinel nodes and second echelon nodes more reliable. In this paper we report on our initial experience with this modality as an additional tool for localising sentinel nodes laparoscopically, in a group of patients with urological malignancies.
METHODS

Patients
We evaluated the use of the portable gamma camera (Sentinella, Oncovision, Valencia, Spain) in twenty patients with urological malignancies: Sixteen patients with prostate cancer, two patients with renal cell carcinoma and two patients with testicular cancer. All patients were treated for their malignancies in the Netherlands Cancer Institute between February 2007 and December 2007.

After informed consent, patients without clinical evidence of lymph node metastases were evaluated. Patient characteristics are outlined in Table 1. In prostate cancer, only patients of the intermediate and poor prognostic group were included: clinical stage >T2b, or PSA level >10.0 ng/ml, or Gleason sum score >6.

In renal cell carcinoma stage T1 or T2 patients were included and in testicular cancer inclusion was restricted to stage 1 patients (tumour clinically limited to testis).

Preoperative procedure
Patients received preoperative lymphoscintigraphy after injection of 99mTechnetium-nannocoloid (GE Healthcare, Eindhoven, The Netherlands). In prostate cancer patients, the tracer was injected intra/peritumourally in one depot of 0.1ml per quadrant, guided by transrectal ultrasonography. Each depot of 0.1ml was followed by flushing with approximately 0.7ml of saline. In renal cell carcinoma, intratumoural injection, in two depots of 0.2ml, was guided by ultrasonography and in testicular cancer one depot of 0.2ml was injected intratesticular. Rest radioactivity in the injection device was subtracted from the injected dose to calculate net injected doses.

All patients received planar lymphoscintigraphy and SPECT/CT to evaluate the lymphatic drainage. Planar lymphoscintigraphy was performed at least two times: fifteen minutes after injection of the radiopharmaceutical and two hours after injection of the radiopharmaceutical. SPECT (128x128 matrix, 60x25-s frames) was combined with CT (130Kv, 17 mA, B60s kernel) using a hybrid camera (SymbiaT, Siemens) at after the delayed planar images. After correction for attenuation and scatter, the SPECT was fused with CT and analysed using two-dimensional orthogonal re-slicing.

The nodes appearing first on planar lymphoscintigraphy were considered to be the sentinel nodes. Nodes appearing later in the same stations were considered to be second echelon nodes. Late appearing nodes in caudal areas were also considered to be sentinel nodes.
The levels of the sentinel nodes were marked on the skin to provide a (external) centring point for the laser pointer of the portable gamma camera during operation.

**Intra-operative procedure**

All patients with prostate cancer and testicular cancer were operated within four to six hours after injection of the tracer. Patients with renal cell carcinoma were operated within 20–24 hours after tracer injection. During laparoscopy, we used the portable gamma camera, in combination with the laparoscopic gamma probe, for sentinel node localisation.

This portable gamma camera was equipped with a 4mm pinhole collimator and uses a CsI(Na) continuous scintillating crystal. The pinhole collimator was used to be able to visualise the whole surgical field. With this collimator the field of view depends on the distance between the camera and the imaging plane, while the parallel collimator has a fixed field of view. The field of view is 4x4cm when placed at 3cm from the imaging plane and increases to 20x20cm when placed at a distance of 15cm. Intrinsic spatial resolution is 1.8mm, while extrinsic spatial resolution values are 7mm and 21mm for a distance of 3cm and 15cm respectively. Detection sensitivity for this collimator depends on the distance to the imaging plane, being 708 and 41 cpm/uCi for distances of 3cm and 15cm respectively. These and other technical details of this portable gamma camera are described by Sanchez et al.9 Figure 1 shows the portable gamma camera, which was set to display two separate signals during operation: the signal of 99mTc (indicating the location of the sentinel nodes) and the signal of the 125I seed, placed on the laparoscopic gamma probe (shown as a yellow circle, enabling the visualisation of sentinel node seeking). Before the start of laparoscopy, the 125I seed (10Mbq) was placed on the top of the laparoscopic gamma probe (Europrobe, Euro Medical Instruments, Londen, UK) as shown in figure 1. During the operation this 125I seed is used as a pointer, being displayed separately (as a yellow circle) on the screen of the portable gamma camera. To provide better orientation for the surgeon and to avoid attenuation of the signal, the location of the 125I seed on the top of the laparoscopic gamma probe was marked with a thin black line. In this way, the location of the seed on the probe is visible on screen during laparoscopy after introduction of the probe. The same thin black line was applied to the grip of the laparoscopic gamma probe to directly show the surgeon the upper side of the seed location, during introduction of the probe.

During laparoscopy, the collimator of the portable gamma camera was sterile wrapped to allow manipulation by the surgeon and placed above the previously marked sentinel node levels, using a laser pointer. Matching of the two signals on the screen of the portable gamma
camera indicated correct localisation of the sentinel node, which was subsequently removed. Figure 2 shows the screen of the portable gamma camera, on which two situations are compared. The left view shows the signal of 99mTc (the location of a sentinel node), whereas the right view shows the screen after removal of the sentinel node.

Figure 1 | The portable gamma camera during operation. (A Left) The gamma camera (Sentinella, Oncovision); right: placing the 125I seed on the top of the laparoscopic probe, afterwards marking the location of the seed on the top and grip of the probe to provide visual orientation for the surgeon. (B) Caudal view of the gamma camera during operation, which is placed above the previously marked area (sentinel node level) on the patient’s skin. (C) Cranial view of the gamma camera during operation, which is placed behind the patient’s head. The nuclear medicine physician can use his/her own screen to operate the camera and guide the surgeon. (D) Screen of the gamma camera showing matching of the sentinel node (99mTc) signal and the 125I seed pointer (yellow circle) signal: exact location of the sentinel node by the surgeon’s probe.
Intra-operative radioguidance with a portable gamma camera

All detected hot spots in close proximity to the marked areas (sentinel node level) were considered to be sentinel node and therefore localised with help of the portable gamma camera and removed. Second echelon nodes, as identified preoperatively were left in place. All removed nodes were examined by experienced pathologists.

RESULTS

Patient characteristics as well as sentinel node biopsy results of all patients are outlined in table 1. The patients with renal cell carcinoma were 55 and 51 years old and received a mean injected dose of 228 MBq. The patients with testicular cancer were both 31 years old and they received a mean injected dose of 88 MBq. The mean age of the prostate cancer patients was 64 years and these patients received a mean injected dose of 218 MBq.
Table 1 | Patient characteristics and sentinel node biopsy results

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Age</th>
<th>Stage</th>
<th>Net injected dose</th>
<th>Preoperative imaging (including SPECT/CT): areas of drainage</th>
<th>Excised nodes</th>
<th>Visualisation of excised SN with mini gamma camera</th>
<th>Pathology SN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>73</td>
<td>T3 Gleason 6 PSA 18</td>
<td>238 MBq</td>
<td>Left iliac area</td>
<td>3 SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>62</td>
<td>T3 Gleason 9 PSA 24</td>
<td>207 MBq</td>
<td>Right iliac area</td>
<td>3 SN, 3 non-SN</td>
<td>Yes</td>
<td>Positive (1/6)</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>T3 Gleason 8 PSA 6</td>
<td>230 MBq</td>
<td>Left iliac area</td>
<td>4 SN, 2 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>66</td>
<td>T3 Gleason 8 PSA 6</td>
<td>238 MBq</td>
<td>Left iliac area</td>
<td>4 SN, 3 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>58</td>
<td>T3 Gleason 8 PSA 31</td>
<td>190 MBq</td>
<td>Left iliac area</td>
<td>3 SN, 6 non-SN</td>
<td>No</td>
<td>Positive (2/9)</td>
</tr>
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<td>Prostate</td>
<td>61</td>
<td>T3 Gleason 6 PSA 35</td>
<td>184 MBq</td>
<td>Right iliac area</td>
<td>1 SN, 5 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>62</td>
<td>T3 Gleason 9 PSA 35</td>
<td>195 MBq</td>
<td>Right iliac area</td>
<td>3 SN, 6 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>66</td>
<td>T3 Gleason 7 PSA 22</td>
<td>239 MBq</td>
<td>Left iliac area</td>
<td>4 SN, 8 non-SN</td>
<td>Yes</td>
<td>Positive (3/12)</td>
</tr>
<tr>
<td>Prostate</td>
<td>70</td>
<td>T3 Gleason 6 PSA 16</td>
<td>249 MBq</td>
<td>Right iliac area</td>
<td>4 SN, 3 non-SN</td>
<td>Yes</td>
<td>Negative</td>
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<tr>
<td>Prostate</td>
<td>60</td>
<td>T3 Gleason 8 PSA 15</td>
<td>224 MBq</td>
<td>Right iliac area</td>
<td>3 SN, 6 non-SN</td>
<td>No</td>
<td>Positive (3/9)</td>
</tr>
<tr>
<td>Prostate</td>
<td>65</td>
<td>T3 Gleason 8 PSA 10</td>
<td>225 MBq</td>
<td>Right iliac area</td>
<td>4 SN, 1 non-SN</td>
<td>Yes</td>
<td>Positive (1/5)</td>
</tr>
<tr>
<td>Prostate</td>
<td>58</td>
<td>T3 Gleason 8 PSA 11</td>
<td>194 MBq</td>
<td>Left iliac area</td>
<td>4 SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Age</td>
<td>Stage</td>
<td>Net injected dose</td>
<td>Preoperative imaging (including SPECT/CT): areas of drainage</td>
<td>Excised nodes</td>
<td>Visualisation of excised SN with mini gamma camera</td>
<td>Pathology SN</td>
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<tr>
<td>Prostate</td>
<td>66</td>
<td>T3, Gleason 7 PSA 22</td>
<td>226 MBq</td>
<td>Right iliac area, Left common iliac area, Presacral area, Left inguinal area</td>
<td>4 SN, 1 non-SN</td>
<td>Yes</td>
<td>Positive (1/5)</td>
</tr>
<tr>
<td>Prostate</td>
<td>61</td>
<td>T3, Gleason 7 PSA 15</td>
<td>193 MBq</td>
<td>Left iliac area, Right iliac area</td>
<td>3 SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostate</td>
<td>57</td>
<td>T3, Gleason 7 PSA 130</td>
<td>239 MBq</td>
<td>Left common iliac area</td>
<td>1 SN</td>
<td>Yes</td>
<td>Positive (1/1)</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>T3, Gleason 6 PSA 6</td>
<td>212 MBq</td>
<td>Left iliac area, Presacral area</td>
<td>5 SN, 7 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>55</td>
<td>T1b</td>
<td>233 MBq</td>
<td>Para-aortic area, Parasternal area</td>
<td>1 SN, 1 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>51</td>
<td>T1b</td>
<td>222 MBq</td>
<td>Para-aortic area</td>
<td>1 SN, 1 non-SN (open surgery)</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Testicular</td>
<td>31</td>
<td>Stage 1</td>
<td>96 MBq</td>
<td>Para-aortic area</td>
<td>2 SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Testicular</td>
<td>31</td>
<td>Stage 1</td>
<td>80 MBq</td>
<td>Para-aortic area</td>
<td>2 SN, 4 non-SN</td>
<td>Yes</td>
<td>Negative</td>
</tr>
</tbody>
</table>

SN: sentinel node
Lymphoscintigraphy in combination with SPECT/CT showed lymphatic drainage in all studied patients. SPECT/CT was made to provide more exact preoperative localisation of the sentinel nodes and it appeared to show additional lymph nodes in uncommon areas in some patients. Furthermore, the SPECT/CT fusion images provided very useful anatomic information in all patients, giving anatomical reference points.

Pelvic sentinel nodes were visualised in all sixteen prostate cancer patients, with bilateral drainage in eleven of them. In seven of these patients uncommonly located sentinel nodes were visualised (presacral area, near the umbilical ligament in the abdominal wall or inguinal). The patients with renal cell carcinoma and testicular carcinoma showed drainage mainly to para-aortic sentinel nodes.

A total of 59 sentinel nodes was found and the portable gamma camera enabled real time sentinel node display / identification in eighteen patients (90%). In the other two patients sentinel nodes could be localised with the laparoscopic gamma probe, but no identification with the portable gamma camera could be accomplished.

Sentinel node metastasis were found in seven patients (all prostate cancer patients), with one positive sentinel node located at an uncommon location (near the umbilical ligament in the abdominal wall). The sentinel nodes of the patients with renal cell cancer and testicular cancer were tumour-free.

**DISCUSSION**

Portable gamma cameras have been designed for radioguided surgery and a possible application of this device can be localising lymph nodes. These cameras have been studied with regards to their use in parathyroidectomy and minimal invasive parathyroidectomy, and recently their use in radio-guided occult lesion localisation in breast cancer has been studied. Concerning lymph node localisation, Kopelman et al. showed good results in an animal model. They achieved exact localisation and excision using a portable gamma camera in nine pigs. Furthermore, Mathelin et al. showed localisation of sentinel nodes in eleven breast cancer patients with the synchronous use of a portable gamma camera and a gamma probe. In these patients they were able to successfully estimate the depth of the sentinel nodes preoperatively using the portable gamma camera.

Accurate staging in urological malignancies is a challenging task. In previous studies the failure rate of sentinel node procedures in prostate cancer, caused by undetectable sentinel nodes, varies from 0% to 18%. To improve detection of sentinel nodes, we introduced
and evaluated the use of an intra-operative portable gamma camera as an additional tool for localising radioactive nodes in laparoscopic procedures for urological malignancies. We are the first to describe this novel technique with localisation by means of an iodine-seed pointer.

In testicular cancer as well as prostate cancer, the use of the sentinel node biopsy has been validated in our hospital.\textsuperscript{1,8} Images after fifteen minutes and two hours appeared to be sufficient and therefore patients could be operated on the same day after the delayed images. This resulted in better identification of sentinel nodes intra-operatively due to higher radioactivity in the time of operation. Therefore we decided to operate all prostate cancer patients and testicular cancer patients in a one day protocol. Our first experience with sentinel node procedures in testicular cancer showed good results in terms of visualisation rates after mean injection of 99 MBq of 99mTc.\textsuperscript{8} Therefore, we decided to aim at injecting approximately 90 MBq of 99mTc in patients with testicular cancer. In prostate cancer, the use of sentinel lymph node mapping has been more extensively described and reported injected doses vary from 200 MBq to 250 MBq.\textsuperscript{3-4} In our experience injection of 225 MBq provided good results,\textsuperscript{1} and therefore we continued using this dosage for prostate cancer patients.

In renal cell carcinoma, sentinel node biopsy is still in the validation phase. Therefore, in those patients delayed images after fifteen minutes, two hours, four hours and six hours were made to ascertain that no sentinel nodes would be missed. Due to logistic reasons, those patients were operated the following morning. Concerning tracer injection, the dose of 225 MBq is being validated.

Our intra-operative method of exact localisation with real time imaging, besides localisation with the gamma probe, provided good results in terms of laparoscopic detection rates of sentinel nodes. The use of the 125I seed enables exact sentinel node localisation and the portable gamma camera provides visual and spatial images.

One of the advantages of this modality is the overview it gives; after removal of radioactive nodes, it clearly shows if there is only background radioactivity or if there is still a hotspot left (another sentinel node which has to be removed, or a second echelon node). In this way, it provides certainty about the completeness of the surgical procedure and is clearly complementary to the intra-operative laparoscopic gamma probe. In several cases the use of the portable gamma camera has led to excision of more tissue, because of remaining activity after excision. Although this leads to a modest prolongation of the length of the procedure it makes the removal of the sentinel nodes more accurate. Overall, the use of the portable gamma camera did not seem to interfere with the operation time since, on the other hand, search
for sentinel nodes can be moderated and accelerated by the exact localisation information provided.

In figure 3, the removal of two para-aortic lymph nodes (testicular cancer) is shown. The portable gamma camera enables visualisation of the nodes, which were located with the seed pointer (on the laparoscopic gamma probe). After removal we performed an ex-vivo check: the portable gamma camera shows that both nodes are radioactive. Since the modality provided clear identification of these radioactive nodes, located deep in the abdomen, it is reasonable to believe that localising sentinel nodes of other deep draining malignancies with a portable gamma camera is beneficial as well.

![Figure 3](image)

Figure 3 | Sentinel node located deeply in the abdomen. (A) SPECT/CT fusion image showing two para-aortic sentinel nodes in a patient with testicular cancer. (B) Intra-operative sentinel node identification with the portable gamma camera. (C) Ex vivo examination of the removed sentinel nodes with the portable gamma camera. (D) The gamma camera shows that both of the removed nodes are radioactive.

Laparoscopic gamma probes, especially in adipose patients, may give insufficient guidance if radio-activity is low or if prostate-activity interferes. In those situations, preoperative SPECT/CT images may show which area has to be resected and how the portable gamma camera can offer intra-operative guidance. With the current portable gamma camera it is not possible to
provide three-dimensional information, therefore the head of the camera has to be moved around the patient to see the exact depth of the 99mTc signal in relation to the location of the signal. Possibly in the future this would be overcome by placing a second detection head for simultaneous lateral viewing.

In our study there was non-visualisation with the portable gamma camera in two cases. With higher uptake by sentinel nodes, guidance with the portable gamma camera became better.

With the use of the portable gamma camera no clinical disadvantages were recorded. Possible concerns may be the cost and time consummation for the nuclear medicine physician. Main advantages are: Real-time imaging and the overview of radioactive hotspots in the whole surgical field the portable gamma camera provides, the differentiation between sentinel node and secondary tier, the exact visual localisation of sentinel node by the iodine-seed pointer besides the auditory localisation by the laparoscopic gamma probe, and the certainty the portable gamma camera provides about the completeness and accuracy of the sentinel node excision. With increasing experience, these aspects will lead to shortening of the procedure and increased reliability of the modality.

**CONCLUSION**

The innovative use of a portable gamma camera equipped for simultaneous 99mTc signal and 125I seed pointer signal display incorporates real time imaging to laparoscopic lymphadenectomy with improved sentinel node identification in prostate cancer and other urological malignancies. In our study, in 90% of the patients, sentinel nodes could be exactly located with the portable gamma camera. To optimize sentinel node identification in urological tumours and other deep draining malignancies, the portable gamma camera can be used as an additional tool, besides preoperative imaging with lymphoscintigraphy and SPECT/CT and the use of a gamma probe. Its relative value, compared to preoperative SPECT/CT imaging, has to be further evaluated.
REFERENCES


