Original

Lymphatic Drainage in Prostate Carcinoma assessed by Lymphoscintigraphy and SPECT/CT: Its importance for the Sentinel Node Procedure

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ABSTRACT

Purpose: The goal was to evaluate the sentinel node procedure in relation to different pathways of lymphatic drainage and the areas of pelvic lymphadenectomy in patients with prostate cancer assessed by lymphoscintigraphy and SPECT/CT study.

Methods: Eighteen patients with prostate cancer of intermediate prognosis were injected with 240 MBq of 99mTc-nanocolloid in the peripheral zone of each quadrant of the prostate, guided by transrectal ultrasonography. Tracer administration was also controlled with a portable gamma camera to assure that there was no diffusion outside the prostate. The injection was followed by planar imaging at 15 min. and 2 h, performing a SPECT/CT study at 2 h, with 2 mm slices. On the same day, a laparoscopic sentinel node lymphadenectomy assisted by a gamma probe and a portable gamma camera was performed.

Results: A total of 55 sentinel lymph nodes (SLNs) were visualized. In 17/18 of patients (94%) SLNs were observed outside the obturator region. Twenty SLNs (36%) were observed along the external iliac artery, 14 in the obturator fossa (25.4%), 6 in internal iliac area (11%) and 4 in common iliac region (7.2%). Three SLNs were visualized in presacral (5.4%), paraaortic (5.4%), and pararectal areas (5.4%) and two in paravesical region (3.6%). SLN metastases were found in 6 patients (33%), and in one of them, a SLN located along the common iliac artery, was the only one with metastases.

Conclusion: Lymphatic drainage from the prostate has high individual variability, and direct drainage outside the pelvic area is observed frequently. With the SLN procedure, SLNs outside the routine area of lymphadenectomy can also be sampled to stage the patient more accurately.

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Drenaje linfático del cáncer de próstata a través de la linfogammagrafía y el SPECT/TAC: su importancia en la técnica del ganglio centinela

RESUMEN

Objetivo: Valorar la técnica del ganglio centinela en relación con los diferentes patrones de drenaje linfático y con las áreas de linfadenectomía pélvica en pacientes con cáncer de próstata a través de la linfogammagrafía y el SPECT/TAC.

Método: Se inyectó un total de 240 MBq de 99mTc-nanocolloide divididos en 4 dosis (una para cada cuadrante) mediante control ecográfico transrectal en 18 pacientes con cáncer de próstata con estado superior a 72h. La inyección también fue controlada con una gammacámara portátil para asegurar que no se producía difusión del trazador fuera de la próstata. Tras la inyección, se realizaron imágenes planares a los 15 min y 2 h, junto a un SPECT-TAC a las 2 h con cortes de 2 mm. El mismo día, se realizó la técnica del ganglio centinela vía laparoscopía guiado por una sonda gamma y una gammacámara portátil.

Resultados: Un total de 55 ganglios centinela (GC) fueron visualizados. En 17/18 de los pacientes (94%) se observaron GC fuera de la fosa obturatriz. Se apreciaron 20 GC a lo largo de la arteria ilíaca externa (36%), 14 en la fosa obturatriz (25,4%), 6 en área de la ilíaca interna (11%) y 4 en la ilíaca común (7,2%). Se localizaron también 3 GC en la región presacra (5,4%), paraaórtica (5,4%), y pararrectal (5,4%) y 2 a en región paravesical (3,6%). Se observaron metástasis en el GC en 6 pacientes (33%) y, en uno de ellos, un GC localizado alrededor de la arteria ilíaca común fue el único con metástasis.

Conclusión: El drenaje linfático del próstata presenta una gran variabilidad individual, y con frecuencia se observan drenajes fuera del área pélvica. Con la técnica del GC, los GC situados fuera del área de rutina de la linfadenectomía pélvica pueden ser extirpados, estudiándose con mayor precisión al paciente.

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Introduction

Nodal stage is an important prognostic factor in solid carcinomas. Unfortunately, conventional imaging techniques are not able to detect very small lymph node (LN) metastases.

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Pelvic node lymphadenectomy (PNL) is currently considered the method of choice for regional staging in patients with apparently localized prostate carcinoma, but the anatomical boundaries of the extent of PNL are still controversially discussed. PNL is mostly related to the area including the obturator fossa which consists of the tissue between the external iliac vein and the obturator nerve. Extended PNL includes the obturator fossa but extends its limits to the external iliac vessels as a rule to the lateral border; further the internal iliac is usually cleared from the bifurcation to just beyond the superior vesical artery, and in most descriptions the common iliac artery is only cleared up to the crossing of the ureter. Therefore, the use of PNL has been found to be associated with various complications (venous thrombosis, lower extremity edema, ureteral injury and lymphocele) and its incidence increases with the number of dissected LNs varying from 10.5% for 1-5 LNs to 24.3% when dissection includes more than 20 LNs.

The concept of the sentinel lymph node (SLN) is based on the hypothesis that the lymphatic dissemination of neoplasm progresses in an orderly fashion. SNLs are the first LNs that might be involved. SLN technique has become a routine staging procedure for several malignances, because assessment of nodal involvement can help to determine a patient’s prognosis and therapeutic regimen. Performing preoperative SLN imaging, including planar lymphoscintigraphy and SPECT/CT has optimized detection of SNLs. Sequential planar imaging will remain important for preoperatively identifying early appearing LNs as SNLs. Anatomic localization of these SNLs, however, is achieved by SPECT/CT. Because the introduction of SPECT/CT in SLN procedures has markedly improved SNLs detection and localization.

SLN mapping has several advantages over PNL. It is a less invasive procedure; causes less morbidity and SNLs outside the area of the extended PNL region can also be sampled. Several groups have validated SLN lymphadenectomy with open as well as laparoscopic procedures. Preoperative anatomical SPECT/CT information about the site of the SNLs is important during laparoscopy for both planning of operation and probe detection. This is the reason to display SPECT/CT in the operation room.

Radioguided SLN lymphadenectomy may be performed using a laparoscopic gamma probe only; however, no visual information is provided, making spatial orientation difficult. Furthermore, discrimination between SNLs and secondary echelon nodes with a gamma probe is often problematic. These limitations may be solved using a portable gamma camera. The portable gamma camera is capable to detect two different signals: the signal of 99mTc-nanocolloid for the visualization of SNLs, plus the signal of a seed pointer (which is placed on the laparoscopic gamma probe) as a seeker of the SNLs localization. This notation only provides exact localization information, but also helps to quantify the amount of radioactive nodes and the extent of radioactivity within the nodes, making discrimination between SNLs and secondary echelon nodes more reliable.

The obturator region has traditionally been considered the primary landing site for LNs metastases, but several studies have demonstrated a more variable lymphatic drainage of the prostate with 19-35% of the metastases outside this standard region for PNL. For this reason, many centers advocate an extended field lymphadenectomy, including the LNs in the obturator fossa, along the external iliac, hypogastric and common iliac artery, and even presacral region.

Lymphatic drainage from the prostate is directed mainly towards pelvic SNLs, but drainage towards SNLs outside the pelvic area has also been described. For this reason, the main of this study was to evaluate the different pathways of lymphatic drainage of prostate carcinoma and its importance for the intraoperative SLN identification. A second main of the study was to compare the SLNs location in relation to the habitual area of PNL.

### Materials and methods

#### Patients

We included 18 patients with prostate cancer from February to August 2011, who presented one or more of the following characteristic: clinical stage greater than T2b, prostate serum antigen level greater than 10.0 ng/ml, or Gleason sum score greater than 6. The patients elected to be treated with external radiotherapy in the Netherlands Cancer Institute. All SNL–negative patients received external-beam radiation therapy to the prostate (78 Gy) and 6 months of hormonal treatment. For SNL–positive patients, further treatment included external-beam radiation therapy to the prostate (70 Gy) and pelvic area (50 Gy), and 3 years of hormonal therapy.

The patients (mean age 65.2 y; range, 57–74 y) were injected with mean dose of 220 MBq of 99mTc-nanocolloid (range 197–246 MBq). The injection was well tolerated by all patients. The mean serum PSA value was 25.4 ng/ml (range 5–187 ng/ml). Gleason score was 6 in two patients, 7 in twelve patients and 8 in four patients. The patients were included after giving informed consent. Clinical patient characteristics are summarized in Table 1.

#### Image Acquisition

At our center, performing SPECT/CT after planar imaging is routine for patients who undergo SLN mapping and who are expected to have intraabdominal drainage. Preoperative planar imaging and SPECT/CT were performed after injection of 99mTc-nanocolloid (mean dose of 220 MBq). The tracer was injected peri and intratumorally using four deports of 0.1 ml was injected in each quadrant of the prostate. Administration was guided by transrectal ultrasonography, and tracer injection was flushed with approximately 0.7 ml of saline. The injections were also controlled with a portable gamma camera (Sentinel, Oncovision, Valencia, Spain), to check that there was no diffusion of the radiotracer out of the prostate (Fig. 1). The remaining radioactivity in the injection device was subtracted from the total dose to calculate the net injected dose.

All patients received a prophylactic antibiotic treatment (Ciprofloxacine) over three days, starting immediately before the planned transrectal injection. The transrectal injection procedure was well tolerated, and no postinterventional bleeding or any infectious complication was observed.

Planar imaging was performed at 15 min and again at 2 h after injection of the tracer. After delayed planar images had

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been obtained, SPECT and CT image were acquired using a hybrid camera (Symbia T; Siemens). This system consists of a dual head variable-angle gamma camera equipped with low-energy high-resolution collimators and a multislice spiral CT component optimized for rapid rotation. The SPECT acquisition (256 × 256 matrix, 60 frames, 20 s/frame) was performed using 6 angular steps in a 20-s time frame. For CT (130 keV, 17 mAs, 860 s kernel), 2 mm slices were obtained.

After correction for attenuation and scatter, corresponding SPECT and CT axial 2-mm slices were generated using an Esoft 2000 application package (Siemens). Images were fused using an Osirix Dicom viewer in a Unix-based operating system (MAC OS X, Mac Pro; Apple Inc.). Furthermore, the images were analyzed using 2-dimensional orthogonal reslicing in axial, sagittal, and coronal directions. Also, a 3-dimensional presentation, using volume rendering, was generated to localize sentinel nodes in relation to anatomic structures. All images were available on a separate SPECT/CT screen in the operation theater.

To identify SLNs some well-defined criteria were applied. The first nodes in each station appearing on early planar imaging were considered to be definitively SLNs. Nodes appearing on delay images in areas more cranial were considered to be second–eighth nodes (low probability SLN). If SPECT/CT showed additional hot spots in caudal areas or on a basin with no other drainage or without previous drainage, those hot spots were considered highly probable SLNs. Radioguided SLN lymphadenectomy was assisted by a laparoscopic gamma-probe (Europrobe; Euro Medical Instruments) and a portable mini gamma camera (Sentinella, Oncovision) in the same day. The portable gamma camera was set to display two separate signals during the operation: the signal of 99mTc (indicating the location of the SLN) and the signal of the 125I seed, placed on the laparoscopic gamma probe (enabling the visualization of SLN seeking). Before the start of laparoscopy, the 125I seed (10 MBq) was placed on the top of the laparoscopic gamma probe. During the operation, this 125I seed is used as a pointer, being displayed separately on the screen of the portable gamma camera.

Results

Lymphoscintigraphy in combination with SPECT/CT showed lymphatic drainage in all patients studied, and 14 patients (77.7%) presented bilateral drainage. SPECT/CT was made to provide more exact preoperative localization of the SLNs and it appeared to show additional LNs in uncommon areas in some patients. The detailed distribution of SLNs is shown in Fig. 2.

A total of 55 SLNs were visualized in 18 patients. The number of SLNs per patient ranged from 1 to 5 (mean: 3.05). SLNs were observed most predominant along external iliac artery (20 SLNs = 36.3%). The second frequently site was in the obturator fossa (14 SLNs = 25.4%) followed by internal iliac area (6 SLNs = 10.9%) and common iliac area (4 SLNs = 7.2%). Others SLNs were visualized in presacral (3 SLNs = 5.4%), paraaortic (3 SLNs = 5.4%), pararectal (3 SLNs = 5.4%) and in paravesical region (2 SLNs = 3.6%). Of all patients, 17 (94.4%) exhibited SLNs outside the obturator region, and 8 patients (44%) presented drainage exclusively outside the obturator fossa. In 9 patients (50%) were visualized simultaneously SLNs in obturator fossa and in other areas. Only 1 patient (5.5%) presented exclusively drainage in obturator fossa. The most frequent combination of visualized SLNs areas was the iliac external and obturator fossa (38.8%). Para-aortic SLNs was seen in three patients and a presacral SLNs were found in two patients (Fig. 3). Two patients had a perivesical SLNs, and two patients presented perirenal SLNs too.

Pathologic examination revealed nodal metastases in six patients (33%), and one of them (16.6%) a SLNs located outside of the pelvic PNL area (common iliac area), was the only one with metastases, downstaging the patient.

Discussion

Surgical removal of the pelvic LNs is still considered the gold standard for LN staging in prostate carcinoma. However, the extent of PLN still is a matter of debate. The major groups of LNs, which may receive drainage from the prostate, follow the iliac vessels. The common iliac LNs are located caudal of the aortic bifurcation. The external iliac LNs are found caudal to the bifurcation of the common iliac vessels and cranial to the inguinal ligament. The internal iliac LNs are located more posterior in the pelvis and includes the lateral sacral nodes, the presacral nodes and the anterior nodes that includes hipogastric nodes. Lymphatic drainage from the prostate is also possible to the paraaortic and perivesical basins. We observed that SLNs is most predominant along external iliac artery (36.3%)
and the most frequent combination of visualized SLNs areas was the iliac external and obturator fossa (38.8%).

In the present study the mean of SLNs found per patient was 3.05. The SLNs visualization rate was 100%, and bilateral drainage was observed in 78% of the patients.

In a study involving 1055 prostate cancer patients, Weckermann et al.\textsuperscript{11} found SLNs outside the obturator fossa in 63% of cases and therefore advise to do either SLN biopsy or extended PLN for staging of the pelvis. In this study, some SLNs were also found in the presacral, pararectal and paravesical area, although numbers and exact location were not specifically mentioned. Jeschke et al.\textsuperscript{12} found SLNs outside the obturator fossa in almost half of their laparoscopic SLNs procedure. In this study, presacral SLNs were found in 8 patients (5.7%), and SLNs not localized on pelvic sidewalls were found in 6 patients (4.3%), though the exact localization was not mentioned. In our population, in 94.4% of patients exhibited SLNs outside the obturator region, and 44% presented drainage exclusively outside the obturator fossa. Only 5.5% of all patients presented exclusively drainage in obturator fossa; furthermore, they would be the only ones with adequately staging with the standard PLN. On the other hand, in 94.5% the standard PLN would be not sufficient for accurate staging and some SLNs would be missed.

In 1999 Wawroschek et al.\textsuperscript{18} published their first results in prostate cancer. SLNs in patients with primary tumours were mainly localized in the pelvic and para-iliac area, but, in concordance with previous findings, a substantial number of these patients also had SLNs in an aberrant location. In previous reports we have demonstrated, that SLNs in aberrant locations can be tumour positive.\textsuperscript{13} With lymphatic mapping followed by SLN biopsy, SLNs outside the area of routine dissection can also be sampled. In our series, 5.4% of SLNs were visualized in paraaortic area, and a 14.4% in presacral, pararectal, and paravesical region. All these SLNs would be missed with extended PLN, therefore, the patients would be inadequately staging. These findings confirm that there is

**Figure 2.** Overview of lymphatic drainage patterns of prostate carcinoma. (A) Coronal volume rendering CT view showing SLNs localization. (B) Axial volume rendering CT view showing SLNs in the vesical, rectal and sacral areas.

**Figure 3.** Planar images after 15 min (A) and 2 hours (B) after \textsuperscript{99m}Tc-nanocolloid injection show two hot spots with directly drainage from the prostate. SPECT/CT and 3-dimensional volume rendering reconstruction of the fused SPECT/CT (C) shows an anatomic overview of a presacral SLNs (green circles and white arrow) in the proximity of the left iliac common vessels. Note that on the right SLN is located along the right external iliac artery.
no preferential site of LNs metastases belonging to different lymph drainage systems. Histological examination revealed nodal metastases in six patients (33%), and one of them (16.6%), a SLN located outside of the PNI area (common iliac area), was the only one with metastases, downsizing the patient.

The detection rate of LN metastases increases with the extent of lymphadenectomy and/or with the use of a gamma probe LN detection procedure. In addition, there are some lines of evidence that SPECT imaging before lymphadenectomy may improve the intra-operative detection rate of SLNs in comparison without doing so or with planar imaging. 19

Sequential conventional planar images after tracer injection show successive steps of lymphatic drainage and thus enable SLNs to be distinguished from nodes farther downstream. 9 During the validation phase of SLN biopsy for prostate cancer at our center, 20 no added value from images acquired more than 2 h after tracer injection was observed.

Accurate staging with SLN lymphadenectomy can be achieved only if all SLNs are detected. Because the LN drainage of tumours draining deeply in the abdomen, such as prostate carcinoma, is often complex, preoperative localization is mandatory. SPECT/CT not only provides useful anatomic information about the localization of SLNs but also has been proven to detect additional SLNs. This is especially relevant for SLNs outside the extend lymphadenectomy area and SLNs near the prostate; a significant number of such nodes will be missed without SPECT/CT. 15 In the last years the CT component of the SPECT/CT gammacamera has been improved. Today, as seen in the present study, it is possible to obtain 2 mm fused SPECT/CT images to despite radioactive SLNs and at the same time to assess the corresponding LNs on CT. SPECT/CT may also give important information for the planning of radiotherapy concerning treatment volume and optimization of irradiation fields in the pelvis. If SPECT/TC and planar imaging do not show the SLNs, extended PLN is the best remaining option for accurate staging, although it is not 100% accurate and it can cause a greater morbidity.

Portable gamma cameras have been designed for radioguided surgery, and a possible application of this device includes localization of LNs by laparoscopy. These cameras have been used also in parathyroidecotomy and in breast cancer. One of the advantages of this modality is the continuous images it gives; after removal of radioactive nodes, it can assess if there is only background radioactivity or if there is still a SLN which has to be removed. In this way, it provides certainty about the completeness of the surgical procedure and is clearly complementary to the intraoperative laparoscopic gamma probe. 2

An important argument for SLN dissection is its lower morbidity compared to extended lymphadenectomy. Especially surgery in the presacral and paraaortal areas is compromised by bleeding from the venous plexus that can be difficult to control. 1

An additional note of caution has to be issued in those patients with macroscopic nodal disease in whom the normal architecture has been destroyed by metastases. In this cases, the visualization of a LN as an SLN may fail because of missing physiologic drainage. 19

This is the main reason for false-negative SLN. Also, a washout of the nanocolloids into the next LN level may occur, depending on the time interval between injection of the tracer substance and sentinel probing. 6

Conclusion

Lymphatic drainage from the prostate has a high individual variability, and direct drainage outside the pelvic area is observed frequently. Integrating high resolution SPECT/CT and intraoperative imaging to the SLN procedure, SLNs outside the routine lymphadenectomy area can also be sampled.

Conflicts of interest

The authors have no conflicts of interest to declare.

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