



## Penile Cancer

# Anatomical Mapping of Lymphatic Drainage in Penile Carcinoma with SPECT-CT: Implications for the Extent of Inguinal Lymph Node Dissection

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### Abstract

**Background:** Knowledge regarding the lymphatic drainage pattern of penile cancer is the basis for the extent of inguinal lymph node dissection for this disease.

**Objective:** To prospectively analyze the lymphatic drainage pattern of penile carcinoma using SPECT-CT and evaluate the implications for the extent of inguinal lymph node dissection.

**Design, Setting, and Participants:** The lymphatic drainage patterns of 50 patients scheduled for dynamic sentinel node biopsy were analyzed using a hybrid SPECT-CT scanner.

**Measurements:** A total of 86 clinically node-negative (cN0) inguinal and pelvic regions was evaluated. The sentinel and higher-tier nodes on SPECT-CT were divided into different zones in the groin and pelvic region. The groin was divided according to Daseler's five zones, four zones obtained by drawing a vertical and horizontal line over the saphenofemoral junction and one zone directly overlying this junction. The nodes in the pelvic region were classified into three zones: the external iliac/obturator zone, the common iliac zone, and the paraaortal zone.

**Results and Limitations:** Lymphatic drainage was visualised in 82 of the 86 cN0 groins (95.3%). A total of 115 sentinel nodes and 182 higher-tier nodes was found. All sentinel nodes were located in superior and central inguinal zones. The higher-tier nodes were located in the groin and pelvic region. No lymphatic drainage was seen to the inferior two regions of the groin. A potential limitation of the study is that the unilateral lymphatic drainage seen in some patients could be normal, but it could also be caused by blockage of lymphatic drainage due to a grossly involved metastatic lymph node. Another possible limitation is that this study relies on the quality and accuracy of lymphoscintigraphy and the subsequent sentinel node procedure.

**Conclusions:** All sentinel and higher-tier nodes were located in the superior and central inguinal zones and the pelvic region. No lymphatic drainage to the inferior inguinal zones was seen. This suggests that the extent of inguinal node dissection in cN0 patients could be reduced to removal of the superior and central inguinal zones. This may decrease the extensive morbidity associated with this procedure.

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## 1. Introduction

More than 95% of penile malignancies are squamous cell carcinomas [1]. Like other squamous cell carcinomas, penile carcinoma has a lymphatic dissemination pattern. Haematogenic spread only occurs in advanced stages of disease [2]. The primary site of metastasis is the inguinal region, and the tumour status of these nodes is the main prognostic factor for survival [3–6]. The treatment of patients with proven tumour-positive inguinal nodes is clear-cut and consists of a radical inguinal lymph node dissection. This procedure is associated with a significant morbidity such as infectious complications and oedema [7].

The management of clinically node-negative (cN0) patients poses a clinical dilemma. Around 20% of cN0 patients have occult inguinal metastasis, and there is evidence that this group of patients benefits from early surgical removal of the inguinal nodes, compared to a wait-and-see policy [8]. However, an elective bilateral inguinal node dissection is unnecessary in the majority of cN0 patients. Predicting the presence of occult nodal metastasis based on primary tumour characteristics is unreliable, and current imaging techniques cannot accurately detect occult metastasis [9]. Dynamic sentinel node biopsy is a suitable technique to identify nonpalpable metastasis, although its use is not widespread [10,11].

Therefore, the current management of cN0 patients consists of an elective bilateral inguinal lymph node dissection in most centres. In 1988, Catalona proposed a modified inguinal node dissection to reduce the area of dissection and decrease the rate of complications in cN0 patients with penile carcinoma [12]. In this modified procedure, the focus of dissection is on the lymph nodes medial and superior to the saphenofemoral junction. However, the oncological safety of this procedure has been questioned, and inguinal recurrences were reported after modified inguinal node dissection in up to 15% of cases [13,14]. Apparently, not all draining nodes of the penis are removed in this modified procedure.

Lymphoscintigraphy to visualise lymphatic drainage is an essential element of sentinel node biopsy. Recently, hybrid single-photon emission computed tomography–computed tomography (SPECT-CT) scanners have become available, allowing for the mapping of lymphatic drainage after injection with a radioactive tracer with unprecedented detail and in relation to anatomical landmarks obtained from the CT images.

The purpose of this study was to prospectively determine the anatomical location of the draining lymph nodes in penile carcinoma with SPECT-CT

and to evaluate the implications for the extent of inguinal lymph node dissection in cN0 patients.

## 2. Methods

We evaluated the drainage patterns of 50 consecutive patients in whom SPECT-CT was performed between August 2006 and August 2007. All patients had a penile tumour >T1/G2 and were scheduled to undergo dynamic sentinel node biopsy [10]. Patient and tumour characteristics are provided in Table 1. In addition to the standard planar lymphoscintigraphic images, SPECT-CT images were acquired in all patients. Only the drainage pattern of cN0 groins and pelvic regions was analyzed in order to avoid groins with possible altered drainage due to tumour blockage in palpable nodes. A preoperative ultrasound was performed in all patients in order to identify potentially involved lymph nodes that were not palpable to further reduce the risk of tumour blockage and rerouting. Of the 50 patients, 14 were unilaterally cN0. Thus, a total of 86 groins and pelvic regions was assessed.

All scans were evaluated by a nuclear physician. A sentinel node was defined as a lymph node that receives lymphatic drainage directly from the primary tumour.

### 2.1. Lymphatic drainage of the penis

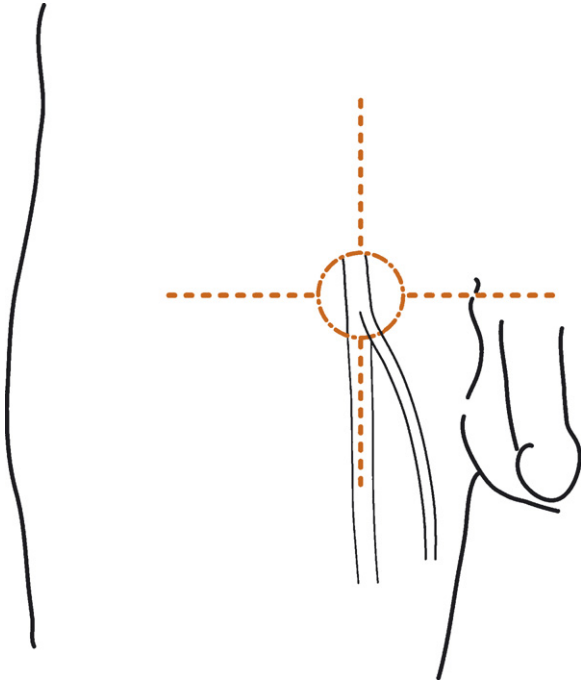
The primary region of lymphatic drainage of the penis is the inguinal region. Daseler et al divided the inguinal region into five zones: four quadrants obtained by drawing two perpendicular lines over the saphenofemoral junction and one zone directly overlying this junction (Fig. 1). For this analysis, we divided the subsequent pelvic and paraaortal lymph nodes into three zones: the trajectory of the external iliac vessels/obturator nerve, the common iliac vessels, and the paraaortal nodes.

### 2.2. Technique of lymphoscintigraphy

Conventional planar lymphoscintigraphic images were obtained from all patients 1 d before sentinel node surgery,

**Table 1 – Patient and tumour characteristics**

No. of patients	50
Median age (range)	64 (34–96)
T-stage	
T1	18
T2	27
T3	4
Tx	1
Tumour differentiation	
Well	8
Intermediate	29
Poor	9
Grade could not be assessed (Gx)	4
Location of the primary tumour	
Glans only	29
Glans/prepuce	18
Glans/prepuce/urethra	1
Shaft	2



**Fig. 1 – Division of the inguinal region into 5 zones according to Daseler.**

after intradermal, peritumoural injection of the technetium-99m nanocolloid (Nanocoll, GE Healthcare, Eindhoven, the Netherlands). Immediate dynamic imaging was performed followed by static imaging at 30 min and 2 h post-injection using a dual-head gamma camera (ADAC Vertex, Milpitas, CA, USA). Anterior and lateral images were routinely obtained with simultaneous transmission scanning using a cobalt-57 flood source to outline the body contour for orientation.

SPECT-CT images were made immediately after the 2-h planar images. The SPECT-CT system (Symbia T,

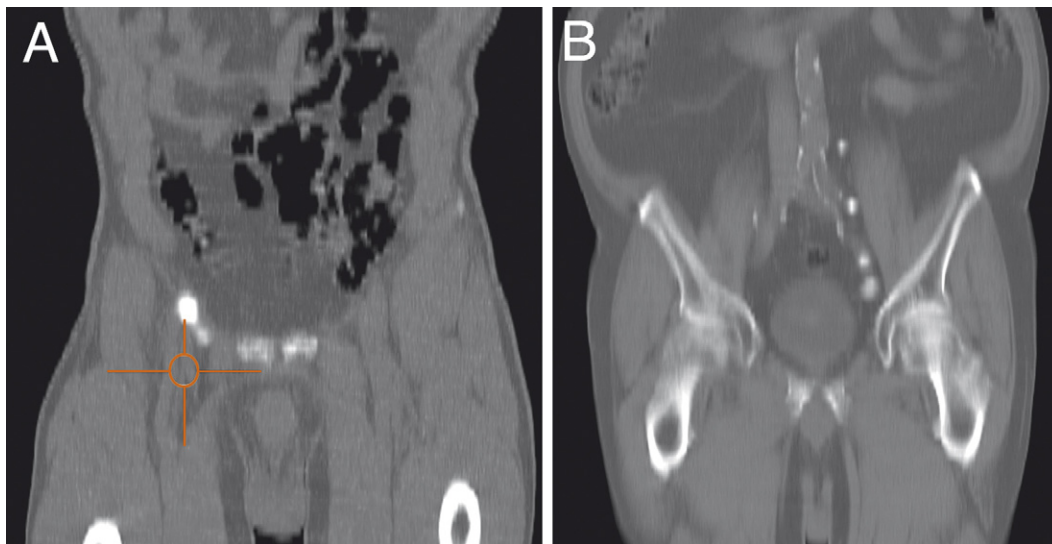
Siemens, Erlangen, Germany) consisted of a dual-head variable-angle gamma camera equipped with low-energy, high-resolution collimators and a spiral CT optimized for rapid rotation. SPECT acquisition (matrix  $128 \times 128$ , 60 frames in a 25 s/frame) was performed using  $6^\circ$ -angle steps. For CT (130 kV, 17 mAs, B60s kernel), 5-mm slices were obtained. After reconstruction, SPECT images were corrected for attenuation and scatter. Both SPECT and CT axial 5-mm slices were generated using an Esoft 2000 application package (Siemens, Erlangen, Germany). These were transferred to picture-archiving and communication systems after generation of Dicom files. Fusion of images was performed using an Osirix Dicom viewer (version 2.7.5) in a Unix-based operating system (MAC OS X, MacPRO, Apple Inc, Cupertino, CA, USA).

### 2.3. Assignment of sentinel and higher-tier nodes

In order to accurately determine the zone in which the radioactive nodes were located, the fused SPECT-CT images were studied using orthogonal reslicing. On the generated coronal images, the saphenofemoral junction was identified in order to project Daseler's zones. The radioactive nodes were then classified according to the five zones of Daseler or their subsequent regions. A distinction was made between the sentinel nodes and higher-tier nodes (Fig. 2).

### 2.4. Sentinel node surgery and pathology evaluation

The day after lymphoscintigraphy and SPECT-CT, all patients underwent surgery to remove the sentinel node(s). Shortly before the operation, 1 ml of patent blue dye (Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected intradermally around the tumour. Sentinel nodes were identified intraoperatively with the aid of the preoperative lymphoscintigraphic and SPECT-CT images, a gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany), and the patent blue dye. All harvested sentinel nodes were



**Fig. 2 – Coronal fused SPECT-CT image showing the right saphenofemoral junction with applied Daseler's zones (A) and radioactive higher-tier nodes along the trajectory of the iliac vessels and aorta (B).**

**Table 2 – Location of sentinel nodes**

Drainage zone	Location of sentinel nodes (n = 115)	Location of higher-tier nodes (n = 182)
Medial superior zone	84 (73%)	20 (11%)
Lateral superior zone	10 (8.7%)	3 (1.6%)
Central zone	21 (18.3%)	8 (4.4%)
Medial inferior zone	0	0
Lateral inferior zone	0	0
External iliac/obturator zone	0	113 (62.1%)
Common iliac zone	0	26 (14.3%)
Paraaortal zone	0	12 (6.6%)

histopathologically analyzed for metastasis with serial sectioning (150- $\mu$ m slices) and immunohistochemical staining.

### 3. Results

On the conventional lymphoscintigraphic images, drainage was seen in 81 of the 86 cNO groins, leading to a visualisation rate of 94.1%. All nodes that were

visualised on the planar images were also visible on the SPECT-CT images. In one groin with nonvisualisation on conventional scintigraphy, a sentinel node could be seen on SPECT-CT images, giving a total visualisation rate of 95.3%. The saphenofemoral junction could be identified on the fused SPECT-CT images in all patients.

#### 3.1. Location of sentinel nodes and higher-tier nodes

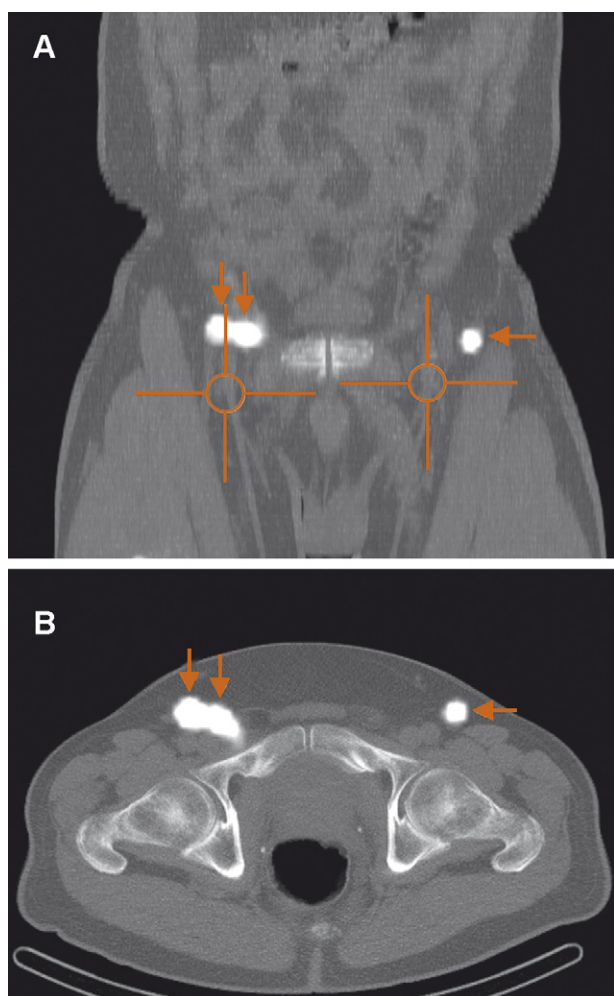
A total of 115 sentinel nodes was found on scintigraphy and SPECT-CT. All sentinel nodes were located in the inguinal region, and no direct drainage (circumventing the inguinal region) to the pelvic lymph nodes was seen (Table 2). The majority (73%) of sentinel nodes was located in the medial superior zone, 8.7% in the lateral superior zone, and 18.3% in the central zone. No drainage was seen to the two inferior quadrants (Fig. 3). The majority (62.1%) of higher-tier nodes were found in the external iliac zone.

#### 3.2. Findings during surgery

Intraoperative use of blue dye did not reveal sentinel nodes in the groins without preoperatively visualised drainage. A total of 122 sentinel nodes was removed and histopathologically analyzed. The higher number of removed nodes compared to the number of preoperatively identified nodes is due to the clustering of nodes. A cluster of sentinel nodes in close proximity to each other cannot always be identified as separate nodes on the preoperative images.

#### 3.3. Histopathological findings

A total of nine tumour-positive sentinel nodes was found in eight patients. All tumour-positive nodes were located in the medial superior quadrant. Patients with a tumour-positive sentinel node underwent a completion radical inguinal lymph node dissection on the affected side. Additional nodal metastases in the inguinal lymph node



**Fig. 3 – Coronal fused SPECT-CT images showing with applied Daseler's zones. Two nodes were classified as lateral superior and one as medial superior (A) and the same nodes in the axial view (B).**

dissection specimen were found in one patient, with 3 of the 17 nodes being positive.

#### 4. Discussion

Several interesting findings regarding the lymphatic drainage of the penis came to light in this study. First, out of 86 examined cN0 groins, no drainage to the inferior quadrants of Daseler's zones was observed. This is in accordance with the results from Riveros et al and Cabañas, who reported on lymphangiographic studies of the penis in which no drainage to the most inferior inguinal nodes was seen [15,16].

Another finding is the absence of sentinel nodes (and thus direct drainage) to the pelvic lymph nodes. Although several anatomical studies have described the possibility of direct drainage of tumours on the glans or urethra to the pelvic nodes [17–19], this has never been confirmed in clinical studies. The majority of tumours in this series were located on the glans of the penis (Table 1). Further confirming the rarity of direct pelvic drainage is a large series of 100 lymphangiographic examinations of the drainage of the penis in which no direct drainage to the pelvic region was found [16].

A third interesting result of this study is the fact that around 10% of the sentinel nodes were located in the lateral superior zone. We could not detect a relation between the primary tumour location and the absence or presence of a sentinel node in the lateral superior zone.

The lateral superior zone is not dissected in the modified inguinal lymph node dissection proposed by Catalona. Although none of the nine tumour-positive nodes in this series were located in this zone, the fact that sentinel nodes are occasionally present is, in our opinion, a reason to expand the modified inguinal lymph node dissection to include the lateral superior zone. We speculate that the reason that no tumour-positive node was found in the central or lateral superior zone is due to chance because of the low total number (nine in eight patients) of positive nodes in this series.

There are some potential limitations to this study. In this series, lymphatic drainage could be visualised in 95% of cN0 groins, with unilateral drainage of the tumour in four cases. Unilateral drainage of the penis could be the normal physiological situation in some people, but it could also be caused by blockage of lymphatic drainage due to a grossly involved metastatic lymph node. The role of blockage was probably limited in this study, because all patients in this series underwent preoperative ultrasound in order to

identify nodes with substantial disease [10,20]. Another possible limitation is the fact that this study relies on the quality and accuracy of lymphoscintigraphy and the subsequent sentinel node procedure. The use of sentinel node biopsy to manage cN0 patients is still not widespread, and the feasibility of this procedure in lower-volume centres is the subject of debate [21–23]. Because of the limited follow-up time in this series, a potential false-negative sentinel node due to nonvisualisation on the lymphoscintigraphic images and that was not discovered with the preoperative ultrasound could not have become clinically evident. However, in a recent analysis of the sentinel-node procedure for penile carcinoma in patients with a follow-up of at least 2 yr, a sensitivity of 95.2% was found [10]. Furthermore, our technique for lymphoscintigraphy is proven to provide reproducible results [24]. We believe that these results form a solid basis for this study.

Based on the results of this study, we are currently prospectively analyzing the radical inguinal lymph dissection specimens of patients undergoing a completion dissection after a tumour-positive sentinel node. Using markings that are added during the operation, the pathologist classifies any additional tumour-positive node(s) into Daseler's zones. If this analysis confirms the results from this study, this clears the path for definite introduction of the reduced (to the superior and central zones) inguinal lymph node dissection at our institute.

#### 5. Conclusions

Penile cancer drains directly to nodes in the superior and central zones of Daseler. This implies that a modified inguinal lymph node dissection should include all three of these zones, but not the inferior two zones. Furthermore, this study confirms the absence of lymphatic drainage to the inferior zones of the groins as well as the absence of direct drainage to the pelvic region.

**Author contributions:** Joost Leijte had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Leijte, Valdés Olmos, Nieweg, Horenblas.

*Acquisition of data:* Leijte, Valdés Olmos.

*Analysis and interpretation of data:* Leijte, Valdés Olmos.

*Drafting of the manuscript:* Leijte, Valdés Olmos, Nieweg, Horenblas.

*Critical revision of the manuscript for important intellectual content:* Leijte, Valdés Olmos, Nieweg, Horenblas.

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Supervision: Horenblas.

Other (specify): None.

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### Editorial Comment on: Anatomical Mapping of Lymphatic Drainage in Penile Carcinoma with SPECT-CT: Implications for the Extent of Inguinal Lymph Node Dissection

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Indications and extension of inguinal lymph node dissection are the mainstays in the treatment of patients with squamous cell carcinoma of the penis [1]. Clinical stage of the groin lymph nodes, pathologic variables of the primary tumour, and, for those urologists who are experienced in dealing with the technique, dynamic sentinel node biopsy (DSNB), are the most commonly used tools to plan the treatment of the groin nodes [2–4]. According to European Association of Urology (EAU) guidelines, bilateral modified lymphadenectomy, involving the preservation of the saphenous vein and restricting resection medial to the femoral vessels, might be indicated in the case of prophylactic lymphadenectomy. However, bilateral radical lymphadenectomy has to be advised in cases involving therapeutic procedures, as well as in cases of positive nodes at frozen section during modified dissection (reference 1 in the text).

Leijte et al reported an anatomical study of the lymphatic drainage in patients with squamous cell carcinoma of the penis. The study dealt specifically with single-photon emission computed tomography (SPECT-CT) and DNSB in 50 patients with cN0 squamous cell carcinoma of the penis. The authors showed that SPECT allowed the visualization of the lymphatic drainage in 95.3% of the patients. All the sentinel nodes were located in the inguinal region (73% in the medial superior zone, 8.7% in the lateral superior, and 18.3% in the central one, as described in the Daseler zone system), with the nine tumour-positive ones identified in the medial superior quadrant [5].

The study reproduced with modern technologies the original studies of Cabañas with lymphangiography (references 15 and 16 in the text). The findings from SPECT-CT and DSNB allow some interesting conclusions to be drawn about the extension of lymphatic drainage, which seems not to extend to the most inferior Daseler zones, but occurs mainly in the medial superior zone and the lateral superior zone (in about 10% of cases). Consequently, it may be time to evaluate a modification of the template for inguinal lymphadenectomy, including all the inguinal nodes placed cranially or at the level of the saphenofemoral junction, laterally and medially to the femoral vessels and excluding the distal ones. Further studies on the pathologic specimens of inguinal lymphadenectomy, submitting the lymph nodes from the different areas separately for pathologic evaluation, are clearly needed. Moreover, to be of real clinical value, it has to be shown that a reduction in the complication rates of lymphadenectomy might be obtained avoiding the dissection of the inferior nodes.

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After optimizing the reliability and safety of dynamic sentinel node biopsy in cNO penile cancer patients, reducing false negative and complication rate to 4.8% and 5.7% respectively [1], the Netherlands Cancer Institute Penile Cancer Group studied the anatomical mapping of the lymphatic drainage of penile cancer in 50 consecutive patients (August 2006–August 2007!) who underwent SPECT-CT imaging immediately after dynamic and static imaging, 30 min and 2 h after injection of technetium-99m nanocolloid [2]. The inguinal regions were divided according to the five Daseler zones [3] and the nodes of the pelvic regions were classified separately. Lymphatic drainage was visualized in 82 of the 86 category cNO-groins, and a total of 115 sentinel nodes were found on scintigraphy and SPECT-CT. A total of 122 sentinel nodes were removed and only 9 tumour positive sentinel nodes were found in 8 patients. All tumour-positive nodes were located in the medial superior quadrant, but 9% of sentinel nodes were located in the lateral superior quadrant and another 18% were found in the central zone. No sentinel nodes were found both in the two inferior quadrants nor in the pelvic regions. This group of patients with few metastatic

sentinel nodes can lead one to the conclusion that early nodal metastases may be expected in the central and the two superior Daseler regions, but not in the two lower regions, which can be spared lymph node dissection in early disease. The advantage of this lymph node mapping over the one used by Cabañas is simplicity and improved technology: The principle of lymphangiograms via the dorsal lymphatics of the penis was good, but the defined location of the sentinel lymph node center was not as clear [4,5].

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