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ARTICLE

DaPeCa-8: drawing the map of lymphatic drainage in patients with invasive penile cancer – evidence from SPECT/CT and sentinel node surgery

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ABSTRACT

Background: Anatomy of the lymphatic drainage guides the extent of inguinal lymph node dissection in penile cancer.

Objective: To prospectively assess the lymphatic drainage of penile cancer with single-photon emission computed tomography CT (SPECT-CT) and implications for the extent of inguinal lymph node dissection.

Methods: We assessed the lymphatic drainage of 62 patients with at least unilateral clinical lymph node-negative (cN0) status with SPECT-CT at our tertiary referral centre. We evaluated 122 cN0 inguinal basins and compared them to the histopathological outcome. The inguinal regions were divided into ten different Daseler zones on SPECT-CT. The surgical team filled in a corresponding scheme at sentinel node biopsy and sent lymph nodes from each Daseler zone individually for histopathological examination.

Results: SPECT-CT successfully visualized lymphatic drainage in 116 of the 122 cN0 inguinal basins (95.1%). The vast majority of sentinel nodes and all metastatic nodes were located in central and superior inguinal zones, including six metastatic nodes in lateral superior zones. Minimal lymphatic drainage was seen to the inferior Daseler zones and no metastatic deposits were located here. No direct pelvic drainage was observed.

Conclusions: Penile cancer lymphatic drainage is primarily to sentinel in the superior and central zones of Daseler. Colleagues practicing a modified inguinal lymph node dissection as a standard in cN0 patients are encouraged to include all these zones, while the inferior zones can be omitted. This study confirms the absence of lymphatic drainage directly to the pelvic region and supports the practice of omitting pelvic nodes from sentinel node biopsy.

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Introduction

Penile cancer together with breast cancer and melanoma became a model disease for the development of the sentinel node concept [1]. The histopathology of malignant primary penile tumours is dominated by penile squamous cell carcinomas (pSCC) which account for over 95% of cases. The predominant pattern of dissemination for squamous cell carcinomas is via the lymphatic system and in this respect, pSCC is no exception with a predictable lymphatic dissemination pattern to first inguinal, later pelvic and para-aortic lymph nodes [2]. Haematogenic dissemination only very rarely occurs as the primary route but is observed in advanced stages of disease [3]. Inguinal lymph node status is an important prognostic factor in pSCC [4–7]. Clinically lymph node-positive (cN+) patients are treated with inguinal lymph node dissection (ILND) and have a high risk of treatment-associated morbidity [8–10]. The dilemma inherent to clinically node-negative (cN0) patients carries the risk of overtreatment with associated morbidity of 75–80% of pathologically negative (pN0) patients on the one side and the fear of missing beneficial early surgical removal of inguinal metastases in 20–25% of pN + patients in a wait-and-see approach [11]. Nomograms based on primary tumour characteristics have failed to reliably predict the presence of occult nodal metastasis and the same is true for imaging [12–15]. Sentinel node biopsy (SNB) is a minimally invasive technique to identify non-palpable metastasis with an acceptable morbidity profile [16,17]. Some centres have been hesitant to incorporate SNB into practice and still perform an elective bilateral ILND. Catalona et al. proposed a modified inguinal node dissection to reduce morbidity in cN0 patients [18]. The Catalona procedure limits the boundaries of dissection to the lymph nodes medial and superior to the saphenofemoral junction. The oncological safety of this technique was questioned by some studies [19–21] but supported by single-photon emission computed tomography CT (SPECT-CT)-based anatomical mapping study [2]. The purpose of this study was to add data to this controversy by investigating the anatomical location of the draining lymph nodes

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Table 1. Patient characteristics of 62 penile squamous cell carcinoma patients with at least unilateral clinical lymph node negative (cN0) status.

Patients, No.	62
Inguinal basins, No.	122[a]
Age at diagnosis, year., median (IQR)	68.7 (62.0–73.4)
Body mass index, kg/m^2, median (IQR)	27.6 (24.0–31.4)
EAU risk group, no. (%)	
Low risk (pT1G1)	19 (30.6)
Intermediate risk (pT1G2, no LVI)	5 (8.1)
High risk ($\geq$pT2, G3, or LVI)	38 (61.3)
Penile Treatment, No. (%)	
Local resection	25[b] (40)
Partial penectomy	31[c] (50)
Total penectomy	6 (10)
Histopathological subtype, No. (%)	
Classical	45 (73)
Verrucous	6 (10)
Basaloid	7 (11)
Sarcomatoid	2 (3)
Mixed	2 (3)
Pathological N stage, No. (%)	
N0	48 (77)
N+	14 (23)
N1	8 (13)
N2	2 (3)
N3	4 (6)

IQR: interquartile range; EAU: European Association of Urology; LVI: lympho-vascular invasion.
[a]Two inguinal basins excluded due to unilateral clinical lymph node positive findings, positive fine needle aspiration cytology and direct inguinal lymph node dissection. [b]Includes circumcision alone, local resection and laser. [c]Includes glansectomy.

with SPECT-CT in a tertiary referral centre in Denmark and to assess the necessary extent of inguinal lymph node dissection in cN0 patients.

Materials and methods

We analysed the drainage patterns on SPECT-CT scans of 62 patients treated for invasive pSCC during a four year period. All patients were scheduled to undergo at least unilateral SNB. Patient characteristics are summarized in Table 1. Exclusively the drainage pattern of cN0 inguinal basins was evaluated. In this way, we hoped to minimize the potential risk of altered drainage due to tumour blockage from bulky tumour deposits in palpable nodes. Of the 62 patients, 2 were unilaterally cN0 leaving a total of 122 inguinal basins to be evaluated.

Scans were evaluated by a nuclear physician. The sentinel node was defined as a lymph node receiving lymphatic drainage directly from the primary tumour. This is typically one or two nodes per inguinal basin. Higher tier nodes receiving the radio-active tracer 99mTc nanocolloid at a delayed time point or with a relatively low tracer uptake compared to the sentinel nodes were marked and described as secondary draining nodes.

Daseler zones

The primary lymphatic drainage of the penis is via the inguinal regions. Daseler divided the inguinal regions into five zones on each side totaling ten zones. Perpendicular lines cross at the sapheno-femoral junctions dividing the left and right inguinal region into lateral superior zones and medial superior zones, lateral inferior zones, and medial inferior zones and the central zones above the sapheno-femoral junctions (Figure 1) [22].

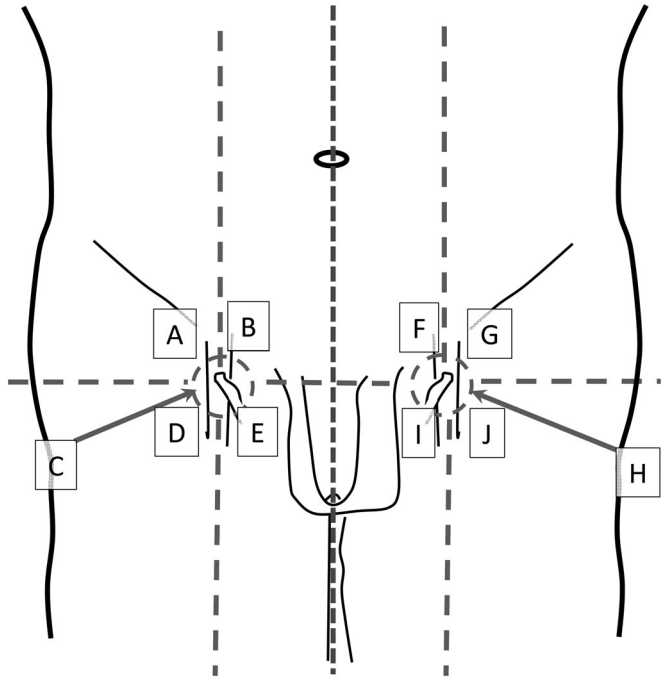

Figure 1. Inguinal regions divided into ten Daseler zones, A–J. Perpendicular lines cross at the sapheno-femoral junctions dividing the left and right inguinal region into lateral superior zones A + G, medial superior zones B + F, lateral inferior zones D + J, medial inferior zones E + I and the central zones above the sapheno-femoral junctions C and H.

Sentinel lymph node biopsy (SNB)

The SNB technique and diagnostic accuracy has previously been described in detail [16,17]. In addition to the EAU guidelines recommendation of invasive nodal staging for bilateral clinically node-negative (cN0) patients with $\geq$ T1G2 pSCC, the national Danish guidelines include the possibility of performing SNB on T1G1 patients. Briefly, the day before surgery 2–4 intradermal injections (0.2–0.4 ml) with a total of 80–110 MBq 99mTc nanocolloid (Nanocoll®, GE Healthcare, Milan, Italy) were injected in the vicinity of the primary penile tumour. After 1–3 h a single-photon emission computed tomography-CT (SPECT-CT) with a 64 slice General Electric Discovery 690 PET/CT, GE, Little Chalfont, UK was recorded. After reconstruction, SPECT-CT images were corrected for attenuation and scatter and transferred to picture-archiving and communication systems. To accurately determine the zone in which the radioactive nodes were located, the fused SPECT-CT images were studied using coronal images after orthogonal reslicing. 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. Possible sentinel nodes were marked on the electronically available images with permanent markings available in the system.

Surgical scheme

The day after SPECT-CT, all patients underwent surgery to remove the sentinel lymph nodes. During surgery, lymph nodes were located with aid of the preoperative imaging, thorough intra-operative palpation of the exposed wound, and a handheld gamma probe, and nodes were harvested through small inguinal incisions. The exploration of an inguinal basin ceased when the radioactivity counts reached background levels and no further palpable lymph nodes were identified in the field. Obvious higher tier nodes located in the pelvis or further cranially were not removed. In the case of a radio-tracer silent inguinal basin, the inguinal basin was surgically explored and at least one lymph node was located by palpation and removed as the SLN. For this study, the surgical team marked a Daseler scheme with the relevant locations of the removed nodes.

Histopathology

The histopathological inguinal lymph node findings were used as the standard reference to compare with the imaging results. SLNs were cut longitudinally in 2 mm sections and paraffin-embedded. One slide was stained with haematoxylin and eosin (H&E). If no metastases were detected, all paraffin-embedded blocks were step-sectioned at 3–500 μm intervals. At each level, two sections were stained with H&E and the immunohistochemical marker cytokeratin A1/A3 (a mixture of the cytokines CK10, CK13-16 and CK19). The SLN were recorded positive if metastases were detected by H&E, cytokeratin positivity or both.

Study approval

This study received approval by the regional authorities and the Danish Data Protection Agency, file numbers 1-16-02-95-13 and 2007-41-0630 as well as from the Danish Health and Medicines Authority.

Results

Lymphatic drainage was observed in 116 of the 122 (95.1%) cN0 inguinal basins and it was possible to localize the saphenofemoral junction on the SPECT-CT in all patients. None of the 6 non-visualized inguinal basin harboured metastatic deposits after surgical exploration. Of the two patients with excluded cN + inguinal basins, one had no metastasis in the included contralateral side, whereas the other turned out to have a positive sentinel node and went on to complete inguinal lymph node dissection.

Inguinal SPECT-CT mapping

Table 2 summarizes the SPECT-CT and SNB Findings of 122 Inguinal basins in 62 patients.

We visualized 156 lymph nodes on SPECT-CT. All primary draining nodes were located in the inguinal region, and no direct drainage to pelvic lymph nodes was observed. Sentinel nodes were visualized by SPECT-CT in the medial superior zone in 47 of 122 inguinal basins (39%), in the lateral superior zones in 43 inguinal basins (35%) and in the central zones in 26 inguinal basins (21%). No sentinel nodes were localized in the inferior zones. Secondary draining nodes were found in all zones but mainly in the lateral superior zones.

Table 2. Findings in 122 inguinal basins and 363 lymph nodes of 62 patients with at least unilateral clinical lymph node negative (cN0) status.

	Left inguinal basins	Right inguinal basins	Total
All Patients			
Excluded inguinal basins; cN+	1	1	2
Included inguinal basins; cN0	61	61	122
SPECT-CT			
Visualization of drainage to inguinal basins by SPECT-CT	59	57	116
Zones with detected lymph nodes (1 or 2 nodes), zones with sentinel nodes (%)/zones with secondary draining nodes			
lateral superior	23 (38)/12	20 (32)/11	43 (35)/23
medial superior	25 (41)/1	22 (36)/1	47 (39)/2
central	11 (18)/3	15 (25)/2	26 (21)/5
lateral inferior	0/5	0/2	0/7
medial inferior	0/2	0/2	0/4
radiotracer silent inguinal basins	2 (3)	4 (7)	6 (5)
Visualized lymph nodes by SPECT, *n*	86	70	156
Removed lymph nodes at SNB	130	124	254
Negative lymph nodes	116	115	231
Positive lymph nodes	14	9	23
Negative inguinal basins; pN0	50	55	105
Positive inguinal basins; pN+	11	6	17
Removed lymph nodes at post SNB inguinal lymph node dissections (17 inguinal basins in 14 patients)	68	41	109
Further positive lymph nodes at post SNB inguinal lymph node dissection (3 inguinal basins in 3 patients)	1	3	4[b]

SPECT-CT: single photon emission computed tomography CT; SNB: sentinel node biopsy; ILND: inguinal lymph node dissection.
[a]All non-visualized inguinal basins were surgically explored and at least one sentinel lymph node was harvested from all groins. [b]All four metastatic deposits in the post SNB ILNDs were located in the deeper aspect of the superior/ central part of the specimen. No metastases were found in inferior Daseler zones.

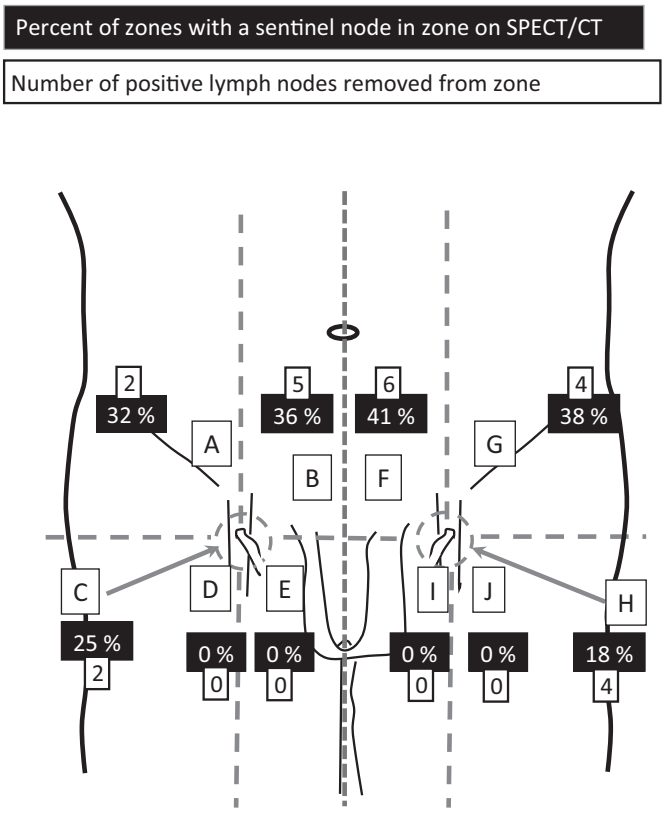

Figure 2. Lymph node map. Inguinal regions divided into ten Daseler zones, A–J, White on black: for 122 inguinal basins in 62 SPECT/CT scanned patients, the percent of inguinal basins with a sentinel node (primary radioactive tracer draining lymph) in the zone. Black on white: The number of metastatic lymph nodes removed from the zone.

Sentinel node biopsy and histopathological examination

The surgical team removed 254 lymph nodes at SNB which were subjected to histopathological examination. A total of 23 nodes from 17 inguinal basins in 14 patients harboured metastatic deposits.

With the aid of the surgical schemes and the handling of lymph node specimens from each Daseler zone individually it was possible to locate the metastatic lymph nodes to zones (Figure 2). Six metastatic lymph nodes were removed from the central zones, six from the lateral superior zones and eleven metastatic lymph nodes were removed from the medial superior zones.

Inguinal lymph node dissection

The 17 tumour-positive inguinal basins found by SNB were subjected to completion ILND revealing a mere 4 additional positive nodes in 3 inguinal basins. All four metastatic deposits in the post SNB ILNDs were located in the deeper aspect of the superior/central part of the ILND specimen. No metastases were found in inferior Daseler zones.

Characteristics of patients with metastatic inguinal nodes

All patients with inguinal metastases, except for one sarcomatoid, SCC T1G3 presented with TNM-2009 T2 ($n = 10$) and T3 tumours ($n = 3$). Two had a vascular invasion of tumour in the penile specimen and all except one T3G1 tumour were G2 ($n = 6$) and G3 ($n = 7$). Four had the extra nodal extension of metastasis in the sentinel node specimen.

Discussion

In this study, we investigated SPECT-CT lymph node visualization in 122 cN0 groins of 62 patients in our tertiary referral centre. Of noteworthy clinical interest is the finding of sentinel nodes only in superior and central inguinal quadrants. This finding is in accordance with the findings from a previous SPECT-CT study by Leijte et al. [2]. In another SPECT-CT-based mapping study by Omorphos et al. the authors located sentinel nodes to inferior zones in 2 of 60 patients, but no metastases were found here [21]. Importantly we were also able to confirm the findings of no direct drainage to the pelvic lymph nodes reported by Leijte and Omorphos [2,21]. This supports our current practice of omitting pelvic lymph nodes with tracer uptake in our daily sentinel biopsy practice in cN0 patients.

The SPECT-CT of our current study visualized a total of 156 lymph nodes, whereas the number of lymph nodes removed by the surgical team was markedly higher at 254. The higher number of removed lymph nodes has at least two reasons. First, the nuclear physician is not always able to differentiate the clustering of nodes on the preoperative images. A cluster of lymph nodes in close proximity may be identified as a single node on SPECT-CT. Secondly, our practice of removing radio-active nodes and nodes appearing suspicious by palpation in the exposed wound might lead individual surgeons to remove extra nodes, which did not take up tracer but appeared suspicious in size or consistency due to inflammation or individual variation.

Remarkably 35% of sentinel nodes were located in the lateral superior zone, which is not dissected in the modified inguinal lymph node dissection proposed by Catalona [18]. Six metastatic lymph nodes were located in the lateral superior zone, which should prompt colleagues practicing elective modified Catalona inguinal lymph node dissection as a standard in cN0 patients to expand the modified inguinal lymph node dissection to include the lateral superior zone.

Our current study has some important limitations. First, lymphatic drainage was visualized in 95% of cN0 inguinal basins and ideally, we hoped for complete visualization in all inguinal basins. However, our visualization rate is in line with other SPECT-CT based studies [2,21]. The five percent non-visualized inguinal basins could be due to injection technique and different technical aspects, but could also merely rely on lateralization of the primary tumour and no crossing of lymph drainage in a minority of patients. Our records of primary tumour localization are not sufficiently precise to test this hypothesis on the current material. Unilateral drainage could also be caused by blockage of lymphatic drainage due to bulky tumour deposits in a metastatic lymph node, which was not the case in this study since no metastatic nodes were found by the surgical exploration of radio-tracer silent inguinal basins. Secondly, even if the lymph node yield

of sentinel node biopsy of the current study was high one could argue that the ideal histopathological reference would be a complete inguinal dissection, which in our opinion would have been ethically dubious because of the morbidity of this procedure.

The strengths of our study include the largest SPECT-CT cohort published in penile cancer, prospective study design and long follow-up.

Conclusion

Penile cancer lymphatic drainage is primarily to sentinel in the superior and central zones of Daseler. Colleagues practicing a modified inguinal lymph node dissection as a standard in cN0 patients are encouraged to include all these zones, while the inferior zones can be omitted. This study confirms the absence of lymphatic drainage directly to the pelvic region and supports the practice of omitting pelvic nodes from sentinel node biopsy.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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