

ARTICLE

## DaPeCa-4: outcome in penile cancer patients with N3 disease due to extra nodal extension treated with surgery and chemo-irradiation

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### ABSTRACT

**Objective:** The role of pelvic lymph node dissection (PLND) is still debated in patients with N3 stage penile cancer. In Denmark this subgroup of patients is in general managed with an inguinal lymphadenectomy (ILND) and adjuvant chemoradiation and PLND is not offered as a standard. The objective of this study was to report treatment outcomes of this regimen and compare this with existing literature.

**Materials and methods:** We retrospectively reviewed records of patients with pT1-T4, N3, M0 penile cancer diagnosed between 1st January 2010 and 31st December 2014 in Denmark and treated with curative intent.

**Results:** 21 patients were identified with a median follow up of 74 months (CI 54–94). Management of the penile lesion was local resection in 5 (23.8%), partial penectomy in 10 (47.6%), and total penectomy in 6 (28.6%) of patients. Regarding the most extensive lymph node (LN) surgery: 4 patients (23.8%) went directly to oncological treatment from sentinel node biopsy with no further LN dissection, 6 patients (28.6%) were treated with unilateral ILND, 10 patients (47.6%) with bilateral ILND and a single patient (4.8%) was treated with ILND and PLND. In the adjuvant setting patients were treated with external beam therapy of involved regions and cisplatin-based chemotherapy. Median overall survival was 84 months (CI 0–176). The 5-year probability of surviving penile cancer was 57.1% (CI 36.0–78.3).

**Conclusion:** Treatment with surgery and chemo-irradiation in this national cohort does not show inferior survival outcomes compared to historical cohorts.

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### KEYWORDS

Penile cancer; lymph node dissection; adjuvant therapy; overall survival; prognosis

## Introduction

Penile cancer (PC) has a predictable sequence of metastasizing. From the primary penile lesion, inguinal lymph nodes (LNs) are involved before pelvic LNs. The presence and extent of LN involvement are major prognostic factors for survival [1,2]. Especially patients with extra nodal extension (ENE) of metastasis and/or pelvic LN involvement (i.e. N3 stage) face a poor prognosis. The strategies for pelvic LN management in penile cancer rely on a small number of primarily retrospective studies and the role of pelvic lymph node dissection (PLND) is still debated. The treatment aim is to optimize oncological outcomes while minimizing the treatment associated morbidity. For patients with N3 penile cancer, the European Association of Urology (EAU) guidelines recommend a pelvic lymphadenectomy [3].

In Denmark patients with N3 penile cancer are in general managed with an inguinal lymphadenectomy (ILND) and adjuvant chemoradiation but PLND is not offered as a

standard. The objective of this study was to assess the outcome of this treatment regimen and to compare this with existing literature on this patient subgroup.

## Material and methods

### Patients

PC patients diagnosed between 1st January 2010 and 31st December 2014 were identified in the Danish national penile cancer database. Records were reviewed to identify patients with N3 lymph node disease (tumor-node-metastasis (TNM) classification, 8th edition) either as pathological inguinal ENE and/or as suspicious pelvic LNs on pre-treatment imaging. Patients not undergoing treatment with a curative intent were excluded. ENE was defined as extension of tumor through the lymph node capsule.

### Pre-treatment imaging

Before treatment, patients underwent a CT scan and, in most cases, an FDG-PET/CT.

### Biopsy and surgical lymph node treatment

Inguinal LN involvement was confirmed by fine needle aspiration cytology (FNAC) or by sentinel node biopsy (SNB). Pelvic LNs were not consequently biopsied if overt metastatic involvement was present on pretreatment imaging. Patients were subjected to ILND in inguinal regions with LN involvement. PLND was not performed as a standard.

### Adjuvant lymph node treatment

Patients with N3 disease were subsequently offered adjuvant chemoradiation therapy. External beam radiation therapy (EBRT) was applied as soon as the inguinal surgical wounds had healed sufficiently. EBRT was in general given to bilateral inguinal – external iliacal lymph nodes with some variations depending on the multidisciplinary evaluation of the pre-treatment imaging. In case of suspicion of pelvic lymph node involvement on imaging the field of EBRT was extended to include pelvic nodes. In general, the EBRT dose was 50 Gy (25 fractions of 2 Gy) to the volume with no macroscopic disease and 64 Gy (32 fractions of 2 Gy) to macroscopic disease and/or to sites with known microscopic disease. A cisplatin-based chemotherapy was administered in various regimens. Clinical handling of lymph node involvement is outlined in Figure 1.

### Follow-up strategy

Follow-up of patients with stage N3 penile cancer involved physical examination of the anogenital area and inguinal region including a thoracic and abdominopelvic CT scan every three months for the first two years and every six months from year three to five. Salvage treatment in case of recurrent disease was dependent on the extent of relapse, the patient's condition and previously given treatment.

### Statistics

Basic descriptive statistics were used. Overall survival (OS) and time from progression to death of penile cancer were estimated using the Kaplan–Meier method. Median time of follow-up was calculated using reversed Kaplan–Meier [4]. Time to progression and death was defined from date of the most extensive lymph node surgery to the event. Progression was ascertained clinically, pathologically or by imaging using RECIST criteria [5]. Cumulative incidence of penile cancer death was analyzed using the Aalen–Johansen method for competing risks. Status on survival was set on 15th January 2019. Statistical analyses were performed using SPSS (software version 25; IBM) and R (R Development Core Team, Vienna, Austria).

### Results

A total number of 21 patients were identified in the study period. Complete information was available on all patients and no patient was lost to follow-up. Table 1 shows patient and disease characteristics as well as initial management of the patients.

After examination of the primary tumor of the penile specimen, pathological tumor stage was T1 in 6 of 21 patients (28.6%), T2 in 10 patients (47.6%) and T3 in 5 patients (23.8%). No patient in the current study presented with T4 status. ENE was present in all of the patients. The median number of involved inguinal LNs were 2 (range 1–8) with 66.7% of the patients having bilateral involvement of the inguinal LNs. A total of 85.7% ( $n=18$  patients) had signs of iliac LN involvement on preoperative imaging.

All patients underwent treatment with curative intent with a median of 22 days (range 8–60) from diagnosis to most extensive LN surgery. Regarding the most extensive LN surgery, 4 patients (23.8%) went directly to oncological treatment from SNB with no further LN dissection as a result of a multidisciplinary decision in individual patient cases, 6 patients (28.6%) were treated with unilateral ILND, 10 patients (47.6%) with bilateral ILND and a single patient (4.8%) was treated with ILND and pelvic LND. The median time from LN surgery to EBRT was 47 days (range 17–130).

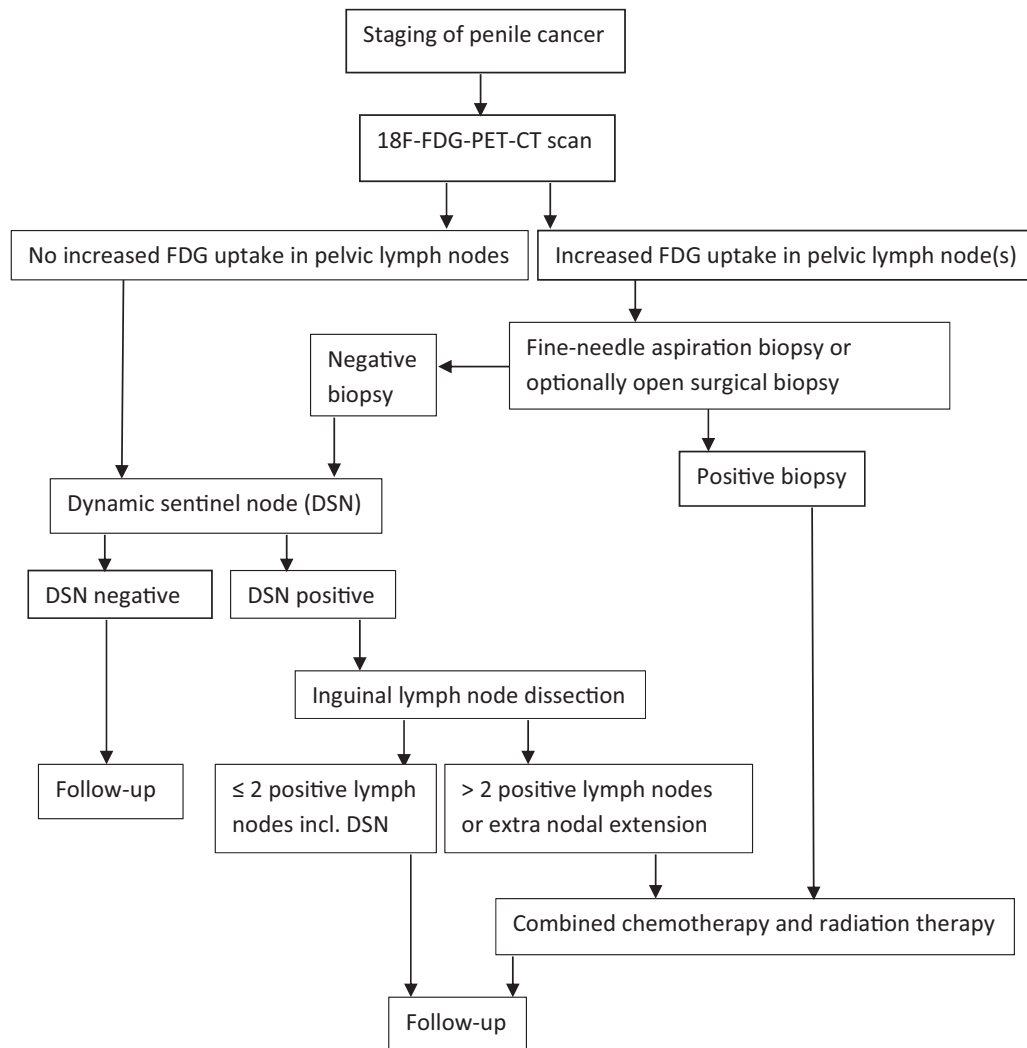
### Outcomes

Median follow-up time was 74 months (CI 54–94). At the end of the study period 12 patients were dead (57.1%) with nine men (42.9%) succumbing to PC and three men (14.3%) dying from other causes. The median OS was 84 months (CI 0–176). In the study period 9 patients (42.8%) had confirmed disease progression with a median time to progression of seven months (range 3–39). Of patients with disease progression all died. Eight patients died of PC and one patient suffered a non-penile cancer related death. Estimated overall median time from progression to death was seven months (CI 5.6–8.3). Figure 2 estimates the cumulative incidence of penile cancer death following lymph node surgery. The 5-year probability of surviving was 57.1% (CI 36.0–78.3). PC specific death happened within 14 months from surgery.

### Discussion

In this study, we present data from a cohort of patients with N3 LN status PC with a long follow-up treated with surgery and adjuvant chemoradiation. In this national cohort, we found an overall median survival of 84 months and a 5-year cumulative probability of surviving penile cancer of 57%.

With a great impact on PC prognosis, LN involvement is at the center of attention of both clinicians and clinical researchers. Available literature on the subject is not equivocal and in Denmark a surgically less radical approach is chosen compared to that recommended by the EAU. PLND is not offered as a standard to patients with N3 LN status in



**Figure 1.** Flowchart outlining the staging and clinical handling of penile cancer patients in Denmark according to DaPeCa (the Danish multidisciplinary Penile Cancer group) guidelines.

Denmark. These patients are in general treated with ILND and adjuvant chemoradiation therapy.

Historically, Ravi et al. in 1993 reported on patients who underwent groin dissection after primary penile treatment and in some cases preoperative radiotherapy [1]. Some patients in this cohort was treated with prophylactic ILND and if positive nodes then subsequently PLND. Others only had an ilioinguinal lymphadenectomy ipsilaterally in case of clinically positive nodes. In the subgroup of patients with perinodal infiltration (of which six also had positive pelvic lymph nodes) they found that 1 in 17 patients (5.9%) of patients survived 5 years and 0% of patients with positive pelvic LNs survived 5 years. Similarly, Pandey et al. in their study found a 5-year OS of 8.9% in the subgroup of patients with ENE and none of the patients with pelvic nodal metastasis survived for 5 years [6]. In this cohort patients had an ipsilateral ilioinguinal block dissection (dissection of superficial and deep inguinal nodes as well as pelvic nodes) with contralateral superficial inguinal block dissection in case of unilateral nodal disease and bilateral ilioinguinal block dissection in case of bilateral nodal disease. The LN treatment

was performed within six months after the primary PC surgery. No adjuvant treatment was given. In 11 cases detection of nodal disease occurred more than six months after their primary penile surgery and in these cases an ipsilateral ilioinguinal block dissection was performed.

These earlier studies lack early up-front lymph node management which is known to be of great importance for the prognosis [7]. In 2009 Svatek reported on outcomes in N3 disease patients reclassified according to the TNM 7 classification ( $n = 13$ ) [8]. This cohort all underwent bilateral superficial ILND in the presence of high-risk primary tumor features even without clinical evidence of nodal involvement. Subsequent deep ILND and PLND were done when  $\geq 1$  positive LNs were identified on frozen section analysis. Patients with clinically evident inguinal or pelvic nodal involvement underwent ipsilateral ilioinguinal lymphadenectomy with contralateral superficial inguinal or ilioinguinal dissection. In this study they found an estimated 5-year disease specific survival of 0% for patients with N3 disease.

The current EAU recommendation of PLND for patients with two or more inguinal LN metastases on one side and/or

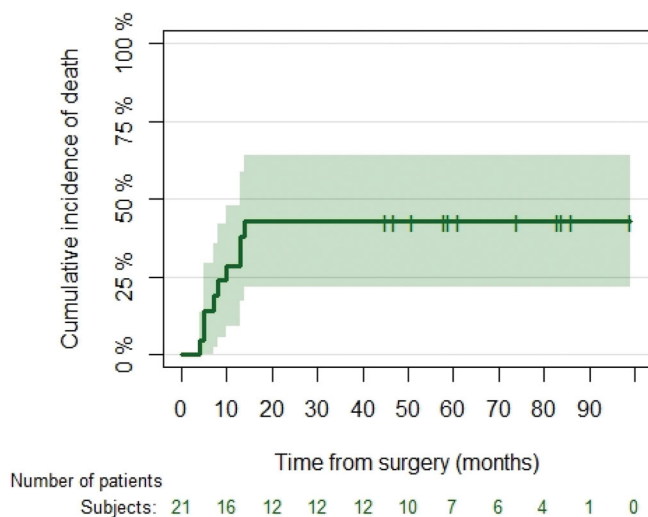
**Table 1.** Patient characteristics and initial management.

Total number of patients , n	21
Median age (range)	68 years (46-81)
T-stage	
T1, n (%)	6 (28,6)
T2, n (%)	10 (47,6)
T3, n (%)	5 (23,8)
Extra nodal extension of any regional lymph node metastasis, n (%)	21 (100)
Median number of lymph node metastases <sup>a</sup> , n (range)	2 (1-8)
Bilateral lymph node involvement, n (%)	14 (66,7)
Pre-treatment imaging	
CT, n	21
FDG PET, n	18
Scintigraphy, n	17
MR, n	1
Ultrasound, n	6
Primary penile surgery	
local resection, n (%)	5 (23,8)
partial penectomy, n (%)	10 (47,6)
total penectomy, n (%)	6 (28,6)
Most extensive lymph node surgery	
bilateral sentinel node, n (%)	4 (19,0)
unilateral inguinal lymph adenectomy, n (%)	6 (28,6)
bilateral inguinal lymph adenectomy, n (%)	10 (47,6)
inguinal plus iliac lymph adenectomy, n (%)	1 (4,8)
Chemotherapy	
none, n	2 <sup>b,c</sup>
Cisplatin, n	10
Cisplatin + 5FU, n	7
Taxan + cisplatin + 5FU, n	1
5FU, n	1
Radiation therapy	
unilateral inguinal (50-64 gy) n	1
bilateral inguinal (64 gy), n	1
unilateral iliacal (50-64 gy), n	4
bilateral inguinal + iliacal (60 + 64 gy), n	1
bilateral iliacal (50 + 64-64 + 64 gy), n	12
bilateral extended/other (50 + 50 – 50 + 64 gy), n	2

<sup>a</sup>A fixed or gross nodal mass was registered as 1 lymphnode regardless of size, and as ENE

<sup>b</sup>Cisplatin not given due to polyneuropathy.

<sup>c</sup>The patient did not want chemotherapy.



**Figure 2.** Cumulative incidence of death of penile cancer following lymph node surgery.

ENE is based on the risk of positive pelvic nodes increases with the number of positive inguinal nodes or ENE [3]. In 2015 Veeratterapillay et al. reported contemporary results on PC patients from a UK Supraregional Center [9]. These included patients with N3 disease treated according to the

current EAU guidelines. They also received adjuvant cisplatin-based chemotherapy but did not receive radiotherapy in comparison to patients in the present study. They reported a median OS of 10 months (range 5–14 months) and a 5-year CSS of 33% for the group of patients with pN3 disease. The cohort, however, consisted of patients with recurrent disease also. Furthermore, the group of N3 patients accounted for only 6 patients.

One of the largest series with a long follow-up reporting on PC patients with N3 disease is by Djajaningrat et al. [10]. In the subgroup of pN3 patients from 2001 to 2012 ( $n = 91$ ), patients had an ipsilateral radical ILND performed in case of a positive SNB. If histopathology revealed  $\geq 2$  positive inguinal LNs and/or ENE in the removed inguinal specimen, a subsequent ipsilateral PLND and adjuvant inguinal radiotherapy followed. In this study they reported a 5-year CSS of 37% (CI 27–52).

Another recent large multicenter study specifically analysed the outcomes of N3 disease PC patients [11]. This study included 93 patients who had at least unilateral LN dissection. Performance of PLND was in general performed if two or more positive inguinal LNs, ENE, or suspicious pelvic imaging. Some patients were treated with chemo- and/or radiation therapy in the adjuvant setting. In this setting they found a median OS of 10.58 months.

To our knowledge, only one study directly comparing N3 PC patients who did and did not undergo PLND has been conducted [12]. In this retrospective multicenter study 102 patients either underwent ILND or ILND plus PLND with adjuvant therapy performed in almost all cases. In their propensity matched analysis, the PLND, with short follow up did not result in statistically significantly higher 1- and 3-year DSS rates than the no-PLND group.

There are several obvious limitations to our study including the non-comparative, non-randomized, retrospective design, the wide heterogeneity of treatments offered as well as the very small study cohort. However, most studies on this rare patient sub-population are small and only recently have an international consortium, The International Penile Advanced Cancer Trial (InPACT), taken initiative to examine different lymph node treatment regimen in a randomized multicenter set-up. Those patients with a high risk of relapse following ILND will be randomized to undergo prophylactic PLND versus no prophylactic PLND.

Another important limitation is the lack of histological confirmation of pelvic lymph node involvement. Literature on the role of FDG-PET/CT for the detection of metastatic pelvic lymph nodes is scarce [13]. To our knowledge, the only study evaluating the diagnostic accuracy of FDG-PET/CT scan found a sensitivity of 91% and a specificity of 100% [14]. N3 stage patients with ENE only and those with pelvic lymph node metastasis have a significantly different 3-year CSS of 47.9% versus 28.6%, respectively [15]. Strengths of the current study include the population-based national platform collecting each and every case prospectively in a database set-up and the access to complete follow-up data on all patients.

## Conclusion

In this study, we demonstrated an overall median survival of 84 months and a 5-year cumulative probability of surviving penile cancer of 59% for the group of penile cancer patients with N3 nodal disease undergoing surgery and adjuvant chemo- and radiation therapy. Direct comparison with previous studies reporting on outcomes for the group of patients with N3 stage disease is difficult because of considerable heterogeneity in study cohorts in terms of treatment of primary lesion, lymph node surgery, inclusion of recurrent disease, size of cohorts, and length of follow-up. Furthermore, outcome measures are not all identical either. However, our result suggests that PLND is not associated with better survival outcome than less radical lymph node surgery with adjuvant chemo- and radiation therapy.

## Disclosure statement

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

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