

Summary

A brief overview of the incidence, etiology and current management of penile carcinoma is provided in **chapter 1**. The incidence trends and survival of patients with primary malignant penile cancers in the Netherlands diagnosed between 1989 to 2006 is described in **chapter 2**. On the basis of nation-wide population-based data from the Netherlands Cancer Registry, three-year moving average European age-standardised incidence and ten-year survival estimates were calculated. In the 17-year study period, 2000 primary penile cancers were diagnosed in the Netherlands of which 1883 (94%) were of the squamous cell carcinoma subtype. The three-year moving average incidence rate of patients with penile squamous cell carcinoma increased slightly, but significantly, from 1.4 per 100,000 person-years in 1989 to 1.5 in 2006 with an estimated annual percentage of change of 1.3%. This increase was mainly contributable to the rising incidence of carcinomas in situ. Ten-year relative survival of patients according to the stage 0–II groups was fairly good of 93%, 89%, and 81%, respectively. Patients with stage III and IV tumours have poor survival with nine-year survival of 50% and a two-year survival of 21%, respectively.

Penile squamous cell carcinoma has a typical lymphogenic dissemination pattern. Presence of lymph node metastasis is the single most prognostic factor for survival. The continuous search towards accurate non-invasive and minimally-invasive staging procedures is driven by the significant overtreatment in patients with nonpalpable lymph nodes, that are those with clinically node-negative (cN0) groins, who undergo elective lymphadenectomy. Several issues on the treatment of such cN0 patients have been addressed by the studies in this thesis. At two European tertiary referral institutes dynamic sentinel node biopsy (DSNB) is used to stage the cN0 groin. In **chapter 3**, the prognostic value of several typically available histopathologic penile tumour factors and accuracy of the high-risk European Association of Urology (EAU) subgroup were assessed in a two-institutional analysis of 342 cN0 patients who had undergone DSNB. The EAU guidelines advise a bilateral inguinal lymphadenectomy in this high-risk subgroup. Presence of occult metastases was established by preoperative ultrasound and tumour-positive fine-needle aspiration cytology, tumour-positive sentinel node(s) and groin metastases during follow up after negative DSNB procedure. Median follow up was 31 months. Sixty-eight of 342 patients (20%) and 87 of 684 inguinal basins (13%) had occult nodal involvement, including six patients (2%) with groin metastases after negative DSNB. Corpus spongiosum invasion, corpus cavernosum invasion, histological grade and lymphovascular invasion (LVI) were each significant prognosticators for occult metastases on univariate analysis. Of note, urethral invasion had no prognostic value. On multivariate analysis, grade (odds ratio 3.3 for intermediate and 4.9 for poor, respectively) and LVI (odds ratio 2.2) remained independent predictive factors. Two hundred forty-five patients (72%) were classified high-risk according to the EAU guidelines. Among them, the incidence of occult metastases of 23%. Consequently, strict adherence to EAU guidelines would have led to unnecessary bilateral inguinal lymphadenectomy

up to 77% of cN0 high-risk patients. These results are in accordance with a previously published study with a smaller patient cohort of 33 cN0 high-risk patients.¹ Although DSNB is not without shortcomings either (i.e. missing of micrometastatic disease in 2% of clinically node-negative patients), we consider it the most suitable staging procedure at this moment.

The search for other non-invasive staging procedures goes on. Two studies with ¹⁸F-FDG positron emission tomography / computed tomography (¹⁸F-FDG PET/CT) showed promising results in assessing the inguinal lymph nodes of patients with penile carcinoma, with a sensitivity of 88%–89% and specificity of 98%.^{2,3} We were unable to reproduce these promising figures. In **chapter 4**, the value of hybrid PET/CT is evaluated as an alternative strategy for staging patients with nonpalpable lymph nodes. In 24 patients with 42 cN0 groins scheduled to undergo DSNB, a preoperative hybrid PET/CT scan was performed to assess the nodal status of the cN0 groins. The histopathological status of the removed sentinel nodes was used as the standard of reference to evaluate the PET/CT results. One of the five tumour-positive cN0 groins was correctly predicted with PET/CT (sensitivity of 20%). All four false-negative PET/CT scans contained metastases ≤10mm. Of the remaining 37 tumour-negative groins, 34 were correctly predicted with PET/CT (specificity 92%). It is concluded that the role of PET/CT in the evaluation of the cN0 groins in penile cancer is limited due to its low sensitivity. The main reason for the difference in sensitivity with both abovementioned published series is patient inclusion. The subgroup of patients who may benefit most from non-invasive staging procedures are men with cN0 penile carcinoma. Both abovementioned studies have also included patients with clinically node-positive disease, while we have only included cN0 groins. Consequently, the sensitivity of PET/CT is overestimated. No current available non-invasive staging procedure is reliable enough to omit surgical staging.⁴ Although imaging modalities such as ultra small super paramagnetic particles of iron oxide (USPIO) combined with diffusion weighted magnetic resonance imaging (DW-MRI) have shown very promising results in staging regional lymph nodes,^{5,6} USPIOs are not commercially available. There remains so far a need for (minimally-invasive) surgical staging.

The indications for DSNB continue to evolve towards more subcategories as more data become available. This minimally-invasive procedure is usually done simultaneously with primary tumour treatment. **Chapter 5** describes the results of nodal staging by DSNB after previous therapeutic primary tumour resection. Forty patients and 60 cN0 groins who had undergone DSNB after previous penile carcinoma resection with histopathologically tumour-negative margins were analyzed. A sentinel node visualization rate of 93%, identification rate of 100% and detection of occult metastases in 12% of cN0 groins was found. No recurrences developed in the groins from which one or more tumour-free sentinel nodes had been taken during a median follow up of 28 months after the primary tumour resection. These figures indicate this minimally-invasive procedure is feasible and seems reliable. Although the relatively short follow up and limited cohort number prevent firm conclusions about its sensitivity, the

results so far seem comparable with the favourable results of DSNB with the primary tumour present. The subcategory of patients with a resected primary tumour has practical consequences. Patients can safely undergo primary tumour treatment at the referring hospital and nodal staging at the referral centre.

In **chapter 6**, the role of repeat DSNB in 12 cN0 patients with locally recurrent penile carcinoma after previous penile surgery and DSNB is explored. Five of these patients had previously undergone a unilateral inguinal node dissection for groin metastases. The median disease-free interval was 18 months. The protocol and technique of “normal” DSNB and the repeat procedure were similar. No sentinel nodes were seen on conventional lymphoscintigraphy in the five groins that had previously been dissected. A sentinel node was visualized on conventional lymphoscintigraphy in the remaining 19 non-dissected groins. Histopathological analysis showed involved sentinel nodes in four groins of three patients. During a median follow up of 32 months after the repeat DSNB, one patient developed a groin recurrence 14 months after the removal of a tumour-negative sentinel node. This study shows that repeat DSNB is technically feasible in cN0 patients with locally recurrent penile carcinoma and discovers metastatic inguinal nodes. Furthermore, our results demonstrate that every local recurrence can lead to new lymphatic spread, yielding a new sentinel node. Renewed nodal staging is therefore important both for prognosis as well as for optimal treatment.

While the management of patients with nonpalpable lymph nodes has evolved, treatment strategies of those who present with lymph node metastases has remained almost identical during the last decades. The most important prognostic factor in penile carcinoma is presence of pathological nodal metastases (pN+).⁷ A number of previously published studies have shed light on the prognostic significance of the extent of nodal involvement in patients with pN+ disease.⁸⁻¹² Nodal factors, such as extranodal extension, bilateral metastases, and pelvic nodal involvement are considered poor prognostic variables.⁸⁻¹² However, previously published studies that reported on prognostic factors in pN+ penile cancer have several drawbacks which are largely related with the low incidence of this disease. The number of patients investigated were relatively small ranging from 78–102 men,^{8,9,11,12} the definition for extranodal extension is not always reported,^{8,9,11} follow up details are unknown,^{8,9,11} and the results reflect older series with patients treated between 1950–1980,⁸ 1962–1986,⁹ 1987–1998,¹¹ and 1956–2001,¹² respectively. Finally, data were collected retrospectively.^{8,9,11,12} An important focus of the studies in this thesis is the management of those patients at risk for cancer-specific death. We analysed a large patient cohort treated uniformly with a regional lymphadenectomy and postoperative external radiotherapy. Data was collected prospectively.

Chapter 7 reports the study in which the prognostic significance of extranodal extension (extension of tumour through the lymph node capsule into the perinodal fibrous-adipose tissue) amongst several other risk factors in 156 patients with pN+ penile cancer were analysed. All patients had undergone therapeutic regional lymphadenectomy without induction treatment. Postoperative external radiotherapy was indicated if histopathological analysis revealed more tumour than one intranodal metastases.

Seventy patients (45%) received adjuvant radiotherapy. Patients with extranodal extension had significant decreased five-year cancer-specific survival compared with patients without this feature (42% vs. 80%). Other prognostic variables on univariate analysis were bilateral metastatic involvement (vs. unilateral), ≥ 3 unilateral metastatic inguinal nodes (vs. ≤ 2), tumour positive margin status of the inguinal lymphadenectomy (vs. tumour negative), and presence of pelvic nodal involvement. Pathological T-stage or grade of differentiation were not significant predictors for outcome. In the multivariate analysis extranodal extension (hazard ratio 2.37) and pelvic nodal involvement (hazard ratio 2.20) remained associated with a decreased cancer-specific survival. This study demonstrates that despite the fact that patients with high-risk pN+ factors are treated more extensively, extranodal extension and pelvic nodal involvement are independent prognostic factors for cancer-specific death.

The TNM classification of penile squamous cell carcinoma was recently revised in 2009. The most important change in pathologic nodal (pN) staging is inclusion of extranodal extension. In **chapter 8** the prognostic value of the new 2009 pN category is evaluated and compared with the previous 1987 pN-classification. We analyzed all 334 patients with penile carcinoma without distant metastases staged pathologically by dynamic sentinel node biopsy and/or lymphadenectomy at a tertiary European referral institute between 1994 and 2008. All patients were (re)staged using the 1987 and 2009 pN-classification. Five-year cancer-specific survival (CSS) was estimated using the Kaplan-Meier method. The predictive abilities of the 1987 and 2009 pN staging systems were compared using the concordance probability estimate. At a median follow up duration of 55 months, 55 patients (16%) had died from penile cancer. The main impact of the 2009 pN revision was a shift of 41 patients (31% of 133 pN+ patients) from 1987 pN1–2 categories to 2009 pN3 because of extranodal extension. Extranodal extension was a poor prognostic factor in the subgroup of patients with inguinal metastases. Estimated 5-yr CSS rates by the 2009 pN category were 97.9%, 76.8%, 83.9% and 38.4% in patients with pN0, pN1, pN2 and pN3 cancers, respectively. The concordance probability estimate of both staging systems was essentially similar: 0.735 for 2002 pN and 0.741 for 2009 pN. We concluded that extranodal extension has a prognostic role in the patients with inguinal metastases and inclusion of this factor in pN-staging seems rational. Nevertheless, predictive capability of the 1987 and 2009 pN-classification of 2009 remains similar. Future studies are needed to evaluate new prognostic factors to further improve discrimination capability.

Several studies have shown that local recurrence only has little impact on survival in patients with penile carcinoma. There are, however, few data on inguinal recurrence following therapeutic lymphadenectomy. In our experience, inguinal relapses are difficult to manage and cause a lot of suffering because of pain, foetor and lymph oedema, leaving the patient often bedridden and debilitated. **Chapter 9** describes a study in which treatment results and outcome of patients with pN+ penile carcinoma who experienced an inguinal recurrence after therapeutic lymphadenectomy were investigated. Clinicopathological features predictive of such recurrences were determined. Data of

161 patients with pN+ penile carcinoma who had undergone contemporary treatment consisting of regional lymphadenectomy were evaluated. Postoperative external radiotherapy was indicated if histopathological analysis revealed more tumour than one intranodal metastases. The five-year incidence of inguinal recurrences was estimated using a competing risk analysis considering death a competing risk. Twenty-six patients developed an inguinal recurrence following lymphadenectomy after a median of 5.3 months. The overall estimated five year inguinal recurrence rate was 16%. Among the 26 patients with inguinal recurrence, ipsilateral adjuvant radiotherapy was indicated in 22, but given in 11 patients. The other 11 patients recurred in the groin before start of adjuvant radiotherapy, because they experienced rapid recurrence during recovery time from surgery with or without postoperative delay because of complications (e.g. wound healing problems). Median survival after inguinal recurrence was 4.5 months. Pronounced differences in estimated recurrence rates were found among a subgroup of “high-risk” patients with ≥ 3 unilateral metastatic inguinal nodes, and/or extranodal extension, and/or pelvic nodal involvement. This study shows that most inguinal recurrences following therapeutic lymphadenectomy in pN+ penile carcinoma occur within short time. Patients experiencing such a recurrence have poor outcome with limited salvage options. Several patients suffer from distant relapse after locoregional treatment, especially those men considered high-risk. Therefore, induction systemic treatment before definitive locoregional therapy is considered a more attractive approach in the high-risk pN+ subgroup compared with more extensive postoperative treatment. Moreover, patients are generally more fit to undergo preoperative multimodality treatment, they can be monitored for response during treatment and chemotherapy has shown to reduce the risk of developing distant metastases by eliminating micrometastatic cells at distant sides.¹³ This needs to be evaluated in clinical trials.

The major disadvantage of induction treatment is postponement of definitive local treatment. Induction treatment should ideally obtain high response rates in the shortest possible time, without compromising subsequent treatment due to prolonged or delayed toxicities. Although penile carcinoma has been considered a relatively chemorefractory disease, further study is required to determine whether systemic treatment before definitive treatment leads to survival benefit. In head and neck carcinoma taxane-based combined chemotherapy have shown promising results.^{14,15} These chemotherapy regimens have also suggested meaningful clinical responses in patients with penile carcinoma.^{16,17} Close monitoring is essential to identify non-responders at the earliest moment.

Accurate selection of high-risk pN+ penile cancer preoperatively is problematic as most of the high-risk characteristics investigated are only found after surgery (e.g. extranodal extension and pelvic nodal involvement). **Chapter 10** presents the results of ¹⁸F-FDG PET/CT in determining pelvic nodal involvement and further metastatic spread in patients with tumour-positive inguinal nodes. Eighteen patients with (uni- or bilaterally) cytologically tumour-positive inguinal disease who had undergone whole-body ¹⁸F-FDG PET/CT for tumour staging were evaluated.

Histopathological results of the pelvic basins when available, radiologic imaging, and clinical follow up (with a minimum of one year) served as reference standard. Of the 11 tumour-positive pelvic basins, ten were correctly predicted by PET/CT scan as were all 17 tumour-negative pelvic basins. The calculated sensitivity was 91% (95% CI, 58–100%) with specificity of 100% (95% CI, 80–100%) and diagnostic accuracy of 96% (95% CI, 82–100%). In addition, PET/CT-scan showed distant metastases in five patients. Among four of them distant metastases could be confirmed. It was concluded that PET/CT-scan appears promising in detecting pelvic lymph node metastases with great accuracy and identifies distant metastases in penile carcinoma patients with inguinal lymph node involvement. In our practice PET/CT-scan has become part of routine staging in such patients. We recognize the fact that PET/CT may still miss small metastases. The patients most likely to benefit from direct pelvic lymphadenectomy are those with occult pelvic metastases, i.e. not detected preoperatively by any imaging procedure(s). A negative PET/CT scan is therefore no reason to omit pelvic lymphadenectomy if histopathological analysis of the inguinal dissected specimen reveals two or more metastatic lymph nodes or extranodal extension. However, we consider induction chemotherapy instead of direct regional lymphadenectomy if PET/CT shows FDG avid pelvic lymph nodes. Patients with pelvic nodal involvement have a poor prognosis and the specificity of PET/CT in our study was 100%.

The role of CT imaging in cN0 patients with penile carcinoma is limited because of the low spatial resolution and unreliability in detecting small metastases. On the other hand, most patients with high-risk pN+ disease have clinically palpable lymph nodes. CT imaging may play a role in identifying “high-risk” characteristics. **Chapter 11** reports the study in which radiographic criteria for the preoperative identification of high-risk pN+ patients is established. Preoperative diagnostic CT studies of 30 penile carcinoma patients with proven unilateral or bilateral lymph node metastases were reviewed independently by two radiologist blinded for patient data. All CT images were analyzed per side ($n = 60$). Several radiographic criteria were assessed for lymph nodes with short-axis diameter of at least 8 mm. Histopathological analysis of the removed sentinel nodes and/or regional lymphadenectomy specimen was used as standard of reference. Sides were characterized as high-risk if histopathological analysis revealed three or more metastatic inguinal nodes, and/or extranodal extension, and/or pelvic nodal involvement. Presence of central nodal necrosis and/or irregular nodal border of the regional lymph nodes on the preoperative CT-scan confirmed the high-risk subgroup with a sensitivity of 95% (21/22) and a specificity of 82% (31/38). All seven sides falsely designated as high-risk harboured inguinal metastases, but they were classified “low-risk”. Furthermore, the interobserver agreement of each radiographic parameter was almost perfect. It was concluded that presence of central nodal necrosis and/or irregular nodal border of the regional lymph nodes on preoperative CT-images are accurate and simple criteria to identify high-risk pN+ penile cancer. These criteria can be used for patient counselling and clinical trial eligibility.

In **chapter 12** the first clinical results of ^{18}F -FDG PET/CT for monitoring

treatment response in eight patients with primary inoperable (i.e. advanced) penile carcinoma treated with induction chemotherapy is described. The metabolic tumour response provided by PET/CT was compared with the radiological evaluation provided by CT imaging. PET/CT showed hypermetabolic uptake of FDG matching with malignancy in all eight patients. According to the reference, six patients were responders and two non-responders after two cycles of chemotherapy. The metabolic tumour response was considered accurate in all eight patients, while the radiological tumour response was accurate in seven patients. In three patients correctly identified as responder, the radiological tumour response was deemed suboptimal compared with the metabolic assessment. This study shows that ^{18}F -FDG-PET/CT imaging is feasible for monitoring response in patients with advanced penile carcinoma treated with induction chemotherapy. PET/CT may potentially be more accurate in identifying responders than CT alone.