Chapter 14

Summary / Samenvatting
Summary
Penile carcinoma primarily metastasizes to the inguinal lymph nodes. Even in case of lymphatic metastasis many patients can still be cured. Most penile carcinoma patients have no suspicious lymph nodes in their groins but this observation does not exclude the presence of disease. Approximately 25% of the patients harbor occult metastases in these lymph nodes. An important issue in the management of penile carcinoma patients is how to identify these metastases. Elective lymph node dissection is an option but will lead to overtreatment in about 75% of the patients. Moreover, inguinal lymphadenectomy is associated with major morbidity. On the other hand, a wait-and-see policy may have a negative impact on survival. Dynamic sentinel node biopsy is a minimally invasive procedure that enables detection of occult metastasis in clinically node-negative groins. This technique was introduced for penile carcinoma at The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital in 1994. The aim of this thesis is to evaluate various aspects of dynamic sentinel node biopsy in patients with penile carcinoma.

Chapter 1 contains a brief introduction on penile carcinoma and describes the outline of this thesis.

In chapter 2, a review on penile carcinoma is provided focusing on the management of patients with clinically tumor-free regional lymph nodes.

The indication for dynamic sentinel node biopsy is discussed in chapter 3. Stage and malignancy grade of the primary tumor are important predictive factors for the presence of occult lymph node metastases. By combining these two histopathologic characteristics, one can estimate the risk of nodal spread in patients with a T1-2/G1-3 primary. This risk ranges from 7% to 45%. Relying solely on these characteristics for the decision to perform regional node dissection leads to unacceptable false-negative and false-positive rates. Only patients with a T1G1 primary tumor have a relatively low risk of occult lymph node metastases. Patients with these tumors may be good candidates for a surveillance policy. For all other patients, immediate histological assessment of the regional nodes is necessary. We suggest dynamic sentinel node biopsy for this purpose.

In chapter 4, the clinical outcome of early versus delayed excision of lymph node metastases in penile carcinoma patients is investigated. This concerns one of the most controversial issues in the management of this disease. Forty patients with proven lymph node metastases were retrospectively included in this study. All patients presented initially with bilateral impalpable lymph nodes. In twenty patients, the metastases were removed at the time of clinical appearance during meticulous follow-up. The other twenty patients underwent early resection of their inguinal metastases detected by dynamic sentinel node biopsy before they became palpable. Disease-specific three-year survival of patients with positive lymph nodes detected during surveillance was 35% and in early resected cases this was 84% (p<0.01). Thus, early resection of lymph node metastases improves disease-specific survival.
The morbidity of dynamic sentinel lymph node biopsy compared to inguinal lymph node dissection in penile carcinoma is reported in chapter 5. Complications following dynamic sentinel node biopsy occurred in 7% of the groins, whereas after inguinal lymph node dissection this was 68% (p<0.001). All complications of dynamic sentinel node biopsy were minor and easily managed. Thus the conclusion is that the dynamic sentinel node biopsy is associated with a limited morbidity.

A case of an unusual sentinel node localization is described in chapter 6. On the preoperative lymphoscintigraphy images, a prepubic sentinel node was depicted. This node could be surgically identified and proved to be tumor-positive. This case illustrates one of the advantages of dynamic sentinel node biopsy in penile carcinoma: lymphoscintigraphy can identify lymph nodes outside the usual nodal basins.

The six false-negative dynamic sentinel node cases that were encountered in our study population are analyzed in chapter 7. In one of these, one groin was not explored because lymphoscintigraphy did not identify a sentinel node there. Non-visualization of the sentinel node may have been caused by massive tumor involvement blocking the lymphatic inflow. In a second patient, additional serial sectioning and immunohistochemical staining of a sentinel node that was initially reported to be disease-free revealed metastasis after all. In three patients, lymphatic inflow blockage and rerouting of lymph flow due to gross tumor involvement of the sentinel node were possibly the causes of the failure. The true sentinel node in this situation is bypassed and the tracers are diverted to another node that is falsely labeled as the sentinel node. In the sixth patient with a false negative result, a sentinel node that was visualized on the scintigram could not be retrieved during surgery because of the low radioactivity content in this node.

Based on these failures, adaptations have been made in our indications for sentinel node biopsy and in our technique. In case of unilateral drainage on the lymphoscintigram, exploration of the non-visualized groin is advised. Exploration after injection of the blue dye can still reveal a blue vessel leading to a non-blue, non-radioactive sentinel node. Intra-operative palpation of the groin was introduced to detect suspicious nodes that could not be palpated through the skin. High-resolution ultrasonography with fine-needle aspiration cytology has been added as a routine examination before patients are scheduled for dynamic sentinel node biopsy. False-negative cases caused by gross involvement of the sentinel node with tumor blocking will hopefully be avoided by this approach because these are the very nodes picked up by the ultrasound. We also modified the routine pathological analysis because of the pathological sampling error. Sentinel nodes are now serially sectioned and immunohistochemistry is used in addition to standard hematoxylin and eosin staining.

A varying lymphatic drainage pattern could also be a cause of a false-negative dynamic sentinel node procedure and this is studied in chapter 8. The reproducibility of
lymphoscintigraphy in the assessment of the location and the number of sentinel nodes was prospectively determined in twenty patients. Lymphoscintigraphy was performed twice in an identical fashion with a mean time interval of 21 hours. At least one sentinel node was visualized in all patients on the first lymphoscintigram. A total of 56 sentinel nodes were seen in 38 basins. The second lymphoscintigram revealed the same drainage pattern in all patients: the same number of sentinel nodes was visualized at identical locations. All sentinel nodes that were visualized on the first lymphoscintigram showed an unequivocal increase in radioactivity after repeat injection of the radioactive tracer. The reproducibility of penile lymphoscintigraphy was 100% (95% CI: 85-100%). Intra-individual variability in lymphatic drainage is thus an unlikely explanation for false-negative results of dynamic sentinel node procedures.

In chapter 9 the accuracy of preoperative high-resolution ultrasonography-guided fine-needle aspiration cytology is evaluated. Sensitivity and specificity of ultrasound-guided fine-needle aspiration cytology were 39% and 100% respectively. The quantity of groins on which a dynamic sentinel node procedure was performed was reduced by 11%. The sensitivity of 39% demonstrates that ultrasound guided fine-needle aspiration cytology cannot replace dynamic sentinel node biopsy. However, this technique proved to be a useful tool for preoperative screening of the clinically node-negative groins. By detecting occult metastases, patients can immediately be scheduled for complete inguinal lymphadenectomy, avoiding unnecessary staging surgery.

In chapter 10, the incidence and causes of non-visualization of sentinel lymph nodes on the preoperative lymphoscintigram are analyzed as well as the implications for further management. Preoperative lymphoscintigraphy visualizes a sentinel node in 89% of the groins. Visualization depends on the administered tracer dose. Unilateral drainage was initially interpreted as a normal physiological phenomenon and non-visualized groins were not explored. After the occurrence of a tumor recurrence in a non-visualized groin, such groins are now explored using blue dye mapping and intraoperative palpation. Sentinel nodes were retrieved in four out of eight such groins of which one contained metastasis.

An evaluation of the overall results of the dynamic sentinel node procedure in 140 patients with a median follow-up of more than four years is presented in chapter 11. Dynamic sentinel node biopsy proved to be of important diagnostic and prognostic value. Sentinel node metastasis was found in 31 patients (22%). Five-year disease-specific survival was 96% and 66% for patients with a tumor-negative sentinel node and tumor-positive sentinel node, respectively (p=0.001).

In Chapter 12, predictive factors for additional (non-sentinel) node involvement are analyzed. Sentinel node metastasis was found in 46 inguinal regions in 37 patients and a complementary lymph node dissection was routinely carried out in these cases. The sentinel node was the only tumor-positive node in 39 of the 46 dissection specimens.
(80%). In uni- and multivariate analysis, the size of the sentinel node metastasis proved to be the only significant prognostic variable for additional lymph node involvement (both $p = 0.02$). No additional lymph node involvement was found when a micrometastasis ($\leq 2\text{mm}$) was present in the sentinel node. Maybe such patients can be spared a complementary inguinal lymph node dissection in the future.