

New Treatment Guidelines for Penile Cancer

Presented by Philippe E. Spiess, MD

Abstract

Although relatively rare in Western countries, penile cancer is associated with high morbidity and mortality. To achieve the most favorable outcomes in men with this malignancy, early medical or surgical treatment is required. Few data are available from prospective, randomized trials, and heterogeneous approaches to care have emerged. In this article, Dr. Spiess presents highlights from the inaugural NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for penile cancer, focusing primarily on treatment strategies for primary penile lesions and regional lymph nodes. NCCN recommendations regarding surveillance and the management of tumor recurrence and metastatic disease are briefly explored. (*JNCCN* 2013;11:659–662).

A high degree of heterogeneity is seen in the care of men with penile cancer around the world, stated Philippe E. Spiess, MD, Associate Member of the Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, Florida, and a member of the NCCN Panel on bladder and penile cancers. With the use of non-evidence-based treatment approaches, outcomes can widely vary. To clarify some of the controversies associated with the treatment of penile cancer, NCCN has created inaugural NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for penile cancer, with input from experts in penile cancer from around the world. This comprehensive protocol is intended to

establish a foundation to help standardize and optimize the care of patients faced with this potentially disfiguring and lethal cancer.

Treatment Strategies for Primary Penile Tumors

Radical surgery (partial or total penectomy with a negative surgical margin) remains the gold standard in managing invasive penile cancer, said Dr. Spiess. However, less invasive options that may improve quality of life are being considered, based on the stage and grade of the tumor.

The new NCCN Guidelines include a variety of options for the primary treatment of superficial lesions (Tis or Ta). Using the NCCN Categories of Evidence and Consensus (Figure 1) category 2A (uniform NCCN consensus based on lower-level evidence) options include topical treatment (with either imiquimod [5%] or 5-fluorouracil [5-FU] cream) or wide local excision with circumcision. Evidence for laser therapy and complete glansectomy is lower level, but panel consensus is that both are appropriate interventions in specific clinical circumstances.

For more extensive tumors (T1), treatment options are based on tumor grade. For instance, for grades 1 to 2 tumors, recommended treatment (category 2A) is wide local excision (possible split-thickness or full-thickness skin graft). Laser or radiation therapy is a category 2B (non-uniform consensus based on lower-level evidence) alternative. For grade 3 or 4 tumors, wide local excision, glansectomy, and partial or total penectomy are indicated. Although radiotherapy is a category 2B option, radiochemotherapy is a category 3 option, with major disagreement on the panel as to its appropriateness. For T2+ tumors, partial or total penectomy is recommended.

Supportive study data on topical therapy and pe-

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Figure 1 NCCN Categories of Evidence and Consensus.

nile-preserving surgery were briefly reviewed. Alnajjar et al¹ studied the use of 5-FU or imiquimod over 10 years in the treatment of 86 patients with carcinoma in situ of the glans penis. Of the 44 men who received topical chemotherapy, 25 (57%) had a complete response. “With 5-FU or imiquimod, you can get excellent outcomes,” stated Dr. Spiess.

One study of the role of penile-preserving surgery was conducted by Feldman and McDougal² (Figure 2). Sixty patients underwent this treatment for squamous cell carcinoma of the penis; about half had carcinoma in situ, and the others had T1 disease. The overall recurrence rate was 21% in both subgroups. At 5 years, about 14% had a late recurrence. “It is important to note that these patients can experience recurrence fairly late and should be followed up for at least 10 years,” noted Dr. Spiess.

Thus, maintaining good penile function is possible in a select patient cohort. However, Dr. Spiess warned, “Clinical stage consideration is pivotal.” This

approach is only indicated for patients with small lesions for which negative margins can be obtained. For patients in whom negative margins are not possible, more radical treatments are best suited.

Management of Regional Lymph Nodes

To predict the probability of metastatic lymph node involvement in men with penile cancer, clinicians have traditionally used standard risk categories (low, intermediate, and high), noted Dr. Spiess. However, the use of nomograms based on clinical stage of groin lymph nodes is also used. For instance, using a nomogram, Ficarra et al³ correctly determined which patients had occult inguinal lymph node metastases 88% of the time. According to Dr. Spiess, “these nomograms outperform our clinical risk categories.”

Dr. Spiess briefly discussed the unclear role of sentinel lymph node biopsy. Studies using dynamic sentinel node biopsy (DSNB) have been somewhat disappointing.^{4,5} For instance, Tanis et al⁴ reported that occult lymph node metastases in penile cancer were detected with a sensitivity of about 80% and a false-negative rate of 18%. Dr. Spiess also shared results from a study he participated in, using preoperative lymphoscintigraphy and DSNB.⁵ He concluded that, with a sensitivity rate of 71%, it remains an insufficient way to detect occult inguinal disease.

Thus, the NCCN Guidelines for managing non-palpable inguinal lymph nodes reflect these findings. For patients at low risk, surveillance is indicated, and DSNB is ranked as a category 2B option. For patients at high risk, inguinal lymph node dissection (ILND) is recommended, and again DSNB is a category 2B recommendation. “We are somewhat cautious in promoting this type of technique [DSNB],” admitted

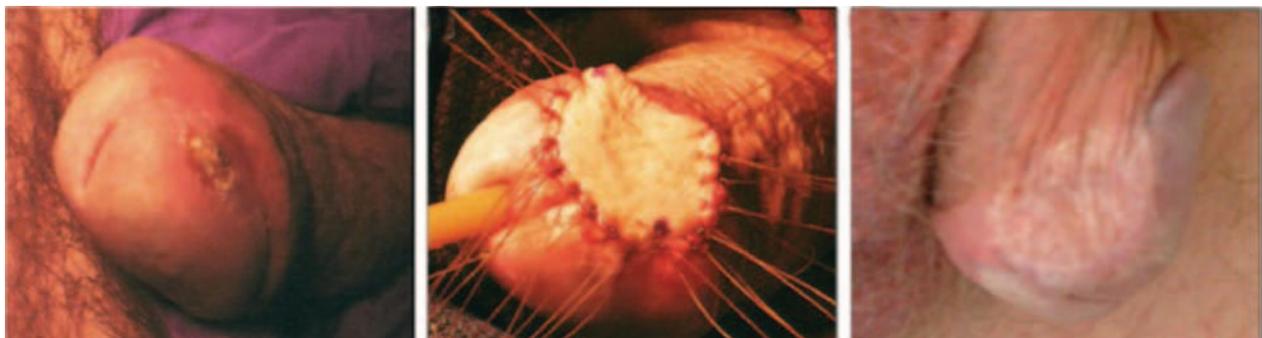


Figure 2 Penile-preserving surgery. Reprinted with permission from Feldman S, et al: Long-term outcome of excisional organ sparing surgery for carcinoma of the penis. *The Journal of Urology*. 2011;186(4):1303-1307. © 2011 Elsevier.

Dr. Spiess. For those with more aggressive primary tumor, the gold standard remains ILND.

For palpable inguinal lymph nodes (nonbulky disease), the NCCN Guidelines are stratified by the size of the unilateral lymph node. For patients with smaller nodes (< 4 cm), fine-needle aspiration is recommended. With a negative result, an excision biopsy would be the next step; with a positive result, the next step would be ILND. For patients with larger nodes (\geq 4 cm), the treatment pathway is the same as that for bulky unresectable inguinal lymph nodes.

“The treatment paradigm for bulky nodal disease is clearly evolving,” revealed Dr. Spiess. With the landmark study by Pagliaro et al,⁶ a multimodal approach has emerged as an effective option. In this small phase II study, patients with penile cancer and bulky nodal metastases (but no distant disease) were treated with neoadjuvant chemotherapy (paclitaxel, ifosfamide, and cisplatin) and then surgical resection. They reported an objective response rate of 50%. “On the whole, this is far superior to what we see traditionally with surgery alone,” declared Dr. Spiess. In addition, improved time to disease progression and overall survival were linked to response to neoadjuvant chemotherapy, absence of bilateral residual disease, absence of extranodal extension, and adjacent skin involvement, he added.

Therefore, the NCCN Guidelines for palpable lymph nodes larger than 4 cm include neoadjuvant chemotherapy as an alternative for those with enlarged pelvic lymph nodes. However, for those with unilateral mobile lymph nodes, ILND is recommended. And for those with multiple or bilateral inguinal lymph nodes, fine-needle aspiration is indicated.

General Surveillance Strategies

Surveillance suggestions are provided in the inaugural NCCN Guidelines for penile cancer. For patients who were treated for primary lesions (topical, laser, radiotherapy, or wide local excision), clinical examination should be performed every 3 months for the first 2 years; every 6 months for years 3 to 5, and every 12 months thereafter. In addition, “those with penile-preserving surgery should be followed up more carefully over the first few years,” noted Dr. Spiess. Patients who were treated initially with partial or total penectomy should undergo follow-up every 6 months for the first few years and then annually.

Similar recommendations are provided for following up patients with lymph node involvement. Clinical examination is indicated every 3 to 6 months for the first few years and then every 6 to 12 months thereafter, depending on the stage of disease. For patients with more extensive disease, chest imaging is recommended every 6 months for the first few years; abdominopelvic imaging with CT or MRI is recommended every 3 months for the first year and then every 6 months thereafter.

Dr. Spiess noted that not much literature is available on surveillance for men with penile cancer. However, patterns of tumor recurrence in men with squamous cell carcinoma of the penis were studied by Leijte et al.⁷ In their retrospective study involving 700 patients, 29% had a tumor recurrence. Of these recurrences, 92% occurred within 5 years of primary treatment. Moreover, a more recent study showed that inguinal recurrence after ILND in node-positive men with penile cancer tends to occur within a short time (about 5 months).⁸ Thus, the NCCN Guidelines recommend following up with patients closely, based on their risk of tumor recurrence.

Guidelines for Recurrent and Metastatic Disease

Dr. Spiess also briefly addressed the NCCN Guidelines for managing both recurrent and metastatic disease. The pathway for recurrence of a penile lesion depends on whether the corpora cavernosa has been invaded. If it has, partial or total penectomy is recommended. If it has not, partial or total penectomy is the primary option, with repeated penile-sparing treatment being a category 2B alternative. For local tumor recurrence in the inguinal region, systemic chemotherapy or external-beam radiotherapy and/or surgical resection should be considered.

For metastatic penile cancer, treatment options include systemic chemotherapy, radiotherapy, and radiotherapy with concurrent chemotherapy. For patients with a complete or partial response, consolidative surgery could be the next choice. However, Dr. Spiess remains hesitant about this step. “I would be cautious and not jump to surgery right away, as these patients are at high risk for subsequent cancer progression,” he noted. For patients who experience no response or disease progression, salvage systemic chemotherapy or radiotherapy or best supportive care could be considered.

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