Sentinel lymph node biopsy in penile cancer: evolution and insights

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Introduction: *Defining the presence or absence of microscopic metastases in the inguinal lymph nodes in patients with invasive penile squamous carcinoma and no palpable adenopathy remains crucial but difficult short of performing inguinal lymphadenectomy.*
Methods: *We reviewed the results of less invasive procedures such as traditional sentinel node biopsy and contemporary dynamic sentinel node biopsy aided by intraoperative lymphatic mapping (IOLM) to determine their role in the management of patients without palpable inguinal adenopathy*
Results: *Inguinal node biopsy directed to the sentinel node area or region although initially promising was associated with a recurrence rate of 16% (24/150) among seven series reported. Extending the dissection to a wider region did not improve these results (20% recurrence, 5/25 patients). Preoperative lymphoscintigraphy combined with IOLM (with blue dye and a hand held gamma probe to detect radioactive counts) routinely detected sentinel nodes in the Netherlands Cancer Institute experience. However IOLM was associated with a false negative rate of 18% (6/34 patients). IOLM using an open incision approach at M.D. Anderson Cancer Center provided evidence for inguinal lymph drainage to alternate areas within the inguinal field confirming proof of principle for IOLM.*
Conclusion: *Inguinal lymph node biopsy directed to the sentinel node area to detect microscopic metastases is no longer recommended. Dynamic sentinel node biopsy utilizing IOLM is a promising technique in evolution that requires further testing among high volume centers for penile cancer. Contemporary superficial and modified inguinal dissection techniques with intraoperative frozen section remain the "gold standard" for defining the presence of microscopic metastases.*

Key Words: penile cancer, sentinel lymph node, intraoperative lymphatic mapping

The dilemma

Squamous penile cancer is a rare neoplasm in developed countries, accounting for only 0.4% to 0.6% of all malignancies among men in the United States and Europe; however, it accounts for up to 10% of malignancies in some Asian, African, and South American countries.[1] Penile cancer has a propensity to spread beyond the primary site via regional lymphatics, which act as conduits for tumor emboli. Metastatic deposits enlarge in inguinal nodal areas, eventually producing ulceration and infection. Death may result from sepsis or hemorrhage due to erosion of tumor into the femoral vessels.[2]

Staging methods include physical examination of the primary lesion or inguinal region, tumor biopsy, chest radiograph, and computerized tomography scan of the abdomen and pelvis. Noninvasive staging of regional disease has long been considered inaccurate, because only 35% to 60% of palpable adenopathy is caused by nodal metastasis—the remainder caused

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by inflammation or infection. A negative physical examination was found to be falsely negative in an average of 25% (range 11% to 62%) of 266 total penile cancer patients from six different series.[3-8] This factor is crucial because 95% of patients with proven nodal metastasis treated conservatively die within 3 years of diagnosis compared with a 5-year survival rate of 77% for patients with nonmetastatic disease.[2]

Inguinal lymph node dissection (ILND) is potentially curative in patients with low-volume inguinal metastases and is therefore the accepted treatment modality for patients with persistent adenopathy, because approximately 50% of patients will benefit. The dilemma that remains is how to detect patients who, despite negative inguinal examinations, harbor micrometastases. Early ILND remains the gold standard treatment; prior series demonstrate 5-year survival rates of 57% to 100% in patients undergoing early ILND versus 8% to 24% in patients subsequently presenting with positive lymph nodes.[9-11] The "price" is high, however, for approximately 60% to 75% of patients with negative inguinal examinations (with pathologically determined negative lymph nodes) who are at risk for the development of leg edema, wound infection/abscess, or skin flap necrosis post surgery.[12]

Sentinel lymph node biopsy and extended sentinel lymph node dissection

In order to decrease the morbidity associated with surgical staging in patients with penile cancer, an anatomically directed biopsy of the sentinel inguinal lymph node was advocated by Cabanas.[13] This concept was based upon the distribution of contrast subsequent injection of penile lymphatics to a specific lymph node group that projected radiographically over the femoral head and was found to reside anatomically (subsequent to dissection) superomedial to the superficial epigastric vein near its junction with the saphenous vein. In patients with positive sentinel lymph node biopsies who subsequently underwent ilioinguinal node dissection, the sentinel de was often the only positive node. Furthermore, there were no cases in which other nodes were positive and the sentinel node was negative or that penile lymphatic drainage bypassed the inguinal lymph node via direct channels to the iliac system. The 5-year survival rate in the face of a negative sentinel lymph node biopsy was 90%. Subsequently however, there were several documented cases of false-negative sentinel lymph node biopsies, and patients relapsed with unresectable disease.[14-15]

Recognizing the potential for false-negative lymph node sampling, an extended sentinel lymph node dissection (ESLND) was performed at The University of Texas M. D. Anderson Cancer Center to identify patients with microscopic inguinal metastases who would benefit from early ilioinguinal lymphadenectomy. The sentinel area is synonymous with the superomedial lymph node quadrant previously reported by Daseler subsequent to anatomical dissection Figure 1.[16] This quadrant contains 0 to 7 lymph nodes and is bounded superiorly by the inguinal ligament laterally by the saphenofemoral vein junction, and inferiorly by a horizontal line through the saphenofemoral junction above the superficial external pudendal vein. Daseler noted that this grouping of nodal tissue as well as lymph nodes over the saphenofemoral junction received the majority of afferent cutaneous lymphatics from the penis.[16] Occasionally, nodal tissue in the superolateral and inferomedial quadrants also received afferent lymphatics from the penis. In our

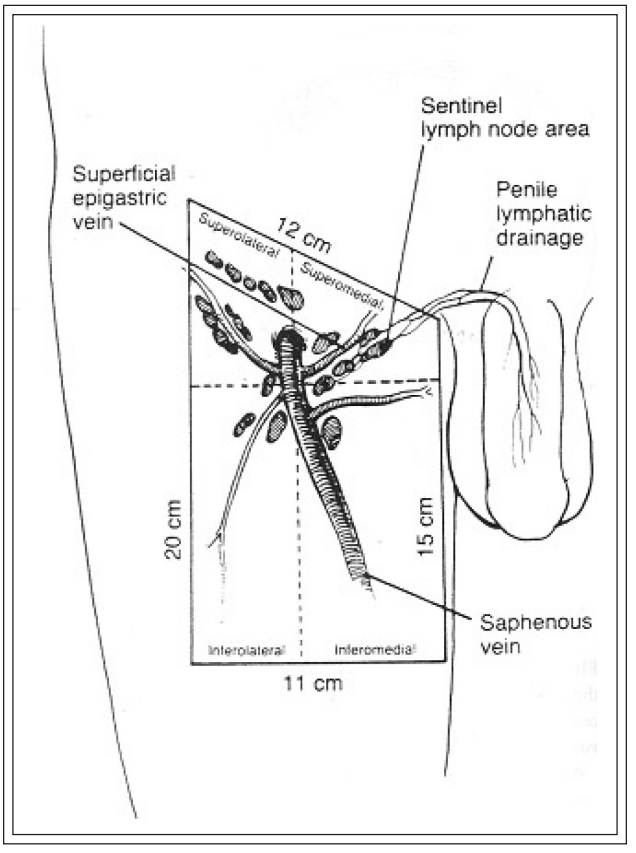

Figure 1. (Reproduced with permission from CA Pettaway, AC von Eschenbach: Surgery of penile carcinoma, in Atlas of Surgical Oncology. KI Bland et al (eds). Philadelphia, WB Saunders, 1995.

TABLE 1. **Penile cancer inguinal lymph node biopsy**

Series	Biopsy type	False negative biopsy (%)
McDougal et al[10]	NS	2/4 (50)
Cabanas[13]	SLNB	3/31 (10)
Perinetti et al[14]	SLNB	1/1 (100)
Wespe et al[15]	SLNB	1/1 (100)
Pettaway et al[17]	ESLND	5/25 (20)
Ravi1[8]	Medial	7/47 (15)
Fossa et al[19]	SLNB	5/41 (12)
Total		24/150 (16)

ESLND = Extended Sentinel Lymph Node Dissection
SLNB = Sentinel Lymph Node Biopsy
NS = Not Specified

experience, the median number of lymph nodes removed in the ESLND specimen was 3 from right-sided dissections and 2 from left-sided dissection. Despite the apparent adequate removal of all lymphatic tissue within the traditional sentinel lymph node area, 5 (25%) patients subsequently developed inguinal metastases. Three of the five patients recurrencies died of progressive disease.[17] Similar findings have been reported by other institutions Table 1. Based on the accumulated data, removal of a designated anatomical lymph node area is insufficient to identify all patients harboring micrometastases. We believe this is most likely due to anatomic variations in the position of the sentinel node.

Intraoperative lymphatic mapping

The goal of intraoperative lymphatic mapping (IOLM) is to determine where in the inguinal lymph node field the sentinel lymph node resides using either visual (vital blue dyes) or gamma emission (lymphoscintigraphy) techniques at the time of surgery. Intraoperative lymphatic mapping offers the potential for precise localization of the sentinel node wherever it may reside in the inguinal field.

Historical perspective

Intraoperative lymphatic mapping was extensively studied by Morton et al[20] in patients with malignant melanoma who required evaluation of the regional lymph nodes. The technique involved intradermal injection of a vital blue dye (isosulfan blue or patent blue) adjacent to the lesion. The dye was transported by the afferent lymphatics to a specific node in the regional nodal basin. This node was designated as the sentinel lymph node. In Morton's series of 237 patients, the sentinel lymph node was identified in 194 patients.[20] These patients then underwent full regional lymphadenectomy; false negative results were observed in only 1% of the cases. This technique has been used at the M. D. Anderson Cancer Center in patients with malignant melanoma and vulvar cancer with good results.[21-22]

Current techniques

Lymphoscintigraphy is a nuclear medicine technique that provides morphologic and functional information about the lymphatic system. In this procedure, Technetium (TC)-labeled particles between 10 nm to 100 nm are injected intradermally, rapidly absorbed into lymphatic capillaries, and retained in draining lymph nodes. When radioactive colloidal material is injected intradermally or subcutaneously, it enters the lymphatic channels and flows to the regional lymph nodes. Lymphoscintigraphy scanning demonstrates the distribution of radioactive colloid within the nodes and the patency of lymph channels. In a study from the Moffitt Cancer Center,[23] preoperative lymphoscintigraphy significantly improved the surgical management of patients with malignant melanoma. Recently, several groups, including our own, have used this technology to assist in defining where in the inguinal field the sentinel node resides in patients with penile cancer.[24-28]

Typically, 0.5 mc of filtered (size < 0.22 micron) Tc-99m sulfur colloid (AN-SULFUR COLLOID; CIS-US, Inc., Bedford, MA) in approximately 0.2 cc is injected intradermally. The injection sites are chosen in surrounding areas adjacent to the lesion. Serial scintigraphic images of the pelvis are obtained using large field-of-view gamma cameras with a low-energy parallel-hole collimator at 140 Kev with a 20% window. Serial 5-minute images of the pelvis (in anterior/posterior and lateral views) are obtained at various intervals until the lymphatic drainage sites are identified. The lateral views are typically used to confirm the direction (anterior or posterior) of the lymphatic drainage to determine whether there is inguinal or iliac nodal involvement. This procedure typically lasts 1.5 to 3 hours.

Preoperative lymphoscintigraphy is typically performed in the nuclear medicine suite within 7 days of the scheduled surgery in order to provide preliminary localization of the sentinel nodes. This evaluation helps to discern whether lymphatic drainage from the penile injection site is unilateral

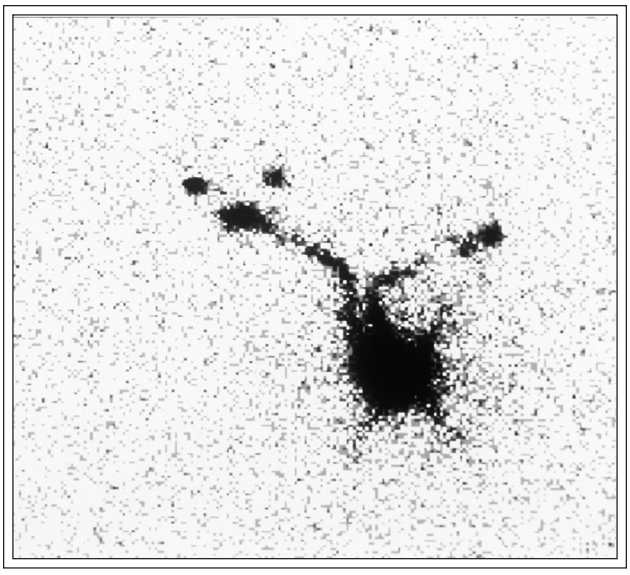

Figure 2. Preoperative lymphoscintigraphy image subsequent to intradermal injection of Tc-99m sulfur colloid adjacent to penile lesion. Inguinal drainage pattern is bilateral.

or bilateral and, potentially, the number of nodal sites involved Figure 2.

To assess the pattern of lymphatic drainage intraoperatively, the patient receives another intradermal dose of Tc-99m sulfur colloid the morning of surgery and proceeds directly to the operating room. Alternatively, a larger dose of Tc-99m sulfur colloid (1.8 mCi) can be given as a single injection at the time of the preoperative study, but the planned surgical procedure must be performed within 24 hours.[27-28]

At surgery, a hand-held gamma probe (NEOPROBE; Neoprobe Corp., Dublin, OH) detects radiotracer activity sequestered in specific lymph nodes and has facilitated the use of smaller surgical incisions and potentially outpatient surgery in both breast and melanoma cancers.[20-21,23,29-30] In one study,[30] lymphoscintigraphy was more sensitive in the identification of the sentinel lymph node in patients with melanoma than vital blue dye staining (83.5% "hot" versus 69.5% "blue"). However, with both techniques, identification of a sentinel node was possible in 96% of cases.[30]

Results in penile cancer

The largest reported experience of IOLM for penile cancer to date is from the Netherland's Cancer Institute.[24,27-28] Candidates for the procedure were patients exhibiting stage T2 or greater primary tumors with no palpable inguinal adenopathy. One hundred twenty-three patients underwent preoperative lymphoscintigrapy followed by IOLM the next day using a hand held gamma probe aided by prior injection of patent blue dye. They have designated the procedure dynamic sentinel lymph node biopsy (DSLNB). Lymph nodes with significant radioactivity and/or that were visibly blue were removed and examined via a standard pathologic protocol.

Preoperative lymphoscintigraphy visualized 121 (98%) of 123 nodes. Bilateral drainage occurred in 83% of patients; the remaining patients had a unilateral pattern. A tumor-positive sentinel lymph node was noted in 28 (23%) of 123 patients. These patients subsequently underwent inguinal dissection with or without pelvic dissection.

Patients with a tumor-negative sentinel lymph node had no additional lymph nodes removed and were observed. After a median of 39 months, six patients developed inguinal relapses despite negative intraoperative findings. The false-negative rate for DSLNB was 6 (18%) of 34 patients with positive lymph nodes. Four of the six patients subsequently died of disease.

Based on their experience over a 9-year period the authors, hypothesized that false-negative findings were related to: 1) inadequate histologic detection, 2) lymphatic obstruction causing rerouting of lymphatic flow, or 3) inadequate injection causing a low signal in the nodal field.[28] Several changes were instituted, including routine serial sectioning of involved lymph nodes along with cytokeratin immunohistochemistry to increase the sensitivity of pathologic detection. In addition, routine exploration of groins with low or no signal subsequent to preoperative or intraoperative studies is now employed. It was felt by the authors that direct palpation of the inguinal field or visualized blue dye could lead to detection of positive lymph nodes that were not detected via gamma emission due to obstruction of lymphatics by cancer.[28] Finally, the authors recommend the use of inguinal ultrasound with fine needle aspiration to detect subtle architectural changes (nonpalpable) in positive lymph nodes that could result in redistribution of lymphatic flow.[28]

At M. D. Anderson Cancer Center we have utilized an open lymphatic mapping technique to define the distribution of lymph nodes within the inguinal field and to define, from a pathologic standpoint, the limits of IOLM in finding microscopic metastases.[26] Thirty-two patients with squamous penile carcinoma (stages T1 to T3) underwent either preoperative lymphoscintigraghy with intraoperative gamma

probe detection and isosulfan blue dye injection (n=16 patients) or intraoperative dye injection alone (n= 16 patients). At the time of surgery, lymph nodes with gamma counts at least 150% over background or that were stained blue were removed and examined pathologically. The site of lymph nodes within the inguinal field with respect to the inguinal quadrants defined by Daseler et al[16] was noted. Irrespective of mapping findings, all patients underwent a complete superficial lymph node dissection.

The pattern of lymphatic drainage was bilateral in 75% of patients with unilateral drainage in the remainder. In 65% of inguinal fields examined, a sentinel node was detected within the superomedial lymph node quadrant Figure 1. This location corresponded to that predicted by Cabanas[13] in his original description of the anatomic location of the sentinel lymph node. However, in 15% of cases, the sentinel node was clearly lateral to the saphenofemoral junction in the superolateral field out of the area described by Cabanas or even that removed by performing an extended lymph node dissection.[13, 17] Thus, using the open-mapping technique, we were able to show that the position of the sentinel node within the inguinal field varies.

Six inguinal fields in five patients contained metastases. Two of the six fields were completely nonpalpable, and four exhibited nonsuspicious adenopathy (i.e, less than 1 cm, "rubbery" nodes). While preoperative lymphoscintigraphy revealed drainage to all six inguinal fields, only four of six fields were detected intraoperatively by significant radioactivity, and only three had visible blue dye. Thus, at best, we would have detected 4 (67%) of 6 patients with metastases had we removed only lymph nodes with significant radioactivity or that were blue.

Direct intraoperative palpation via the open inguinal incision revealed in one of two missed cases a small, firm lymph node that proved to be replaced by cancer. Due to a large body habitus, we failed to palpate this node prior to surgery. We believe that relative obstruction of lymphatic flow occurred in this case and redistribution of the radioactive tracer resulted in a false-negative finding as noted by Kroon et al.[28] The second case involved a microscopic focus of cancer noted in a lymph node located lateral to the saphenofemoral junction (superolateral inguinal quadrant; Figure 1) when the more medially placed sentinel node (positive radioactive counts and blue) was tumor negative. Serial sectioning of this medial sentinel node failed to reveal metastasis upon further examination. The finding of metastases in the lateral nonsentinel node remains unexplained.

Collectively, these data - illustrate that IOLM in penile cancer is technically feasible but the optimal technique remains to be defined. As has been noted with many surgical techniques, the learning curve can be initially challenging, especially given the fact that the disease is rare. It was recently estimated that a surgeon technically capable of correctly identifying sentinel nodes (i.e., 5% false-negative rate) would have a 13% chance that the rate of nonidentification would be higher (i.e., ≥ 10%) if only 25 cases were performed.[31] This decreased with the number of cases performed because 75 to 150 cases were required to decrease the nonidentification rate to 1% to 3%.[31] Thus, the number of cases (i.e., ≥ 25) for most urologists in developed countries where the disease is rare is an impediment to performing IOLM reliably to detect microscopic metastases.

In such cases, standard dissection techniques, including superficial and modified inguinal lymphadenectomy with intraoperative frozen section analysis, represent alternative strategies to define the presence of microscopic metastases with relatively low morbidity.[32,33]

Conclusions

Defining the presence of microscopic metastases in patients with invasive penile cancer remains a challenge. Inguinal node biopsy within designated anatomic areas is no longer recommended due to false-negative findings. Dynamic sentinel node biopsy utilizing IOLM is a promising technique in evolution that requires further testing among high volume centers for penile cancer. Contemporary superficial and modified inguinal dissection techniques with intraoperative frozen section analysis remain the gold standard for defining the presence of microscopic metastases in patients without inguinal adenopathy. □

References

1. Lynch DF Jr, Pettaway CA. Tumors of the Penis. Campbell's Urology Walsh PC, Retik AB, Vaughn Jr, Wein AJ. Philadelphia: Saunders, 2002:2945-2982.
2. Thompson IM, Fair WR. Penile carcinoma. AUA update series, Lesson 1, 9:1990.
3. Srivinas V, Morse MJ, Herr HW, Sogani PC, Whitemore WF Jr. Penile cancer: relation of extent nodal metastases to survival. *J Urol* 1987;137:880.
4. Ornellas AA, Seixas ALC, Marota A, Wisnescky A, Campos F, Rangel De Moraes J. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. *J Urol* 1994;151:1244.

5. Horenblas S, van Tinteren H, Delemarre JF, Moonen LF, Lustig D, van Waardenburg EW. Squamous cell carcinoma of the penis-Part III: Treatment of the regional nodes. *J Urol* 1993;149:492.
6. Beggs JH, Spratt JS. Epidermoid carcinoma of the penis. *J Urol* 1964;91:166.
7. Theodorescu D, Russo P, Zang ZF et al. Outcomes of initial surveillance of invasive squamous cell carcinoma of the penis and negative nodes. *J Urol* 1996;155:1626-1631.
8. Hardner GJ, Bhanalph T, Murphy GP, Albert DJ, Moore RH. Carcinoma of the penis: Analysis of therapy in 100 consecutive cases. *J Urol* 1972;108:428-431.
9. Johnson DE, Lo RK. Management of regional lymph nodes in penile carcinoma: five-year results following therapeutic groin dissections. *Urology* 1984;24:308.
10. McDougal WS, Kirchner FK Jr, Edwards RH, Killion LT. Treatment of carcinoma of the penis: The case for primary lymphadenectomy. *J Urol* 1986;136:38.
11. Fraley EE, Zhang G, Manivel C, Niehans GA. The role of ilioinguinal lymphadenectomy and significance of histological differentiation in treatment of carcinoma of the penis. *J Urol* 1989;142:1478.
12. Johnson DE, Lo RK. Complications of groin dissection in penile cancer: experience with 101 lymphadenectomies. *Urology* 1984;24:312.
13. Cabanas RM. Anatomy and biopsy of the sentinel lymph nodes. *Urol Clin N Amer* 1992;19(2):267.
14. Perinetti E, Crane DB, Catalona WJ. Unreliability of sentinel lymph node biopsy for staging penile carcinoma. *J Urol* 1980;124:734.
15. Wespes E, Simon J, Schulman CC. Cabanas approach: Is sentinel node biopsy reliable for staging penile carcinoma? *Urology* 1986;28:278.
16. Daseler EH, Anson BJ, Reimann AF. Radical excision of the inguinal and iliac lymph glands. *Surg Gyn Obst* 1948;87:679.
17. Pettaway CA, Pisters LL, Dinney CPN, Jularbal F, Swanson DA, von Eschenbach AC, Ayala A. Sentinel lymph node dissection for penile carcinoma: The M. D. Anderson Cancer Center experience. *J Urol* 1995;154:1999.
18. Ravi R. Prophylactic lymphadenectomy vs observation vs inguinal biopsy in node-negative patients with invasive carcinoma of the penis. *Jap J Clin Oncol* 1993;23:53.
19. Fossa SD, Hall KS, Johannessen NB, Urnes T, Kaalhus O. Cancer of the penis. Experience at the Norwegian Radium Hospital 1974-1985. *Eur Urol* 1987;13(6):372-377.
20. Morton DL, Wen D, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392.
21. Gershenwald GE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng C, Lee JJ, Balch CM, Reintgen DS, Ross MI. Multi-institutional lymphatic mapping experience: The prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999;17:976-983.
22. Levenback C, Burke TW, Gershenson DM, Morris M, Malpica A, Ross MI. Intraoperative lymphatic mapping for vulvar cancer. *Obst Gynecol* 1994;84:163.
23. Norman J, Cruse CW, Espinosa C, Cox C, Berman C, Clark R, Saba H, Wells K, and Reintgen DS. Redefinition of cutaneous lymphatic drainage with the use of lymphoscintigraphy for malignant melanoma. *Am J Surg* 1991;162:432-437.
24. Horenblas S, Jansen L, Meinhardt W, Hoefnagel CA, de Jong D, Nieweg OE. Detection of occult metastasis in squamous cell carcinoma of the penis using a dynamic sentinel node procedure. *J Urol* 2000;163:100-104.
25. Akduman B, Fleshner NE, Ehrlich L, Klotz L. Early experience in intermediate-risk penile cancer with sentinel node identification using the gamma probe. [Clinical Trial. Journal Article] *Urology* 2001;58(1):65-68.
26. Kedar D, Izawa J, Tamboli P, Ainslie N, Eddings T, Babaian RJ, Dinney CPN, Pisters LP, Pettaway CA. Intraoperative lymphatic mapping (IOLM) for squamous penile cancer: the M. D. Anderson Cancer Center prospective experience. The American Urological Association 96th Annual Meeting, *J Urol (Suppl)* 2001;165(5):#711,173.
27. Tanis PJ, Lont AP, Meinhardt W, Valdes Olmos RA, Nieweg OE, Horenblas S. Dynamic sentinel node biopsy for penile cancer: Reliability of a staging technique. *J Urol* 2002;168:76-80.
28. Kroon BK, Horenblas S, Estourgie SH, Lont AP, Valdes Olmos, RA, Nieweg OE. How to avoid false-negative dynamic sentinel node procedures in penile carcinoma. *J Urol* 2004;171:2191-2194.
29. Stewart KC, Lyster DM. Interstitial lymphoscintigraphy for lymphatic mapping in surgical practice and research. *J Invest Surg* 1997;10:249-262.
30. Albertini JJ, Cruse CW, Rapaport D, Wells K, Ross M, DeConti R, Berman CG, Jared K, Messina J, Lyman G, Glass F, Fenske N, Reintgen DS. Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. *Ann Surg* 1996;223:217-224.
31. Tanis PJ, Nieweg OE, Har, AAM, Kroon BBR. The illusion of the learning phase for lymphatic mapping. *Ann Surg Oncol* 2002;9(2):142-147.
32. Colberg JW, Andriole GL, Catalona WJ. Long-term follow-up of men undergoing modified inguinal lymphadenectomy for carcinoma of the penis. *Brit J Urol* 1997;79:54-57.
33. Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: The M. D. Anderson Cancer Center experience. *J Urol* 2002;167:1638-1642.