SENTINEL LYMPH NODE BIOPSY IN TREATMENT OF PENILE CANCER

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ABSTRACT

Objectives: The management of lymph node metastases is crucial in penile cancer surgery. Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure used to assess the presence of lymph node metastasis. The objective is to evaluate the efficiency of SLNB in the treatment of penile cancer.

Methods: This retrospective observational study included 31 patients diagnosed with penile cancer who underwent surgery and SLNB at the National Hospital of Dermatology between January 2018 and May 2021.

Results: The average age of patients was 58.4 ± 12.3 years old. The majority of patients had a history of phimosis (87.1%) and a treatment delay of over 1 year (67.7%). All 31 patients with penile cancer had squamous cell carcinoma (SCC) as the histological type, with the majority undergoing partial penectomy (87.1%). Out of 61 inguinal regions examined in 31 patients, lymph node metastasis was detected in one region (3.2%). The average follow-up time was 45.2 ± 12.1 months. One SLNB-negative patient was found to have inguinal lymph node metastasis after 12 months, resulting in a false-negative rate of 50%. The complication rate was 8.2%.

Conclusions: SLNB utilizing a radioisotope tracer can significantly reduce the incidence and severity of complications associated with inguinal lymph node dissection in patients with penile cancer.

Keywords: *Dynamic sentinel node biopsy; inguinal lymph node dissection; penile cancer.*

1. INTRODUCTION

Penile cancer is a rare malignancy, with a global incidence of 1 in 100,000.[1] Squamous cell carcinoma (SCC) constitutes the predominant histological type, accounting for 95% of cases, while basal cell carcinoma, melanoma, and sarcoma are less prevalent. Lymph node metastasis is a critical prognostic factor in penile carcinoma[2], typically progressing from inguinal nodes to pelvic and distant sites.[3] Patients without lymph node

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involvement exhibit a favorable 5-year survival rate of 90%, contrasting with a lower rate of 56% for those with lymph node metastasis.[4] Hence, precise diagnosis and effective management of regional lymph nodes are pivotal in penile cancer treatment.

According to the US National Comprehensive Cancer Network (NCCN) Guidelines for Penile Cancer, lymph node management should be tailored based on the clinical status of lymph nodes[5]. Inguinal lymphadenectomy poses a high risk of postoperative complications, such as skin necrosis, wound infection, and lymphedema, leading to unnecessary overtreatment in 75 - 80% of patients with non-palpable lymph nodes.[6] However, relying solely on clinical monitoring without lymph node dissection can result in missed lymph node metastases during the early stages, negatively impacting patient prognosis.[7] Therefore, the NCCN panel recommends considering sentinel lymph node biopsy (SLNB) for patients with non-palpable lymph nodes or palpable lymph nodes but negative fine needle aspiration.[5]

The sentinel node biopsy procedure was first introduced by Cabañas more than 40 years ago, and SLNB for penile cancer patients was performed in 2000.[8,9] The technique involves injecting a radioisotope tracer around the tumor, followed by lymphoscintigraphy to locate the sentinel lymph nodes. Intraoperatively, a gamma probe measures radioactivity to identify the sentinel lymph nodes. This approach has significantly reduced the complication rate to 5.7% and the false-negative rate to 4.8%.[10] The sensitivity and specificity of SLNB are 88% and 99%, respectively.[11] Despite numerous studies on SLNB in penile cancer patients, most have small sample sizes and yield divergent findings regarding the false-negative rate, reliability, and complication rate.[12,13] The optimal timing for utilizing SLNB remains a topic of debate due to conflicting results.

2. MATERIALS AND METHODS

Study design

The study was conducted at the National Hospital of Dermatology and Venereology in Vietnam. This study was designed as a retrospective observational study.

Subjects

The study cohort comprised individuals diagnosed with penile cancer who underwent both cancer surgery and sentinel lymph node biopsy (SLNB) at the National Hospital of Dermatology between January 2018 and May 2021. The research methodology involved conducting sentinel lymph node biopsies on 31 patients with a total of 61 inguinal regions. Inclusion criteria necessitated that the patients met the dual conditions of being diagnosed with penile cancer and undergoing cancer surgery along with SLNB at the specified hospital. Participation in the study was contingent upon the patient's agreement. Conversely, exclusion criteria encompassed individuals with a follow-up period of less than 2 years and those who declined to participate in the study.

Procedures

Before undergoing surgery, all patients underwent a comprehensive preoperative assessment, including clinical examination, pathological examination, inguinal ultrasound, and basic laboratory tests. Fine needle aspiration was performed for patients with palpable inguinal lymph nodes to identify potential lymph node metastasis. Patients meeting the criteria for

Sentinel Lymph Node Biopsy (SLNB) underwent lymphoscintigraphy 3 to 5 hours before the surgery. A 99mTechnetium (99mTc) nanocolloid was injected at the base of the penis, and intraoperative detection of sentinel lymph nodes was facilitated using a gamma probe. If clinically suspected metastases were detected during surgery, they were also surgically addressed. All harvested lymph nodes underwent treatment, staining with hematoxylin-eosin, and examination by a pathologist. Immunohistochemistry was employed when necessary to confirm the diagnosis.

Following the National Comprehensive Cancer Network (NCCN) guidelines, patients with at least one positive lymph node were recommended for bilateral inguinal lymphadenectomy, while those with at least two positive nodes were advised to consider extending the procedure with pelvic lymphadenectomy on the same side. Patients were closely monitored during their hospital stay, and subsequent follow-ups occurred every 3 months to assess complications, local recurrence, lymph node metastasis, and distant metastasis.

To evaluate the efficacy of SLNB, a false-negative result was defined as a negative SLNB followed by the later detection of regional lymph node metastasis during follow-up, without evidence of a new primary tumor. The false-negative rate was calculated using the standard formula: false-negative inguinal regions / (true-positive inguinal regions + false-negative inguinal regions).

Statistical analysis

The data were encrypted and analyzed using the statistical algorithm with SPSS 20.0. The T-test and the Chi-square test were employed to compare the difference between means and prevalence. The difference was considered statistically significant at $p < 0.05$.

Ethical approval

The study was approved by the Ethical Review Board of the National Hospital of Dermatology and Venereology, Vietnam, and written informed consent was obtained from all subjects before their enrollment in the study.

3. RESULTS

3.1. Characterization of the study population

Table 1. Characteristics of the study population

Number of patients (n)		31	
Average age		58.4 ± 12.3	
Phimosis	Yes	27	87.1%
	No	4	12.9%
Time to treatment	Under 1 year	10	32.3%
	1 year and above	21	67.7%

Histopathological classification	Well differentiated SCC	24	77.4%
	Moderately differentiated SCC	1	3.2%
	Verrucous carcinoma	6	19.4%
Inguinal lymph nodes	Palpable	23	74.2%
	Non-palpable	8	25.8%

The research findings encompassed a cohort of 31 individuals diagnosed with penile cancer who had undergone surgical resection and Sentinel Lymph Node Biopsy (SLNB) involving radioisotope injection. The average age of the patients was 58.4 ± 12.3 years. Notably, 87.1% of the patients had a history of phimosis. A significant portion, constituting 67.7%, had a time to treatment exceeding one year. All 31 patients were diagnosed with squamous cell carcinoma (SCC), with 24 presenting well-differentiated SCC, one with moderately differentiated SCC, and six with Verrucous carcinoma. Additionally, 25.8% of the patients exhibited non-palpable inguinal lymph nodes (as shown in Table 1).

3.2. Surgical resection and dynamic sentinel node biopsy

Table 2. Surgical resection and dynamic sentinel node biopsy

		Number of nodes	Percentage (%)
Type of surgery	Mohs surgery	2	6.5%
	Wide local excision	2	6.5%
	Partial penectomy	27	87.0%
SLNB	One-stage	28	90.3%
	Two-stage	3	9.7%
Number of groins had SLNB	One side	1	3.2%
	Two sides	30	96.8%
Average number of nodes		2.1 ± 0.7	

Among the 31 patients, partial penectomy was performed in 87.0% of cases, and 90.3% underwent simultaneous Sentinel Lymph Node Biopsy (SLNB) and penile surgery. Interestingly, 9.7% of patients underwent SLNB 5 to 7 days after surgical resection, a subgroup identified by preoperative histopathology suggesting a benign tumor, but postoperative histopathology confirmed the presence of penile cancer. The study involved a total of 61 inguinal regions across the 31 patients, with an average removal of 2.1 ± 0.7 lymph nodes per groin during the SLNB procedure (as shown in Table 2).

3.3. Follow-up after surgery

The average postoperative length was 8.9 ± 2.6 days, ranging from 4 to 16 days. The average follow-

up duration was 45.2 ± 12.1 months, with a range of 24 to 62 months.

Table 3. Follow-up after surgery

	Number of patients	%
Lymph node metastasis	1	3.2
Lymph node metastasis after negative SLNB	1	3.2
No metastasis	29	93.6
Total	31	100.0

Following surgery, histopathological examination of the lymph nodes revealed inguinal lymph node metastasis in 1 out of the 61 inguinal regions, corresponding to a rate of 3.2% (as shown in Table 3). This specific patient underwent SLNB on both sides of the inguinal region, detecting 1 metastatic lymph node, followed by bilateral inguinal lymphadenectomy. Throughout the 38-month follow-up period, no local metastasis or nodal recurrence was observed in this patient.

Conversely, another patient who underwent partial penectomy and had a negative SLNB experienced inguinal lymph node metastasis after 12 months. Subsequently, this patient underwent bilateral inguinal lymphadenectomy and received adjuvant radiotherapy. Unfortunately, the patient developed distant metastases and succumbed to the disease 34 months after the SLNB procedure. Consequently, one patient in the study died during the follow-up period due to cancer metastasis, and no other instances of local recurrence were observed.

The study encountered 1 true-positive procedure and 1 false-negative procedure, resulting in a false-negative rate of 50%.

3.4. Complications

Table 4. Complications (n = 61)

Complications	Number of patients	%
Wound infection	2	3.3
Wound lymphedema (no intervention required)	2	3.3
Wound lymphedema (needed aspiration)	1	1.6
Total	5	8.2

Out of the 61 inguinal regions that underwent Sentinel Lymph Node Biopsy (SLNB), complications were observed in 5 inguinal regions among 5 patients, constituting an incidence of 8.2%. Specifically, one patient with wound lymphedema drainage received aspiration and compression bandages, while two patients experienced wound infections. Additionally, two patients presented with wound lymphedema that did not necessitate intervention. Importantly, there were no reported fatalities attributable to these complications (as shown in Table 4).

4. DISCUSSION

The management of regional lymph nodes in penile cancer treatment has been a topic of debate for many years, particularly in patients with non-palpable lymph nodes. Clinical examination alone often detects lymph node metastasis in the advanced stages, while radical inguinal lymphadenectomy carries a high complication rate and may result in overtreatment in a significant number of patients.[6] In line with NCCN guidelines, the consideration of SLNB is recommended for patients with non-palpable lymph nodes or palpable lymph nodes but negative fine needle aspiration.[5]

In our study, the complication rate was 8.2% with mostly mild complications and did not require intervention. Only one patient experienced wound lymphedema and received aspiration and compression bandages. The complication rate of SLNB was lower than that reported in studies on radical inguinal lymphadenectomy, which ranged from 49% to 58% with the rate of serious complications reaching 10%[6]. The complication rate observed in our study is consistent with that reported by several other authors, ranging from 4.7% to 15.8%.[13,14] These findings highlight that SLNB significantly reduces the risk of complications compared to radical lymphadenectomy in penile cancer patients.

While SLNB helps reduce the incidence of excessive inguinal lymphadenectomy, it does carry a risk of false-negative results, leading to delayed detection of lymph node metastases and potentially poor prognosis.[7]

The false-negative rates of SLNB reported in different studies vary considerably. Study of Lam et al. conducted SLNB on 500 groins and reported a false-negative rate of 5% per inguinal region.[13] The Netherlands Cancer Institute reported a false-negative rate of SLNB of 4,8 - 19.2 - 22%.[10,15] In another study by Lena Nemitz et al. involving 76 groins, a false-negative rate of 42.9% was reported[14]. Gonzaga-Silva et al. performed SLNB on 27 patients and reported a false-negative rate as high as 42,8%.[12] In our study, the false-negative rate was 50%. These variations in results can be attributed to factors such as small sample sizes in most studies, heterogeneity in SLNB procedures, and differences in the populations under investigation.

Several possible factors may contribute to false-negative SLNB results. It is plausible that lymph node micrometastases were not detected by histopathology. Additionally, alterations in lymphatic drainage due to tumor compression or enlargement of lymph nodes could lead to changes in the primary portal lymph node.[16]

Although SLNB remains a subject of controversy, it is increasingly being studied and applied more extensively, with ongoing technical improvements aimed at reducing the false-negative rate associated with this procedure in the future.

A limitation of our study is its retrospective design, which may result in incomplete information obtained from medical records. The sample size was relatively small, comprising only 31 patients. Furthermore, only one patient with SLNB had metastases, and one patient had a false-negative result, significantly impacting the false-negative rate. However, this study represents the largest number of cases in Vietnam published on the use of SLNB in penile cancer patients. Most cases in our study had a follow-up period of less than 5 years, and therefore, we cannot rule out

the possibility of detecting further false-negative results in the future.

5. CONCLUSION

The findings from this study show that SLNB with radioisotope tracer can significantly reduce the complication rate and severity of inguinal lymph node dissection in patients with penile cancer. However, due to the small sample size, the false-negative rate is high. We will continue to monitor and study with a larger sample size in the future to get the most accurate results.

REFERENCES

1. Montes Cardona, C. E., & García-Perdomo, H. A. (2017). Incidence of penile cancer worldwide: systematic review and meta-analysis. Revista panamericana de salud publica = Pan American journal of public health, 41, e117. https://doi.org/10.26633/RPSP.2017.117.

2. Horenblas, S., & van Tinteren, H. (1994). Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. The Journal of urology, 151(5), 1239 -1243. https://doi.org/10.1016/s0022-5347(17)35221-7.

3. Wood, H. M., & Angermeier, K. W. (2010). Anatomic considerations of the penis, lymphatic drainage, and biopsy of the sentinel node. The Urologic clinics of North America, 37(3), 327-334. https://doi.org/10.1016/j.ucl.2010.04.013.

4. Djajadiningrat, R. S., Graafland, N. M., van Werkhoven, E., Meinhardt, W., Bex, A., van der Poel, H. G., van Boven, H. H., Valdés Olmos, R. A., & Horenblas, S. (2014). Contemporary management of regional nodes in penile cancer-improvement of survival? The Journal of urology, 191(1), 68-73. https://doi.org/10.1016/j.juro.2013.07.088.

5. National Comprehensive Cancer Network. (2022). Penile Cancer, version 1.2023. NCCN Clinical Practice Guideline in Oncology. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1456.

6. Stuiver, M. M., Djajadiningrat, R. S., Graafland, N. M., Vincent, A. D., Lucas, C., & Horenblas, S. (2013). Early wound complications after inguinal lymphadenectomy in penile cancer: a historical cohort study and risk-factor analysis. European urology, 64(3), 486 -492. https://doi.org/10.1016/j.eururo.2013.02.037.

7. Kroon, B. K., Horenblas, S., Lont, A. P., Tanis, P. J., Gallee, M. P., & Nieweg, O. E. (2005). Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. The Journal of urology, 173(3), 816-819. https://doi.org/10.1097/01.ju.0000154565.37397.4d.

8. Cabanas R. M. (1977). An approach for the treatment of penile carcinoma. Cancer, 39(2), 456-466. https://doi.org/10.1002/1097-0142(197702)39:2<456:aid-cncr2820390214>3.0.co;2-i.

9. Horenblas, S., Jansen, L., Meinhardt, W., Hoefnagel, C. A., de Jong, D., & Nieweg, O. E. (2000). Detection of occult metastasis in squamous cell carcinoma of the penis using a dynamic sentinel node procedure. The Journal of urology, 163(1), 100-104. https://pubmed.ncbi.nlm.nih.gov/10604324/

10. Leijte, J. A., Kroon, B. K., Valdés Olmos, R. A., Nieweg, O. E., & Horenblas, S. (2007). Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. European urology, 52(1), 170-177. https://doi.org/10.1016/j.eururo.2007.01.107.

11. Zou, Z. J., Liu, Z. H., Tang, L. Y., Wang, Y. J., Liang, J. Y., Zhang, R. C., Tang, Y. Q., & Lu, Y. P. (2016). Radiocolloid-based dynamic sentinel lymph node biopsy in penile cancer with clinically negative inguinal lymph node: an updated systematic review and meta-analysis. International urology and nephrology, 48(12), 2001-2013. https://doi.org/10.1007/s11255-016-1405-x

12. Gonzaga-Silva, L. F., Tavares, J. M., Freitas, F. C., Tomas Filho, M. E., Oliveira, V. P., & Lima, M. V. (2007). The isolated gamma probe technique for sentinel node penile carcinoma detection is unreliable. International braz j urol: official journal of the Brazilian Society of Urology, 33(1), 58-67. https://doi.org/10.1590/s1677-55382007000100009.

13. Lam, W., Alnajjar, H. M., La-Touche, S., Perry, M., Sharma, D., Corbishley, C., Pilcher, J., Heenan, S., & Watkin, N. (2013). Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: a prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. European urology, 63(4), 657-663. https://doi.org/10.1016/j.eururo.2012.10.035.

14. Nemitz, L., Vincke, A., Michalik, B., Engels, S., Meyer, L. M., Henke, R. P., Wawroschek, F., & Winter, A. (2022). Radioisotope-Guided Sentinel Lymph Node Biopsy in Penile Cancer: A Long-Term Follow-Up Study. Frontiers in oncology, 12, 850905. https://doi.org/10.3389/fonc.2022.850905.

15. Tanis, P. J., Lont, A. P., Meinhardt, W., Olmos, R. A., Nieweg, O. E., & Horenblas, S. (2002). Dynamic sentinel node biopsy for penile cancer: reliability of a staging technique. The Journal of urology, 168(1), 76-80. https://pubmed.ncbi.nlm.nih.gov/12050496.

16. Leijte, J. A., van der Ploeg, I. M., Valdés Olmos, R. A., Nieweg, O. E., & Horenblas, S. (2009). Visualization of tumor blockage and rerouting of lymphatic drainage in penile cancer patients by use of SPECT/CT. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 50(3), 364-367. https://doi.org/10.2967/jnumed.108.059733.