



## Determining the sentinel lymph node of patients with penile cancer using radioactive nuclides

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### ABSTRACT

Penile cancer is an extremely rare disease among men's oncological diseases. This is most commonly a squamous cell carcinoma, usually developed from the inner part of the foreskin epithelium or penis glans. Penile cancer is often caused by HPV 16 and 18 genotypes. Also, differences in causes of morbidity are considered as differences in the prevalence of risk factors in different populations caused by social and economic factors. Penile cancer can be cured in more than 80% of all cases if the disease is diagnosed at early stage. Having detected the widespread metastases of penile cancer in the adjacent lymph nodes, the 5-year survival rate is reduced to 29%. Examination of the lymph nodes is very important for the diagnosis of the tumor. Determining the sentinel lymph node is a technically very complex procedure which is used as a diagnosis and treatment method.

**Keywords:** penile, cancer, radioactive, nuclides.

### Introduction

Penile cancer is a very rare disease that often appears as the painful wound or ulcer in the penis glans area. This is most commonly a squamous cell carcinoma, usually developed from the inner part of the foreskin epithelium or penis glans. Pathogistologically, penile squamous cell carcinoma is very similar to oropharyngeal epithelium or female genitalia, cervix, vagina or vulvar tumors [1,2]. According to the latest data of the Lithuanian Cancer Registry, from 2000 to 2012, Only 300 cases of penile cancer have been registered in Lithuania (i.e., from 20 to 30 cases per year). In the Western world, primary penile tumors are

also very rare and occur less frequently than 1.00/100,000 in European or American men [1,3]. However, in Africa, in some Asian and South American countries, penile cancer makes up 10-20% of male cancer cases, and it is directly influenced by the prevalence of HPV. HPV DNA is determined in 70-100% of intraepithelial neoplasia cases and in 30-40% of invasive penile tumor cases. Penile cancer is often caused by HPV 16 and 18 genotypes [4,5]. Also, differences in causes of morbidity are considered as differences in the prevalence of risk factors in different populations caused by social and economic factors (low social stratum, frequent sexual partners presence, early start of sexual intercourse, smoking, phimosis, chronic

inflammatory processes of the penis, such as balanoposthitis, obliterating balanitis, etc.). It is worth mentioning that it is exactly phimosis associated with invasive tumor form. In countries where circumcisions are performed on religious grounds, the number of penile tumors is the lowest – only 0.3/100,000 per year [6,7]. Penile cancer can be cured in more than 80% of all cases if the disease is diagnosed at early stage. Having detected the widespread metastases of penile cancer in the adjacent lymph nodes, the 5-year survival rate is reduced to 29%. Mortality is usually associated with local complications: an infection, bleeding from ulcerated metastases [8,9]. During the diagnosis of primary tumor, physical examination is mandatory for the determination of local lesions. Lymph nodes examination is very important – lymph nodes should be palpated. When the lymph nodes in the groin area are impalpable, micrometastatic probability in the lymph nodes is about 25% [4]. At cN0 stage, dynamic scintigraphy is performed to determine the sentinel lymph node. A nano-colloidal Technetium-99m solution is used for this procedure; it is injected around the tumor a day before the biopsy of the lymph nodes in the groin area. Gamma-ray camera helps to locate the sentinel lymph node or several lymph nodes, and they are removed. Patients are informed about a potentially false negative result, which can occur in 12-15% of all cases, according to literature. If other methods of investigation determine lymph node metastases, inguinal lymphadenectomy is performed [10-12].

### **Indications for treatment of the lymph nodes, if they are not enlarged**

Patients with a low risk of metastases (pTis, pTaG1-2 or pT1G1) are monitored. And in cases when monitoring can not be guaranteed, modified inguinal lymphadenectomy is performed. For medium risk patients (pT1G2) – determination of the sentinel lymph node with radionuclide or modified lymphadenectomy is performed. Lymph node removal can be extended to radical lymphadenectomy if metastases are found in the superficial groin lymph nodes. For high risk patients (pT  $\geq$  2 or G3) – determination of the sentinel lymph node with radionuclide or modified or radical lymphadenectomy is also performed [8,12,13]. If the patient is supposed to be actively monitored after removal of the primary tumor, it is recommended that the groin to be examined every 3 months for a period of two years, later – every 6 months for another three years. If the patient has undergone inguinal lymphadenectomy (pN0), the physical examination is recommended every 3 months

for 2 years, then every year up to 5 years. However, if inguinal lymphadenectomy (pN1-3) has been performed, specific monitoring is recommended – physical examination, CT, chest X-ray, etc. every 3 months for 2 years, then every 6 months up to 5 years. Bone scanning and other tests are recommended for patients with more symptoms [14].

### **Determining the sentinel lymph node using radioactive nuclide**

No special preparation is required for this study. The product used is a human serum albumin colloid with a particle size of ~ 80 microns. It is absorbed from the injection site into the lymphatic vessels and does not absorb into the blood capillaries (due to size). Injection should be made overnight prior to surgery (the day before surgery). The total used activity of the preparation is ~ 100 MBq (megabecquerels). For comparison, bone scintigraphy is performed with 500-600 MBq. The injection is performed intra-subdermally around the tumor at a distance of 5 mm from the tumor edge. The number of injections depends on tumor size, one injection volume – up to 0.1 ml. (Fig. 1) [15]. Subsequently, a visual examination using Siemens Symbia T6 Gamma Camera (Fig. 2) is performed. Two images are taken: the “early” image is recorded right after the injection (approximately ~ 10 minutes), and the “late” image (lymphoscintigraphy, SPECT/CT) on the day of surgery. SPECT/CT helps to determine precisely the location, number, and size of a SLN. (Fig. 3) During the operation, a sentinel, i. e. “radioactive” lymph node is searched using a portable radiometer (Neoprobe 2000) [15,16]. This instrument shortens the operation time and helps to locate other sentinel lymph nodes when radioactivity remains high in adjacent tissues after the removal of the most radioactive lymph node (Fig. 4). On finding the sentinel lymph node the removal of this sentinel lymph node is made. According to the recommendations of the European Nuclear Medicine Association, radiation exposure to operational personnel is low during the detection of the sentinel lymph node, no additional protection or measuring instruments (dosimeters) are required.

### **The sentinel lymph node determinations performed in NCI**

In the National Cancer Institute, dynamic scintigraphy was performed for 4 patients with penile cancer for determination of the protective lymph node. The radioactive nuclide was used to locate the

sentinel lymph node, which was surgically removed later. However, no modified lymphadenectomy was performed. During the research, all patients were monitored for 2 years: they were examined by CT and US. Summarizing the results: 1 micrometastasis was found using radionuclide method in one of four patients. Due to lymphadenopathy, lymphadenectomy was performed for one patient and biopsy for another. No more metastases were found.

## Figures

Fig. 1 Injection using human serum albumin colloid.



Fig. 2. Visual examination using Siemens Symbia T6 Gamma Camera is performed.



Fig. 3 Lymphoscintigraphy

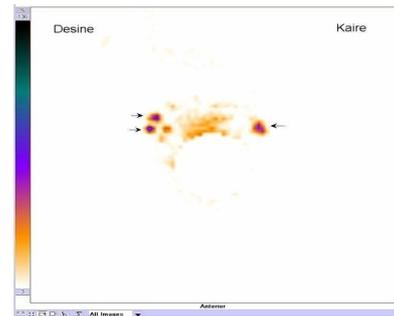


Fig. 4. Radiometer.



## Conclusions

Determination of the sentinel lymph node when having penile cancer is used as a diagnostic and treatment method. It is technically complex and may be associated with an erroneous negative lymph nodes detection rate. However, the use of complex non-invasive visualization methods (SPECT/CT) reduces the number of postoperative complications and false negative lymph nodes.

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