

## Oncology

## Penile cancer with positive nodes: A case of HPV p16-positivity and its significance, implication of data from head and neck cancer



Cam Nguyen<sup>a,\*</sup>, Stephen Leslie<sup>b</sup>, John Gross<sup>c</sup>, Nicholas Dietz<sup>c</sup>, Subodh M. Lele<sup>d</sup>, Gopi Sirineni<sup>e</sup>

<sup>a</sup> Division of Radiation Oncology, Creighton University Medical Center, Omaha, NE, USA

<sup>b</sup> Department of Urology, Creighton University School of Medicine, Omaha, NE, USA

<sup>c</sup> Department of Pathology, Creighton University Medical Center, Omaha, NE, USA

<sup>d</sup> Department of Pathology, University of Nebraska Medical Center, Omaha, NE, USA

<sup>e</sup> Department of Radiology, Creighton University Medical Center, Omaha, NE, USA

## ARTICLE INFO

## Keywords:

Penile cancer  
Anal cancer  
Chemotherapy  
Radiotherapy  
HPV  
p16

## ABSTRACT

Penile cancer is normally discovered in an early stage due to its visibility to the patient. This case report demonstrates a morbidly obese patient with a locally advanced penile cancer hidden by fatty tissue. Biopsy showed P16-positive tumor cells, which responded to concurrent chemo-radiotherapy with no evidence of disease at 24 months of follow-up. We also review the significance of p16-positive cell biology.

## Introduction

Penile cancer is a rare malignancy, accounting for <1% of all neoplasms among men in the United States. In terms of histology, approximately 95% are squamous cell carcinoma, with the rest being melanoma, basal cell carcinoma, adenocarcinoma (Paget disease of the penis) and sarcoma.<sup>1</sup>

Recently, HPV vaccine using Gardasil®9, has been advocated for young females and males.<sup>2</sup>

HPV-negative penile carcinogenesis is less well understood, however it has been linked to p53 mutations. It appears that tumor cells that express p16 respond better to cytotoxic treatment such as chemotherapy and/or radiotherapy.<sup>3</sup>

## Case presentation

A 54 year-old man presented with urinary obstruction and a penile mass, and due to his morbid obesity, was not diagnosed until the penile tumor was far advanced, i.e., unresectable. Initial physical exam showed a patient with morbid obesity, weighing 150 kg with the tip of the penis barely visible. The entire penis was involved with tumor, attempt at placement of Foley catheter was not successful, thus the need for suprapubic catheterization.

The PET-CT scan showed a highly hypermetabolic 7-cm mass in distal penis with a SUV of 39.8. There was also non-specific pelvic lymphadenopathy with hypermetabolic activity ranging from 2.7 to 5.3 SUV. The most prominent of these lymph nodes included a right external iliac node that measured 1.9 cm, left inguinal lymph node that measured 1.3 cm and a left external iliac lymph nodes which measured 1.7 cm (Fig. 1).

The biopsy H&E section showed squamous cell carcinoma, moderately differentiated type. The HPV P16 stain was strongly positive (Fig. 2).

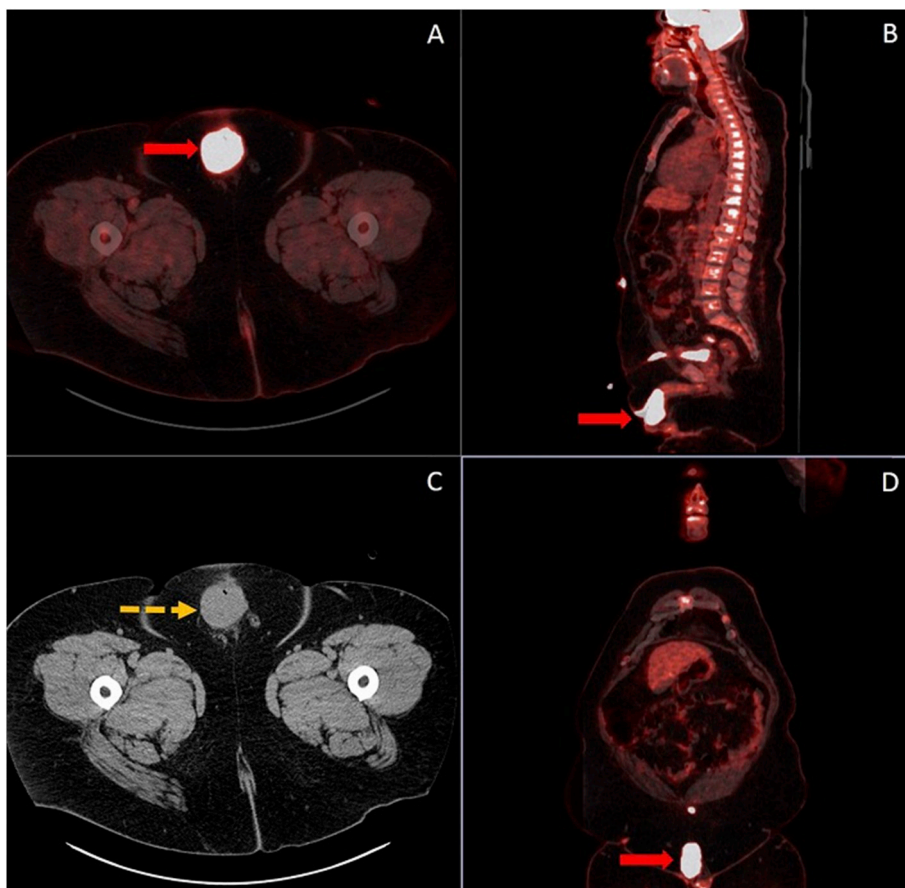
Pt was treated with definitive therapy, delivered using concurrent chemo-radiotherapy using weekly i.v. Cisplatin and a total radiotherapy dose of 5940 cGy. The radiotherapy treatment program is similar to the anal cancer protocol, which has been well established for the last 40 years, also known as Nigro protocol.<sup>3</sup>

A follow-up MRI at 24 months showed complete resolution of the abnormality (Fig. 3). Repeat biopsy at 24 months showed no tumor (Fig. 2C).

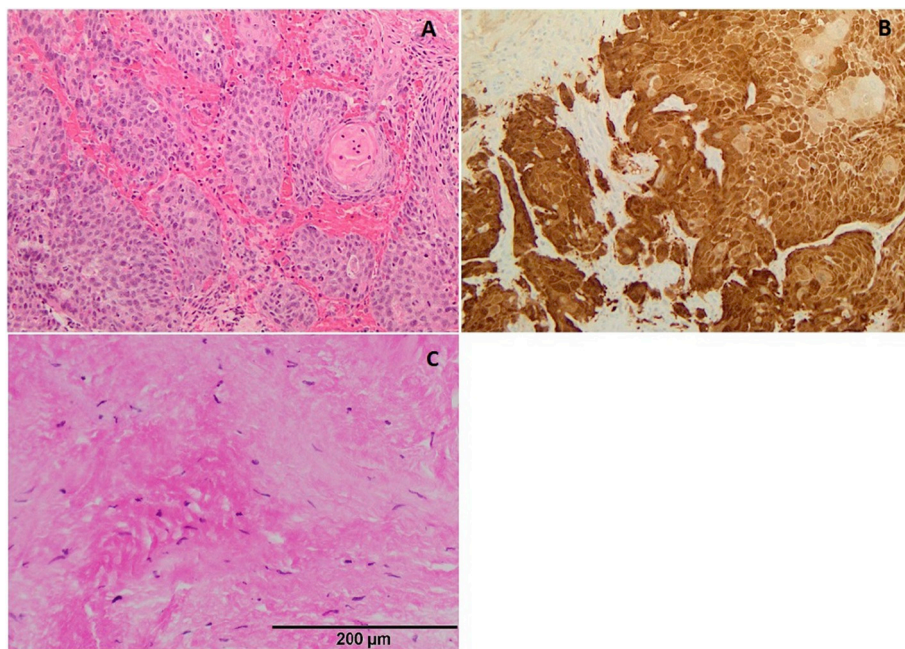
In contrast to head and neck cancer, where p16 data is now maturing and affects the latest AJCC staging system, there is virtually very little data in penile cancer on the prognostic significance of p16, due to the fact that penile cancer is very rare. We thereby present this case to bring awareness of p16 in penile cancer.

\* Corresponding author. Division of Radiation Oncology, Creighton University Medical Center, 7500 Mercy Rd, Omaha, NE, 68124, USA.

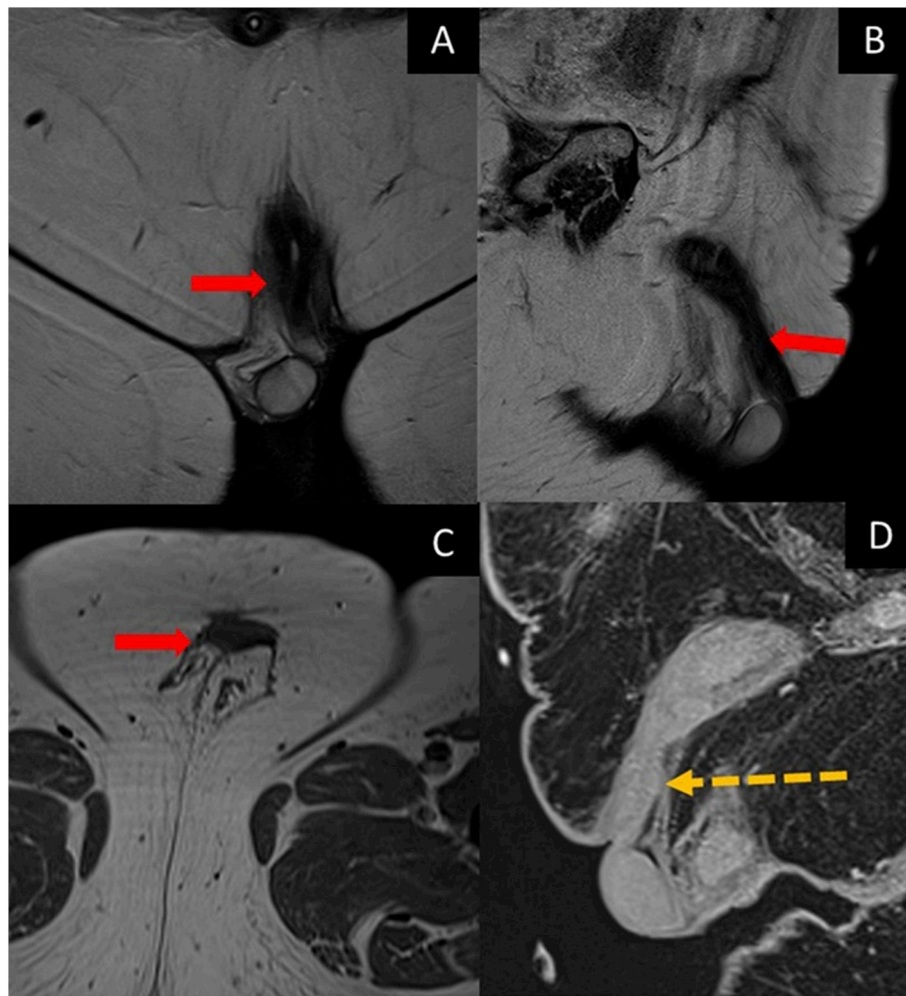
E-mail address: [camnguyen@creighton.edu](mailto:camnguyen@creighton.edu) (C. Nguyen).



**Fig. 1.** (A–D): Initial FDG PET CT demonstrating a highly hypermetabolic penile mass (red arrows) on fused CT-PET axial (A), coronal (B) and sagittal (D) images. Soft tissue density penile mass (yellow dashed arrow) on axial CT imaging (D) portion of the PET CT. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 2.** (A) Nest of invasive squamous cell carcinoma (H&E). (B) Immunohistochemical stain for p16: 90+% positive, 200x. (C) Repeat biopsy at 24 months post-treatment showed only benign fibrous tissue with collagen deposition without cancer.



**Fig. 3.** Post radiation therapy - T2W MRI showed complete resolution of penile mass with residual scar (red arrows) on coronal (A), sagittal (B), and axial (C) images. Post-contrast T1W VIBE sagittal images (D) shows no abnormal enhancement of the penile corpus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

## Discussion

Penile cancers with bulky or extensive disease not amenable to limited excisions are likely to require a partial or total penectomy. A partial penectomy is performed when the tumor can be completely removed surgically with an appropriate margin of resection while leaving an adequate penile length for voiding. If this cannot be accomplished with a partial penectomy, then a total penectomy will be required. The most common complication of partial penectomies is meatalstenosis which occurs in 4–9% of all such procedures. In most series, the local recurrence rate following penectomy is about 10% or less.

In the field of head and neck cancer, particularly oropharyngeal cancers such as tonsil or base-of-tongue cancers, the p16-positivity is now incorporated into the AJCC staging system for head and neck cancer. As an example, a T3N2 tonsil cancer was classified as stage III in AJCC 7th edition, but in the AJCC 8th edition (which is the most recent edition that takes into account the importance of p16), the very same tumor T3N2 tonsil cancer with p16-positivity is now classified as stage I. Psychologically, a patient would be pleased to know that he/she has a stage I cancer rather than stage III.<sup>3</sup>

Given the similar biology of HPV-induced cancers of the oropharynx, cervix, and anus, penile cancer biopsy specimens should be analyzed for p16 stains. A patient should be informed of this test as it has potential prognostic significance.<sup>3</sup>

As mentioned above, anal cancer has been treated primarily with definitive chemo-radiotherapy for the last 40 years, with the main regimen being 5-FU and mitomycin C, or 5-FU and cisplatin. The radiotherapy dose is generally in the range of 5400–6000 cGy with 180 cGy per fraction. The majority of anal cancer is p16-positive, and responds favorably to chemo-radiotherapy with excellent outcome, even for the advanced anal cancer.<sup>4</sup>

There have been a few case reports where penile cancer was treated with neoadjuvant chemotherapy, followed by surgical resection without radiotherapy.<sup>5</sup> Our case was treated with definitive chemo-radiotherapy, similar to the anal cancer regimen with successful outcome at 2 years of follow-up.

## Conclusion

This particular case of advanced penile cancer showed that, especially when it is p16-positive, can be successfully treated with definitive chemo-radiotherapy as seen in post-treatment MRI, PET-CT studies, and repeat biopsies that showed complete resolution of the disease.

In head and neck cancer, the implication of p16 positivity is significant: current research trials are investigating on de-escalation of treatment. For example, a patient with *p16-negative* tumor will require full radiotherapy dose such as 7000 cGy, while patients with *p16-positive* tumor may be successfully treated with lower radiotherapy dose (such as 5600–6000 cGy) with similar outcome.

We strongly believe that locally advanced penile cancer has similar prognosis as an anal cancer patients with similar volume of disease. Hopefully, data for p16 for penile cancer will accumulate over time in Urology literature, allowing physicians to inform the patients of the potential prognostic value of p16.

#### Funding

No funding was used for preparation of this manuscript.

#### Conflicts of interest

The authors disclose no conflict of interest.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at

<https://doi.org/10.1016/j.eucr.2019.101009>.

#### References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA A Cancer J Clin*. 2016 Jun;66(1):7-30. <https://doi.org/10.3322/caac.21332>.
2. White MD. Pros, cons, and ethics of HPV vaccine in teens—why such controversy? *Transl Androl Urol*. 2014 Dec;3(4):429–434. <https://doi.org/10.3978/j.issn.2223-4683.2014.11.02>.
3. Lydiatt WL, Patel SG, O'Sullivan B, et al. Head and neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA A Cancer J Clin*. 2017 Jan;67(2):122–137. <https://doi.org/10.3322/caac.21389>.
4. Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. *J Clin Oncol*. 2012 Dec;30(35):4344–4351. <https://doi.org/10.1200/JCO.2012.43.8085>.
5. Asghar AM, McIntosh AG, Kutikov A, Chen DYT, Geynisman DM. Neoadjuvant chemotherapy for penile cancer enabling organ preservation: a case of individualized management for bilateral lymph node metastasis and a bulky primary tumor. *Urol Case Reports*. 2019 Mar;(23):3–5. <https://doi.org/10.1016/j.eucr.2018.11.002>.