Comprehensive Genomic Profiling of Advanced Penile Carcinoma Suggests a High Frequency of Clinically Relevant Genomic Alterations

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Penile cancer • Sequencing • Targeted therapy • Mutation • Genomic profiling • Human papillomavirus

ABSTRACT

Background. Advanced penile squamous cell carcinoma (PSCC) is associated with poor survival due to the aggressiveness of the disease and lack of effective systemic therapies. Comprehensive genomic profiling (CGP) was performed to identify clinically relevant genomic alterations (CRGAs).

Materials and Methods. DNA was extracted from 40 μm of formalin-fixed, paraffin-embedded sections in patients with advanced PSCC. CGP was performed on hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of 692 X for 3,769 exons of 236 cancer-related genes plus 47 introns from 19 genes frequently rearranged in cancer. CRGAs were defined as genomic alterations (GAs) linked to targeted therapies on the market or under evaluation in mechanism-driven clinical trials.

Results. Twenty male patients with a median age of 60 years (range, 46–87 years) were assessed. Seventeen (85%) cases were stage IV and three cases (15%) were stage III. CGP revealed 109 GAs (5.45 per tumor), 44 of which were CRGAs (2.2 per tumor). At least one CRGA was detected in 19 (95%) cases, and the most common CRGAs were CDKN2A point mutations and homozygous deletion (40%), NOTCH1 point mutations and rearrangements (25%), PIK3CA point mutations and amplification (25%), EGFR amplification (20%), CCND1 amplification (20%), BRCA2 insertions/deletions (10%), RICTOR amplifications (10%), and FBXW7 point mutations (10%).

Conclusion. CGP identified CRGAs in patients with advanced PSCC, including EGFR amplification and PIK3CA alterations, which can lead to the rational administration of targeted therapy and subsequent benefit for these patients. The Oncologist 2016; 21:1–7

Implications for Practice: Few treatment options exist for patients with advanced penile squamous cell carcinoma (PSCC). Outcomes are dismal with platinum-based chemotherapy, with median survival estimated at 1 year or less across multiple series. Biological studies of patients with PSCC to date have principally focused on human papillomavirus status, but few studies have elucidated molecular drivers of the disease. To this end, we performed comprehensive genomic profiling in a cohort of 20 patients with advanced PSCC. Findings of frequent mutations in CDKN2A, NOTCH1, PIK3CA, and EGFR (all in excess of 20%) point to potential therapeutic avenues. Trials of targeted therapies directed toward these mutations should be explored.

INTRODUCTION

In 2015, the incidence of penile cancer in the United States is estimated to be 1,800, and approximately 320 deaths will occur because of the disease [1]. However, the annual incidence groups penile squamous cell carcinoma (PSCC) cases of different stages, for which survival varies markedly. In a large series, patients with stage I disease have an estimated 10-year survival of 89% [2]. In contrast, patients with penile cancer with metastatic disease have only an estimated survival of 21% at 2 years [2].

Despite the poor prognosis of patients with advanced PSCC, National Comprehensive Cancer Network guidelines are predicated largely on small prospective studies or
retrospective series rather than randomized trials because of the rarity of the disease [3]. Systemic therapy is typically chemotherapy; data from a single-arm phase II trial supports the use of paclitaxel, ifosfamide, and platinum (TIP) as neoadjuvant therapy for patients with clinical evidence of nodal involvement [4]. For metastatic disease, TIP is also the preferred first-line regimen, although historical regimens such as 5-fluorouracil with cisplatin may also be considered [5]. Cetuximab has been seen to be active in a subset of patients with PSCC; one patient in one non-epidermal growth factor (EGFR)-stratified series had a response rate of 23.5% to cetuximab with chemotherapy backbone [6–8]. EGFR expression was assayed in four other patients, with a range from 1+ to 3+, but expression did not correlate well with response [6–8].

A challenge in developing novel systemic strategies for penile cancer is the limited understanding of the heterogeneity of the oncogenic drivers of disease, particularly human papillomavirus (HPV) infection. HPV has been associated with 50%–70% of cases of squamous penile cancer across multiple series, but these studies amalgamate early, and patients with late-stage PSCC who likely have distinct clinicopathologic features and biology [9–14]. Broader molecular studies of penile carcinoma have been performed in a limited series of patients, but interpretation is again confounded by heterogeneity of the stage of disease and diagnostic methodologies used [15, 16]. Herein, we report results from comprehensive genomic profiling (CGP) in a cohort of patients with advanced penile cancer.

**RESULTS**

Among the 20 male patients included in the analysis, the median age was 60 years (range, 46–87 years). Seventeen patients (85%) had stage IV disease, and the remaining three (15%) had stage III disease. CGP revealed 109 GAs, with an average of 5.45 GAs per patient, and of the 109 GAs, 44 GAs (40%) were CRGAs, occurring at a mean frequency of 2.2 per case. TP53 was mutated in 13 cases (65%) and was the most common GA (Fig. 1). At least one CRGA was detected in 19 patients, and the most common CRGAs were CDKN2A (8 patients [40%]), NOTCH1 (5 patients [25%]), PIK3CA (5 patients [25%]), CCND1 (4 patients [20%]), EGFR amplification (4 patients [20%]), BRCA2 insertions/deletions (2 patients [10%]), RICTOR amplifications (2 patients [10%]) and FBXW7 point mutations (2 patients [10%]) (Table 1). Less frequent alterations in our series included FGF amplification and mutation of chromatin remodeling genes (e.g.,

![Figure 1](image.png)

**Figure 1.** Frequency of genomic alterations in advanced penile cancer. Long-tail plot outlining all observed clinically relevant genomic alterations in a series of 20 patients with advanced penile cancer.

**MATERIALS AND METHODS**

Formalin-fixed, paraffin-embedded (FFPE) slides or blocks were obtained for a series of 20 patients with advanced squamous cell penile cancer. DNA was extracted with a minimum threshold of 20% of DNA derived from tumor. CGP based on targeted next-generation sequencing was performed using hybridization-captured, adaptor ligation-based libraries in a Clinical Laboratory Improvement Amendments-certified laboratory (Foundation Medicine, Inc., Cambridge, MA). DNA was extracted from 40 μL of FFPE sections in patients with advanced PSCC. Cases were sequenced with a median coverage exceeding 500× across 3,769 exons in 236 cancer-related genes and 47 introns derived from 19 genes frequently rearranged in cancer. Bayesian algorithms were used to detect substitutions. Comparison with healthy control specimens was used to ascertain copy number alterations. Finally, local assembly algorithms were used to detect insertions and deletions. The genomic alterations (GAs) linked to approved or investigational targeted agents were termed clinically relevant genomic alterations (CRGAs). Only deidentified data were used for the current analysis. Pathologic stage was determined by review of available medical records. Local site permissions were used for this study.
<table>
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<tr>
<th>Patient</th>
<th>Tissue of origin</th>
<th>Age</th>
<th>Median exon depth</th>
<th>Known somatic short variants</th>
<th>Likely somatic short variants</th>
<th>Known CNAs</th>
<th>Likely rearrangements</th>
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<td>744</td>
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<td>725</td>
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<th>Patient</th>
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<td>NOTCH3:NM_0000435:c.1416_1417delGT_p.C473fs*3 [0.23,448], NOTCH3:NM_0000435:c.1378+2_1378+3TGT_p.splice site 1378→2_1378+3TGT_p.CNAs None</td>
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<td>452</td>
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<td>445</td>
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<td>CDKN2A:NM_000077:c.234_256del23_p.T79fs<em>33 [0.16,337], CDKN2A:NM_000077:c.301_307delGCCGG_p.R103fs</em>33 [0.15,1243], TP53:NM_0000546:c.367_368insCTTG_p.T125fs<em>25 [0.28,382], TP53:NM_0000546:c.367_368insCTTG_p.T125fs</em>25 [0.28,382], TP53:NM_0000546:c.367_368insCTTG_p.T125fs*25 [0.28,382]</td>
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<td>None</td>
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<td>None</td>
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</table>

Variants present in the Catalogue of Somatic Mutations in Cancer (COSMIC) that have been previously confirmed somatic are reported as known somatic alterations, whereas nonsynonymous variants in known oncogenes not found in the Single Nucleotide Polymorphism Database or COSMIC are reported as likely somatic variants. Abbreviations: CNA, circulating nucleic acids; HPV, human papillomavirus.
The 4 patients harboring *EGFR* amplification harbored between 9 and 46 copies, and they did not harbor any alterations of RAS (*HRAS*, *KRAS*, *NRAS*) family members. Alterations in RAS family members were identified in 2 patients (10%) and were *HRAS* G12D and *HRAS* G13D; HPV-16 was detected in 2 patients (10%), HPV-6 was detected in 1 patient (5%), and HPV-18 was not detected in any patients (Table 1; Fig. 2). Of the three patients who were HPV-positive, the patient who was HPV-6 positive (case 9) harbored a *TP53* alteration, and patient 14 harbored a *TP53* alteration and HPV-16 (Fig. 2).

**CONCLUSION**

Currently, outcomes for advanced penile cancer are poor, with a 2-year survival of only 21%, and little data exists to guide treatment beyond small nonrandomized studies using platinum-based chemotherapy [2]. The current series of 20 cases represents the largest ever cohort of patients with advanced PSCC assessed with CGP. To that end, CRGAs that could guide the rational use of targeted therapy were observed in all but one case.

Previously, anecdotal reports have described striking clinical benefit with cetuximab in patients with PSCC. For these patients, pretreatment testing of *EGFR* expression was performed with immunohistochemistry, which is qualitative at best, and it is also likely biased by the nonreporting of failure of cetuximab treatment in PSCC [6–8]. The frequency of 20% of patients with PSCC in this series harboring *EGFR* high-level amplification suggests that the basis of occasional benefit from cetuximab is indeed linked to *EGFR* amplification. Moreover, if an analogy is made to the contraindication for anti-EGFR inhibitor treatment in *RAS*-mutated colorectal carcinoma, only 10% of patients with PSCC here harbored RAS family alterations [17].

Twenty-five percent of patients with advanced PSCC harbor alterations in *PIK3CA*, which suggests possible response to inhibitors of the mammalian target of rapamycin.
(mTOR)/phosphatidylinositol 3-kinase pathway, such as rapamycin analogs, as observed in other tumor types [18]. One patient also harbored a FBXW7 alteration, but it was wild type for PIK3CA, which also predicts sensitivity to rapamycin analogs such as temsirolimus [19]. Importantly, these patients harboring PIK3CA and/or FBXW7 alterations (30%) did not also harbor EGFR amplifications (25%) because these groups of alterations occurred in a mutually exclusive fashion.

Alterations of CDKN2A, which encodes p16, occur in 40% of cases, and CCND1 amplifications occur in 20% of cases [20]. Aberrations in p16 appear to increase sensitization to the novel CDK4/6 inhibitor palbociclib in preclinical models, but this finding has not yet been well borne out in clinical studies [21–24]. Cyclin D1 coactivates CDK4, but a small phase II trial in breast carcinoma did not demonstrate correlation between either p16 status or CCND1 alteration and response to palbociclib [25]. It remains to be seen in PSCC whether either of these alterations confer sensitivity to cell cycle inhibitors.

HPV positivity and TP53 mutation occur in a largely mutually exclusive fashion in squamous cell carcinomas driven by HPV [26–28]. The frequency of high-risk HPV infection in this PSCC series is much lower than cervical carcinoma (95%+) and anal carcinoma (90%+) (Fig. 2), which is consistent with the high frequency (65%) of p16 alteration. PIK3CA alterations are enriched in squamous carcinomas driven by high-risk HPV, and interestingly are also somewhat enriched in this PSCC series, although occurring solely in patients with a negative HPV test result.

High-risk HPV viruses (16, 18, 6, and 11) are members of the α-HPV family and exclusively infect nonkeratinized squamous mucosa, such as in the cervix, anus, and oropharyngeal tract, but they are currently thought to not infect cutaneous keratinizing squamous epithelium of the skin. PSCC of the foreskin, which has keratinized outer and nonkeratinized inner squamous epithelium, is classically HPV positive with pre-existing small or giant condylomas. This series is likely primarily HPV-negative PSCC of the glans or shaft, given that these are Western patients who have likely undergone circumcision [29]. Understanding the diversity of PSCC genomic profiles and possible correlation to clinicopathologic characterization may add insight into the open question of the role of HPV infection in the oncogenesis of PSCC, particularly in the context of a circumcised versus uncircumcised population.

Whether in the setting of practice or clinical trials, CGP offers the possibility of guiding the rational use of targeted therapy for individuals with advanced PSCC, who have a very poor prognosis under standard care regimens at present. In particular, 55% of patients in this small study harbor either EGFR amplification or PIK3CA/FBXW7 alterations, suggesting possible clinical benefit from treatment with cetuximab or mTOR inhibitors, respectively. Ideally, larger cohorts can be assembled to validate the findings of the current study. Furthermore, prospective trials should be designed to determine whether the alterations specified herein predict activity of corresponding targeted therapies.

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Author Contributions


Provision of Study Material or Patients: Siraj M. Ali, Sumanta K. Pal, Norma A. Palma, Eric Sanford, Mark Bailey, Jie He, Julia A. Elvin, Juliann Chmielecki, Rachel Squillace, Edward Dow, Deborah Morosini, Jamie Buell, Roman Yelensky, Doron Lipson, Garret M. Frampton, Peter Howley

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Data Analysis and Interpretation: Siraj M. Ali, Sumanta K. Pal, Kai Wang, Norma A. Palma, Eric Sanford, Mark Bailey, Jie He, Julia A. Elvin, Juliann Chmielecki, Rachel Squillace, Edward Dow, Deborah Morosini, Jamie Buell, Roman Yelensky, Doron Lipson, Garret M. Frampton, Peter Howley, Jeffrey S. Ross, Philip J. Stephens, Vincent A. Miller

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References


