INTRODUCTION

Penile squamous cell carcinoma (pSCC) is the most common type of penile cancer, and its incidence is generally low, but it remains a serious health problem in developing countries. Patients with advanced/recurrent pSCC in the inguinal region carries a dismal prognosis, especially these patients with pelvic lymph node (PLN) metastases, with a 5-year survival rate of 0%-17%.1,2 Currently, cisplatin-based chemotherapy in combination with radiotherapy is regarded as a standard treatment among these patients with PLN metastases/recurrence.3,4 However, there is no clear consensus on the optimal second-line treatment upon disease progression or deterioration of the patient’s general condition after advanced first-line treatment. In this context, we reported a clinical case of cetuximab (an anti-EGFR monoclonal antibody) combined with anlotinib (a multi-targeted small-molecule tyrosine kinase inhibitor) in the treatment of recurrent penile squamous cell carcinoma.

CASE PRESENTATION

A 36-year-old man unintentionally found a palpable, visible lesion on the penis in September 2012, and was further diagnosed with pSCC invading into corpus cavernosum in January 2013, through biopsy (Figure 1A), and treated with partial penectomy. Later, in February 2013, just one month after the diagnosis of pSCC, the patient found the enlarged lymph nodes in the left groin (1 cm*1 cm*1 cm) without pressure pain. At that time, the bilateral inguinal
lymph node dissection was performed again. The postoperative pathological examination indicated that tumor invasion was positive in the left inguinal lymph node, revealing IIIA stage (pT2N1M0) (Figure 1B). In January 2014, eleven months after surgery, he again found a dorsal subcutaneous mass at the root of the penis with pressure pain and a hard node in the left inguinal area without redness, swelling, and bleeding. Subsequently, the biopsy revealed squamous cell carcinoma (moderate to low differentiation) with focal keratinization at the root of the penis (Figure 1C,D), which suggested tumor recurrence. He received excision of the penile root mass and left inguinal region mass on February 20, 2014, with complete resection of the lesion and no evaluable lesion postoperatively. Furthermore, after surgery, he continued to receive postoperative chemotherapy including five cycles of TPF regimen chemotherapy with paclitaxel (120 mg/m², day 1), cisplatin (25 mg/m², days 1–3), and fluorouracil (500 mg/m², days 1–5), repeated every 3 weeks. He was followed up regularly afterwards and remained in a stable condition for half of the year.

On May 16, 2015, contrast-enhanced computerized tomography (CT) of the abdomen revealed a metastatic lymph node (largest approximately 2.6 cm × 2.5 cm) adjacent to the left external iliac vessels (Figure 2A). He received radiotherapy with 60 Gy/30 fractions and three cycles of TPF chemotherapy. At the end of treatment, on Sep 28, 2015, CT suggested complete remission (CR). However, after only three months of stability, the lesion recurred in January 2016. Contrast-enhanced CT of the abdomen
suggested additional enlarged lymph nodes in the right external iliac artery. Considering the patient's previous chemo-radiotherapy was effective, two cycles of TPF chemotherapy in combination with radiotherapy (64 Gy/32 fractions) was added, and the efficacy was assessed as CR.

Twenty months after remission, until September 20, 2018, CT scans indicated metastases in the right inguinal soft tissue. The tumor invaded the right wall of the bladder, the right external iliac artery, the right ureter, and the left lateral wall of the rectum (Figure 2C1). The patient was retreated with one cycle of TPF regimen. However, the cancer progressed rapidly leading to severe symptoms and much worse physical status (Figure 2D1). The patient developed severe right leg edema, which severely limited and that any further change in chemotherapy regimen to improve due to the high toxic side effects. Based on limited clinical experience, cetuximab monotherapy or cetuximab in combination with anlotinib may be effective. He was administered cetuximab (400 mg/m² on day 1, every week) and anlotinib (12 mg on day 1–14) in December 2018. After one cycle, the edema of right leg obviously reduced (Figure 3B). Follow-up CT scans (Figure 2E1) after two cycles discovered that metastasis center was significantly shrank. The patient continued to receive treatment. But his right femoral artery was suddenly ruptured and hemorrhaged, and underwent immediate endovascular therapy. Anlotinib and cetuximab were discontinued in March 2019. Less than a month after the drug was stopped, metastatic lesions were found in the liver (Figure 2F3), and he died on May 25, 2019. Patients survived for more than 6 months from the start of treatment with anlotinib and cetuximab.

3 | DISCUSSION

The degree of lymph node involvement in the inguinal region is an important indicator for assessing the prognosis of pSCC. The five-year cancer-specific survival rate can reach 85%–100% for patients without inguinal lymph node metastases; 79%–89% for patients with a single inguinal lymph node metastasis; 17%–60% for patients with bilateral or multiple inguinal lymph node metastases; 0%–17% for patients with pelvic lymph node metastases. Chemotherapy in combination with radiotherapy is regarded as a standard treatment among these patients with tumor recurrence or metastases after lymph node dissection and partial resection in the inguinal region. Patients with tumor recurrence have significantly prolonged survival time after radiotherapy intervention. In terms of chemotherapy, cisplatin-based regimens is the first-line option. In line with adjuvant indications, both TIP (paclitaxel, ifosfamide, and cisplatin) and TPF (using 5-FU instead of ifosfamide) are recommended as reasonable options. TPF regimen can contribute to durable remission up to 52.6% after a median follow-up of 42 months, and was recommended for adjuvant chemotherapy of patients with N2-N3 stage in the 2020 EAU (European Association of Urology) guideline. Herein, after complete surgical resection, we chose TPF as adjuvant chemotherapy and observed a sustained response. Because there are virtually no consistent data on systemic treatment options. Upon disease progression, TPF continued to be used as the first or subsequent line therapy of advanced/relapsed pSCC. Tumor growth was successfully controlled for a long time. Our patient had survived over 5 years.

Anlotinib, a novel multi-targeted small-molecule tyrosine kinase inhibitor (TKI), targets vascular endothelial growth factor receptor (VEGFR2/3), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), and plays an important role in inhibiting tumor angiogenesis and suppressing tumor growth. Currently, anlotinib treatment has been reported in advanced non-small cell lung cancer, soft tissue sarcoma, renal cell carcinoma, and other solid tumors. In addition, the EGFR-RAS-RAF signaling pathway plays an important role in tumor cell proliferation, invasion, and metastasis. Recently, it has been reported that cetuximab, an anti-EGFR monoclonal antibody, has antitumor activity in metastatic penile cancer and may enhance

![Figure 3](https://example.com/figure3.png) Edema of right leg. (A) is a pre-treatment image; (B) is a post-treatment image
the effect of cisplatin-based chemotherapy. The median overall survival with EGFR-targeted therapy can reach 29.6 weeks in metastatic squamous carcinoma. Our patient had difficulty tolerating subsequent chemoradiotherapy, and we used anti-angiogenesis agents and observed an effective response, which may provide a new strategy for metastatic/recurrent pSCC, especially for patients who have no more chemotherapy options available or refuse to continue chemotherapy.

Of note, prior to the use of anlotinib and cetuximab, the tumor has invaded and encircled the blood vessels. Furthermore, the edema subsided rapidly, and the center of the tumor shrank significantly after treatment. These two factors may be the cause of femoral artery rupture and bleeding. It is generally believed that anlotinib is an effective and safe drug for cancer patients that shows tolerable and manageable toxicity. However, to date, one case has been reported in which the drug was discontinued due to gastrointestinal bleeding during the use of anlotinib. So the possibility of bleeding caused by anti-angiogenic drugs cannot be ruled out either. On the other hand, some studies indicated that the adverse effects of anti-angiogenic drugs may be correlated with their efficacy. All in all, this treatment is not recommended for patients with a bleeding tendency. Before using it, you must carefully assess bleeding risk including whether the tumor invades the vessel wall and the degree of invasion.

In conclusion, the available drugs to treat advanced/recurrent pSCC are very limited. Here, the efficacy of anlotinib and cetuximab was verified, and the results suggest a potential treatment option for advanced or refractory pSCC, which deserves further in-depth study and exploration.

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CONFLICT OF INTEREST

The author reports no conflict of interest in this work.

AUTHOR CONTRIBUTIONS

All authors take responsibility for the integrity and accuracy of the data, and approved the final version. S.D., Y.Y.L., T.L., and Y.Z involved in data acquisition; S.D. and Y.Y.L. wrote original draft; Pro. L involved in writing, review and editing.

ETHICAL APPROVAL

We have obtained the informed consent of patient’s family for the use of data and publication of this study, and approvals from concerned review boards/committees (human) are documented.

CONSENT

Written patient consent was signed and collected in accordance with the journal’s patient consent policy.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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