

Squamous cell carcinoma of the scrotum: A look beyond the chimneystacks

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Core tip: Scrotal squamous cell carcinoma (SCC) although rare, represents one of the most common forms of scrotal malignancy. The epidemiology of SCC has changed over time and iatrogenic conditions (psoralens and ultraviolet A radiation, immunosuppression, *etc.*) and human papilloma virus infection play a significant role as associated conditions. Surgery is the cornerstone of treatment and primary excision with a risk stratified approach for staging and treatment of regional lymph node is advisable. Sentinel lymph node biopsy can mitigate the morbidities of unwarranted inguinal lymph node dissection in selected cases. For locally advanced and metastatic disease palliative chemotherapy is advocated. Targeted therapies might hold promise for management of advanced SCC.

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Abstract

Despite the low incidence, squamous cell carcinoma (SCC) remains the most common scrotal malignancy with a propensity for recurrence and metastasis. In recent years there has been a significant change in the epidemiology of scrotal SCC. Surgery is the mainstay of treatment for resectable disease. Sentinel lymph node dissection adapted from experience with penile SCC can reduce the morbidity of routine lymph node dissection. Emerging treatments for advanced and metastatic SCC are at the cusp of significantly changing management of this disease. We have performed a comprehensive review of scrotal SCC with a focus on these topics.

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INTRODUCTION

Squamous cell carcinoma (SCC) is the most common scrotal malignancy^[1,2]. Despite awareness and removal of occupational carcinogens over the last century, after initial reduction in incidence, scrotal SCC has maintained a steady incidence rate. Due to significant associated morbidity and mortality it remains an important urogenital malignancy for the urologist. Our aim was to review recent published literature on scrotal SCC and highlight changing epidemiology as well as emerging therapies.

HISTORICAL BACKGROUND

The earliest accounts of scrotal SCC date back to the Persian nomads who used to transport pots of burning coal between their legs to keep warm as they travelled^[3]. The first clinical descriptions of cases occurring were by Bassius and Treyling in the mid 1700s, with Treyling describing a case in a Cavalryman^[4]. Sir Percival Potts in 1775 was the first to link the chronic lodgment of soot in the rugal folds of the scrotum occurring in chimney sweeps to development of scrotal SCC^[5-7]. It hence became known as the first described occupational disease. The active carcinogen discovered later was 3,4-benzpyrene. Occupational scrotal SCC was also later described in association with other occupations with chronic carcinogen exposure including cotton mule spinners, paraffin and tar workers, creosote workers, shale oil workers, lathe workers, pitch workers and machine tool setters and operators^[4,8-12]. More recently it has been described in car mechanics, car and airplane manufacture, gas workers, engineers, steel manufacture and aluminum workers^[11,13-15]. The majority of occupationally related scrotal SCC can be attributed to exposure to carcinogenic polycyclic aromatic hydrocarbons^[10].

EPIDEMIOLOGY

In order to assess recent trends in the epidemiology of scrotal SCC, we examined all clinical studies published on scrotal SCC since the year 2000.

There were six case series published including two Surveillance Epidemiology, and End Results (SEER) based analyses, one Netherlands Cancer Registry (NCR) based analysis, one prospective multi-institutional study and two retrospective studies^[1,2,16-19].

Studies in the mid-to-late 1900s reported that scrotal SCC accounting for the majority (80%-100%) of all scrotal malignancies but in more recent reports it only accounts for one-third of all scrotal malignancies^[1,2,16,20,21]. However scrotal SCC still remains the most common scrotal malignancy^[1,2,16]. Other scrotal malignancies include extramammary Paget's disease (EMPD), sarcoma, basal cell carcinoma, melanoma, Bowen's disease (SCCIS) and adnexal skin tumors. Median age at diagnosis ranges from 52-57 years^[1,18,19]. Most cases occur in Caucasian men followed by Black and Asian men and other ethnicities.

Verhoeven *et al*^[1] reported the age-standardized 5-year incidence rate of all histologic types of scrotal cancer in the Netherlands and this varied between 0.9 and 1.8 per 1000000 male person-years from 1986 to 2006 with no statistically significant change over time^[1]. Age-standardized incidence rate of scrotal SCC varied between 0.34 and 0.44 per 1000000 male person-years from 1986 to 2006. Over a similar time period Wright *et al*^[2] reported on the age-adjusted incidence rate of scrotal cancer in the United states which increased from 0.49 per 1000000 persons in 1973 to 0.95 per 1000000 persons in 2002. While

specific incidence rate of scrotal SCC was not provided they did report no change in incidence rates by histologic type^[2]. The incidence reported from the Connecticut Tumor registry data from 1935 to 1979 showed stable incidence rates of all scrotal malignancies and epithelial scrotal malignancies^[22]. It has been speculated that the reason for this sustained incidence despite occupation carcinogen avoidance has been the emergence of new risk factors such as phototherapy for the treatment of skin diseases and human papilloma virus (HPV).

Johnson *et al*^[16] reported on the largest SEER series of scrotal squamous cell carcinoma with 269 patients focusing on histologic subtypes. They categorized scrotal SCC, melanoma and adnexal skin tumors as high-risk scrotal cancer and scrotal basal cell carcinoma, EMPD and sarcoma as low-risk based on median overall survival of 118 mo for the high-risk group and 166 mo for the low-risk group^[16]. Survival for scrotal SCC was 115 mo (range 97-133), which was the second lowest with lowest being adnexal skin tumors with median overall survival of 114 mo^[16]. Wright *et al*^[2] reported statistically significant worse survival for those with SCC than for those with other histologic types. SCC comprised 35% of all scrotal tumors in whites compared to 69% in blacks^[2]. Dutch researchers reported 77% 5-year survival for scrotal SCC^[1].

In early 1990s, Goldolf *et al*^[23] reported that the incidence of scrotal SCC despite increase in the rates of UV exposure through sunbeds and sunlamps has not changed. However psoralens and ultraviolet A radiation (PUVA) used for the treatment of psoriasis and other inflammatory skin diseases has been implicated with the development of scrotal SCC^[24,25]. In 1990 Stern reported on a prospective 12.3 year study in 892 men who had undergone ultraviolet radiation as part of their psoriasis treatment, out of which 14 developed genital tumors including 5 patients who developed 9 invasive scrotal SCC and one scrotal SCC in situ (SCCIS)^[26]. They found that patients with high dose PUVA had 286 times the risk of the general population to develop invasive genital SCC, low dose PUVA had 16.3 times the risk and high dose UVB was associated with 4.6 times elevation of the risk^[26]. Authors recommended genital protection for men undergoing UV radiation for treatment of skin diseases.

Increasing incidence of oropharyngeal SCC has been attributed to increasing prevalence of oral mucosal HPV^[27,28]. HPV viral oncoproteins E5, E6 and E7 have an important role in carcinogenesis with p53 tumor suppressor gene and Rb oncogene being the major targets^[29]. HPV infection in scrotal SCC has only been reported in a few case reports or small series^[18,30-33]. Andrews *et al*^[32] reported a total of 6 (42.9%) out of 14 cases were associated with HPV.

Matoso *et al*^[18] reported on 29 patients with scrotal SCC and found high-risk HPV in 7 cases (24.1%) assessed by *in-situ* hybridization. These authors also reported p16 positivity and elevated Ki67 in HPV positive scrotal SCC. These cases were also more likely to display a basaloid or

Table 1 Risk factors associated with scrotal squamous cell carcinoma

Occupations Chimney sweepers, tar and paraffin workers, occupations with exposure to mineral and cutting oils, printing, metal working, car and aeroplane manufacture, car mechanics, commercial printing, aluminum worker, shale oil workers, pitch workers, engineering, steel production, cavalrymen
Carcinogenic metals Arsenic, nickel, chromium
Chronic mechanical irritation
Chronic inflammatory states Chronic lymphedema, infective and surgical scars
Lifestyle Poor personal hygiene, smoking
Viruses HPV
Ionizing Radiation
Iatrogenic Coal tar, PUVA, radiotherapy, nitrogen mustard, Fowler's solution
Immunosuppression Acquired and inherited immunodeficiency, post transplant immunosuppression

HPV: Human papilloma virus; PUVA: Psoralens and ultraviolet A radiation.

warty morphology. They suggested p16 stain to be used for screening for HPV infection with addition of Ki67 in cases with equivocal p16. If indeed the true proportion of HPV associated scrotal SCC lies between 24%-42% as in these small series, it has important implications for preventive therapy with the availability of HPV vaccines.

Chronic mechanical irritation has been associated with scrotal SCC. Long-term rubber urinal use^[34], topical nitrogen mustard^[35] and coal tar^[36] have been reported to be associated with scrotal SCC. Initially scrotal SCC was thought to be uncommon among non-Caucasian ethnicities however subsequent reports in Africans, African Americans and other ethnicities including Chinese refuted this hypothesis^[37,38].

Both preceding and subsequent increased malignancy risk has been described in patients with scrotal SCC^[39]. Verhoeven reported 18% of patients with scrotal malignancy developed one or more tumors after the scrotal tumor with lung cancer, skin SCC and second scrotal tumor being the most common second malignancy^[1].

DIAGNOSIS

The most common presentation of scrotal SCC is of an erythematous scrotal nodule or plaque^[40]. Ulceration and pruritus often accompany the lesion. It occurs most commonly in the left scrotum, lower and anterior areas^[40,41]. It can uncommonly present as abscess or ulcer^[42]. The main differential diagnoses are extramammary Paget's disease, verrucous carcinoma and bowenoid papulosis^[43-46]. Pigmented scrotal SCC and scrotal SCCIS have been rarely reported^[38,47]. Multiple scrotal SCCs in the same patient have often been described^[26,48]. Table 1 lists the risk factors that have been associated with scrotal SCC.

Table 2 Lowe's staging of scrotal squamous cell carcinoma

A1	Disease localized to scrotum
A2	Locally extensive disease involving adjacent structures (penis, perineum, testis or cord, and pubic bone) by continuity but without evident metastasis
B	Superficial lymph node metastasis, resectable
C	Pelvic lymph node metastasis or any unresectable metastasis
D	Distant metastasis beyond regional nodes

STAGING

In 1983, Lowe modified the initial staging system proposed by Ray and Whitmore and this staging system is still in use as outlined in Table 2^[49].

The American Joint committee on Cancer (AJCC), TNM classification for scrotal SCC is similar to TNM classification for SCC in other locations (with the exception of Eyelid, Vulva and Penis) and is shown in Table 3.

For staging, clinical examination including the assessment of extension and depth of the scrotal lesion and examination of inguinal lymph nodes is mandatory. Plain chest X-ray for evaluation of the lungs is recommended. MRI scan and ultrasonography can be used for assessing the depth of the lesion and evidence of involvement of underlying structures where this is suspected. For inguinal lymph node imaging CT scan can detect enlarged inguinal and pelvic lymph nodes but is unable to identify small metastatic deposits in normal sized nodes. For nodal disease ultrasound and fine needle biopsy of suspicious lymph nodes similar to penile cancer might be of diagnostic value^[50]. Similarly with improvement in sensitivity and specificity profile, 18F-FDG PET/CT might have a role in further staging of inguinal lymph nodes in patients with scrotal SCC^[51]. For high-risk cases sentinel lymph node biopsy at the time of excision of primary lesion similar to penile cancer has been advocated^[52].

MANAGEMENT

Few case series have been reported since 2000 (Table 4).

Primary tumour

Wide local excision of the lesion with a negative margin is the goal for the treatment of primary tumor. A surgical margin of 2-3 cm has been advocated by some authors^[53], however the available guidelines for the management of cutaneous SCC recommend a 4mm radial margin for small (< 2 cm) lesions with well define edges and a radial margin of 6mm for larger lesions with poor defined edges and risk of subcutaneous extension^[54]. Based on evidence from penile SCC, for < T2 disease a margin of ≥ 3 mm is considered safe where for ≥ T2 disease a surgical margin of 5-10 mm is considered appropriate^[55]. Given the redundancy and laxity of scrotal skin primary scrotal closure is usually possible, but after large tumor resection primary closure might not be achievable. The defect can be reconstructed with simple closure, flap,

Table 3 TNM staging system for squamous cell carcinoma

Stage	Primary tumour	Regional lymph nodes	Distant metastasis
Stage 0	Tis = carcinoma in situ	N0 = no regional lymph node involvement	M0
Stage I	T1 = tumour 2 cm or less	N0	M0
Stage II	T2 = tumour > 2 cm but < 5 cm T3 = tumour > 5 cm	N0	M0
Stage III	T4 = Invasion of deeper extradermal structures	N0	M0
Stage IV	Any T	N1 = regional lymph node spread.	M0
	Any T	Any N	M1 = distant metastasis.

Table 4 Case series with epidemiology, management and outcomes of scrotal squamous cell carcinoma published after 2000

Ref.	n	Design	Cohort characteristics	Summary
Stern <i>et al</i> ^[17] , 2002	17	Prospective multi-institutional cohort study	892 men first treated with PUVA	Dose-dependent increase in the risk of genital tumors in men treated with PUVA
Seabra <i>et al</i> ^[19] , 2007	6	Retrospective single institution	Age: 52 (31-89) Race: Ca: 2; Bl: 2; Oth: 1; Unknown: 1 Staging: LC: 4, RL: 1, DD: 1	4/6 WLE; 1/6 WLE + SLNB; 1/6 was unresectable: 1 developed LN metastasis and was treated with chemo/radiation Patient with unresectable disease and was treated with chemotherapy and subsequently died
Wright <i>et al</i> ^[2] , 2008	151	SEER (1973-2002)	Age: 68 ² Race: Ca 117 (77.5); Bl 24 (15.9); Oth 10 (6.6)	SCC had the worse survival compared to other histological subtypes
Verhoeven <i>et al</i> ^[1] , 2010	53	NCR (1989-2006)	Age: 56.5 Staging: Stg 0: 1 (1.9), Stg 1: 22 (41.5), Stg 2: 18 (34), Stg 3: 2 (3.8), Stg 4: 0, Unk: 10 (18.9)	SCC had the worse survival compared to other histological subtypes: 1 yr relative survival 93% 3 yr relative survival 80% 5 yr relative survival 77%
Johnson <i>et al</i> ^[16] , 2013	269	SEER (1973-2006)	Age: 65.4 ² ± 14.9 Race: Ca 206 (76.6%), Bl 43 (16.0%), As 12 (4.5%), Hi 18 (6.7%), Oth 8 (3.0%) Staging: LC 205 (76.2%), RL 54 (20.1%), DD 10 (3.7%)	The median OS for patients with SCC was 115 (95%CI: 97-133) mo
Matoso <i>et al</i> ^[18] , 2014	29	Retrospective multi-institutional	Age: 55 (30-74) Race: Ca 19 (65.5%), Bl 10 (34.5%) Follow up: 37 mo	25/29 WLE; 1/29 WLE + LND; 3/29 imiquimod post WLE: 13 (45%) with ¹ margins required re-excision 3/29 local recurrence: 2 WLE; 1 WLE/RT 3 /29 with lymphadenopathy lost to follow-up

¹Positive; ²Mean. As: Asian; Bl: Black; Ca: Caucasians; DD: Distant disease; Hi: Hispanics; LC: Local disease; NCR: Netherlands Cancer Registry; OS: Overall survival; Oth: Other; PUVA: Psoralens and ultraviolet A radiation; RL: Regional lymph node; SCC: Squamous cell carcinoma; SEER: Surveillance, Epidemiology and end results; SLNB: Sentinel lymph node biopsy; Stg: Stage; WLE: Wide local excision.

split thickness skin graft, mesh grafts or myocutaneous grafts. Hemiscrotectomy is required for more advanced disease. Contralateral testicular transposition is an option if preservation of testis is preferable^[56].

For patients with significant co-morbidities in whom surgical management is not suitable less invasive treatments such as CO2 laser for invasive SCC and 5-fluorouracil, photodynamic therapy or imiquimod for SCCIS may be considered^[57,58]. Imiquimod has also been used as adjuvant to surgery post-excision^[18]. Superficial small SCC and SCCIS are also amenable to mohs micrographic surgery which offers full evaluation of the surgical margins at the time of surgery and skin-sparing surgery with good functional and aesthetic outcomes^[59,60].

Inguinal lymph node

Morley observed early on in the 20th century that the raphe of the scrotum does not provide a physical barrier to

scrotal lymphatic drainage and the scrotum has bilateral inguinal drainage^[61]. This observation forms the basis for bilateral inguinal assessment when treating patients with scrotal SCC. Data from early series suggest that similar to penile cancer only half of the patients with inguinal lymphadenopathy at the time of diagnosis, harbor metastatic disease at inguinal lymph node dissection (ILND) questioning the need for routine ILND in patients with inguinal adenopathy^[62]. The authors advocated a period of follow-up (2-3 mo) after excision of primary lesion and ipsilateral ilioinguinal dissection if patient developed biopsy proven evidence of metastasis, and to defer contralateral node dissection until clinical verification of metastasis is evident.

The more contemporary algorithm for treatment of inguinal lymph node in patients with scrotal SCC has many similarities to patients with penile cancer^[63]. A risk based approach to minimize morbidity associated with

ILND advocates the use of inguinal sentinel lymph node biopsy^[49], with subsequent complete ILND in cases where sentinel lymph node biopsy is positive^[64]. Due to rarity of this condition data from large case series are lacking and the current recommendations are largely based on experts' opinions and extrapolation of data from series with penile SCCs.

Locally advanced and metastatic disease

Adjuvant chemotherapy has been utilized in advanced stage and metastatic disease. Systemic chemotherapy is also indicated for inoperable scrotal SCC. Combination chemotherapy with methotrexate, bleomycin and cisplatin has been reported in inoperable or metastatic SCC of male genital tract with response rate of 72%, however median response duration was only 6 mo and only 14% achieved complete response^[65]. Bleomycin has been utilized in the neoadjuvant setting. Adjuvant radiation has been shown to not change outcomes^[32].

EMERGING THERAPIES

The era of targeted molecular and immunotherapies holds promise for management of advanced squamous cell carcinoma. Cetuximab an anti-epidermal growth factor receptor (EGFR) monoclonal antibody is an approved agent for treatment of head and neck SCC^[66]. Emerging therapies for head and neck SCC include EGFR tyrosine kinase inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, insulin-like growth factor receptor (IGF-1R) inhibitors and inhibitors of the PI3K/AKT/mTOR pathway may have a role in the treatment of patients with scrotal SCC in future^[67]. Unfortunately currently data on the efficacy of such therapies for patients with scrotal SCC is lacking.

Recently Lavens *et al*^[68] showed increased EGFR expression in penile SCC. Carthon *et al*^[69] evaluated EGFR targeted therapy in patients with advanced penile or scrotal cancer in a retrospective case series of twenty-four patients. Only one of twenty-four patients had scrotal SCC. This patient developed metastases to right groin with disease progression despite paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy. The addition of EGFR targeted therapy lead to reduction in tumor burden and allowed resection of residual disease. He was reported to be disease free 38 mo post EGFR therapy.

Further studies need to focus on establishing EGFR status in scrotal SCC tissue before prospective evaluation of benefits of EGFR targeted therapies. Due to low incidence of scrotal SCC, multi-institutional collaboration would be a more feasible approach. Further genomic and molecular characterization of scrotal SCC would be important in identifying key pathways and developing therapeutic targets.

CONCLUSION

Scrotal SCC is a rare clinical entity that represents one of

the most common forms of scrotal malignancy. Although historically considered as an occupational disease, its epidemiology has changed in recent years and iatrogenic conditions (PUVA, Immunosuppression, *etc.*) and HPV infection play a significant role as associating conditions. Surgery is the cornerstone of the treatment algorithm for scrotal SCC. Excision of the primary lesion and a risk stratified approach for staging and treatment of regional lymph nodes is advisable. For patients with high-risk disease and negative clinical lymph nodes, sentinel lymph node biopsy can mitigate the morbidities of unwarranted ILND. For locally advanced and metastatic disease palliative chemotherapy is advocated. Future endeavors with focus on targeted therapies might hold promise for management of advanced squamous cell carcinoma. Given the rarity of this condition, multi-institutional trials in conjunction with trials for the treatment of penile SCC are likely to provide us with further knowledge in this field.

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