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Mohs Micrographic Surgery Versus Wide Local Excision in the Treatment of Anogenital Squamous Cell Carcinoma: A Systematic Review

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ABSTRACT

Primary anogenital squamous cell carcinoma (SCC) is a locally aggressive malignancy that requires careful consideration of surgical margins. Anogenital SCC impacts the quality of life due to tissue removal, scarring, and sexual dysfunction. Mohs micrographic surgery (MMS) offers a compelling alternative to wide local excision (WLE) due to its complete margin control and potential tissue-sparing properties. This analysis systematically reviews surgical modalities used for the management of anogenital SCC. Articles meeting eligibility criteria were identified using MEDLINE (via PubMed), Embase, Cochrane, and Scopus databases. All studies investigating surgical management of anogenital SCC with WLE (including vulvectomy) or MMS were considered. A total of 70 studies met inclusion criteria: 46 examined WLE patients, 8 utilized vulvectomy, and 24 examined MMS patients. MMS patients experienced lower local recurrence rates; regional and distant recurrence rates did not differ. The local, regional, and distant recurrence rates for WLE were 17.7%, 5.1%, and 6.0%, respectively, and 5.0%, 3.8%, and 4.3% for MMS. Local recurrence was more likely in patients treated with WLE ($p < 0.0001$). No differences were noted in regional recurrence ($p = 0.444$) and distant recurrence ($p = 0.420$). Study limitations include differences in tumor characteristics and follow-up durations between the groups. The WLE group had larger tumors at presentation. Overall, MMS had superior outcomes for local recurrence compared to WLE and vulvectomy, making it a reasonable option for managing anogenital SCC.

1 | Introduction

Primary cutaneous squamous cell carcinoma (SCC) of the anogenital region is a locally aggressive malignancy that requires careful consideration of surgical margins for removal. The incidence of anogenital SCC in the United States varies by location, with vulvar SCC being the most common at an estimated 2–3 cases per 100,000 and penile SCC affecting approximately 2000 men each year [1]. In the anogenital region, SCC can present across a spectrum, ranging from squamous cell carcinoma in situ (SCCIS), invasive SCC, and the distinct histologic variant, verrucous carcinoma (VC) [2]. Anogenital SCC predominantly affects individuals over 50 years of age, with a slight female preponderance, primarily attributed to a higher incidence of vulvar SCC [2]. Genital SCC can present clinically as erythematous plaques, warty and exophytic lesions, or flat ulcerated tumors [3]. Key risk factors include human papillomavirus infection, immunosuppression,

smoking, and lichen sclerosis, particularly for vulvar lesions. Other contributing factors have been identified, such as lack of circumcision, poor genital hygiene, ultraviolet radiation exposure, sexually transmitted infections, and advanced age [2, 4, 5]. Due to its location and variable clinical presentation, genital SCC can easily be misdiagnosed, delaying diagnosis and treatment. Although anogenital SCC is a locally aggressive tumor, regional and distant metastases have been reported [6]. The National Comprehensive Cancer Network (NCCN) guidelines recommend wide local excision (WLE) as the preferred approach for early-stage vulvar SCC and radical vulvectomy for larger or more advanced tumors [7]. For early-stage penile SCC, options include WLE, Mohs micrographic surgery (MMS), glansectomy, or partial penectomy, with more advanced cases needing a total penectomy [8]. Topical chemotherapy and radiation are recommended for the treatment of perianal SCC [9]. Although WLE is more frequently utilized for SCC of the vulva and penis, it is associated with local recurrence rates ranging from 18.7% to 46.2% for vulvar SCC, 26% to 32% for penile SCC, and 19% to 75% for VC [8, 10]. Recurrence rates for MMS in the genital area have been reported to range from as low as 0.8% to 10.5%, with higher rates observed in certain high-risk cases or studies with limited follow-up [11, 12] Because MMS allows for 100% histologic margin evaluation while preserving healthy tissue, it might offer a treatment advantage over WLE [13]. This study systematically reviews surgical modalities for treating anogenital SCC, specifically MMS and WLE, including vulvectomy. We aim to outline treatment recommendations based on recurrence rates in cases treated with both surgical methods.

2 | Materials and Methods

2.1 | Search Strategy

This review was designed and executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An extensive literature search was conducted using databases MEDLINE (via PubMed), Scopus, Embase, and Cochrane. We identified eligible articles from database inception to September 1, 2024, and included articles from January 1, 1939, to March 4, 2024. The search terms were expanded to ensure inclusivity and to capture relevant studies potentially missed in the initial search. The final search strategy included combinations of keywords across several categories. Anatomical terms included "anogenital," "genital," "vulvar," "penile," "scrotal," "perianal," and "labia". Tumor types were limited to "Invasive squamous cell carcinoma", "squamous cell carcinoma in situ," and "verrucous carcinoma" Treatment modalities included "Mohs surgery," "Mohs micrographic surgery," "wide local excision," "vulvectomy" and "local excision." Outcome-related terms included "recurrence," "local recurrence," "regional metastasis," "distant metastasis," "patient-reported outcomes," and "margin assessment." Boolean operators (AND, OR) were used to combine these terms for a comprehensive search systematically. Only articles written in English were included. There were no limitations on article type. After the selection process, reference lists of relevant articles were reviewed to identify additional studies. The review protocol is registered with PROSPERO (CRD42024606921), https://www.crd.york.ac.uk/prospero/.

2.2 | Study Eligibility, Selection Criteria, and Screening

After eliminating duplicates, two authors independently reviewed the titles and abstracts of each article to identify those that satisfied the inclusion criteria. Disagreements were resolved through discussion with a third author. All studies reporting one or more cases of anogenital SCC treated with MMS or WLE (including vulvectomy) were included. The following studies were excluded: those reporting any type of primary treatment modality other than MMS or WLE, studies that failed to assess recurrence, studies including pediatric population, patients presenting first with metastatic disease before surgery, cases where adjuvant or neoadjuvant therapy was used in addition to surgery, and cases where tumor was not completely resected or resected with a positive margin. In addition, articles from National Databases and other systematic reviews were excluded to avoid data duplication.

2.3 | Data Extraction and Statistical Analysis

The following variables were gathered as available: age, sex, tumor location (vulvar, scrotal, penile or perianal), method of tumor excision (WLE or MMS), size of the tumor, subtype of SCC (SCCIS, conventional SCC, VC), American Joint Committee on Cancer (AJCC) staging, number of layers required to achieve tumor-free margins for MMS cases, margin size for WLE cases, average follow-up time, and recurrence rate (local, regional, or distant). Local recurrence refers to the reappearance of the tumor at the site of the surgical scar following treatment with MMS or WLE. Regional recurrence is defined as metastases confined to regional lymph nodes following the primary treatment with MMS or WLE. Metastases to distant organs or non-regional lymph nodes characterize distant recurrence. Statistical analysis was performed using IBM SPSS version 25 (IBM, Armonk, NY).

3 | Results

3.1 | Systematic Search Results

A total of 70 articles were included (Figure 1). The total number of patients was 1271, and the majority were treated with WLE ($n = 911$, 71.7%) [14–60]. Patients with MMS [3, 4, 10–13, 45, 61–77] made up 28.3% of the study sample ($n = 360$, 28.3%). Most of the articles were retrospective cohort studies (54.3%), followed by case reports (35.7%) and case series (10%). A summary of the studies is included in Table S1.

3.2 | Tumor and Patient Characteristics

The mean age of the cohort was 57 years. Gender distribution was approximately 1:1, with a slight preponderance in males (51.1%). Caucasians were the most commonly affected racial

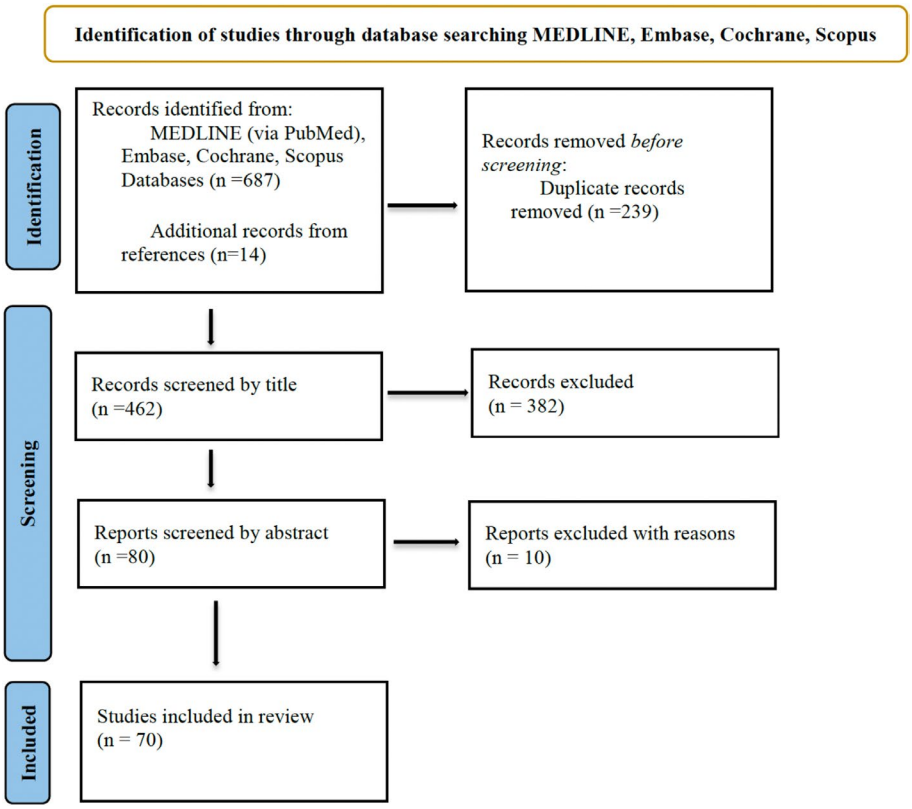

FIGURE 1 | Study selection flow diagram.

group overall. Among females, the majority of tumors were located on the vulva ($n = 508$, 86.1%). For males, the penis was the most commonly affected site ($n = 503$, 81.6%), followed by the perianal region ($n = 9.4\%$) and the scrotum ($n = 55$, 8.9%). The average tumor size of the entire cohort was 3.2 cm, and the average time to diagnosis was 26 months. The majority of the patients had invasive SCC (50.5%), followed by SCCIS/Bowen's (45.6%) and VC (3.9%). AJCC staging was only available in 8.6% of articles.

3.3 | Wide Local Excision

A total of 911 patients were treated with WLE, including vulvectomy. Anatomical location was reported in all patients, with 49.0% of SCCs occurring in the vulvar region and 37.3% involving the penis. The average tumor size was 4.18 cm, and the average time to diagnosis was 24.6 months. The local recurrence rate was 17.7% ($n = 161/911$), the regional recurrence rate was 5.1% (18/350), and the distant recurrence rate was 6.0% (14/235). The mean follow-up time was 39 months.

3.4 | Mohs Micrographic Surgery

A total of 360 patients were treated with MMS. Anatomical location was reported in all patients, with the most common area being the penis (72.2%), followed by the vulva (17.7%). The average tumor size was 2.4 cm, a lower mean size compared to patients who underwent WLE with statistical significance ($p = 0.021$), and the average time to diagnosis was 32 months. Mean number of stages needed to achieve tumor clearance was 2.7. The average follow-up time was 30 months. The local, regional, and distant recurrences were 5.0% (18/360), 3.8% (9/237), and 4.3% (10/233), respectively. Patients treated with WLE were more likely to have a local recurrence than patients treated with MMS (OR: 4.075, 95% CI: 2.5–6.9, $p < 0.0001$). However, no differences were noted regarding regional recurrence (OR: 1.373, 95% CI: 0.6–3.2, $p = 0.444$) and distant recurrence (OR: 1.405, 95% CI: 0.6–3.3, $p = 0.420$).

3.5 | WLE Versus MMS for Vulvar Squamous Cell Carcinoma

A subgroup analysis was conducted for vulvar tumors treated with WLE versus MMS, involving a total of 508 patients. Four hundred and forty-four patients were treated with WLE and sixty-four with MMS. The mean age for the WLE group was 61 years, and 59 years for the MMS group. Tumor size was similar to the WLE and MMS group, averaging 2.8 cm. Local recurrence was observed in 16.7% (74/444) of cases in the WLE group versus 4.6% (3/65) in the MMS group, which was statistically significant (OR: 4.126, 95% CI: 1.4–13.0, $p = 0.011$). Regional recurrence was reported in 4.9% (14/285) of WLE cases and 4.5% (2/44) of MMS cases (OR: 1.081, 95% CI: 0.2–4.9, $p = 0.29$), and distant metastases occurred in 5.6% (11/198) of WLE cases and 2.4% (1/41) of MMS cases (OR: 2.347, 95% CI: 0.3–18.7, $p = 0.79$). These findings suggest that MMS is associated with a lower local recurrence rate compared to WLE, while there were no significant differences in regional or distant recurrence rates between the two groups.

3.6 | WLE Versus MMS for Penile Squamous Cell Carcinoma

A subgroup analysis was conducted for penile tumors treated with WLE versus MMS, involving a total of 503 patients; 243 cases were treated with WLE and 260 with MMS. The mean age for the WLE group was 61 years compared to 53 years for the MMS group. Local recurrence was observed in 16.8% (41/243) of cases in the WLE group versus 5.4% (14/260) in the MMS group, which was statistically significant (OR: 3.54, 95% CI: 1.9–6.7, $p = 0.0001$). Regional recurrence was reported in 3.5% (1/29) of WLE cases and 4% (7/175) of MMS cases (OR: 0.86, 95% CI: 0.1–7.2, $p = 0.65$), and distant metastases occurred in 4.7% (9/192) of MMS cases and were not reported in WLE cases that were included in our study. MMS is associated with a lower local recurrence rate compared to WLE, while there were no significant differences in regional recurrence rates between the two groups.

4 | Discussion

This study evaluates two common surgical approaches for treating anogenital SCC. Although WLE is a widely employed treatment for various skin cancers, its use in the anogenital area can adversely impact the quality of life due to the potential for extensive tissue removal, scarring, and sexual dysfunction [5, 15]. WLE is commonly paired with vulvectomy, particularly for larger tumors or multifocal vulvar SCC, with recommended 0.8–1 cm margins to reduce recurrence [4]. Similarly, a 1 cm margin is often suggested for penile SCC [12, 14]. MMS is more suitable for this location due to its complete assessment of deep and peripheral margins and tissue-sparing capabilities [4]. Although MMS is a well-established approach for the management of cutaneous SCCs, the literature on its use in the anogenital region remains limited, with promising results reported mainly for treating penile SCCs [4]. While our study included a larger sample of 911 cases for WLE, the available literature on MMS for anogenital SCC was limited, comprising only 360 cases. Limited MMS cases make it challenging to compare the efficacy of these two surgical approaches reliably. In our analysis, a higher proportion of patients who underwent WLE experienced local recurrence; however, no statistically significant difference was found between regional, distant recurrences compared to those treated with MMS; additionally, the WLE group, on average, presented with larger tumors. The average number of stages needed to achieve negative histologic margins in the MMS group was 2.7. The need for two or more stages to achieve negative margins may be a result of smaller margins at each stage due to unique anatomical considerations in the anogenital region.

Most tumors in our analysis were not staged. Among studies that reported staging, the most prevalent stage, according to the AJCC staging system for cutaneous SCC, was Stage II, T2 N0. Due to their hidden nature, anogenital SCCs are more likely to present at later stages. VC is a subtype of SCC characterized by low metastatic potential but is locally aggressive. There were 41 cases of VC included in our analysis, of which 31 were treated with WLE and 10 with MMS. Comparative analysis demonstrated similar local recurrence rates between the two groups. However, the small sample size makes it difficult to draw reliable comparisons. No evidence of regional or distant metastases was noted in either group. Recurrence rates ranging from 16% for MMS to 19–75% for WLE have been reported for verrucous carcinoma in previous literature [13].

A subgroup analysis was conducted for vulvar and penile SCCs, as these comprised the majority of anogenital SCCs. There were 508 cases of vulvar SCC, 444 of which were treated with WLE and 64 with MMS. Patients treated with WLE were more likely to experience local recurrence, which was statistically significant. The difference was not statistically significant despite slightly increasing regional and distant recurrences in the WLE group. In a subgroup analysis of penile tumors, 503 patients were included; 243 patients were treated with WLE and 260 with MMS. A statistically significant difference was found between the WLE and MMS groups for the local recurrence rate, but no difference was found for the regional recurrence rate.

Our study found a statistically significant difference in local recurrence rates between the two approaches; however, no statistical difference was observed in regional and distant recurrence rates. MMS offers a key advantage in providing 100% histologic margin assessment, in contrast to the 1% with WLE [11, 13]. Complete margin evaluation allows MMS to integrate reconstruction as part of the same surgery, reducing the need for multiple procedures. This benefit is particularly crucial in complex cases requiring extensive flaps or intricate reconstruction to maintain function in the anogenital region. MMS can decrease scarring, especially in the vulvar and penile areas [4, 12].

Study limitations include variability among studies included, differences in follow-up durations, and tumor characteristics between the two groups. Additionally, several factors may affect overall survival in anogenital SCC, including age, primary tumor size, and comorbidities; our study did not examine survival outcomes. MMS's complete margin control, lower recurrence rates, and tissue-sparing nature result in better functional and cosmetic outcomes, enhancing the patient's quality of life [4–6]. While continued research is needed to elucidate the benefits of MMS in this context, the existing evidence strongly supports its consideration as a primary treatment option. Both Boettler et al. and Machan et al. demonstrate the superiority of MMS in VC and penile SCC, and their margin assessment and tissue preservation principles apply to other anogenital malignancies [4, 11]. The findings of this study reinforce the AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for treating anogenital SCC with MMS [78].

5 | Conclusion

The role of MMS in managing anogenital SCC is becoming increasingly recognized. Our study demonstrates that MMS may lead to a lower local recurrence rate when compared to WLE. Therefore, it should be considered a viable option that can achieve superior outcomes with more precise tissue loss and possibly improved quality of life. Among the limitations of this study are varying follow-up lengths, heterogeneity among the included studies, and differences between the two cohorts on tumor characteristics. Additionally, our analysis did not address disease-specific

survival, underscoring the need for long-term follow-ups and additional research. Despite these limitations, our findings reinforce the growing consensus that MMS is an appropriate treatment option for anogenital SCC, aligning with earlier studies demonstrating favorable outcomes in similar patient populations [11, 77]. While our review includes articles from multiple databases, more studies examining MMS for treating anogenital SCC are needed to strengthen the available comparative data.

Conflicts of Interest

Dr. Tolkachjov is a speaker/investigator for CASTLE Biosciences, Kerecis, and Boehringer Ingelheim, which is unrelated to this study. The other authors have no conflicts of interest to disclose.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.