

Mohs Micrographic Surgery in Female Genital Cancers: A Systematic Review

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ABSTRACT

Background: Mohs micrographic surgery (MMS) has shown promising efficacy in female genital cancers, including Extramammary Paget's disease (EMPD), dermatofibrosarcoma protuberans (DFSP), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). However, limited consolidated research exists on the clinical outcomes following MMS in female genital cancers. The aim of this systematic review is to synthesize and evaluate recent literature on the application and utility of MMS in the management of female genital cancers.

Methods: A comprehensive search was conducted of the PubMed and EMBASE databases on October 16, 2024, using the keywords "Mohs surgery" or "Mohs micrographic surgery" and "female genital" or "vulvar cancer" or "vaginal cancer" or "genital cancer" or "vulva" or "vagina." Studies were included if they directly discussed MMS for female genital cancers, particularly EMPD, DFSP, SCC, and BCC, with attention to clinical outcomes, were of the correct study type, and were published in peer-reviewed journals in English.

Results: Our results identified a 95% curative rate following MMS for EMPD, DFSP, SCC, and BCC, following analysis of 166 treated cases.

Conclusion: MMS provides superior outcomes compared with traditional excisional approaches, potentially secondary to its precision-guided approach and histological analysis. Future studies should utilize larger patient cohorts and investigate rarer malignancies and combination therapies to optimize treatment guidelines for female genital cancers.

J Drugs Dermatol. 2025;24(11):1080-1086. doi:10.36849/JDD.9167

INTRODUCTION

Mohs micrographic surgery (MMS) has emerged as a highly effective and precise treatment for skin cancer, offering exceptional cure rates while preserving healthy tissue.¹ MMS involves the sequential removal of horizontal layers of the tumor, which are processed in real time to determine if the margins are cancer-free.² This stepwise approach is designed to maximize the conservation of healthy tissue by allowing the surgeon to suspend tissue removal once cancer-free margins are detected.² The American Academy of Dermatology has determined guidelines for excision and management by MMS with the appropriate use criteria (AUC). Some examples of AUC for MMS include tumor recurrence, aggressive histology, and anatomic location.³

MMS has been used to treat various vulvar and perineal cancers, such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Extramammary Paget's disease (EMPD), and dermatofibrosarcoma protuberans (DFSP).⁴ However, female cutaneous genital cancers have historically been managed with methods such as partial or total vulvectomy, or wide local excision (WLE) with consideration of lymph node dissection based on dermal invasion and probability of metastasis.⁵ The

anatomy of the female genitalia poses unique challenges for surgical management, particularly in cancer cases. The vulva is a complex structure with histologically diverse tissue types, including keratinized epithelium, non-keratinized mucosa, and underlying connective tissue.⁶ There are many critical structures in close proximity within the female genital region, including the urethra, anal sphincter, and clitoris. These are often located extremely close to potential tumor sites; therefore, surgical precision is of utmost importance to avoid damage that could compromise urinary or fecal continence, sexual function, and sensory integrity of the area.⁷ Thus, when compared to conventional approaches like vulvectomy, MMS potentially offers the benefits of maximizing tissue conservation for more superficial skin cancers where lymph node biopsy or dissection is not indicated.

While there has been increasing evidence on the utility of MMS in female genital cancers, limited consolidated research on these methods remains, as delineated by a previous systematic review on vulvar malignancies.⁸ This systematic review aims to synthesize and evaluate recent literature on the application and utility of MMS in the management of female genital cancers.

MATERIALS AND METHODS

A comprehensive search was conducted of the PubMed and EMBASE databases was conducted on October 16, 2024, using the keywords "Mohs surgery" or "Mohs micrographic surgery" and "female genital" or "vulvar cancer" or "vaginal cancer" or "genital cancer" or "vulva" or "vagina." After the removal of duplicate articles, our search retrieved 87 studies for screening. Identified articles were independently screened by their title and abstract to assess for relevance. Article abstracts lacking sufficient information to include or exclude were assessed using a full-text evaluation to establish eligibility. Studies were included if they directly discussed MMS for female genital cancers, particularly EMPD, DFSP, SCC, and BCC, with attention to clinical outcomes, were of the correct study type, and were published in peer-reviewed journals in English. Exclusion criteria consisted of studies not relevant to the topic, incorrect publication types (ie, review articles or commentaries), and publications in languages other than English. Studies that did not specifically comment on clinical outcomes following MMS treatment of female genital cancers were excluded. Articles were screened by reviewer SS and validated by reviewers IR or SA.

Any disagreements were resolved through discussion between reviewers. After analysis of 38 full texts, 14 were excluded due to incorrect intervention (n=3), outcome measures (n=4), study design (n=5), or patient population (n=2). Ultimately, 24 articles met our criteria. Quality assessment included validating study methodology, population characteristics, intervention details, and outcome measurement tools for all included studies. Data extraction and synthesis consisted of extracting pertinent information from eligible studies, organizing and summarizing the findings, and synthesizing key insights. A PRISMA diagram with included studies can be found in Figure 1. Key findings from the included studies can be found in Table 1. A brief review of each cancer is also included in our results.

RESULTS

Extramammary Paget's Disease

Extramammary Paget's disease (EMPD) is a rare, slow-growing cutaneous malignancy arising from the apocrine glands. It often presents in the anogenital area; the vulva is the most common anatomical area affected, making up around 65% of all cases. While there are no defining clinical features specific to EMPD, it

FIGURE 1. PRISMA diagram.⁴³

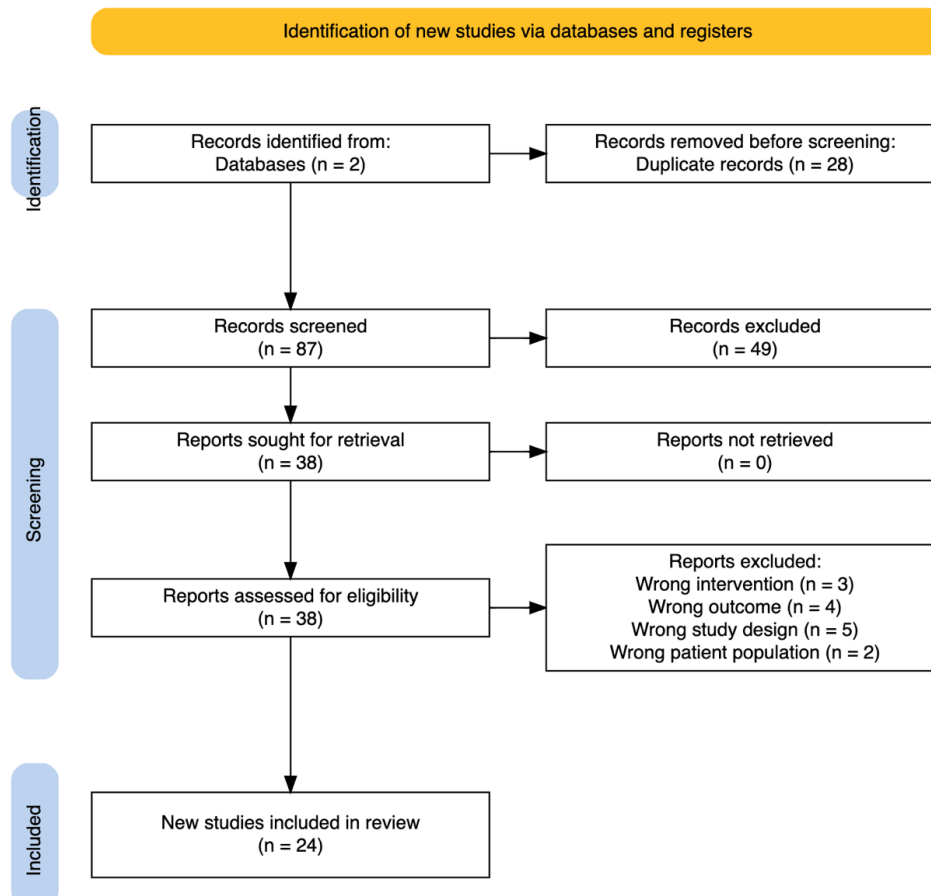


TABLE 1.

Characteristics of Studies Included						
Author name / Year / Reference	Type of Cancer	Number of Cases Reported	MMS Stages	Site	Type of Closure	Outcome
Barmon et al. 2023 (17)	EMPD	2	NR	Vulva	Flap	No recurrence at 2 years
Bruce et al. 2023 (14)	EMPD	24	1-5, median 2	Vulva, perineum	Primary closure, flap, graft	6.7% recurrence at 3 years
Chang et al. 2021 (11)	EMPD	1	4	Vulva	Primary closure, flap	No recurrence at 6 months
Coldiron et al. 1991 (10)	EMPD	1	>1	Genitalia	Secondary intention, primary closure	Recurrence at 5 months in scar line, retreated with MMS with no recurrence at 25 months
Damavandy et al. 2019 (16)	EMPD	10	1-14, mean 5	Vulva, perineum	NR	No recurrence at mean of 43.5 months (1-120 months)
Hendi et al. 2004 (18)	EMPD	7	1-4, mean 2.5	Vulva, perineum	Secondary intention, flap	One case of recurrence at 29 months; retreated with MMS with no evidence of recurrence at 76.2 months mean follow-up time No recurrence in remaining cases between 12- and 101-months follow-up
Nugent et al. 2023 (13)	SCCIS, BCC, EMPD, SCC, DFSP, MM, MIS, atypical spindle cell neoplasm	57	1-9, mean 1.9	Vulva, perineum	Secondary intention, primary closure, flap	5.6% recurrence rate within 54 patients presenting with a mean follow-up time of 61.1 months (1.1-191.8 months)
Qi et al. 2014 (12)	EMPD	3	2	Vulva, groin	Primary closure, flap	No recurrence in the 3 patients at 39, 37, and 84 months respectively
Spiker et al. 2019 (15)	SCCIS, EMPD, BCC, SCC, verrucous carcinoma, basosquamous carcinoma, DFSP	41	1-5, mean 2	Vulva	NR	No recurrence at least 1 year follow up in 18 patients (range, 1-11 years), no recurrence at less than 1 year follow up in 10 patients, and 8 lost to follow up *41 cases were examined in 36 patients
Doufekas et al. 2003 (20)	DFSP	1	NR	Vulva	Primary closure	No recurrence at 3 years
Hammonds et al. 2010 (21)	DFSP	1	2	Vulva	Primary closure	No recurrence at 4 months and 2.5 years
Pascual et al. 2010 (22)	DFSP	1	3	Vulva	Secondary intention	No recurrence at 15 months 27% recurrence rate per chart review and case report at 0.5-7.5 years (mean 3.34 years)
Dudley et al. 1998 (23)	SCC and SCCIS	15	2	Vulva	Secondary intention	One case report showed local recurrence at 6 months; studies revealed metastatic SCC with a pelvic mass Despite radiation therapy, the patient expired 3 months later due to metastasis to the lungs
Boaz et al. 2007 (24)	SSCIS	1	NR	Vulva	NR	No recurrence at 1 year
Siegle et al. 1983 (25)	SCC	1	3	Vulva	Primary closure	No recurrence at 2 years
Asilian et al. 2022 (29)	BCC	1	NR	Vulva	Secondary intention	No recurrence at 13 months
Comstock et al. 2019 (33)	BCC	1	5	Vulva	Secondary intention	No recurrence at 6 months
Muñoz et al. 2023 (30)	BCC	3	NR	Vulva	NR	No recurrence at 1 year
Poppens et al. 2023 (32)	BCC	1	NR	Vulva	NR	No recurrence at 4 months
Renati et al. 2019 (31)	BCC	1	NR	Vulva	NR	No recurrence at 3 years
Sinha et al. 2019 (28)	BCC	7	NR	Vulva	Secondary intention, primary closure, flap	No recurrence at 3 years
Stiller et al. 1993 (34)	BCC	1	NR	Vulva	Secondary intention	No recurrence at 1 year and 13 years
Abbott et al. 2006 (42)	Adeno-carcinoma	1	>1	Vulva	NR	No recurrence at 26 months

often presents as an erythematous plaque with white scales and crusting. WLE is the long-standing treatment of choice for non-invasive EMPD due to the discontinuity of the disease; however, MMS has shown benefits in some cases.⁹

Upon review, there were 68 cases of female patients with EMPD located in the vulvar, inguinal, and perineal regions who were treated surgically using MMS.¹⁰⁻¹⁸ Two of 68 cases documented in the literature experienced recurrence following treatment with MMS, with an overall curative rate of 97%.^{10,18} Specific recurrence rates for EMPD and other malignancies can be found in Figure 2. In one case, Coldiron et al noted recurrence after 5 months in the scar line; this was retreated with MMS and remained recurrence-free 25 months later.¹⁰ Hendi et al documented recurrence in one of 7 vulvar and perineal EMPD cases treated with MMS. Following retreatment with MMS, no evidence of recurrence was noted at approximately 76.2 months of follow-up time.¹⁸ Nugent et al quantified functional outcomes for EMPD cases treated with MMS, reporting that 2 patients experienced worsened urinary function after MMS. However, these patients also had extensive tumor mucosal invasion that required an average of 4.7 MMS stages.¹³ Importantly, 6 EMPD cases throughout the literature received MMS therapy following recurrence with WLE.^{11,15,16} Five patients received total or partial vulvectomies, one patient received CO2 laser treatment, and one patient received imiquimod treatment for EMPD with inadequate control before MMS treatment.^{15,16} In all of these cases, including those following excision, MMS provided a successful cure.^{11,15,16} Bruce et al compared 24 cases of EMPD

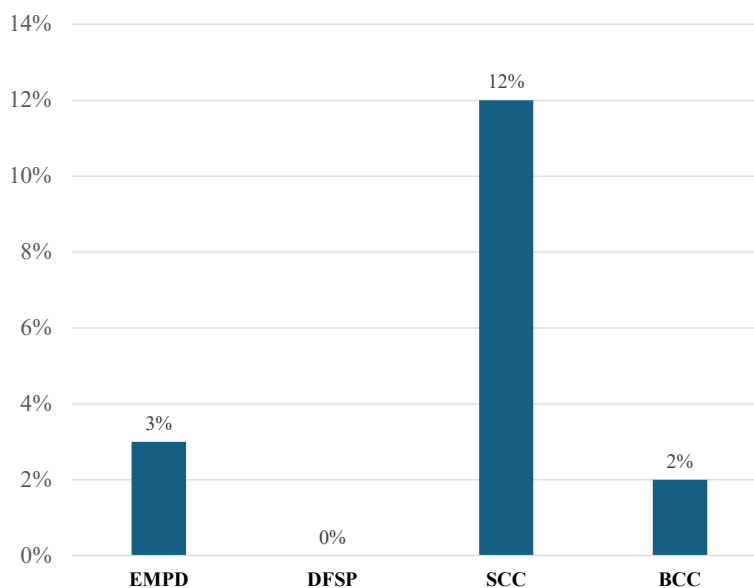
with MMS-guided wide local excisions to 63 traditional WLEs. The prospective cohort (MMS) saw a 6.7% recurrence at 3 years, compared to a 34.1% recurrence rate for the retrospective cohort (WLE).¹⁴

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a slow-growing neoplasm that presents as a painless pink or purple plaque thought to arise from the dermis. Vulvar DFSP is rare, with less than 70 cases currently documented in the literature according to a recent systematic review.¹⁹ The gold standard of treatment has been surgical excision with negative margins, most commonly treated with WLE. However, treatment with MMS has been used in a few emerging cases.¹⁹

With a review of current literature, 8 cases of genital DFSP diagnosed in female patients were found; no cases of recurrence followed treatment with MMS.^{13,15,20-22} Three cases were documented as case reports of MMS-treated DFSP, with no recurrence reported after 1-3 years.²⁰⁻²² Hammonds et al reported no evidence of deformity of the vulva following MMS, regarding cosmetic and functional outcomes.²¹ Four more cases of DFSP treated with MMS were described by Nugent et al's retrospective case series, with no evidence of recurrence at the mean follow-up time of 61.1 months.¹³ Finally, Spiker et al reported one case of DFSP treated with MMS with no evidence of recurrence following treatment failure with WLE in their single institution review.¹⁵

FIGURE 2. Recurrence rates for EMPD, DFSP, SCC, and BCC.



EMPD: Extramammary Paget's disease
DFSP: Dermatofibrosarcoma protuberans
SCC: Squamous cell carcinoma
BCC: Basal cell carcinoma

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is one of the most common malignancies of the vulva, accounting for approximately 60% of vulvar cancers. It is associated with significant morbidity and mortality, particularly in cases of late-stage or metastatic disease.^{4,23} Clinically, vulvar SCC often presents as a persistent, ulcerated lesion, but can also present as a scaly plaque or nodule. The gold standard for treatment usually involves wide local excision or vulvectomy and a lymph node assessment to check for metastasis. However, these approaches can result in significant tissue loss and subsequent functional impairment, resulting in increased interest in the use of MMS.⁴

A review of the literature yielded 51 total cases of either SCC or squamous cell carcinoma in situ (SCCIS) of the vulva and perineum treated with MMS. Six out of 51 cases experienced recurrence, indicating an 88% curative rate.^{13,15,23-25} Four cases of vulvar SCC or SCCIS in Dudley et al faced recurrence occurring between 0.5 and 3.5 years; 2 of these patients died of disease following recurrence.²³ In Dudley's cohort, 4 patients had previous vulvectomies, 3 previous excisions, and 3 other medical treatments (eg, laser, radiation), before treatment with MMS.²³ Out of the 26 cases documented in Nugent et al, there was one case of local recurrence in a patient with a history of vulvar SCCIS, detected 23 months after MMS, with biopsy showing invasive SCC. After subsequent local excision, there was no evidence of disease at 9 months.¹³ Another patient in Nugent et al's cohort with SCC of the labia majora developed regional nodal metastasis at 13 months after MMS and partial vaginectomy. Sentinel node biopsy was not performed at the time of initial surgery.¹³ Spiker et al reported 18 cases of vulvar SCC and SCCIS, including 2 cases in which MMS was performed following nonsurgical treatment of SCCIS with topical imiquimod. Both cases experienced recurrence after 2 years of topical treatment, with no recurrence following MMS.¹⁵

Basal Cell Carcinoma

Cases of basal cell carcinoma (BCC) in the vulvar region are relatively rare, with vulvar BCC accounting for less than 5% of all vulvar cancers, primarily affecting postmenopausal women.²⁶ Clinically, vulvar BCC can present as an ulcerated lesion, a nodular growth, or an erythematous plaque, often mimicking a benign condition. Due to its non-specific presentation, a delay in diagnosis can allow for growth, often resulting in larger lesions that require more extensive treatment.²⁷ The gold standard for vulvar BCC continues to be surgical excision with negative margins, with MMS increasingly being used.⁴

A review of the literature identified 39 cases of vulvar or perineal BCC treated with MMS, with only one case of documented recurrence and follow-up rates of up to 13 years.^{13,15,28-34} The results amount to a curative rate of 98%. Nugent et al included 12 cases of vulvar or perineal BCC in their analysis, with one

patient experiencing local recurrence at 48 months following MMS. This case of BCC on the labia majora was treated again with MMS and no recurrence was observed at the 18-month follow-up.¹³

DISCUSSION

Overall, our findings indicate that recurrence rates were low following primary or secondary treatment with MMS for EMPD, DFSP, SCC, and BCC in the female genital region. MMS may be particularly beneficial for tumors located in sensitive genital areas due to its systematic approach, which facilitates gradual tissue removal and immediate histological evaluation of margins.

For EMPD, an overall recurrence rate of 3% following MMS from our review contrasts rates as high as 58% (with an average of 37%) following WLE, according to prior reports.¹⁴ Our aggregate recurrence rate is more favorable than a previous systematic review and meta-analysis in EMPD patients which found that WLE was associated with a 2.67 times higher risk of recurrence than MMS (95% CI: 1.47–4.85; $P=.001$).³⁵ Despite criticisms that margin-controlled approaches for EMPD may lead to larger excision sizes and higher morbidity, the results of this review suggest that MMS offers similar excisions with potentially superior curative rates.^{14,36} The use of cytokeratin 7 (CK7) immunohistochemical stains during MMS for EMPD has been evaluated in the included studies. Results support earlier evidence that utilization of CK7 staining may enable even lower recurrence rates for genital EMPD lesions.^{14,16,37} This staining technique may circumvent difficulties in visualizing tumor cells on hematoxylin and eosin-stained section slides.¹⁶ It is important to note that the majority of EMPD patients included in our review required several MMS stages for clearance with Bruce et al conferring that MMS-guided cases required significant reconstructive procedures for wound closure.¹⁴ These results may be attributed to the structural complexity often seen in genital EMPD lesions.

Eight cases of DFSP in the female genital skin were reviewed, all treated with MMS as the primary modality, with a 0% recurrence rate over a 3- to 5-year follow-up period from our review. Although systematic reviews comparing MMS to wide WLE for DFSP in female genital skin are lacking, a retrospective cohort of 79 patients with DFSP who underwent WLE (n=38) or MMS (n=41) on the trunk and extremities between 1990 and 2005 showed that 5 patients in the WLE group experienced recurrence, whereas none in the MMS group did.³⁸ Given the aggressive nature of DFSP, genital lesions can pose a significant risk to nearby functional structures making the precision-guided technique of MMS particularly valuable in such cases. Our findings support the most recent National Comprehensive Cancer Network (NCCN) guidelines that recommend MMS as the first line for DFSP.³⁹

For SCC, there were 51 total patients treated with MMS; 6 had recurrence, and 2 subsequently died, amounting to a recurrence rate of 12% from our review. Prior authors suggest that MMS may be useful in not all cases of vulvar SCC, but particularly those in early stages when the lesion is intraepithelial or minimally invasive with no prior excision or treatment.^{8,23,40} This is in line with the most recent NCCN guidelines that recommend WLE over SCC as the primary treatment modality for vulvar SCC.³⁹ Although there are no comparative studies examining WLE vs MMS in female SCC cohorts, cumulative data, including male patients, suggest WLE incurs recurrence rates as high as 15 to 33%.⁴ Several cases in our review employed MMS following unsuccessful medical and surgical treatments for vulvar SCC, including instances of invasive SCC.^{15,23,25} These results indicate MMS should be considered alongside WLE for certain cases of female genital SCC, as it offers substantial cure rates, including for complex cases, and demonstrates efficacy following prior treatments.

Thirty-nine cases of BCC in the female genital skin were examined; there was one episode of recurrence when treated with MMS revealing a recurrence rate of 2% from our review. This is in comparison to prior literature that suggests recurrence rates following WLE for female genital BCC may be as high as 10-20%.^{31,41} NCCN guidelines suggest MMS for cases of BCC; however, utilization remains low.³⁹ The low incidence of utilization of MMS in BCC may be attributed to internal referrals among gynecologists, which may also pose an issue for other genital cancers such as SCC. In a review of 35 cases of vulvar BCC, treatments included WLE (46%), vulvectomy (37%), MMS (11%), and electrodesiccation with curettage (6%), all with no recurrence.³⁰ Mean surgical margins were 3 mm for MMS, 4.4 mm for excision, and 6 mm for vulvectomy, with most cases (77%) identified and managed by gynecology. These authors' findings align with our cumulative results, supporting the prioritization of MMS in suitable cases to minimize surgical margins while providing efficient curative rates.

While MMS appears to be a strong alternative, if not superior treatment to WLE in female genital cancers, there remains a need for personalized approaches given the complexity of female genital anatomy. By customizing excision techniques, wound closure strategies, and anesthesia to the unique characteristics of each patient and tumor, MMS provides an effective method for achieving oncologic control while maintaining both function and aesthetics in the complex genital area.

Our investigation has several limitations, notably the variability in study methodologies and sample sizes, with many articles relying on small patient cohorts. Time to follow-up differed greatly, highlighting the need for standardized, long-term studies to ensure consistency in the assessment of treatment efficacy. Larger and more comprehensive cohorts focused on

female genital cancers are essential to developing optimal guidelines for both common and more rare vulvar malignancies.

CONCLUSION

In our analysis of MMS for skin cancers in the female genital region, including EMPD, DFSP, SCC, and BCC, the majority of patients achieved favorable outcomes on their first treatment of MMS, with an aggregate 5% recurrence rate observed across all 4 skin cancer types reviewed. MMS was also utilized as a second-line treatment in cases of recurrence following standard excision, with few instances of recurrence following MMS re-excision. Future investigations should focus on prospective studies looking at MMS in the management of more common and rare vulvar malignancies, as well as the potential for combining MMS with adjunctive therapies, including immunotherapy, to enhance treatment efficacy and patient outcomes.

DISCLOSURES

The authors have no conflicts of interest to declare.

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