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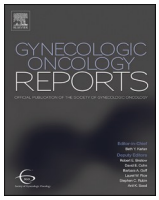

Research Report

Cost-effectiveness analysis of margin-controlled surgery for vulvar Paget's disease

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ABSTRACT

Objectives: To determine the cost of two surgical treatment approaches for vulvar Paget's disease and model the cost-effectiveness considering differences in recurrence and reoperation over time.
Methods: We assessed cost-effectiveness between excision guided by Mohs micrographic surgery (MMS-E) and traditional wide local excision (WLE). We examined billing data from patients with vulvar Paget's disease who underwent MMS-E (cases, n = 24, 2018–2022) or WLE (controls, n = 64, 1990–2020). We created typical treatment bundles incorporating physician-administered services and facility costs standardized to Medicare reimbursements in 2022 United States Dollars (USD). The primary measure of effectiveness was disease-free years of life. A secondary analysis estimated quality-adjusted life years (QALY). A Markov model simulated treatment pathways over a 10-year time horizon. Transition probabilities were based on institutional recurrence rates (3-year RR 6.7 % for MMS-E vs 34.1 % for WLE). We used a willingness-to-pay threshold of 100,000 USD per QALY.
Results: The cost of a single surgical episode was 34,664 USD for MMS-E and 14,969 USD for WLE. In the setting of lower recurrence rates with MMS-E, the incremental cost was 12,789 USD per disease-free year gained. A secondary analysis incorporating QALY showed an incremental cost of 72,820 USD per QALY.
Conclusions: MMS-E appears to be a cost-effective treatment for vulvar Paget's disease compared to historic standard of care. Our ability to estimate quality of life gained by avoiding disease recurrence was limited by scant data for this rare condition; thus, future studies incorporating health utility values are needed to facilitate a more comprehensive analysis.

1. Introduction

Vulvar Paget's disease (VPD) is an uncommon malignancy of the female genital skin. Although rare, the reported incidence has increased more than two-fold over the last three decades (Kilts, 2020). VPD presents as a symptomatic red, itchy patch that may involve sensitive areas such as the clitoris, urethra, vagina, perineum, or anus. Symptoms vary in severity depending on disease extent, location, and whether the disease is primary or recurrent. Treatment options include surgery, topical immune-modulating creams, radiation therapy, carbon dioxide laser ablation, and phototherapy (van der Linden, 2016; Kibbi et al., 2022). Currently, surgery is standard of care and has the added advantage of ruling out invasive disease (Kibbi et al., 2022). There are two main surgical approaches: traditional surgical excision, such as wide local excision (WLE) or simple vulvectomy, and margin-controlled surgery, such as excision guided by Mohs micrographic surgery (MMS-E).

Recurrences are common after traditional surgical excision (Long, 2017; Matsuo, 2021), with an estimated aggregate recurrence rate of 37 % (Kibbi et al., 2022). Recurrences after MMS-E are less common (Bae, 2013; Merritt et al., 2019; Kim, 2017), with an estimated aggregate rate of 11 % (Kibbi et al., 2022), although rates may be less than 5 % with optimized protocols (Merritt et al., 2019). Our group recently published oncologic outcomes from the first prospective cohort of VPD treated with MMS-E (Bruce, 2023). Like previous studies, we found superior recurrence-free survival with MMS-E (Bruce, 2023). Our results, coupled with recent expert consensus guidelines (Kibbi et al., 2022), encourage a

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wider adoption of the MMS-guided surgical technique, but certain concerns remain. Specifically, MMS-E is a resource-intensive intervention that requires unique equipment and staff with special training; thus, there is apprehension about the cost of its routine use.

No prior studies have described the cost of MMS-E for the treatment of VPD. Studies of MMS-E for other types of non-melanoma skin cancers report higher upfront costs compared to traditional surgical excision (Puri, 2020; Wilson, 2012), but these studies do not account for the differences in treatment effect, such as length and quality of life. Economic evaluations that factor in length and quality of life are called cost-effectiveness analyses (CEAs) (Gray et al., 2011). CEAs comparing MMS-E to traditional excision for cutaneous squamous cell carcinoma and dermatofibrosarcoma protuberans suggest that MMS-E is cost-effective (Udkoff, 2022; Udkoff, 2022). Unfortunately, extrapolating this conclusion to VPD is inappropriate given differences in the pathophysiology of disease and complexity of the multidisciplinary surgical approach. Thus, we sought to 1) estimate the cost of treatment for VPD and 2) compare the long-term cost-effectiveness of MMS-E vs traditional excision.

2. Methods

2.1. Study design and patient population

We conducted a cost-effectiveness analysis comparing MMS-E to WLE. Methods and results are reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022, supplemental file) (Husereau, 2022). We created a Markov model using TreeAge Pro 2020 R1.0 software (TreeAge Software, LLC). Our primary Markov model considered the risk of local disease recurrence and all-cause death from a health care payer perspective (Fig. 1). Each theoretic subject in the model began at age 70, based on the mean age at diagnosis published in a systematic review (Kibbi et al., 2022). Subjects were allowed to transition in and out of health states (remission, local recurrence, and death) based on a set of investigator-determined transition probabilities (Table 1). Transitions were allowed in annual intervals over a 10-year time horizon. We chose a 10-year time horizon because the median time to recurrence is 2–3 years, but recurrences can occur up to 10 years from diagnosis, and patients may have multiple recurrences (Kibbi et al., 2022).

2.2. Determination of cost

Our first objective was to determine the cost of a single surgical episode for an average patient undergoing one of two surgical treatment approaches for VPD: excision guided by Mohs surgery (MMS-E) or traditional excision (WLE). To do this, we created typical treatment bundles. Treatment bundles included physician-administered services (defined using Current Procedural Terminology or CPT codes) as well as hospital-billed services and facility costs. We included costs from preoperative assessment, surgical intervention, and postoperative care up to 30 days. The bundles were informed by billing data from individual patients who underwent either surgical approach at our institution.

Table 1
Markov model inputs.

Costs	Base-case values	Model	Ref.
Cost of MMS-E	$34,663.91	Primary	CS
Cost of WLE	$14,968.71	Primary	CS
Cost of recurrence	Same as index†	Primary	CS
Cost of invasive disease*	$38,947.74	Scenarios B-C	(Yabroff, 2008)
Cost of disease-specific death*	$41,853.05	Scenarios B-C	(Yabroff, 2008)
Probabilities (Annual)**			
Prob remission to recurrence – WLE, national	0.124	Scenario A	(Kibbi et al., 2022)
Prob remission to recurrence – WLE, institutional	0.130	Primary	(Bruce, 2023)
Prob remission to recurrence – MMS-E, national	0.033	Scenario A	(Kibbi et al., 2022)
Prob remission to recurrence – MMS-E, institutional	0.023	Primary	(Bruce, 2023)
Prob remission or recurrence to invasive disease	0.017	Scenarios B-C	(van der Linden, 2019)
Prob disease-specific death with carcinoma in situ	0	Primary	CS
Prob disease-specific death with invasive disease	0.030	Scenarios B-C	(van der Linden, 2019)
Prob death other causes	Age-specific life tables	Primary	(Arias and Xu, 2022)
Utilities			
Utility remission	0.89	Scenario C	(Dominiak-Felden, 2013)
Utility recurrence	0.72	Scenario C	(Dominiak-Felden, 2013)
Utility invasive disease	0.60	Scenario C	(Conway, 2012; Marcellusi, 2015; Monk, 2023; Perrone, 2021)
Utility death	0	Scenario C	NA

Abbreviations: MMS-E, Mohs micrographic surgery; WLE, wide local excision; prob, probability; ref; reference; CS, current study; NA, not applicable.
†Cost of each recurrence was $34,663.91 for theoretic patients in the MMS-E group and $14,968.71 for theoretic patients in the WLE group.
*Costs identified in the literature were inflated to 2022 United States Dollars.
**Transition rates identified in the literature were converted to annual probabilities using a published procedure for converting transition rates to probabilities for multistate Markov models (Jones et al., 2017).

Patients who underwent MMS-E (cases, n = 24) were part of a prospective observational trial (NCT03564483) and received care between 2018 and 2022. Patients who underwent WLE (controls, n = 64) were part of a historic, retrospective cohort and received care between 1990 and 2020. The study was approved by the Mayo Clinic Institutional

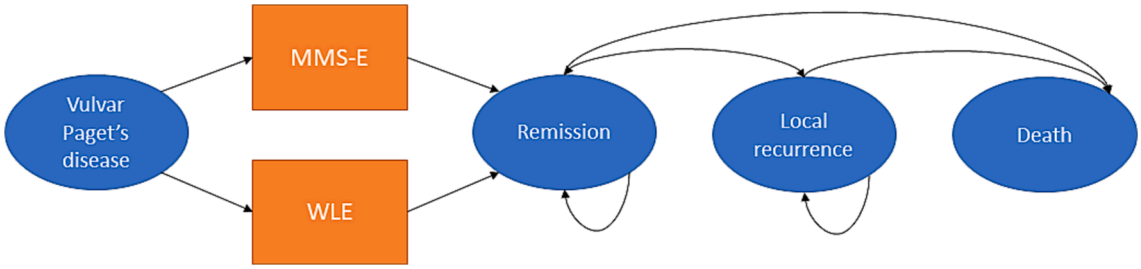

Fig. 1. Markov transition state diagram for primary model and scenario A.

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Details of each treatment protocol and the resulting oncologic outcomes can be found in a prior publication (Bruce, 2023). Briefly, both approaches included surgical consultation, excision under general anesthesia, and postoperative care. The MMS-E approach additionally included the following services: multidisciplinary consultations, mapping biopsies, and office-based MMS-E. There was variation in specific procedures involved based on the location and complexity of an individual patient's VPD lesion. For instance, some cases involved critical medial structures and required intraoperative frozen section pathology and vulvar reconstruction for wound closure. To account for these variations in complexities, we estimated the proportion of cases involving specific interventions within each care bundle (MMS-E vs. WLE) and used the proportions as "weights" to develop a weighted cost for each care bundle (Supplemental Tables 1 & 2). We determined weights based on the clinical characteristics of the MMS-E and WLE cohorts in our previous publication (Bruce, 2023). For the MMS-E cohort, we assumed that 79 % of cases would involve plastic surgery consultation, 12.5 % would require radical vulvectomy, and 67 % would involve a medial lesion and necessitate intraoperative frozen pathology for margin clearance (Bruce, 2023). We assumed that 14 % of cases would require complex wound repair by plastic surgery and 57 % would require repair with an advancement or rotational flap. Given the rarity of use, skin grafting was not modeled. For the historic WLE cohort, plastic surgery was rarely involved. We assumed that 19 % of cases would require radical vulvectomy, 46 % would require intra-operative frozen pathology to aid in excisional planning, and 27 % would require flap reconstruction (unpublished data).

We estimated the base cost for each CPT code using current Centers for Medicare & Medicaid Services reimbursement rates. Some codes were billed multiple times; for instance, pathology codes were billed per specimen submitted. To determine the frequency of such codes, we calculated the average frequency from the actual patients in each treatment cohort. Base costs were multiplied by a weight as described above to account for complexity of procedures that are required for a subset of patients only. Costs for hospital-billed services were standardized using the Medicare Cost-to-Charge ratio for the year 2022 and were then averaged for the 24 patients who underwent the MMS-E-guided approach. Facility costs for WLE were determined using the most recent patient treated with the approach in 2020, given that components of a single surgical encounter have changed significantly since 1990. All costs were valued in 2022 US Dollars. Costs were inflated using the Gross Domestic Product Implicit Price Deflator (U.S. Bureau of Economic Analysis Gross Domestic Product: Implicit Price Deflator, 2023). The CPT codes, base costs, and weights for each step of the treatment bundle are documented in Supplementary Tables 1 and 2.

2.3. Primary cost-effectiveness analysis

We set the recurrence rate at 34.1 % for WLE and 6.7 % for MMS-E over 3 years based on recently published data from our institution (Bruce, 2023). Rate of all-cause, age-specific death was determined using the 2020 United States life tables (Arias and Xu, 2022). We assumed that patients who recurred were treated with the same surgical approach for each subsequent episode of locally recurrent disease. The model output was the incremental cost-effectiveness ratio (ICER) comparing cost in United States dollars (USD) to effectiveness measured in disease-free years of life. Disease-free years was defined as the total time a theoretic patient was alive and in remission during the 10-year model time horizon. A year in recurrence was counted as zero disease-free years. Costs and outcomes were discounted at 3 %. No specific willingness-to-pay (WTP) threshold was set given that quality of life data were not available.

2.4. Scenario analyses

We performed several additional analyses to consider the effects of different assumptions. First, we used institution-specific data for the probability of local recurrence, which may not accurately reflect outcomes nationwide. Thus, we performed a scenario analysis using recently published national data that estimated recurrence risk to be 37 % for WLE and 11 % for MMS-E over a median of 3.5 years (Scenario A, Table 1) (Kibbi et al., 2022). Second, our main model was based on a simplistic transition state diagram that assumed 100 % disease-specific survival (DSS) for VPD (Fig. 1). While DSS has been noted to be excellent for carcinoma in-situ or microinvasive disease (98–100 %), one cohort study noted an 8 % (7/87) risk of progression from carcinoma in-situ to invasive disease over a median of 5 years (van der Linden, 2019). In that study, among the 7 patients who progressed to invasion, 1 died of disease, leading to an estimated DSS of 85.7 % (6/7) (van der Linden, 2019). Therefore, we ran an alternative model to account for the possibility of progression and disease-specific death (Supplemental Figure; Scenario B, Table 1). In this scenario, it was assumed those with disease progression would stay in the invasive disease state until death.

Finally, since VPD is a rare condition and MMS-E is an emerging treatment, comprehensive and reliable health utility values are not available. Thus, we had to rely on disease-free-years as an effectiveness measure rather than quality-adjusted life years (QALY). Given the potential difficulty in interpreting these results compared to a typical cost-effectiveness analysis, we present a scenario analysis incorporating health utility values extrapolated from related health conditions (Scenario C). Utility values for remission (0.89) and local recurrence (0.72) were derived from a study of women with vulvar intraepithelial neoplasia (VIN) and age-matched, female controls in the United Kingdom (Dominiak-Felden, 2013). This study quantified quality of life using the EQ-5D-3L, which accounts for five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQol. EQ-5D., 2023). We assumed a utility for invasive disease of 0.60 based on values from HPV-associated lower genital tract carcinomas (Conway, 2012; Marcellusi, 2015; Monk, 2023; Perrone, 2021). These estimates are not an exact representation of health-related quality of life for VPD, and care should be taken while interpreting our findings. For instance, although VIN is a pre-invasive lesion that likely confers a similar level of anticipatory anxiety as compared to EMPD, the symptom burden is unlikely to be identical, as symptoms from large EMPD lesions can be severe and persistent. For this reason, we intended this final scenario analysis to serve only as a rough guide for interpreting cost-effectiveness. Due to the uncertainty of health utility value estimates, we completed a variety of sensitivity analyses. We varied all parameters by plus or minus 25 %, except for disease-specific death, which we varied from 0 % to 50 % within 5 years. We varied health utility values by plus or minus 0.10. The ICER resulting from scenario C can be compared to common willingness-to-pay (WTP) thresholds in the United States, which, in modern day, are set between 100,000 – 150,000 USD (Neumann et al., 2014; ICER, 2020). For our scenario analysis and sensitivity analyses, we used a WTP of 100,000 USD per QALY.

3. Results

3.1. Primary cost-effectiveness analysis

Our primary CEA evaluated a simplistic model of local recurrence and all-cause death. The cost of a single surgical episode was 34,664 USD for MMS-E and 14,969 USD for WLE (Table 1). The single episode cost for MMS-E included 7,606 USD for the Mohs procedure and IHC stains; facility fees were calculated separately (Supplemental Table 1). The average 10-year cost and effectiveness for a patient in the CEA model was 41,261 USD and 7.83 disease-free years for MMS-E compared to 30,902 USD and 7.02 disease-free years for WLE (Table 2). This resulted in an incremental cost-effectiveness ratio (ICER) of 12,789 USD

Table 2
Results of primary and secondary (scenario) analyses.

Model	Recurrence risk	DSD?	MMS-E Cost / Effect	WLE Cost / Effect	ICER
Primary	Institutional	No	$41,261 / 7.83	$30,902 / 7.02	$12,789 / DFY
Scenario A	National	No	$44,096 / 7.76	$30,134 / 7.06	$19,946 / DFY
Scenario B	Institutional	Yes	$46,460 / 7.24	$35,537 / 6.47	$14,186 / DFY
Scenario C	Institutional	Yes	$46,460 / 7.91	$35,537 / 7.76	$72,820/ QALY

Abbreviations: DSD, disease-specific death; MMS-E, Mohs micrographic surgery; WLE, wide local excision; ICER, incremental cost-effectiveness ratio; DFY, disease-free year; QALY, quality-adjusted life year.

per one additional disease-free year of life (DFY).

3.2. Scenario analyses

We completed three scenario analyses. Scenario A used national recurrence rate estimates and resulted in an ICER of 19,946 USD per DFY (Table 2). Scenario B included the potential for progression of disease and disease-specific death and resulted in an ICER of 14,186 USD per DFY (Table 2). Scenario C included rough estimates of health utility values so that QALY could be calculated as an effectiveness measure. In this model, the average 10-year cost and effectiveness were 46,460 USD and 7.91 QALY for MMS-E compared to 35,537 USD and 7.76 QALY for WLE, resulting in an ICER of 72,820 USD per QALY; we considered this cost effective based on a WTP threshold of 100,000 USD. In sensitivity analyses, increasing the cost of Mohs, decreasing the cost of WLE, increasing the utility of the local recurrence health state, decreasing the utility of the remission health state, or decreasing the probability of recurrence for WLE resulted in an ICER that was no longer cost effective.

4. Discussion

In this cost analysis of surgical treatments for VPD, we estimated the cost of a single surgical episode to be 34,664 USD for excision guided by Mohs surgery (MMS-E) and 14,969 USD for traditional wide local excision (WLE). A Markov model incorporating the different risks of local recurrence and reoperation resulted in an incremental cost of 12,789 USD per disease-free year gained for MMS-E compared to WLE. While there is no standard willingness-to-pay (WTP) threshold when comparing disease-free years, it seems reasonable to use a threshold of 100,000 USD per equal value life year gained, as suggested by the Institute for Clinical and Economic Review (ICER, 2020). In this context, a cost of approximately 13,000 USD to gain a year without disease seems quite reasonable.

Despite superior oncologic outcomes and increasing use in penoscrotal Paget's disease (Kibbi et al., 2022), MMS-E is not widely used for VPD. Potential explanations include concerns of cost and facility limitations to a multidisciplinary treatment approach. Our study appears to be the first to report cost and cost-effectiveness of MMS-E for VPD. As we anticipated, we found that MMS-E was more costly upfront as compared to WLE by approximately 20,000 USD, with large contributions from pathologic examination using specialty immunohistochemical (IHC) staining. Over 5,000 USD were spent on mapping biopsies prior to MMS-E, largely due to the expense of IHC. That said, mapping biopsies and cytokeratin-7 IHC staining are critical steps in the current MMS-E approach and were employed in the study suggesting favorable oncologic outcomes with MME-E (Bruce, 2023). MMS-E for VPD is not yet common, and protocol refinements are ongoing. Alternative mapping strategies are under investigation, including intravenous fluorescein mapping, which may provide similar preoperative planning at a lower cost (Wagar, 2023; Askew et al., 2022). MMS-E has the best oncologic outcomes for VPD among available treatments (Kibbi et al., 2022). By reporting the costs of various portions of the protocol, our results may help institutions optimize this treatment in a cost-efficient manner.

Our study had multiple strengths. First, we used billing data from actual patients to define the cost of certain treatment steps. Additionally, we completed scenario analyses to understand the impact of various assumptions we made in the Markov model. Our analysis was limited by the quality of data available for model inputs, including the absence of randomized controlled trials for VPD to inform recurrence risk. In addition, due to a lack of data, our model assumes that annual recurrence risk is static over a 10-year time horizon. Quality of life data was not available for VPD, and therefore, we were constrained by using the narrowed perspective of disease-free years as an effectiveness measure. CEAs conventionally measure effectiveness using QALY, which account for quality of life in addition to length of life or time in remission. Calculation requires valuation of health-related quality of life using detailed methods such as rating scales, time trade-offs, standard gambles, or multi-attribute utility systems (e.g., EQ-5D) (EuroQol. EQ-5D., 2023). Such health utility values are not available for VPD. Importantly, if readers choose to compare our results to other CEAs that use QALY as an effectiveness measure, they must be cautioned that this assumes that patients who are disease-free after MMS-E and WLE have identical quality of life, which is not known. We did complete a secondary analysis using quality of life data extrapolated from other symptomatic vulvar conditions treated with a surgical approach (e.g., VIN and vulvar cancer), which found MMS-E to be cost-effective. Because time spent in recurrence with VPD is significantly more symptomatic for some women based on disease extent or location, our secondary analysis likely underrepresents the health utility detriment of an active VPD lesion and thus undervalues the benefit of lower recurrence rates. In sensitivity analyses, the results were sensitive to multiple utility values, which supports the need for high quality, disease-specific data for these parameters.

Additional considerations include the population studied in this analysis. Patients referred to our institution for MMS-E are likely more complex than the average patient with VPD. For example, 25 % of patients presented for treatment of recurrent disease, often after multiple prior lines of therapy. Two thirds of patients had large or complex lesions that required some type of reconstruction. This may signify that the costs calculated in this analysis are higher than could be observed in a more routine practice. Finally, it is important to note that Mohs surgery at our institution was performed in a setting that takes into account both physician-administered services and hospital fees. Cost breakdown may be different in dermatologic surgery practices outside of a hospital system setting.

In conclusion, MMS-E appears to be a cost-effective surgical approach for treating VPD. Providers who treat VPD may use this analysis when considering the value of adopting MMS-E protocols. Recognizing the lack of quality of life data to measure the value of durable remission from this symptomatic but rare disease, we encourage future researchers to define QALY for VPD using standard health economic instruments.

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CRediT authorship contribution statement

Kelly H. Bruce: Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **James P. Moriarty:** Writing – review & editing, Validation, Methodology, Formal analysis. **Bijan J. Borah:** Writing – review & editing, Supervision, Methodology,

Conceptualization. **Ruchita Dholakia:** Writing – original draft, Methodology, Investigation, Data curation. **Mary E. Lohman:** Writing – review & editing, Resources, Investigation. **Jerry D. Brewer:** Writing – review & editing, Supervision, Resources, Conceptualization. **Nahid Y. Vidal:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **Jamie N. Bakkum-Gamez:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **William A. Cliby:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kelly H Bruce: mentorship through related NIH grant; James P Moriarty: none; Bijan J Borah: Consultant for Boehringer Ingelheim and Exact Sciences Corporation for unrelated projects; Ruchita Dholakia: none; Mary E Lohman: none; Jerry D Brewer: Assistant editor of the Journal of Dermatologic Surgery; Nahid Y Vidal: none; Jamie N Bakkum-Gamez: NIH/NCI grants unrelated to this research, licensing agreements between Mayo Clinic and Exact Science unrelated to this research ($0 in royalties), board member - Foundation for Women's Cancer; William A Cliby: salary support from a philanthropic named professorship within Mayo Clinic, division member - American Board of Obstetrics and Gynecology.

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Appendix A. Supplementary data

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