Premalignant Vulvar lesions Medical vs. Surgical Treatment

PROF. AMR EL-SHALAKANY, MD FRCOG.

GYNECOLOGICAL ONCOLOGY UNIT

EARLY CANCER DETECTION UNIT

AIN SHAMS UNIVERSITY

CAIRO, EGYPT

Conflict of interest

None Declared

Take home message

- Majority of VIN are the HPV related u VIN type
- Prophylactic HPV vaccines have a protective and a possible therapeutic effect
- Being more common in young women with a multifocal chance and a tendency to recur, warrants a rational tailored use of surgery and the favorability of finding comparably effective medical treatment .
- No evidence of the superiority of any particular surgical modality.
- Imiquimod and cidofovir have proved comparable effectiveness in the treatment of VIN
- No available evidence comparing medical versus surgical options (ongoing trials)

VIN ISSVD classification 2004

VIN 1 is no longer included

VIN2 & VIN3 amalgamated in one category

- **VIN, usual type (HPV related)**
  - VIN, warty
  - VIN, basaloid
  - VIN, mixed
- **VIN, differentiated type (Non- HPV related)**

2012 LAST (Lower Anogenital Squamous Terminology)

(ASCCP and College of American Pathologists)
Darragh et al. 2012

Low squamous intra-epithelial lesion (LSIL) (VIN I)

High squamous intra-epithelial lesion (HSIL) (VIN 2/3)

2014 WHO Classification of Tumours of the Vulva

Crum et al. 2014

Epithelial: **Squamous cell tumours and precursors**

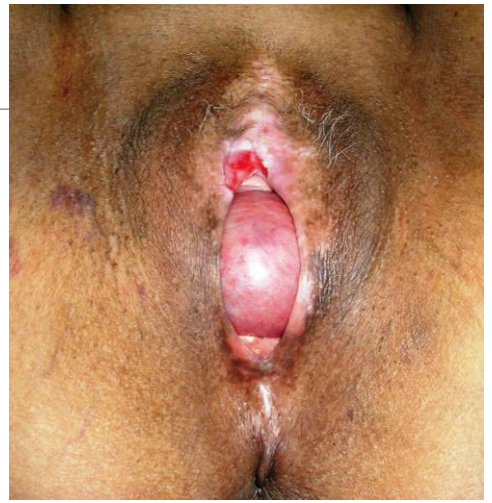
- **SILs** (LSIL, HSIL and differentiated type VIN)
- **Squamous cell carcinoma**
  (Keratinizing, Non-keratinizing, Basaloid, Warty, Verrucous)
- **Basal cell carcinoma**
- **Benign squamous lesions**
  (Condyloma accuminatum, vestibular papilloma, seborrhoeic keratosis)

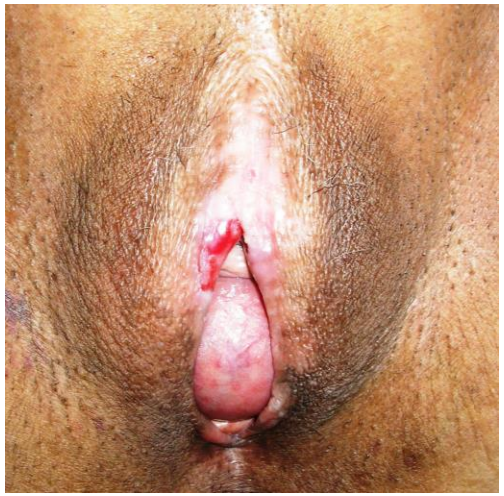
The 2015 International Society for the Study of Vulvovaginal Disease Terminology of Vulvar Squamous Intraepithelial Lesions

- Low grade squamous intraepithelial lesion (Flat condyloma or HPV effect)
- High grade squamous intraepithelial lesion (VIN usual type)
- Vulvar Intraepithelial neoplasia, differentiated-type

Vulval intraepithelial neoplasia (VIN) Management approach objectives

- Prophylactic HPV vaccines can be protective against future development of VIN.
- Exclude invasiveness.
- Control patients' symptoms with preservation of sexual function.
- Long term follow up for optimal handling of any recurrence.





Role of HPV vaccines and VIN

PREVENTION

TREATMENT

PREVENT RECURRENCE

Author manuscript
J Low Genit Tract Dis. Author manuscript; available in PMC 2017 August 11.

ished in final edited form as:
J Low Genit Tract Dis. 2012 October ; 16(4): 471–479. doi:10.1097/LGT.0b013e3182472947.

Prevalence of Human Papillomavirus (HPV) Types in Invasive Vulvar Cancers and VIN3 in the United States Before Vaccine Introduction

Julia W. Gargano, PhD[1,2], Edward J. Wilkinson, MD[3], Elizabeth R. Unger, PhD, MD[2], Martin Steinau, PhD[2], Meg Watson, MPH[4], Youjie Huang, DrPH, MD[5], Glenn Copeland, MBA[6], Wendy Cozen, DO[7], Marc T. Goodman, PhD[8], Claudia Hopenhayn, PhD[9], Charles F. Lynch,

Nearly all VIN3 and two thirds of invasive vulvar cancer were HR-HPV positive.
HPV prevalence ranged from 49.1%-100% in all SCC histological subtypes.
Prophylactic vaccines have the potential to decrease the incidence of vulvar neoplasia.

Published OnlineFirst September 29, 2009; DOI: 10.1158/1940-6207.CAPR-09-0031

Cancer **Prevention** Research

A Pooled Analysis of Continued Prophylactic Efficacy of Quadrivalent Human Papillomavirus (Types 6/11/16/18) Vaccine against High-grade Cervical and External Genital Lesions

Susanne K. Kjaer,[1] Kristján Sigurdsson,[2] Ole-Erik Iversen,[3] Mauricio Hernandez-Avila,[4] Cosette M. Wheeler,[5] Gonzalo Perez,[6] Darron R. Brown,[7] Laura A. Koutsky,[8] Eng Hseon Tay,[9] Patricia García,[10] Kevin A. Ault,[11] Suzanne M. Garland,[12] Sepp Leodolter,[13] Sven-Eric Olsson,[14] Grace W.K. Tang,[15] Daron G. Ferris,[16] Jorma Paavonen,[17] Matti Lehtinen,[18] Marc Steben,[19] F. Xavier Bosch,[20] Joakim Dillner,[21] Elmar A. Joura,[13] Slawomir Majewski,[22] Nubia Muñoz,[23] Evan R. Myers,[24] Luisa L. Villa,[25] Frank J. Taddeo,[26] Christine Roberts,[26] Amha Tadesse,[26] Janine Bryan,[26] Roger Maansson,[26] Shuang Lu,[26] Scott Vuocolo,[26] Teresa M. Hesley,[26] Alfred Saah,[26] Eliav Barr[26] and Richard M. Haupt[26]

Vaccine efficacy against HPV 6/11/16/18–related high-grade vulvar and vaginal lesions in the per-protocol and intention-to-treat populations was 100.0% (95% CI, 82.6-100.0) and 79.0% (95% CI, 56.4-91.0), respectively

IJC
International Journal of Cancer

Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: *Post-hoc* analysis from a randomized controlled trial

Suzanne M. Garland[1], Jorma Paavonen[2], Unnop Jaisamrarn[3], Paulo Naud[4], Jorge Salmerón[5], Song-Nan Chow[6], Dan Apter[7], Xavier Castellsagué[8†], Júlio C. Teixeira[9], S. Rachel Skinner[10,11], James Hedrick[12], Genara Limson[13], Tino F. Schwarz[14], Willy A.J. Poppe[15], F. Xavier Bosch[8], Newton S. de Carvalho[16], Maria Julieta V. Germar[17], Klaus Peters[18], M. Rowena Del Rosario-Raymundo[19], Grégory Catteau[20], Dominique Descamps[20], Frank Struyf[20], Matti Lehtinen[21], and Gary Dubin[22] for the HPV PATRICIA Study Group

No VIN was reported and one woman in each group had VaIN2+ 60 days or more post-surgery. *Garland et al. 2016*

Gynecologic Oncology 154 (2019) 110–117

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ygyno

Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population☆,☆☆

Anna R. Giuliano [a,*], Elmar A. Joura [b], Suzanne M. Garland [c,d,e], Warner K. Huh [f], Ole-Erik Iversen [g,h], Susanne K. Kjaer [i,j], Alex Ferenczy [k], Robert J. Kurman [l,m], Brigitte M. Ronnett [l,m], Mark H. Stoler [n], Oliver M. Bautista [o], Erin Moeller [o], Michael Ritter [o], Christine Shields [o], Alain Luxembourg [o]

A significant reduction in the incidence of vulvar and vaginal disease was observed among women negative at baseline to all nine HPV types for lesions related to HPV 6, 11, 16, or 18 (any grade: 94.9%,; condyloma: 95.0%,) and HPV 31, 33, 45, 52, or 58 (any grade: 98.2%,; condyloma: 100%,).

Bryan et al. BMC Women's Health (2019) 19:3
https://doi.org/10.1186/s12905-018-0707-9

BMC Women's Health

RESEARCH ARTICLE Open Access

HPV vaccine in the treatment of usual type vulval and vaginal intraepithelial neoplasia: a systematic review

Stacey Bryan[1*], Cynthia Barbara[2], Jane Thomas[2] and Adeola Olaitan[2]

- 93 articles, 7 studies included. No RCTs.
- Reduction in lesion size varied from no response to 83% overall (partial and complete) response.
- Symptom relief varied from no change to 68.4% of women symptom free
- HPV clearance varied between 8 and 74%
- Histological regression with (lesions down graded from a high to low-grade) varied from 0 up to 63%.

Bryan *et al. BMC Women's Health* (2019) 19:3
https://doi.org/10.1186/s12905-018-0707-9

BMC Women's Health

RESEARCH ARTICLE Open Access

HPV vaccine in the treatment of usual type vulval and vaginal intraepithelial neoplasia: a systematic review

Stacey Bryan[1*], Cynthia Barbara[2], Jane Thomas[2] and Adeola Olaitan[2]

Conclusions: This review finds the evidence relating to the use of HPV vaccine in the treatment of women with VIN/VaIN is of very low quality and insufficient to guide practice. Further longitudinal studies are needed to assess its use in prevention of progression to cancer.

HPV therapeutic vaccines and VIN

[CANCER RESEARCH 63, 6032–6041, September 15, 2003]

Immunological and Clinical Responses in Women with Vulval Intraepithelial Neoplasia Vaccinated with a Vaccinia Virus Encoding Human Papillomavirus 16/18 Oncoproteins[1]

Emma J. Davidson, Christopher M. Boswell, Peter Sehr, Michael Pawlita, Anne E. Tomlinson, Rhona J. McVey, Jennifer Dobson, John St. C. Roberts, Julian Hickling, Henry C. Kitchener, and Peter L. Stern[2]

Immunology Group, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester, United Kingdom [P. L. S., E. J. D.]; University Department of Obstetrics and Gynaecology, St. Mary's Hospital, Manchester, United Kingdom [E. J. D., A. E. T., R. J. M., H. C. K.]; Xenova Research, Ltd., Cambridge, United Kingdom [C. N. B., J. D., J. S. R., J. H.]; and Applied Tumor Virology, Deutsches Krebsforschungszentrum, Heidelberg, Germany [P. S., M. P.]

British Journal of Cancer (2010) 102, 1129 – 1136

www.bjcancer.com

Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulval intraepithelial neoplasia

S Daayana[1,2], E Elkord[2], U Winters[1,2], M Pawlita[3], R Roden[4], PL Stern[*,2] and HC Kitchener[*,1]

[1]Academic Unit of Obstetrics and Gynaecology, University of Manchester, St Mary's Hospital, Whitworth Park, Manchester M13 0JH, UK; [2]Cancer Research UK Immunology Group, Paterson Institute for Cancer Research, University of Manchester, Christie Hospital NHS Trust, Manchester M20 4BX, UK; [3]Department of Genome Modifications and Carcinogenesis, German Cancer Research Centre (DKFZ), Im NeuenheimerFeld 280, Heidelberg, Germany; [4]Department of Pathology, Johns Hopkins University, Baltimore, MD 21231, USA

Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA)

JAMA Netw Open. 2019 Apr; 2(4): e190819.
Published online 2019 Apr 12.
doi: 10.1001/jamanetworkopen.2019.0819: 10.1001/jamanetworkopen.2019.0819

PMCID: PMC6481452
PMID: 30977845

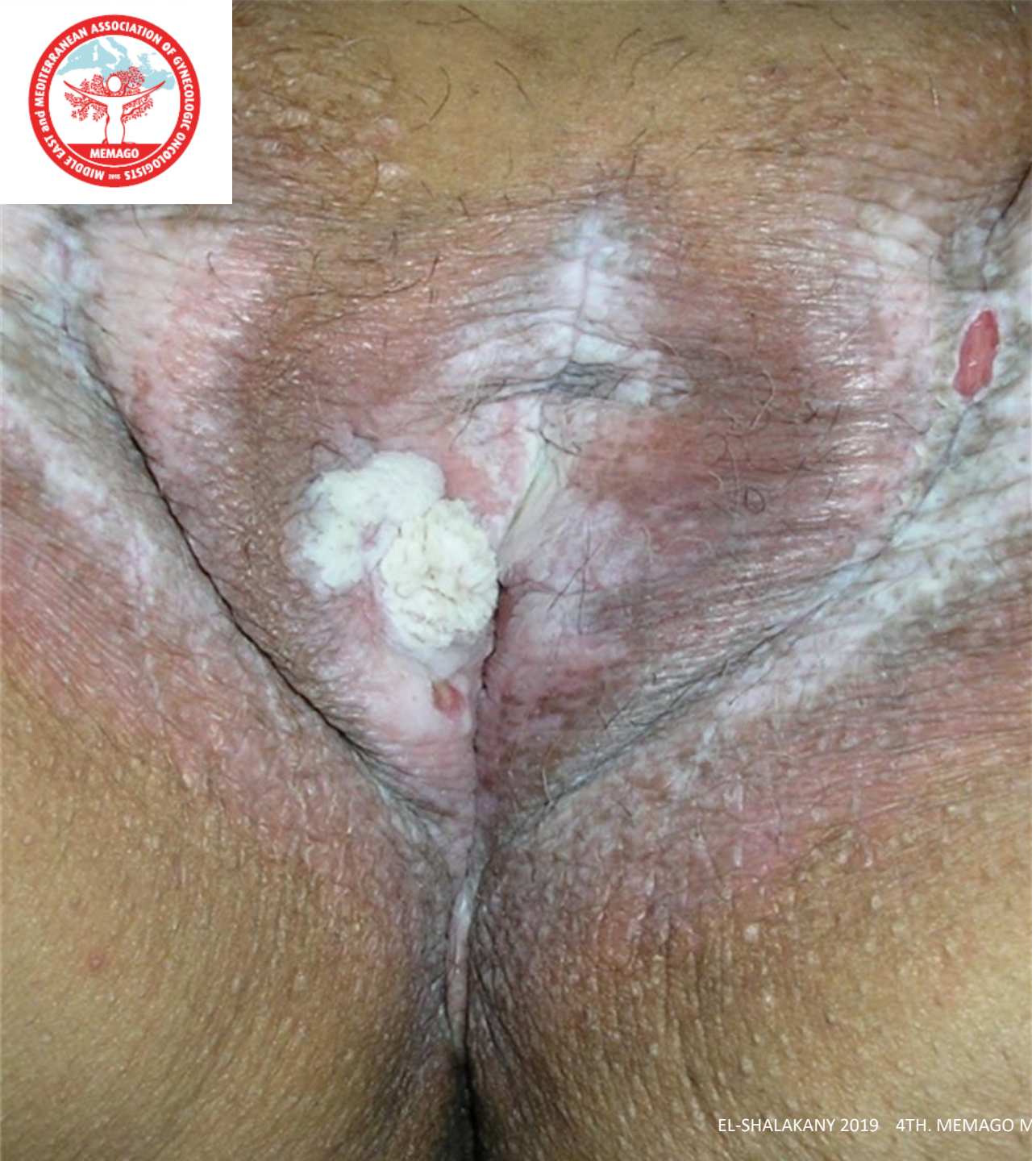
Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA)

A Trial Protocol

Helen C. Stankiewicz Karita, MD,[✉1] Kirsten Hauge, MPH,[1] Amalia Magaret, PhD,[2,3,4] Constance Mao, MD,[5] Jeffrey Schouten, MD, JD,[1,3,6] Verena Grieco, MD,[7] Long Fu Xi, PhD,[8] Denise A. Galloway, PhD,[9,10] Margaret M. Madeleine, PhD,[8,10] and Anna Wald, MD, MPH[1,3,4,8]

[1]Department of Medicine, University of Washington, Seattle
[2]Department of Biostatistics, University of Washington, Seattle
[3]Division of Vaccine and Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington
[4]Department of Laboratory Medicine, University of Washington, Seattle
[5]Department of Obstetrics and Gynecology, University of Washington, Seattle
[6]Department of Surgery, University of Washington, Seattle
[7]Department of Pathology, University of Washington, Seattle
[8]Department of Epidemiology, University of Washington, Seattle
[9]Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington
[10]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington
[✉]Corresponding author.

Article Information



VIN medical treatment

- OUTDATED (5FU, DNCB, BLEOMYCINE, IFN-A,..).
- POTENTIALLY BENEFICIAL (IMIQUIMOD, CIDOFOVIR, I3C, PDT).

VIN medical treatment

Imiquimod, an immune response modifier, approved for the treatment of genital warts (Moore 2001)

Cidofovir is a deoxycytidine monophosphate analogue with potent antiviral activity against a broad range of DNA viruses including HPV. Cidofovir probably mediates its effects by causing death in HPV-infected cells (Tristram 2005)

Indole-3-carbinol (I3C) acts as a potent inducer of 2-hydroxylation of oestradiol, decreasing production of the carcinogen, 16-alpha-hydroxyestrone and increasing production of the anti-proliferative metabolite 2-hydroxyestrone (Newfield 1998).

Photodynamic therapy (PDT) causes direct destruction of lesions using the interaction between a tumour-localising photo-sensitiser and light of an appropriate wavelength to bring about molecular oxygen-induced cell death. It is usually used in conjunction with a topical cream containing 5-aminolaevulinic acid (ALA), since the resultant chemical reaction reduces incidental damage to surrounding normal tissues (Dougherty 1998).

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Medical interventions for high-grade vulval intraepithelial neoplasia (Review)

Pepas L, Kaushik S, Nordin A, Bryant A, Lawrie TA

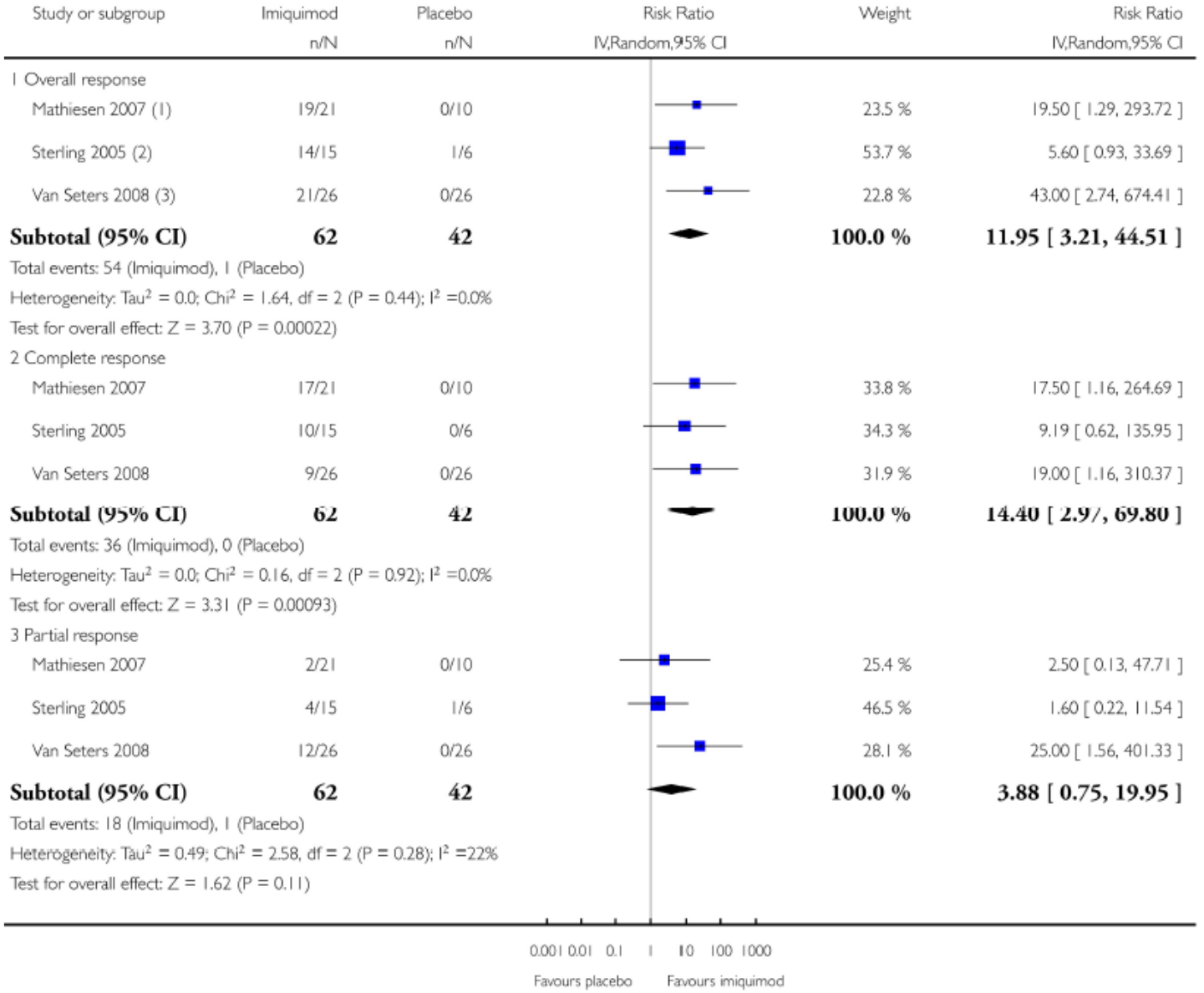
Pepas L, Kaushik S, Nordin A, Bryant A, Lawrie TA. Medical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD007924. DOI: 10.1002/14651858.CD007924.pub3

Medical interventions for high-grade vulval intraepithelial neoplasia.

Pepas L, Kaushik S, Nordin A, Bryant A, Lawrie TA. Medical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015,

- 5 RCTs involving 297 women.
- 3 trials assessed imiquimod vs. placebo,
  - Sterling et al. 2005
  - Mathiesen et al. 2007
  - Van Seters et al. 2008 FU 2011
- One RCT assessed imiquimod vs cidofovir, (Tristram 2014).
- one RCT compared 2 different doses of indole-3-carbinol (Naik et al. 2006)

Topical imiquimod versus placebo, Response to treatment at 5-6 months.



- Sterling et al. 2005.
- Mathiesen et al. 2007.
- Van Seters et al. 2008, 7-year FU Terlou et al. 2011.

Topical imiquimod versus placebo, Response to treatment at 12 months.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Difference IV,Fixed,95% CI	Risk Difference IV,Fixed,95% CI
1 Overall response				
Van Seters 2008	19/24	2/23		0.70 [0.51, 0.90]
2 Complete response				
Van Seters 2008	9/24	0/23		0.38 [0.18, 0.57]
3 Partial response				
Van Seters 2008	10/24	2/23		0.33 [0.10, 0.56]

7-year follow-up data from Van Seters 2008 (Terlou 2011) suggests only 1 of 9 complete responders in this trial experienced a recurrence, and none progressed to vulval cancer.

Topical imiquimod versus cidofovir, Response to treatment at 6 months.

Study or subgroup	Imiquimod n/N	Cidofovir n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 Overall response				
Tristram 2014	52/91	55/89		0.92 [0.73, 1.18]
2 Complete response				
Tristram 2014	42/91	41/89		1.00 [0.73, 1.37]
3 Partial response				
Tristram 2014	10/69	14/72		0.75 [0.36, 1.56]

Statistically non-significant higher total adverse events were slightly more in the imiquimod group with slightly more discontinuations occurring in this group.

- Martin-Hiersch et al. 1998
- Kurwa et al. 2000
- Hillemanns et al. 2000
- Fehr et al. 2001
- Abdel-Hady et al. 2001
- Campbell et al. 2004
- Zawislak et al. 2009
- Choi et al. 2015

biomedicines

MDPI

Review

The Role of Photodynamic Therapy in the Treatment of Vulvar Intraepithelial Neoplasia

Giulio Tosti [1,*], Anna Daniela Iacobone [2], Eleonora Petra Preti [2], Sabina Vaccari [3], Alessia Barisani [3], Elisabetta Pennacchioli [1] and Carmen Cantisani [4]

1 Division of Melanoma, Soft Tissue Sarcomas and Rare Tumors, Istituto Europeo di Oncologia, Via G. Ripamonti 437, 20141 Milano, Italy; elisabetta.pennacchioli@ieo.it
2 Preventive Gynecology Unit, Istituto Europeo di Oncologia, 20141 Milano, Italy; AnnaDaniela.Iacobone@ieo.it (A.D.I.); eleonora.preti@ieo.it (E.P.P.)
3 Unit of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, Policlinico Sant'Orsola-Malpighi, 40138 Bologna, Italy; sabina.vaccari@aosp.bo.it (S.V.); alessiabarisani@gmail.com (A.B.)
4 Department of Dermatology, Policlinico Umberto I, Sapienza University of Rome, 00185 Rome, Italy; carmencantisanister@gmail.com
* Correspondence: giulio.tosti@gmail.com; Tel.: +39-025-7489-318

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Overall, complete histological response ranged between 20% and 67% and symptom response rates ranged between 52% and 89% according to different studies and case series.

VIN surgical treatment

WHEN LESS IS MORE

VIN surgical treatment

As HPV infection is common, uVIN is becoming more common in younger women (under 50 years of age).

Treatments are aimed at relief of distressing symptoms and to ensure that the condition does not become cancerous.

The most common treatment option for women with this condition has been surgery to remove the affected skin areas.

Surgery, however, does not guarantee a cure, can be disfiguring, and may result in physical and psychological problems in younger women who are sexually active.

VIN surgical treatment

No clinical appearance helps in distinguishing uVIN with stromal invasion.

12–17% of excised VIN show unrecognised invasion (Powel et al. 1986, Husseinzadah et al.1999, Jones et al. 2005)

More limited surgery is now being used in order to alter morphology as little as possible and to preserve vulvar function.

Irrespective of the surgical treatment used recurrence rates are high (van Seter et al. 2005, Jones et al. 2005)

All local excision techniques seem to have a similar efficacy (scalpel, laser, electrosurgery)

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von Gruenigen et al. Surgical treatments for vulvar and vaginal dysplasia: a randomized controlled trial. Obstetrics and Gynecology 2007;109(4):942–7.

Surgical interventions for high-grade vulval intraepithelial neoplasia (Review)

Kaushik S, Pepas L, Nordin A, Bryant A, Dickinson HO, Lawrie TA

- Only one RCT, 30 women,
- CO2 laser surgery versus cavitational ultrasonic surgical aspiration (CUSA).
- No differences in the risks recurrence after one year of follow-up, pain, scarring, dysuria or burning, adhesions, infection, abnormal discharge or eschar
- Lacked statistical power (small number of women and the low number of observed events).
- Low risk of bias.
- NO reliable evidence regarding the effectiveness and safety of the 2 surgical techniques for VIN treatment

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Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia (Review)

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011837. DOI: 10.1002/14651858.CD011837.pub2

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Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia (Review)

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L

- Low-quality evidence from the best included NRS indicated,
- Adjusted data show little difference in the risk of VIN recurrence between surgical excision and laser vaporisation.
- Recurrence occurred in 51% of women overall, at a median of 14 months,
- Recurrence was more common in multifocal than unifocal lesions (66% versus 34%).
- Vulval cancer occurred in 15.1% overall at a median of 71.5 months
- Vulval cancer risk did not differ significantly between excision and laser vaporisation

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Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia (Review)

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L

- Alternative surgical procedures that might be as effective include Cavitron ultrasonic surgical aspiration (CUSA) and loop electrosurgical excision (LEEP) procedures, based on low- to very low-quality evidence, respectively.
- Photodynamic therapy may be a useful treatment option.(Very low quality)
- Only one ongoing RCT of medical treatment (imiquimod) compared with surgical treatment

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Authors conclusions

Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia (Review)

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L

- No evidence on how medical treatment compares with surgical treatment.
- 50% chance of the condition recurring one year later after surgery , irrespective of whether by surgical excision or laser vaporisation.
- Multifocal uVIN lesions are at a higher risk of recurrence and progression.
- If occult cancer is suspected, surgical excision remains the treatment of choice.
- If occult cancer is not a concern, treatment needs to be individualised (site and extent of disease, and a woman's preferences).

Take home message

- Majority of VIN are the HPV related uVIN type
- Prophylactic HPV vaccines have a protective and a possible therapeutic effect
- Being more common in young women with the multifocal chance and the tendency to recur warrants a rational tailored use of surgery and the favorability of finding comparably effective medical treatment .
- No evidence of the superiority of any particular surgical modality.
- Imiquimod and cidofovir have proved comparable effectiveness in the treatment of VIN
- No available evidence comparing medical versus surgical options (ongoing trials)

Thank you for listening