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

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

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TABLE OF CONTENTS

[Intervention Review]

Surgical interventions for high-grade vulval intraepithelial neoplasia

Sonali Kaushik[1], Litha Pepas[2], Andy Nordin[3], Andrew Bryant[4], Heather O Dickinson[4]

[1]Division of Gynaecological Oncology, Cheltenham General Hospital, Cheltenham, UK. [2]Centre of Reproductive Medicine, Barts Health NHS Trust, London, UK. [3]East Kent Gynaecological Oncology Centre, Queen Elizabeth The Queen Mother Hospital, Kent, UK. [4]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Contact address: Sonali Kaushik, Division of Gynaecological Oncology, Cheltenham General Hospital, Cheltenham, Gloucestershire, GL53 7AN, UK. kaushik.sonali@googlemail.com.

Editorial group: Cochrane Gynaecological Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2014.
Review content assessed as up-to-date: 3 December 2013.

Citation: Kaushik S, Pepas L, Nordin A, Bryant A, Dickinson HO. Surgical interventions for high-grade vulval intraepithelial neoplasia. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD007928. DOI: 10.1002/14651858.CD007928.pub3.

ABSTRACT

Background

This is an updated version of an original Cochrane review published in *The Cochrane Library*, 2011, Issue 1.

Vulval intraepithelial neoplasia (VIN) is a pre-malignant condition of the vulval skin. This uncommon chronic skin condition of the vulva is associated with a high risk of recurrence and the potential to progress to vulval cancer. The condition is complicated by its multicentric and multifocal nature. The incidence of this condition appears to be rising, particularly in the younger age group. There is a lack of consensus on the optimal surgical treatment method. However, the rationale for the surgical treatment of VIN has been to treat the symptoms and exclude any underlying malignancy, with the continued aim of preserving the vulval anatomy and function. Repeated treatments affect local cosmesis and cause psychosexual morbidity, thus impacting he individual's quality of life.

Objectives

To evaluate the effectiveness and safety of surgical interventions in women with high-grade VIN.

Search methods

We searched the Cochrane Gynaecological Cancer Group Trials Register and the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 11,2013 and MEDLINE and EMBASE up to December 2013. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies, and contacted experts in the field.

Selection criteria

Randomised controlled trials (RCTs) that compared surgical interventions in adult women diagnosed with high-grade VIN.

Data collection and analysis

Two review authors independently abstracted data and assessed risk of bias.

Main results

We identified one RCT, including 30 women, that met our inclusion criteria; this trial reported data on carbon dioxide (CO_2) laser surgery versus cavitational ultrasonic surgical aspiration (CUSA). There were no statistically significant differences in the risks of disease recurrence after one year of follow-up, pain, scarring, dysuria or burning, adhesions, infection, abnormal discharge or eschar between women who underwent CO_2 laser surgery and those who received CUSA. The trial lacked statistical power due to the small number of women in each group and the low number of observed events, but was at low risk of bias.

Authors' conclusions

The included trial lacked statistical power due to the small number of women in each group and the low number of observed events. The absence of reliable evidence regarding the effectiveness and safety of the two surgical techniques for the management of VIN therefore precludes any definitive guidance or recommendations for clinical practice.

PLAIN LANGUAGE SUMMARY

Comparison of surgical procedures for women diagnosed with precancerous changes of the vulva (high-grade vulval intraepithelial neoplasia)

Background

Vulval intraepithelial neoplasia (VIN) is regarded as a precancerous condition of the skin of the vulva that may further develop into vulval cancer. The condition is usually treated by surgery. The various surgical techniques currently available are either ablative (where the lesion is removed by destruction of tissue using an energy source) or excisional (the lesion is simply 'cut out'); sometimes a combination of the two may be used. There is currently no consensus as to which surgical technique is the most effective and safe. The treatment options available to the individual with VIN are currently based on the preference of the treating physician and his/her skills, and these vary both nationally and internationally. Because there is a high risk of the condition recurring after surgery, multiple treatments may be required. Hence, various conservative surgical and medical modalities of treatment are currently being explored.

Review question

To evaluate the effectiveness and safety of surgical interventions in women with high-grade vulval intraepithelial neoplasia (VIN).

Main findings

This review is based on one randomised controlled trial (RCT) which included 30 participants and therefore the results are restricted to the analyses of a single study. This RCT compared two ablative techniques: carbon dioxide (CO_2) laser surgery and cavitron ultrasonic surgical aspiration (CUSA). There was no evidence for differences in the risks of disease recurrence after one year follow up, pain, scarring, painful/uncomfortable urination (dysuria) or burning on urination, adhesions (fusion of the 'lips' or labia as part of the healing process by the formation of bridges of tissue), infection, abnormal discharge or the presence of dead tissue shedding from healthy skin (eschar) between women who received CO_2 laser surgery and those who underwent CUSA.

Quality of the evidence

Due to the small number of participants with high-grade VIN included in the trial there was insufficient evidence to conclude that either surgical technique is superior over the other. This review highlights the need for further high-quality, well-designed trials.

BACKGROUND

Description of the condition

Vulval intraepithelial neoplasia (VIN) is a condition in which precancerous changes occur in the skin that covers the vulva of the

female external genital organs. VIN can affect women at any age but most recent studies suggest it is more common under the age of 50 years (Jones 2001). VIN is diagnosed by examination of a vulval biopsy and historically has been classified on the basis of histology as either low grade (VIN 1) or high grade (VIN 2/3). In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) modified this classification to reflect the two divergent types of VIN: the human papilloma virus (HPV)-related type, which precedes almost all vulval cancers in women under the age of 45 years, described as usual-type VIN, and the lichen sclerosus-related type, which causes vulval cancer in older women, known as differentiated VIN (van der Avoort 2006). VIN may be asymptomatic or may present with a mixed variety of symptoms such as itching, discomfort, burning, painful intercourse and whitish patches over the vulva. These symptoms alone can lead to considerable morbidity. The main concern with VIN, however, is its potential to progress to cancer of the vulva. The true rate of progression to invasive vulval cancer in women with untreated high-grade VIN is debatable, although some studies suggest a rate as high as 9% (van Seters 2002), whereas the risk of progression in treated lesions over a period of years has been reported as between 2% and 5% (Jones 2001). A woman's risk of developing cancer of the vulva by the age of 75 years varies between countries, and ranges from 0.01% to 0.28%, corresponding to zero to three cases per year in 100,000 women under the age of 75 years (IARC 2002). More recently an increase in vulval cancer in women under the age of 50 years has been documented (Jones 1997; Joura 2000; ONS 2004; WCISU 2004). This rising trend has been linked to an increasing incidence of VIN in younger women, which has been attributed to infection with HPV, smoking or poor immunological status. Effective treatments for vulval cancer are available; however, they are associated with considerable morbidity.

Description of the intervention

The treatment of VIN depends on its grade and location on the vulva. VIN 1 is generally monitored using comprehensive vulvoscopy and inspection of the perianal region; with liberal biopsying of any suspicious areas to ascertain progression to high-grade disease. VIN 2/3 lesions are considered to have a high propensity for malignant conversion; hence, they are managed actively. Traditionally, VIN lesions are either excised or ablated. Popular surgical treatment modalities include carbon dioxide (CO_2) laser vaporisation (a type of ablation) and surgical excision. Laser vaporisation involves destruction of the skin using a pulsed laser; no tissue is provided for histology. Surgical excision involves the removal of diseased tissue, which can be used to provide histological information. Ultrasonic surgical aspiration is another surgical technique which involves the use of a high frequency ultrasonic vibrator which destroys tissue by cavitation. A simultaneous irrigation and aspiration system cleans the operative system and cools the tip of the instrument. Cavitation induces selective tissue fragmentation. This sytem allows precise and selective tissue dissection. Depending on the extent of the lesion, surgery can involve local excision, hemi-vulvectomy or a superficial skinning vulvectomy. However, full vulvectomy is rarely indicated. Due to the disfiguring nature of these procedures and the younger age of the population of women being treated, less-invasive modalities have been developed, many of which are still being evaluated, such as photodynamic therapy (Hillemanns 2000) and, more recently, the topical use of immune modulators (Le 2007; Mathiesen 2007). Following recent studies, the latter treatment has gained popularity and appears to be a promising option for VIN in younger women who wish to remain sexually active and avoid radical surgery provided cancer is absent (Tristam 2005).

Why it is important to do this review

There is no consensus on the optimal management of high-grade VIN. The ideal management of women with VIN is complicated by the broad age range of women affected, and the extent and occasional multifocal nature of this condition, which has a risk of recurrence of over 50%. Surgical intervention is often associated with deformity and loss of vulvar function, which has significant somatic and psychosexual morbidity, factors that need more consideration as VIN and vulval cancer are now being diagnosed in younger women in whom traditional surgical treatment would usually be warranted. A parallel systematic review examining the medical management of women with VIN is being carried out. The impact of various surgical interventions currently available on the risks of recurrence of VIN and its progression to vulval cancer remains unknown; hence, the need for a formal appraisal of the evidence available for the effective surgical management of women with VIN.

OBJECTIVES

To evaluate the effectiveness and safety of surgical interventions in women with high-grade VIN.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

Types of participants

Women aged over 18 years with a confirmed histological diagnosis of high-grade VIN. We included studies involving women with either unifocal or multifocal disease of the vulva and excluded studies involving women with a histological diagnosis of Paget's disease. We also excluded trials that studied the management of vulval carcinoma.

Types of interventions

- Intervention
    - Excision (including wide local excision and simple vulvectomy)
    - Ablation (CO_2 and laser vaporisation)
    - Excision and ablation as a combined technique
- Control
    - Observation

We additionally considered any studies direct comparing excisional and ablative surgical techniques, as well as those comparing excisional and ablative techniques with observation only.

Types of outcome measures

Primary outcomes

1. Response to treatment (based on clinical or histological, or clinical and histological assessment of resolution, regression, persistence or progression of VIN)
2. Recurrence of high-grade VIN on long-term follow up (at two and five years)
3. Progression to vulval cancer

Secondary outcomes

1. Quality of life (QoL), as measured by a validated scale
2. Sexual function, assessed using a validated tool (e.g. the Sabbatsberg sexual self-rating scoring system (Garrat 1995; Naransingh 2000))
3. Control of symptoms (i.e. pain, pruritis, soreness and superficial dyspareunia)
4. Adverse events classified according to CTCAE 2006
    i) direct surgical morbidity (death within 30 days; injury to bladder, ureter, vascular system, small bowel or rectum; wound healing; febrile morbidity; haematoma; local infection; indwelling catheter)
    ii) surgically related systemic morbidity (chest infection, thromboembolic event (deep vein thrombosis and pulmonary embolism), cardiac event (cardiac ischaemia and cardiac failure), cerebrovascular accident)
    iii) long-term pain
    iv) unscheduled re-admission to hospital, delayed discharge

Search methods for identification of studies

We included papers in all languages, which we had translated when necessary.

Electronic searches

Please refer to the methods of the Cochrane Gynaecological Cancer Group, which are used in reviews.
We searched the following electronic databases:

- The Cochrane Gynaecological Cancer Review Group Trial Register;
- Cochrane Central Register of Controlled Trials (CENTRAL), 2013, Issue 11;
- MEDLINE to December 2013;
- EMBASE to December 2013.

The MEDLINE, EMBASE and CENTRAL search strategies aiming to identify RCTs comparing surgical interventions in women with high-grade VIN are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.
We identified all relevant articles found on PubMed and, using the 'related articles' feature, we carried out a further search for newly published articles.

Searching other resources

Unpublished and Grey literature

We searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials.

Handsearching

We handsearched reports of conferences in the following sources:

- Gynecologic Oncology (Annual Meetings of the American Society of Gynecologic Oncologists);
- International Journal of Gynecological Cancer (Annual Meetings of the International Gynecologic Cancer Society);
- British Journal of Cancer;
- British Cancer Research Meeting;
- proceedings of the Annual Meeting of European Society of Medical Oncology (ESMO);
- proceedings of the Annual Meeting of the American Society of Clinical Oncology (ASCO).

Reference lists and Correspondence

We checked the reference lists of included studies and contacted experts in the field to identify further reports of trials. We found two trials listed in the ClinicalTrials.gov register that are underway; the results are yet to be reported (PITVIN 2013; Senn 2013). We contacted two experts (Mr R Naik and Miss A Tristam) in the field, who confirmed that there were currently no other trials underway that assessed surgical interventions for the management of women with VIN.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote. We removed duplicates and the remaining references were examined by two review authors (LP, SK) independently. We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of the full text of potentially relevant references. Two review authors (LP, SK) assessed the eligibility of retrieved papers independently. We resolved disagreements by discussion or by appeal to a third review author (AN) if necessary. We documented reasons for study exclusion.

Data extraction and management

We abstracted the following data from the included study, as recommended in Chapter 7 of Higgins 2008:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- study population:
    - total number enrolled;
    - participant characteristics;
    - age;
    - co-morbidities;
    - previous treatment;
- VIN details:
    - grade;
    - size of lesion;
    - unifocal or multifocal lesion;
- intervention details: surgery or control:
    - for surgical interventions: type of excision or ablation;
- risk of bias in study (see below);
- duration of follow up;
- outcomes - response to treatment, QoL, sexual function, symptom assessment and adverse events:
    - for each outcome: outcome definition (with diagnostic criteria if relevant);
    - unit of measurement (if relevant);
    - for scales: upper and lower limits, and whether high or low score is good
    - results: number of participants allocated to each intervention group;
    - for each outcome of interest: sample size, missing participants.

We extracted data on outcomes as below.

- For dichotomous outcomes (e.g. adverse events or number of participants with disease recurrence if it was not possible to use a hazard ratio), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. subjective pain), we extracted the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm (pain was assessed at one week after treatment, scarring, wound healing and other adverse effects were assessed at a two-four week interval after surgery) at the end of follow up at one year, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and the standard error.

We extracted both unadjusted and adjusted statistics, where reported.
Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.
We noted the time points at which outcomes were collected and reported.
Two reviewers (LP, SK) abstracted data independently into a data abstraction form specially designed for the review. We resolved differences between reviewers by discussion or by appeal to a third review author (AN or AB) when necessary.

Assessment of risk of bias in included studies

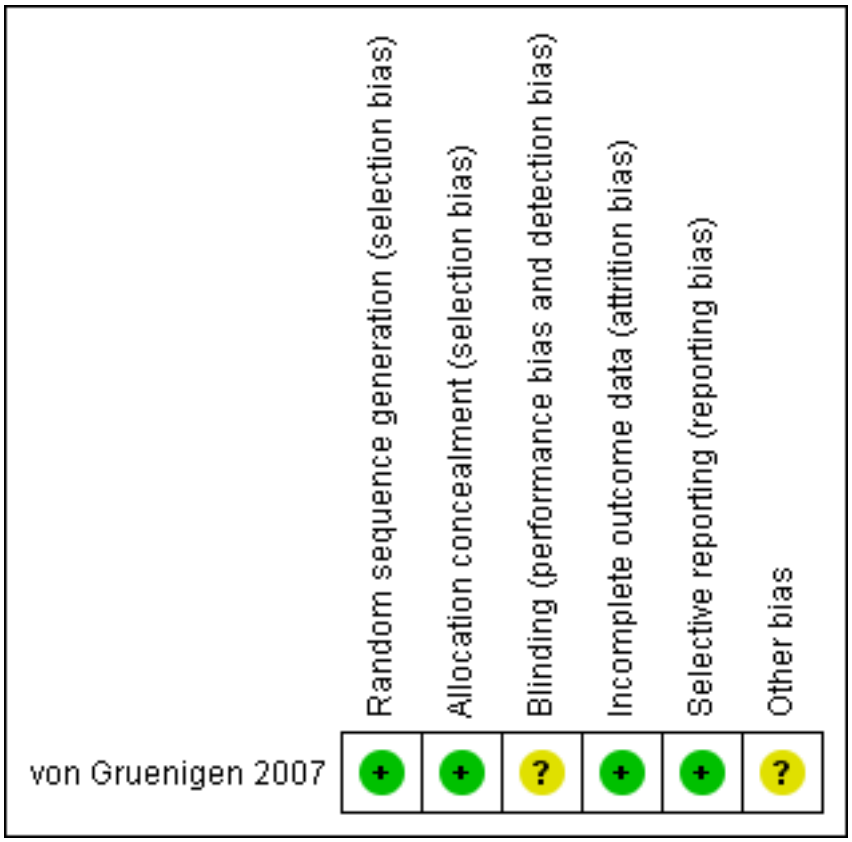
We assessed the risk of bias in the included RCT using The Cochrane Collaboration's tool and the criteria specified in Chapter 8 of Higgins 2008. This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data:

- we recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow up was not reported; we coded the satisfactory level of loss to follow up for each outcome as:
  - yes, if fewer than 20% of participants were lost to follow up and reasons for loss to follow up were similar in both treatment arms;
  - no, if more than 20% of participants were lost to follow up or reasons for loss to follow up differed between treatment arms;
  - unclear, if loss to follow up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (LP, SK) applied the 'Risk of bias' tool independently and differences were resolved by discussion or by appeal to a third review author (AN). We present the results using a 'Risk of bias' summary (Figure 1).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

We used the following measures of the effect of treatment:

- for dichotomous outcomes, we used the RR;
- for continuous outcomes, we used the mean difference between treatment arms.

Dealing with missing data

We contacted the trial authors of von Gruenigen 2007 to request data on the outcomes in only those participants that had high-grade VIN who were assessed.

Data synthesis

We identified only one included trial so it was not possible to perform meta-analyses. It was therefore not relevant to assess heterogeneity between the results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses.

RESULTS

Description of studies

Results of the search

The search strategy identified 2584 unique references in the original review up to September 2010 and an additional 1037 references in this updated review up to December 2013. Two review authors independently read the abstracts, and articles that obviously did not meet the inclusion criteria were excluded at this stage. We retrieved the full text of eight articles, and had them translated into English where appropriate, and we identified updated versions of relevant studies. We excluded seven of these eight references for the reasons described in the table Characteristics of excluded studies. However, we identified one completed RCT that met our inclusion criteria: we describe this study in the table Characteristics of included studies.

We identified no additional trials through searches of the grey literature.

Included studies

The one included trial (von Gruenigen 2007) included women with vulvar and vaginal dysplasia, but reported results for the two diseases separately. Although not reported in the original paper, the trial authors provided us with outcome data for women with high-grade VIN. The trial randomised 110 women, of whom 30 had high-grade VIN and were assessed at the end of the trial.

This multi-centre trial recruited women with vaginal and vulval dysplasia between 2000 and 2005.

The objective of the trial was to compare pain, adverse effects and recurrence in women with VIN or vaginal intraepithelial neoplasia (VAIN) randomised to treatment with CO_2 laser surgery or USA. A preoperative biopsy was performed to confirm the presence of dysplasia. Women aged 18 years or younger and those who were pregnant were excluded from the trial. Participants provided informed consent before being randomly assigned to one of the treatment modalities. Participants completed a visual analogue scale to measure their level of pain one week following surgery and were evaluated at two to four weeks after the intervention to assess scarring, wound healing and adverse effects. Participants returned every three months for one year for a pelvic examination and cytology in order to assess recurrence. Follow-up colposcopy and biopsy were used at the discretion of the treating physician.

Race; marital status; tobacco use; history of sexually transmitted infection, diethylstilbestrol exposure, immunodeficiency, hysterectomy and genital tract neoplasia; and previous treatment were recorded at enrolment.

CO_2 laser surgery was performed to a depth of tissue destruction of 1 mm in non-hairy vulvar regions and 3 mm in hairy vulvar regions. CUSA was performed using the Cavitron Ultrasonic Surgical Aspirator Excel System (Valley-lab, Boulder, Colorado, USA). The handheld tool vibrates and contains separate irrigation and suction channels. Lesions were removed to the reticular layer of the dermis. Surgeries were performed in an outpatient setting, with participants given standard discharge instructions regarding postoperative care.

The outcomes reported were recurrence after one year of follow up, pain, scarring, dysuria or burning, adhesions, abnormal discharge, infection and eschar. Additionally, the authors carried out multiple logistic regression to assess the relative risk of disease recurrence after one year of follow up in the two groups. The odds ratio was adjusted for age (continuous), history of dysplasia and smoking status.

Excluded studies

Seven references were excluded, after obtaining the full text.

- Four references (Bruchim 2007; Hillemanns 2005; Jones 1994; Jones 2005) were not RCTs. Bruchim 2007, Hillemanns 2005 and Jones 1994 were retrospective studies and Jones 2005 was a prospective case series.
- In two references describing one trial (Ferenczy 1992; Ferenczy 1994), half the lesional area in each participant was randomised and treated with either CO_2 laser surgery or loop electrosurgical excision procedure (LEEP). However, 10/25 of the areas were treated with both LEEP and CO_2 laser surgery after relapse prior to the nine-month assessment. The trial also included women with coexisting condylomata of the vagina (n = 5) or intraepithelial neoplasia of the cervix (n = 16).
- One reference (van Seters 2005) was a systematic review that yielded no further included trials.

For further details of all the excluded studies see the table Characteristics of excluded studies.

Risk of bias in included studies

The one included trial (von Gruenigen 2007) was at low risk of bias as it satisfied four criteria used to assess risk of bias (see Figure 1).

The trial reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and

made an effort to conceal this allocation sequence from participants and healthcare professionals involved in the trial. However, it was not reported whether the participants, healthcare professionals and outcome assessors were blinded. No woman with VIN 2 or higher was lost to follow up, and it seemed unlikely that outcomes had been selectively reported as the authors provided us with data on request. It was unclear whether any other bias may have been present.

Effects of interventions

CO_2 laser surgery versus USA

We found only one trial (von Gruenigen 2007), including 30 women, that met our inclusion criteria and this trial reported data on CO_2 laser surgery versus USA. For dichotomous outcomes, we were unable to estimate finite confidence intervals for the RR for presence of scarring and adhesions outcomes, as women in the USA group did not experience any events.

Disease recurrence after one year of follow up

(see Analysis 1.1)
There was no statistically significant difference in disease recurrence after one year of follow up between women who received CO_2 laser surgery and those who received USA (RR 1.53, 95% CI 0.56 to 4.15). The authors also carried out multiple logistic regression, which adjusted for age (continuous), history of dysplasia and smoking status. No statistically significant difference was observed between the two types of surgical procedures (adjusted odds ratio 0.68, 95% CI 0.27 to 1.83). None of the prognostic factors appeared to be predictive of recurrence, although the trial lacked statistical power due to the small number of women in each group and the low number of observed events.

Subjective pain

(see Analysis 1.2)
There was no statistically significant difference in subjective pain between women who received CO_2 laser surgery and those who received USA (mean difference −1.70, 95% CI −26.80 to 23.40).

Presence of scarring

Presence of scarring was observed in five women who received CO_2 laser surgery compared with no women who received USA (5/16 versus 0/14 in the laser and USA groups, respectively).

Dysuria or burning

(see Analysis 1.3)
There was no statistically significant difference in the risk of dysuria or burning in women who received CO_2 laser surgery and those who received USA (RR 0.66, 95% CI 0.18 to 2.44).

Adhesions

There was no statistically significant difference in the risk of adhesions between women who received CO_2 laser surgery and those who received USA. The trial reported only one occurrence of adhesions, in a woman who received CO_2 laser surgery.

Infection (yeast, urinary tract infection, other)

(see Analysis 1.4)
There was no statistically significant difference in the risk of infection in women who received CO_2 laser surgery and those who received USA (RR 0.88, 95% CI 0.14 to 5.42).

Abnormal discharge

(see Analysis 1.5)
There was no statistically significant difference in the risk of abnormal discharge between women who received CO_2 laser surgery and those who received USA (RR 1.75, 95% CI 0.18 to 17.29).

Eschar

(see Analysis 1.6)
There was no statistically significant difference in the risk of eschar in women who received CO_2 laser surgery and those who received USA (RR 0.88, 95% CI 0.14 to 5.42).

DISCUSSION

Summary of main results

We found only one RCT, including 30 women, that met our inclusion criteria and this trial reported data on CO_2 laser surgery versus USA. However, our primary outcomes were incompletely documented and the trial seemed to focus on adverse events. Disease recurrence was assessed in the trial, but follow up was assessed only at one year. Long-term follow up of at least two to five years would have been more informative and would have allowed other outcomes, such as progression to vulvar cancer, to have been investigated.
There was no statistically significant difference in the risks of disease recurrence after one year of follow up, pain, presence of scarring, dysuria or burning, adhesions, infection, abnormal discharge

or eschar between women who received CO_2 laser surgery and those who received USA. There is therefore no evidence as to whether CO_2 laser surgery or USA is the most effective and safe ablative surgical method for the treatment of women with high-grade VIN, and these ablative techniques have not been compared with surgical excision, which is the traditional surgical modality.

There is a paucity of good-quality data with regard to this relatively rare disease. We did not expect to identify a large number of RCTs, but the review was restricted to high-quality evidence because retrospective case series are of inadequate quality and in many instances do not allow for comparison. The main limitation of this review, other than the fact the conclusions are based on analyses of a small single trial, is the fact that follow up was for only one year. Many of the analyses showed the magnitude of the point estimate to be large, but due to the uncertainty, no statistically significant difference was observed. This was largely because the trial reported relatively few events and so lacked the statistical power to detect any difference in risk that might be present.

Overall completeness and applicability of evidence

Overall, the quality of the evidence was low (Atkins 2004), as the study included only a small number of women with high-grade VIN (n = 30) and outcomes were incompletely reported. We could not identify any prospective randomised trials that compared ablative with excisional techniques or observation, or both, so no definitive conclusions can be drawn with respect to the optimal surgical technique for the surgical management of women with high-grade VIN.

The single identified RCT did not investigate response to treatment, long-term disease recurrence or progression to vulval cancer. The absence of QoL and sexual function data do not allow for any firm conclusions to be drawn in these respects.

Quality of the evidence

We reviewed one RCT assessing only 30 participants that evaluated two types of surgical procedure for the treatment of women with high-grade VIN. All participants received the treatment to which they were allocated, with no loss to follow up being reported. The trial was not adequately powered to detect differences in disease recurrence or adverse events, especially as follow up was for only one year (disease recurrence). QoL, response to treatment, recurrence on long-term follow up and sexual function in participants were inadequately documented. Therefore, from the included RCT, we cannot reach any definitive conclusions about the benefit of either type of surgery.

The trial was at low risk of bias. The only obvious risk of bias was from the uncertainty as to whether outcome assessors were blinded to the type of treatment that participants received. The authors did not estimate a hazard ratio, which is the best statistic by which to summarise the difference in risk between two treatment groups over the duration of a trial when there is 'censoring' (i.e. the time to disease recurrence is unknown for some women as they were still disease free at the end of the trial), but given that all participants were followed up for one year, an estimate at this time interval is probably acceptable and is unlikely to cause any major bias.

Few women experienced disease recurrence or adverse events, and outcomes were incompletely reported, so there is a need for more data to ensure higher-quality evidence.

The two treatments examined in this review were both ablative methods, so it was not possible to compare ablative with excisional techniques or observation. Most of the evidence currently available is from non-randomised non-controlled retrospective case series with heterogeneous data sets, which do not allow for comparison. The main methodological limitations of the currently available studies are listed below.

1. Non-use of updated disease classification: in 2004, the ISSVD classification was devised, which excluded VIN 1. Currently, VIN refers to high grade VIN and includes VIN 2 & 3 according to the old grading system. However, the above-mentioned RCT and various other retrospective studies have continued with the use of the old histological classification.
2. Lack of standardisation in the recording of outcome measures negates the comparison of observational studies. The clinical heterogeneity of VIN, uncontrolled and differing treatment modalities, short-term follow up and the varied health professionals involved in the management of VIN severely restrict comparison between studies.
3. Failure to define participants who had received previous multiple treatments with various modalities and the subsequent histological outcomes, which would aid the assessment of a treatment modality in the long term.
4. Difficulty in defining recurrence: the nature of the disease and its associated high risk of recurrence accentuates the difficulty in differentiating between disease persistence and disease recurrence.

Potential biases in the review process

We performed a comprehensive search, including a thorough search of the grey literature; all references were sifted and data extracted by two reviewers independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence, we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias (i.e. studies that did not find the treatment to have been effective may not have been published). We were unable to assess this possibility as the analyses were restricted to the results of a single trial.

Agreements and disagreements with other studies or reviews

The exhaustive literature search identified only one RCT. One systematic review was identified that included 68 studies involving a total of 1921 women treated with surgery for VIN (van Seters 2005). The aim of this systematic review was to assess both the risk of progression of VIN III in untreated women and the effect of surgical treatment in relation to recurrences and progression of VIN III. After conducting a thorough search of the literature in November 2004, the authors' criteria for inclusion were: (1) articles written in English, German or French; and (2) data, clearly retrievable, on the surgical treatment, progression or regression, or all three, of VIN III. Case histories were excluded, except those concerning the regression or progression of VIN III. This review included studies of various designs, mainly retrospective, and did not include any RCTs with the exception of that included in this review (von Gruenigen 2007). The authors reported recurrences after vulvectomy (n = 613) in 19% of participants, after partial vulvectomy (n = 62) in 18%, after local excision (n = 808) in 22%, after laser vaporisation (n = 253) in 23% and after cryocoagulation (n = 16) in 56%. There were no statistically significant differences between recurrences after vulvectomy, partial vulvectomy, local excision and laser vaporisation. Recurrences were significantly lower after free surgical margins than after involved surgical margins (17% of 291 women versus 47% of 189 women, P value < 0.001). A total of 215 invasive vulvar carcinomas (6.5%) were found. There were 107 occult carcinomas (3.2%), and 108 carcinomas (3.3%) were diagnosed during follow up after treatment. In untreated women, the progression rate was found to be 9%.

Numerous studies have also since been published (Athavale 2008; McFadden 2009; Polterauer 2009), which contribute to the available reported non-randomised, non-controlled, retrospective data. Consequently, most of these studies were at a very high risk of bias as they were prone to selection bias or were not scientifically sound as a concurrent comparison was not available.

Two studies suggest a decrease in the age of women diagnosed with VIN probably due to increased awareness, and an absolute increase in incidence (van Seters 2005; von Gruenigen 2007). Participant characteristics, such as smoking and the presence of multicentric disease, were found to be related to a diagnosis of VIN in some studies (Athavale 2008; von Gruenigen 2007). All authors suggest that treatment was performed not only for the relief of symptoms, but also to remove the lesion for the purpose of cosmesis, and exclude or prevent progression to invasive disease, or both. One systematic review and one large retrospective case note series quote the incidence of symptoms such as pain and pruritis to be 60% to 85% in women with VIN (Jones 2005; van Seters 2005).

The therapeutic efficacy of an excisional procedure (LEEP) compared with ablation (CO_2 laser surgery) was studied in 28 women with VIN in an open trial where half the lesional area received either treatment (Ferenczy 1994). Treatment results are reported for the 25 women who were compliant both with their short-term (6 to 24 weeks) and longer-term (9 to 26 months, mean 12 months) follow-up schedule. At each visit, each woman received a physical and colposcopic examination, and a biopsy was obtained to obtain histological ascertainment of the disease in those in whom disease recurred.

A complete response was arbitrarily defined as no clinically visible disease at nine months after the last treatment (maximum six treatment sessions). Women with recurrent disease at nine months or earlier were considered non-responders. Of the 25 women who were compliant with a minimum of nine months follow up, a complete response at nine months or longer was observed in 12 of 25 (48%) women after a single laser/LEEP treatment, and 7 of 13 (53%) who experienced recurrence after a single treatment became disease free for nine months or longer after two to six (mean three) treatments with CO_2 laser surgery/LEEP. The linear extent of the lesional area in 11 of the 12 women who responded after a single laser/LEEP was 6 cm^2 or less, whereas all but one woman in the multiple treatment group (mean three) had lesions larger than 6 cm^2. Most recurrences (86%) were observed at the first six-week post-treatment visit, and the remaining 14% developed between four and six months. Recurrence rates were similar between the LEEP- and CO_2 laser-treated areas (P value = 0.5). This study reported an overall complete response rate of 48%, with a recurrence rate of 52% after either a single LEEP or laser treatment. The potential advantages of LEEP over CO_2 laser surgery include lower cost and greater accuracy of lesion excision. Occult cancers are also more likely to be detected after an excisional technique for treatment rather than after ablation.

This trial of Ferenczy 1994 did not randomise participants to either treatment, but either side of the lesion was assigned to one of the two treatments by computer and the randomisation numbers appeared on each woman's trial record. Ten of the 25 women received both treatments prior to the nine-month follow-up assessment, with many of the recurrences observed at the first six week follow up. It is therefore not possible to assess the benefits of either treatment in terms of recurrence. This trial was therefore excluded from our analyses.

In a recent paper by Frega 2013, 80 women with high-grade VIN were enrolled in a prospective study to compare the complete response rate, recurrence rate and risk factors for relapse following treatment with 5% imiquimod or surgical excision with a cold knife. All women were followed up at six-monthly intervals for five years. Multifocal lesions and VIN 3 were associated with a higher risk of relapse. The recurrence rate was statistically higher in the surgically treated group, but the relapse rate was higher in the imiquimod group. The overall complete response rate was higher in the surgical group, thus indicating that this modality of treatment was more favourable when considering the outcomes relapse and complete response rates. Kushnir 2013 retrospectively reviewed the use of argon beam coagulation(ABC) for the first time in 29 patients for the treatment of multifocal VIN3. The advantages of

ABC were cosmesis with preservation of vulval anatomy allowing multiple treatments. The recurrence rate was 48.3% at one year of follow up.

One prospective observational study (Jones 2005) comparing surgical excision and laser ablation in 405 women with VIN was unable to draw reliable conclusions. This study reported that the clinical heterogeneity of VIN, uncontrolled and differing treatment modalities, short-term follow up, and the various physician specialties involved in the management of women with VIN severely restricted comparison between different treatment methods. To further illustrate this, of the 405 women in the study, 194 had an initial excisional treatment, of whom 34% (95% CI 28% to 41%) required further treatment, whereas of the 118 women undergoing initial laser vaporisation, 39% (95% CI 31% to 48%) required further treatment (P value = 0.4). A small number of women with extensive disease (sometimes involving almost the entire vulva) were deliberately managed with two or more treatments, often combining excisional and laser vaporisation techniques. Other treatments included 5-fluorouracil and imiquimod. Of the 198 treated unifocal lesions, 69% (95% CI 62% to 75%) received a single treatment, whereas a smaller proportion of 120 treated multifocal lesions (58%, 95% CI 49% to 67%) received a single treatment (P value = 0.05).

To assess the degree of agreement between preoperative vulva biopsy findings and the outcomes of surgery in women with VIN 2 and VIN 3 in one study, 186 consecutive women with VIN 2/3 were observed (Polterauer 2009). These women were treated with local wide excision or skinning vulvectomy. VIN 2 and 3 were correctly diagnosed by preoperative vulva biopsy in 56% (29/52) and 88% (118/134) women, respectively. Underdiagnosis occurred in 44% (23/52) and 12% (16/134) of preoperative vulva biopsies, with an occult cancer rate of 4% (2/52) and 12% (16/ 134) for VIN 2 and 3, respectively. Complete resection was achieved in 43% (80/186) of women. The presence of multifocal VIN was the only factor that was associated with incomplete resection in the study population under univariate and multivariate analyses (P value = 0.001). In another study, preoperative vulval biopsies failed to exclude early stromal cancer (7%) in a series of 48 women treated using skinning vulvectomy (Rettenmaier 1987). A recent study reviewed the histological reports of 1309 specimens from 802 women and analysed the proportional risk of metachronous or subsequent squamous cell carcinoma of the vulva (VSCC) associated with pre-malignant conditions of the vulva (Eva 2009). Five hundred and eighty women had biopsy specimens containing a pre-malignant pathological condition, which was classified as either differentiated VIN, usual VIN, Lichen scleroses or squamous hyperplasia. The results showed a significant association between the presence of differentiated VIN and the risk of developing VSCC, with an odds ratio of 15.3 compared with an odds ratio of 0.5 for usual VIN and an odds ratio of 0.6 for Lichen scleroses

The recurrent nature of VIN indicates the possible need for multiple treatments, which can alter the cosmetic appearance of the vulva. Case studies suggest that following vulval surgery women report a reduction in sexual function and global QoL (Andersen 1983). The psychological component is further impacted by the possibility of underlying cancer, which recurs with every treatment. A study conducted by Likes 2007 examined sexual function after vulvectomy. This study in 43 women concluded that older age and more-extensive vulvar excision were associated with poorer sexual function and QoL in women following surgical treatment for VIN.

A small prospective pilot study in eight women found that careful observation is not a realistic option for most of those with a new diagnosis of VIN 2/3 (McFadden 2009): a majority will eventually require surgical treatment. In addition, VIN appears to have an adverse impact on QoL and sexual functioning in these women. This led to the authors abandoning plans for a RCT of initial observation versus immediate primary surgical treatment in women with VIN.

AUTHORS' CONCLUSIONS

Implications for practice

The included trial lacked statistical power due to the small number of women in each group and the low number of observed events. The absence of reliable evidence regarding the effectiveness and safety of the two surgical techniques for the management of VIN therefore precludes the drawing of any definitive conclusions.

Implications for research

Further retrospective case series are unlikely to reveal significant new insights into the management of women with VIN. Good-quality prospective multi-centre randomised trials are required, and there is a need to examine excisional surgical techniques and observation as well as ablative techniques. One trial that is currently recruiting participants with the aim of comparing primary imiquimod therapy with surgical excision will report results in 2016 (PITVIN 2013). It is essential that this and other trials are adequately powered to allow for a satisfactory comparison of outcomes. Future trials should report long-term outcomes for a recommended duration of two to five years to allow for the assessment of treatment response, recurrence and progression to vulval cancer. Definitions of disease persistence, recurrence and the participants must be standardised for the purposes of the trial. QoL and sexual function scores using appropriate validated scales or tools should be considered as outcomes in women with high-grade VIN receiving these surgical interventions in future trials. These outcomes are extremely important and may also contribute to the psychological well-being of women with VIN. The results of an observational study that is looking at reported symptoms

following surgery for vulvar disease are still awaiting psychometric analysis for use in future trials (Senn 2013).

ACKNOWLEDGEMENTS

We thank Chris Williams and Jo Morrison for clinical and editorial advice, Jane Hayes for designing the search strategy, and Gail Quinn and Clare Jess for their contribution to the editorial process. We thank the referees for their helpful comments and Dr Heidi Frasure and her clinical colleagues in Ohio, USA, for providing us with important data on women with high-grade VIN. We would like to acknowledge assistance from Miss Amanda Tristam, Senior Lecturer in gynaecological oncology, Cardiff University, and Mr Raj Naik, Consultant Gynaecological Oncologist, Queen Elizabeth Hospital, Gateshead, UK, as experts contacted for information on ongoing trials.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, the National Health Service or the Department of Health

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

von Gruenigen 2007

Methods	Multicentre randomised controlled trial. Age (50 years or younger and older than 50 years) and site location were used as stratification variables in the randomisation assignment
Participants	30 women with high-grade vulval intraepithelial neoplasia (VIN) of a total of 110, which included those with VIN 1 and all-grade vaginal intraepithelial neoplasia; 16 of the 30 women with high-grade VIN were randomised to carbon dioxide laser surgery and 14 women to ultrasonic surgical aspiration
Interventions	**Interventions:** **Carbon dioxide laser surgery:** Depth of tissue destruction was 1 mm in non-hairy vulvar regions and 3 mm in hairy vulvar regions **Ultrasonic surgical aspiration:** Surgery was performed with the Cavitron Ultrasonic Surgical Aspirator Excel System (Valley-lab, Boulder, Colorado, USA). The handheld tool vibrates and contains separate irrigation and suction channels. Lesions were removed to the reticular layer of the dermis Surgeries were performed in an outpatient setting, with participants given standard discharge instructions regarding postoperative care. The use of topical postoperative symptom control therapies (e.g. silver sulfadiazine) were ordered at the discretion of the attending physician All participants were seen preoperatively and treated by one of three gynaecological oncologists
Outcomes	• Recurrence (dysplasia) • Pain (visual analogue scale) • Presence of scarring • Infection • Dysuria, burning • Adhesions • Abnormal discharge • Eschar
Notes	Participants were followed up quarterly for a year. Fifty-three per cent of participants treated in this study had received prior therapy for intraepithelial disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Blocked randomization was carried out by a computer-generated table of random numbers corresponding to treatment assignment"

Allocation concealment (selection bias)	Low risk	"Randomization assignment was given to the treating physician by personnel not involved in the patient's medical care"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Percentage analysed: 30/30 (100%).
Selective reporting (reporting bias)	Low risk	It seems unlikely that outcomes were selectively reported as trial authors provided us with data for VIN 2 or higher-grade women on request
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bruchim 2007	This study was a retrospective non-randomised non-controlled case-series evaluation
Ferenczy 1992	Abstract that was later published in full in 1994 and is one of the excluded studies in the review (Ferenczy 1994)
Ferenczy 1994	This study was an RCT. Each participant had half the lesional area treated with CO_2 laser excision/vaporisation and the other half was electro-excised/fulgurated. However, 10 of the areas were treated with both LEEP and CO_2 laser after relapse prior to the 9-month assessment. Consequently, the primary objective could not be assessed in the treatment arm. The trial also included women with coexisting condylomata of the vagina (n = 5) or intraepithelial neoplasia of the cervix (n = 16)
Hillemanns 2005	This study was a retrospective case note analysis of 93 cases, eight of which were VIN 1. The treatment methods were subject to selection bias and were based on surgeon choice. Treatment failure, persistence of VIN and recurrence are not well defined
Jones 1994	This study was a retrospective case note analysis to assess the outcome of untreated VIN in relation to the development of cancer
Jones 2005	Prospective case series review of 405 cases.
van Seters 2005	This systematic review of surgical interventions in women with VIN3 did not include any RCTs with the exception of that included in this review (von Gruenigen 2007),

Characteristics of ongoing studies *[ordered by study ID]*

PITVIN 2013

Trial name or title	Primary imiquimod treatment versus surgery for VIN (PITVIN)
Methods	The primary purpose of this study is to evaluate the efficacy, defined as complete clinical response 6 months after the start of treatment, of Imiquimod compared to standard treatment (surgery) for VIN Study design: randomised design. Endpoint classification: safety/efficacy study. Intervention model: parallel assignment. Masking: open label. Study arms: • Experimental: primary treatment with imiquimod will be self-administered by participants for a period of 4 months with a possible extension to 6 months. A thin layer of imiquimod cream should be applied to the lesion and remain overnight without a cover. Application will be once a week for 2 weeks, then twice a week for the following 2 weeks and, if tolerated, 3 times a week for the last weeks. In case of severe side effects, the number of applications can be reduced; a treatment-free period of no more than 1 week is permitted. • Active comparator: primary surgery - the type of surgery (excision or ablation) will be based on clinical findings and the judgement of the surgeon. After excision, the specimen will be histologically analysed to assess resection margins and rule out invasion.
Participants	110 participants are to be enrolled; those enrolled to date have an age range of 18 to 90 years Inclusion criteria: • histologically confirmed VIN (only usual type, formerly VIN 2/3); • visible, measurable lesion(s); • contraception (for premenopausal women). Exclusion criteria: • evidence of invasion; • history of cancer or severe inflammatory dermatosis of the vulva; • pregnancy, lactation; • immunodeficiency; • any treatment for VIN within the previous 3 months; • known hypersensitivity to imiquimod.
Interventions	• Drug: imiquimod • Procedure: surgery (more specifically excision/ablation)
Outcomes	Primary outcome • Complete clinical response at 6 months (no clinical evidence of vulvar lesion, i.e. 100% reduction in primary lesion size). Secondary outcomes • Partial/non-response/lesion size at 6 and 12 months: vulvar lesions will be described, measured with callipers, mapped and photographed. Digital photos will be analysed using a computer programme (ImageJ) to calculate the total lesion size in cm^2. Results will be classified as: no response (reduction in lesion size of 25% or less), weak partial response (26% to 75% reduction), strong partial response (76% to 99% reduction) and complete response (100% reduction). • Histological response at 6 months: at baseline, punch biopsies will be taken from the affected areas. The site of the initial biopsy will be photo documented to ensure that the follow-up biopsy at 6 months is taken from the same site. Histological results will be classified as response - complete disappearance of usual-

	type VIN or reduction to VIN 1 - or no response. All biopsy samples will be analysed independently by two experienced gynaecological pathologists unaware of the treatment allocation. • Extent of surgery: the number, types and extent of surgical procedures will be recorded. The extent of surgery will be recorded as total operated lesion size (in cm^2, as measured on preoperative photographs) and relative operated lesion size (percentage of operated lesion size compared with the original pretreatment lesion size). • HPV status at 6 and 12 months: HPV status will be measured with the qualitative cobas® HPV Test (Roche) and the APTIMA® HPV assay (Gen-Pro).
Starting date	June 2013
Contact information	Gerda Trutnovsky, MD. Email address: gerda.trutnovsky@medunigraz.at
Notes	

Senn 2013

Trial name or title	A new participant-reported outcome instrument to assess symptom experience in women with vulvar neoplasms (WOMAN-PRO)
Methods	Observational study
Participants	Postsurgery symptom experience in women with VIN or vulvar cancer Inclusion criteria: • over 18 years old; • able to read and write German; • diagnosed with vulvar neoplasms; • treated with vulval surgery during the prior 6 months. Exclusion criteria: • cognitive impairment; • participant concurrently under psychiatric treatment or terminally ill.
Interventions	Creating and validating a participant-reported outcome instrument to assess symptom experience related to surgical wounds in women with vulvar neoplasms - a mixed methods study
Outcomes	Postsurgery complications in women with vulvar neoplasms (VIN and vulvar cancer) are still high and an instrument assessing participant self-reported post-vulval surgery symptom experiences is missing. The study aims to develop and validate a postoperative instrument to assess symptom experiences in women with vulvar neoplasms. In this mixed-method project, 20 women were interviewed, the WOMAN-PRO instrument was developed, and content validity was tested by 6 experts and 10 participants. The instrument's psychometric properties and the prevalence of symptoms will be examined in a cross-sectional study in the University Hospitals Munich, Freiburg, Berlin, Düsseldorf (Germany), Zurich, Basel, Berne, and the Cantonal Hospital St. Gallen (Switzerland) (n = 150). The goal of this project is that symptom assessment becomes a standard component of clinical practice (to promote the early detection and treatment of symptoms) and research
Starting date	January 2009
Contact information	Prof. Dr. Rebecca Spirig, Institute of Nursing Science, University of Basel

Senn 2013 (*Continued*)

Notes	

DATA AND ANALYSES

Comparison 1. Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease recurrence after 1 year follow-up	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2 Subjective pain	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Dysuria or burning	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4 Infection (yeast, UTI, other)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5 Abnormal discharge	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6 Eschar	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 1 Disease recurrence after 1 year follow-up.

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 1 Disease recurrence after 1 year follow-up

Study or subgroup	Laser n/N	USA n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
von Gruenigen 2007	7/16	4/14		1.53 [0.56, 4.15]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 7 (Laser), 4 (USA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.2. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 2 Subjective pain.

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 2 Subjective pain

Study or subgroup	Laser N	Mean(SD)	USA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
von Gruenigen 2007	16	44.2 (35.2)	14	45.9 (34.8)		-1.70 [-26.80, 23.40]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						

Analysis 1.3. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 3 Dysuria or burning.

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 3 Dysuria or burning

Study or subgroup	Laser n/N	USA n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
von Gruenigen 2007	3/16	4/14		0.66 [0.18, 2.44]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 3 (Laser), 4 (USA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.4. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 4 Infection (yeast, UTI, other).

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 4 Infection (yeast, UTI, other)

Study or subgroup	Laser n/N	USA n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
von Gruenigen 2007	2/16	2/14		0.88 [0.14, 5.42]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (Laser), 2 (USA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

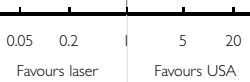
Analysis 1.5. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 5 Abnormal discharge.

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 5 Abnormal discharge

Study or subgroup	Laser n/N	USA n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
von Gruenigen 2007	2/16	1/14		1.75 [0.18, 17.29]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (Laser), 1 (USA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 1.6. Comparison 1 Carbon dioxide laser versus ultrasonic surgical aspiration, Outcome 6 Eschar.

Review: Surgical interventions for high-grade vulval intraepithelial neoplasia

Comparison: 1 Carbon dioxide laser versus ultrasonic surgical aspiration

Outcome: 6 Eschar

Study or subgroup	Laser n/N	USA n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
von Gruenigen 2007	2/16	2/14		0.88 [0.14, 5.42]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (Laser), 2 (USA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE 1950 to December 2013

1. (VIN or VIN2 or VIN3).mp.
2. (vulva* adj5 intraepithelial neoplasia).mp.
3. 1 or 2
4. exp Vulva/
5. vulva*.mp.
6. 4 or 5
7. exp Precancerous Conditions/
8. (pre-cancer* or precancer*).mp.
9. dysplasia.mp.
10. unifocal.mp.
11. multifocal.mp.
12. exp Carcinoma in Situ/
13. carcinoma in situ.mp.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. 3 or 15

key: mp=title, original title, abstract, name of substance word, subject heading word

Appendix 2. EMBASE search strategy

EMBASE Ovid 1980 to December 2013

1. (VIN or VIN2 or VIN3).mp.
2. (vulva* adj5 intraepithelial neoplasia).mp.
3. 1 or 2
4. exp Vulva/
5. vulva*.mp.
6. 4 or 5
7. exp Precancer/
8. (pre-cancer* or precancer*).mp.
9. dysplasia.mp.
10. unifocal.mp.
11. multifocal.mp.
12. exp Carcinoma in Situ/
13. carcinoma in situ.mp.
14. 8 or 11 or 7 or 13 or 10 or 9 or 12
15. 6 and 14
16. 3 or 15

key: mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 3. CENTRAL search strategy

CENTRAL Issue 11, 2013

1. (VIN or VIN2 or VIN3):ti,ab,kw
2. (vulva* near/5 intraepithelial neoplasia):ti,ab,kw
3. (#1 OR #2)
4. MeSH descriptor Vulva explode all trees
5. vulva*
6. (#4 OR #5)
7. MeSH descriptor Precancerous Conditions explode all trees
8. pre-cancer* or precancer*
9. dysplasia
10. unifocal
11. multifocal
12. MeSH descriptor Carcinoma in Situ explode all trees
13. carcinoma in situ
14. (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
15. (#6 AND #14)
16. (#3 OR #15)

key: ti,ab,kw = title, abstract, keyword

WHAT'S NEW

Last assessed as up-to-date: 3 December 2013.

Date	Event	Description
27 March 2014	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2011

Date	Event	Description
8 January 2014	New search has been performed	New search conducted December 2013
8 January 2014	New citation required but conclusions have not changed	Trial data information added

CONTRIBUTIONS OF AUTHORS

LP, SK and AN drafted the clinical sections of the review; AB and HOD drafted the methodological and statistical sections of the review. All authors agreed the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Restriction to RCTs

In the protocol we stated that we expected to find few RCTs of surgical interventions; we intended to include the following types of non-randomised studies with concurrent comparison groups:
quasi-randomised trials, non-randomised trials, prospective and retrospective cohort studies, and case series of 30 or more participants.
The search strategy identified one RCT that met our inclusion criteria, so we restricted the review to RCTs as they provide the best level of evidence. We were also concerned about the threat of selection bias in non-randomised studies.

Searches

In the protocol, we stated:
"The main investigators of any relevant ongoing trials will be contacted for further information, as will any major co-operative trials groups active in this area."
However, we did not find any relevant ongoing trials or active trials groups, so we did not make these contacts.

Risk of bias

As the review was restricted to RCTs, risk of bias was not examined in non-randomised studies, as had been proposed in the protocol.

Time-to-event outcome data

Time-to-event outcome data were not reported in the trial of von Gruenigen 2007, so the sections in the protocol which discussed the handling of data for survival outcomes were removed as they were unnecessary:

Data synthesis

We identified only one included trial so it was not possible to perform meta-analyses. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses. The following sections of the protocol were therefore removed:

- assessment of heterogeneity;
- assessment of reporting biases;
- data synthesis;
- subgroup analysis and investigation of heterogeneity;
- sensitivity analysis;
- subgroup analysis and investigation of heterogeneity;
- sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinoma in Situ [pathology; *surgery]; Lasers, Gas [*therapeutic use]; Precancerous Conditions [pathology; *surgery]; Randomized Controlled Trials as Topic; Suction [methods]; Ultrasonic Therapy [instrumentation; *methods]; Vulvar Neoplasms [pathology; *surgery]

MeSH check words

Adult; Female; Humans