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Primary groin irradiation versus primary groin surgery for early vulvar cancer (Review)

van der Velden J, Fons G, Lawrie TA

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Primary groin irradiation versus primary groin surgery for early vulvar cancer.
Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224.
DOI: [10.1002/14651858.CD002224.pub2](https://doi.org/10.1002/14651858.CD002224.pub2).

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[Intervention Review]

Primary groin irradiation versus primary groin surgery for early vulvar cancer

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 2, 2016.

Citation: van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No.: CD002224. DOI: [10.1002/14651858.CD002224.pub2](https://doi.org/10.1002/14651858.CD002224.pub2).

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ABSTRACT

Background

Despite changes in technique, morbidity after surgery for vulvar cancer is high and mainly related to the groin dissection. Primary radiotherapy to the groin is expected to result in lower morbidity. However, studies on the efficacy of primary radiotherapy to the groin in terms of groin recurrences and survival show conflicting results.

Objectives

To determine whether the effectiveness and safety of primary radiotherapy to the inguino-femoral lymph nodes in early vulvar cancer is comparable with surgery.

Search methods

We searched The Cochrane Gynaecological Cancer Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE from 1966 to July 2010 for the latest update in 2011. We searched again in January 2016 and no additional trials were identified.

Selection criteria

We selected randomised clinical trials (RCTs) comparing inguino-femoral lymph node dissection and primary radiotherapy of the inguino-femoral lymph nodes for patients with early squamous cell cancer of the vulva.

Data collection and analysis

Two reviewers independently assessed study quality and extracted results. Primary outcome measures were the incidence of groin recurrences, patient survival and morbidity.

Main results

No new RCTs were identified by the updated search. Out of twelve identified papers only one met the selection criteria. From this one small RCT of 52 women, there was a trend towards increased groin recurrence rates (relative risk (RR) 10.21, 95% confidence interval (CI) 0.59 to 175.78), lower disease-specific survival rates (RR 3.70, 95% CI 0.87 to 15.80), less lymphoedema (RR 0.06, 95% CI 0.00 to 1.03) and fewer life-threatening cardiovascular complications (RR 0.08, 95% CI 0.00 to 1.45) in the radiotherapy group. Primary surgery was associated with a longer hospital stay than primary groin irradiation (RR 0.28, 95% CI 0.13 to 0.58).

Authors' conclusions

Primary radiotherapy to the groin results in less morbidity but may be associated with a higher risk of groin recurrence and decreased survival when compared with surgery. Due to the small numbers in this trial and criticisms regarding the depth of radiotherapy applied, corroboration of these findings by larger RCTs using a standardised radiotherapy method, is desirable. However, until better evidence is available, surgery should be considered the first choice treatment for the groin nodes in women with vulvar cancer. Individual patients not physically able to withstand surgery may be treated with primary radiotherapy.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence that radiotherapy works as well as surgery for treating groin nodes in early vulvar cancer.

Cancer of the vulva is mainly a disease of elderly women. Surgery involves removal of the tumour and surrounding lymph nodes, occasionally followed by radiotherapy. Although survival rates are high if the tumour is found early enough, removal of the lymph nodes causes odema (swelling), particularly in the legs. Wound healing and psychosexual problems are also common. While radiotherapy may be effective in the short term, there is not enough evidence from trials to show that it is as effective as surgery in preventing tumour regrowth in the lymph nodes of the groin.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Primary Groin Radiotherapy compared to Primary Groin Surgery for Early Vulvar Cancer

Primary Groin Radiotherapy compared to Primary Groin Surgery for Early Vulvar Cancer

Patient or population: patients with Early Vulvar Cancer

Settings: Hospital

Intervention: Primary Groin Radiotherapy

Comparison: Primary Groin Surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primary Groin Surgery	Primary Groin Radiotherapy				
Groin recurrence	Study population ¹		RR 10.21 (0.59 to 175.78)	52 (1 study)	⊕⊕⊕⊕ low 2,3	See footnotes
	Low risk population ¹					
	20 per 1000	204 per 1000 (12 to 1000)				
Disease specific mortality	Study population		RR 3.70 (0.87 to 15.8)	52 (1 study)	⊕⊕⊕⊕ low 2,3	See footnotes
	80 per 1000	296 per 1000 (70 to 1000)				
	Low risk population					
	100 per 1000	370 per 1000 (87 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ The control risk is of groin recurrence after surgery is assumed to be 2% based on incidence of groin recurrence after surgery by van der Velden 1996.
- ² The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.
- ³ Radiotherapy was applied to a depth of 3cm only. The mean depth of deeper groin nodes is estimated at 4.5-6.1cm, therefore the radiotherapy dose used in this trial may have been insufficient for deep nodes.

BACKGROUND

Description of the condition

Vulval cancer is predominantly a disease of elderly women with a mean age at diagnosis of approximately 70 years. The incidence in industrialised countries is around 3 per 100,000 women per year (UKStats 2000). According to population-based studies, approximately 75% of vulvar malignancies are squamous cell carcinomas (Platz 1995; Van der Velden 1996) although this figure may be as high as 90% (de Hulle 2004). Primarily the tumour metastasises to the inguinofemoral lymph nodes (Hacker 1994; Morley 1976).

With the older (pre-1988) clinical International Federation of Gynecology and Obstetrics (FIGO) staging, early vulvar cancer was categorised as stage I or II disease. After 1988 the FIGO staging became pathological. However, for the purposes of this review, we used the TNM classification of malignant tumours where early vulvar cancer is defined as cancer in which the primary tumour is confined to the vulva without clinically suspicious groin nodes or clinical suspicion of distant metastases i.e. patients with cT1 to T2, N0 to T1, M0 tumours (see Appendix 1 for staging classifications).

Pre-treatment risk of groin lymph node metastases appears to be of the order of 15% for T1 to T2 N0 patients (Sedlis 1987) and 10% for T1 N0 patients (Manavi 1997; Sedlis 1987; Van der Velden 1996). Groin lymph node metastases are associated with a poorer prognosis (Homesley 1991).

Description of the intervention

Current standard treatment for patients with clinical T1 to T2 N0 M0 tumours is primary surgery, followed by radiotherapy if indicated (Hacker 1993). Surgery usually consists of radical excision of the tumour and bilateral inguinal and femoral lymph node dissection. This treatment policy results in excellent survival figures, and the incidence of tumour recurrences in the groin after surgery in patients with clinically non-suspicious (N0) lymph nodes is often reported as less than 2% (Petereit 1993, Stehman 1992; Van der Velden 1996). Unfortunately, surgery is associated with high complication rates: wound healing problems are observed in a large proportion of patients, and in the long term, lymphoedema and psychosexual complications are frequently seen. In one study, 49% of patients experienced wound breakdown and 27% experienced chronic lymphoedema following this radical surgery (Homesley 1991), however some studies report even higher figures. The high complication rates have prompted many investigators to look for less radical surgery and a more individualized approach (Hacker 1993). As morbidity is mainly related to the dissection of the inguinal-femoral lymph nodes, modifications in the surgical approach have been introduced into practice, specifically, a triple incision technique instead of an en-bloc resection, and a unilateral groin dissection instead of a bilateral groin dissection. These changes in surgical technique have been the subject of another Cochrane review (Ansink 1999). Recently the sentinel node technique has been introduced into the diagnostic workup and treatment of early vulvar cancer whereby sentinel nodes are identified using a radioactive tracer and blue dye, and removed (van der Zee 2008). In an observational study by van der Zee 2008, only 6 out of 259 women (2.3%) with T1 to T2 N0 vulvar cancer experienced a groin recurrence after a negative sentinel node was reported. Despite the changes in technique of groin dissection, morbidity is

still considerable for the group of patients who are not candidates for the sentinel node procedure.

Some investigators recommend radiotherapy for the primary treatment of groin lymph nodes in early vulvar cancer which has a lower risk of acute and late morbidity than primary surgery (Petereit 1993). Primary radiotherapy for the groin in early vulvar cancer results in less tumour recurrences in the groin compared with a 'wait and see' policy (Manavi 1997). Groin recurrence rates after primary radiotherapy range from 0% to 14% in non-randomised studies (NRS) (Hallak S 2007; Katz 2003, Manavi 1997, Perez 1998) which all have methodological shortcomings, e.g. data on early vulvar cancer often cannot be extracted separately from other stages of disease (Perez 1998; Petereit 1993), or non-standard surgical procedures have been used (Katz 2003). Similarly, reliable survival figures on primary radiotherapy for early vulvar cancer are scarce.

Why it is important to do this review

Clarity is needed on the role, if any, of primary radiotherapy to inguinofemoral lymph nodes in early vulvar cancer and how it compares to primary surgery with respect to recurrence, morbidity and survival rates.

OBJECTIVES

To determine whether the effectiveness and safety of primary radiotherapy to the inguinofemoral lymph nodes in early squamous cell carcinoma of the vulva is comparable with primary surgery.

METHODS

Criteria for considering studies for this review

Types of studies

All well-conducted RCTs comparing primary radiotherapy with primary surgery for clinical T1 to T2 N0 M0 vulvar cancer were considered for inclusion. As it was anticipated that only a very small number of RCTs exist on this topic, we examined NRS too. Contributions from these NRSs are considered in the Discussion section of this review.

Types of participants

Women diagnosed with early squamous cell carcinoma of the vulva i.e. clinical T1 to T2 N0 M0.

Types of interventions

Inguinal and femoral lymphadenectomy is defined as removal of all lymph node bearing fatty tissue between the inguinal ligament, the sartorius muscle and the adductor longus muscle, and dissection of the femoral lymph nodes located in the fossa ovalis medial to the femoral vein.

Radiotherapy to the groin is defined as radiotherapy to a volume including the inguinal and femoral lymph nodes. This volume is limited cranially by the inguinal ligament, medially by the fossa ovalis up to 2 cm lateral from the midline, laterally by the superior iliac spine and caudally by the crossing of the sartorius and adductor longus muscle (which means 6 cm caudal to the middle of the inguinal ligament). Dorsally this volume is limited by the level of the femoral vessels.

Types of outcome measures

Primary outcomes

- Recurrence - overall, and groin recurrence;
- Mortality - overall, disease specific, and mortality related to treatment;
- Morbidity/complications including severe life-threatening complications, wound healing, lymphoedema, thrombosis, infection, pain and psychosexual problems.

Secondary outcomes

- Length of hospital stay

Where possible, studies will be stratified according to radiotherapy dose and/or technique.

Search methods for identification of studies

Electronic searches

The Cochrane Gynaecological Cancer Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched (The Cochrane Library Issue 3, 2010) ([Appendix 2](#)). MEDLINE search (1966 to week 1, July 2010) ([Appendix 3](#)) using Mesh term 'vulvar neoplasms' and text word 'vulva' was performed. EMBASE search (1988 to week 28, 2010) ([Appendix 4](#)) using terms: vulvar neoplasm and vulva was performed. Publications on the effectiveness of primary radiotherapy treatment of cT1-2 N0-1 M0 squamous cell carcinoma of the vulva were selected. In addition, we used our own publication archives. We searched again in January 2016 and no additional trials were identified.

Searching other resources

We carried out a prospective handsearch of publications from 1986 to July 2010 on the treatment of vulvar cancer in the following journals: American Journal of Obstetrics and Gynecology, British Journal of Obstetrics and Gynaecology, Cancer, Gynecologic Oncology, Obstetrics and Gynecology and International Journal of Radiation Oncology Biology, Physics. In addition, the International Journal of Gynecologic Cancer has been handsearched from the first issue (1991 to July 2010). Publications that met the set criteria were selected. A further search was done by checking the reference lists of the relevant publications. The reference lists of textbooks on gynaecological cancer were also searched, as well as abstracts from the meetings of the Society of Gynecologic Oncologists, the British Gynaecological Cancer Society and The International Gynaecological Cancer Society, from 1989 to July 2010.

Data collection and analysis

Selection of studies

The original selection of studies was done independently by both JV and AA and included only one RCT ([Stehman 1992](#)). For this update JV and GF independently identified three NRSs ([Katz 2003](#), [Hallak S 2007](#), [Talaat 2009](#)) but no new RCTs.

Data extraction and management

For the methodology of the original review see [Appendix 5](#). For the update, we designed a new form to extract data. JV and TL independently extracted data for the only RCT ([Stehman 1992](#)) as

it had not been done in the original review. Any disagreements between reviewers were resolved by discussion.

Assessment of risk of bias in included studies

JV and TL independently assessed the risk of bias for the only eligible study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion.

1. Sequence generation (checking for possible selection bias)

We described for the included study the method used to generate the allocation sequence. We assessed the method as:

- Adequate (any truly random process, e.g. random number table; computer random number generator);
- Inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or;
- Unclear.

2. Allocation concealment (checking for possible selection bias)

We described for the included study the method used to conceal the allocation sequence. We assessed the method as:

- Adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- Inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- Unclear.

3. Blinding (checking for possible performance bias)

We described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We assessed the methods as:

- Adequate, inadequate or unclear for participants;
- Adequate, inadequate or unclear for personnel;
- Adequate, inadequate or unclear for outcome assessors.

4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for the included study the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), and reasons for attrition or exclusion where reported. We assessed methods as:

- Adequate;
- Inadequate;
- Unclear.

5. Selective reporting bias

We described for the included study how we investigated the possibility of selective outcome reporting bias. We assessed the methods as:

- Adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- Inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- Unclear.

6. Other sources of bias

We described for the included study any important concerns we had about other possible sources of bias.

Measures of treatment effect

Dichotomous data are presented as the summary risk ratio with 95% confidence intervals (CI) using [RevMan 2011](#).

RESULTS

Description of studies

Results of the search

Twelve studies were identified as potentially pertinent to this review (nine studies from the original search and three from the updated searches ([Hallak S 2007](#); [Katz 2003](#), [Hallak S 2007](#)). However, only one RCT was identified ([Stehman 1992](#)).

Included studies

One RCT was included ([Stehman 1992](#)). This was a small study of 52 patients with early vulvar cancer. For more details see [Characteristics of included studies](#).

Excluded studies

Eleven studies were excluded due to methodological shortcomings e.g. they were NRS: case-controlled and observational studies (for more details of these studies see [Characteristics of excluded studies](#)).

Risk of bias in included studies

[Stehman 1992](#) was the only RCT included and we consider it to be of low to moderate risk of bias. Randomisation was done in blocks and balanced across participating institutions. However, no details of allocation concealment are described. Patients and personnel could not be blinded to intervention group allocation for obvious reasons. Of the 58 patients initially randomised, six were withdrawn after randomisation due to incorrect staging (five) or due to the incorrect primary site (one), leaving 52 for analysis (27 in the radiotherapy group and 25 in the surgery group). Investigators had planned to recruit 300 patients but the trial was stopped early when 5 out of 27 patients in the radiotherapy group experienced groin recurrences. All pre-specified outcomes were addressed, although morbidity data were not clearly presented and could not all be extracted for comparison here. Patients in the radiotherapy group were slightly younger and had a better 'performance status', however we considered that these differences were unlikely to have impacted substantially on the findings.

Effects of interventions

See: [Summary of findings for the main comparison Primary Groin Radiotherapy compared to Primary Groin Surgery for Early Vulvar Cancer](#)

Recurrence

Groin recurrence occurred in 5 out of 27 women (18.5%) in the radiotherapy group compared with 0 out of 25 women (0%) in the surgery group. These numbers are small and do not reach significance on review analysis (RR 10.21; 95% CI 0.59 to 175.78).

Mortality/Survival

There was a trend towards better overall survival (10 deaths versus 3 deaths; RR 4.31, 95% CI 1.03 to 18.15) and better disease-specific survival in the surgery group (8 deaths versus 2 deaths; RR 3.70, 95% CI 0.87 to 15.80). One death in the surgery group occurred as a result of massive pulmonary embolism.

Morbidity

Lymphoedema occurred less in the radiotherapy group (none versus 7 patients; RR 0.06, 95% CI 0.00 to 1.03). There was a trend towards more severe life-threatening cardiovascular complications in the surgery group (none versus 5 patients; RR 0.08, 95% CI 0.00 to 1.45]. Primary surgery was associated with a longer hospital stay than primary groin irradiation (RR 0.28, 95% CI 0.13 to 0.58).

DISCUSSION

Vulvar cancer is a rare disease, therefore conducting RCTs on the treatment thereof is difficult. However, it becomes clear how important these RCTs are when one considers the shortcomings of the existing observational and case-control studies.

Summary of main results

Based on one small RCT reviewed here, there was no statistically significant difference in groin recurrence or disease-specific survival between the radiotherapy and surgery groups although the trend favours the surgery group. As expected, morbidity outcomes favoured the radiotherapy group.

Overall completeness and applicability of evidence

High quality evidence is sparse in this field. None of the outcomes addressed by this review have been answered completely by the available data. The controversy over the radiotherapy method and dose limits the applicability of the [Stehman 1992](#) study. See [Agreements and disagreements with other studies or reviews](#) below.

Although not many studies are available, it is obvious that morbidity after primary radiotherapy is low. Reversible grade I skin reactions are the main problem, while the incidence of lymphoedema is significantly less than reported after surgery. There is no doubt that additional problems after surgery such as infection and wound separation are not seen after radiotherapy. The occurrence of severe life-threatening cardiovascular complications occurred in five out of 25 patients (20%) in the surgery group in the [Stehman 1992](#) trial, reinforcing the risks associated with this radical procedure.

Agreements and disagreements with other studies or reviews

The incidence of groin recurrence was much higher in the [Stehman 1992](#) study compared with some NRS ([Manavi 1997](#), [Katz 2003](#)); however the risk of selection and other biases in these studies was high e.g. by selecting patients with a low pre-treatment risk of nodal metastases for radiotherapy. The study by [Stehman 1992](#) has been criticised in the radiotherapy literature ([Lanciano 1993](#); [Petereit 1993](#)) because the technique of radiotherapy applied was insufficient to sterilise subclinical lymph node metastases in the groin. The mean depth of the deeper groin nodes (the femoral group of nodes, under the fascia lata, at the level of the femoral vessels) is between 4.5 cm ([McCall 1995](#)) and 6.1 cm ([Koh 1993](#)). In [Stehman 1992](#), the radiotherapy was dosed at a depth of 3 cm and this suggests that many of the patients were under-dosed at the level of the deeper, femoral lymph nodes. This casts doubt on the reliability of the data.

AUTHORS' CONCLUSIONS

Implications for practice

Although primary radiotherapy for the groin results in less short term and long term morbidity compared with inguinal and femoral groin dissection, there is not enough evidence to prove that it is as effective regarding control of tumours in the groin. In the only RCT, tumour recurrence and survival were both better in the surgery arm overall, although the irradiation dose may have been inadequate. In daily practice this means that surgery is the first choice treatment for the groin lymph nodes in early vulvar cancer. When the condition of the patient is such that the increased risk of morbidity with

the use of surgery outweighs the chances of cure, then primary radiotherapy is a good alternative treatment.

Implications for research

The role of radiotherapy in primary groin treatment remains uncertain. There is a need for a large well-conducted RCT, comparing primary radiotherapy of adequate dose, depth and volume with primary surgery, to address this uncertainty. However, the debate about primary radiotherapy or primary surgery for the groin in early vulvar cancer is now definitely influenced by the outcome of the 'sentinel node' studies. In these studies, the area around the vulvar tumour is injected with a radioactive colloid. The first lymph node in the groin to pick up the radioactive colloid is considered the 'sentinel node'. It is hypothesised that the presence or absence of tumour involvement in this node will predict whether the remaining nodes in the groin are affected. When the predictive value of the 'sentinel node' is sufficiently high, 80% of T1-2 N0 vulvar cancers will not need treatment for the groin because of a negative sentinel node. However, when a positive sentinel node is found, primary radiotherapy may have a role to play. An observational study is currently underway on this subject, and a RCT comparing radiotherapy versus lymph node dissection for sentinel positive nodes in early vulvar cancer would be desirable.

ACKNOWLEDGEMENTS

Clare Jess and Gail Quinn provided editorial support. Dr P Eifel gave unpublished information from the study by [Katz 2003](#). We thank her for this information. L Uitterhoeve, radiotherapist, critically reviewed the original manuscript. We would like to thank Anca Ansink for all her work on previous versions of this review as an author.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Stehman 1992

Methods	Randomised controlled trial. No details on allocation concealment or blinding. Original study accrual goal was for 300 participants but only 58 were recruited. There were 6 post-randomisation exclusions. Study was stopped due to the high groin recurrence rate in the radiotherapy group.
Participants	52 patients with primary, previously untreated, squamous cell carcinoma of the vulva (T1-3 N0-1 M0). A radical vulvectomy had to suffice to remove the lesion; patients with T1 tumours were eligible only if there was vascular space involvement or if invasion > 5 mm; no suspicious lymph nodes (N0-1); no distant metastases. Needle aspiration was required if there was any concern over lymph node status. Excluded if: medically unfit for surgery, previous radiation therapy or chemotherapy, any previous malignancy other than non-melanoma skin cancer.
Interventions	Radiotherapy: radical vulvectomy followed by groin radiation therapy within 4 weeks of the operation. Dose 200 cGy/day, to a total of 50Gy over 5 weeks. Depth to 3 cm. Photon beam energy of 4-6 Me V, 50% with electrons. Surgical: radical vulvectomy with bilateral inguinal-femoral lymphadenectomy. Patients found to have microscopic evidence of nodal disease received radiotherapy to the affected side.
Outcomes	Site of recurrence; progression-free interval (defined as the time from study entry to physical or radiological evidence of disease recurrence or date last seen); survival (time from study entry to death or date last seen); adverse effects including wound complications, lymphoedema and length of hospitalisation. Groin recurrence: 5 out of 27(18.5%); Survival: overall 63% vs 88%; Disease specific: 67% vs 92%; Disease free interval: 68% vs 92%

Stehman 1992 (Continued)

Notes Three patients in the Rt group declined to complete the radiation therapy. None of these patients experienced groin recurrences during the course of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks balanced across institutions and T/N subgroup classification.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described. Blinding not possible for patient and personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were six post-randomisation exclusions, five due to incorrect staging and one due to incorrect primary site.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Unclear risk	Patients in the Rt group were slightly younger and had a better performance status.

Rt = radiotherapy

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Daly 1974	Non-randomised study. Insufficient numbers.
Edsmyr 1961	Non-randomised study. Incidence of groin recurrences cannot be analysed separately.
Hallak S 2007	<p>Retrospective observational study. 294 cases of vulvar cancer were given post-operative radiotherapy after standard surgery which included inguinal lymphadenectomy in only 27 cases. 110 patients had Stage I disease.</p> <p>Two separate inguinal fields were irradiated with combined photon (6MeV) and electron (12 MeV) beams. Dose 47.5 Gy to 54 Gy; depth: relative depth dose > 100 from 2 till 7 cm. Three different fraction schedules were used.</p> <p>Follow-up was for a minimum of 10 years. Overall, 127 recurrences were recorded (43%) - 15/110 patients with Stage 1 disease (14%). The 5-year survival of the Stage I group was 69% and relapse free survival (RFS) was 60%. RFS rate was not associated with the type of surgery performed (total/partial vulvectomy or local tumour excision) The inguinal relapse free rate was 75% both for patients treated with adjuvant inguinal irradiation without lymphadenectomy (n=201) and patients treated with primary lymphadenectomy ± inguinal irradiation (n=27). It was not possible to identify the inguinal relapse free rate for the stage I/II patients who had radiotherapy as sole treatment for the groins separately. Post-op complications were significantly more frequent in the subgroup undergoing lymphadenectomy.</p>
Henderson 1984	Non-randomised study. Incidence of groin recurrences cannot be analysed separately.

Primary groin irradiation versus primary groin surgery for early vulvar cancer (Review)

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Study	Reason for exclusion
Katz 2003	Retrospective review of 227 patients with vulvar cancer, including 14 cases given radiotherapy to inguinal nodes in T1-2 N0 M0 stage. Dose: 45 Gy; type: electrons and photons combined; depth: not stated (CT panning). Groin recurrence occurred in 0/14 cases. The majority of the patients in this surgery group had only a superficial (inguinal) lymph node dissection performed. This is a sub-optimal procedure and makes comparison difficult.
Leiserowitz 1997	Non-randomised study. Incidence of groin recurrences cannot be analysed separately.
Manavi 1997	Case-control study of T1 N0-1 M0 patients. Control = 'wait and see'. 65 patients received radiotherapy to inguofemoral nodes, 70 received no treatment to nodes. 5 patients had non-squamous cell carcinoma. No significant difference in relapse rates and survival. Radiotherapy dose: 60Gy; type: telecobalt; depth: 45 Gy at 5cm. Groin recurrence = 3/65 (4.6%) versus 7/70 (10%). "Low" morbidity: 5/65 (vaginal stenosis: 2, inguinal pain, recto-vaginal fistula, infection) versus 2/70 (vaginal stenosis). Survival overall = 91% (? disease specific; ? disease free).
Perez 1998	Observational study of 87 women with T1-2 N0-1 M0 vulvar cancer (7 with non-squamous cell carcinoma): 19/87 women received radiotherapy to inguofemoral lymph nodes. Dose: 50-70Gy; type: photons (electron boost); depth: at 4cm. Groin recurrence occurred in 2/19 cases (10.5%). No survival data.
Petereit 1993	Non-randomised study. Incidence of groin recurrences cannot be analysed separately in relation to early stage disease.
Pirtoli 1982	Non-randomised study. Site of recurrence not mentioned.
Talaat 2009	Retrospective series of 23 over 80 year old women with various stages of vulvar cancer. Insufficient numbers.

DATA AND ANALYSES

Comparison 1. Primary radiotherapy versus primary surgery to inguofemoral lymph nodes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence overall	1	52	Risk Ratio (M-H, Random, 95% CI)	3.70 [0.87, 15.80]
2 Groin recurrence	1	52	Risk Ratio (M-H, Fixed, 95% CI)	10.21 [0.59, 175.78]
3 Mortality - overall	1	52	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.96, 9.94]
4 Mortality - disease specific	1	52	Risk Ratio (M-H, Fixed, 95% CI)	3.70 [0.87, 15.80]
5 Mortality - related to treatment	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.26]
6 Morbidity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Lymphoedema	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Severe life-threatening cardiovascular complications	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.45]
7 Hospital stay > 12 days	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.13, 0.58]

Analysis 1.1. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 1 Recurrence overall.

Analysis 1.2. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 2 Groin recurrence.

Analysis 1.3. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 3 Mortality - overall.

Analysis 1.4. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 4 Mortality - disease specific.

Analysis 1.5. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 5 Mortality - related to treatment.

Analysis 1.6. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 6 Morbidity.

Analysis 1.7. Comparison 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes, Outcome 7 Hospital stay > 12 days.

APPENDICES

Appendix 1. TNM classification of vulvar cancer and corresponding FIGO staging

TNM Categories/FIGO Stages

Primary tumour = T

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- Tis/0: Carcinoma *in situ* (preinvasive carcinoma)
- T1/I: Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension
- T1a/IA: Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion no greater than 1 mm.
- T1b/IB: Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion greater than 1 mm.
- T2/II: Tumor confined to the vulva or vulva and perineum, more than 2 cm in greatest dimension
- T3/III: Tumor of any size with contiguous spread to the lower urethra and/or vagina or anus
- T4/IVA: Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, or is fixed to the pubic bone

Regional lymph nodes = N

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1/III: Unilateral regional lymph node metastasis
- N2/IVA: Bilateral regional lymph node metastasis

Distant metastasis = M

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1/IVB: Distant metastasis (including pelvic lymph node metastasis)

Appendix 2. CENTRAL search strategy

CENTRAL Issue 3 2010 2006-2010

- #1 MeSH descriptor Vulvar Neoplasms explode all trees
- #2 vulva* near/5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*)
- #3 (#1 OR #2)
- #4 MeSH descriptor Radiotherapy explode all trees
- #5 Any MeSH descriptor with qualifier: RT
- #6 radiotherap*
- #7 irradiation
- #8 radiation

#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Surgical Procedures, Operative explode all trees
#11 Any MeSH descriptor with qualifier: SU
#12 lymphadenectom*
#13 lymph node* near/5 (excis* or dissect*)
#14 surg*
#15 (#10 OR #11 OR #12 OR #13 OR #14)
#16 (#3 AND #9 AND #15)
#17 (#16), from 2006 to 2010

Appendix 3. MEDLINE search strategy

MEDLINE Ovid 2006 to July week 1 2010

- 1 Vulvar Neoplasms/
- 2 (vulva* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*)).mp.
- 3 1 or 2
- 4 exp Radiotherapy/
- 5 radiotherapy.fs.
- 6 radiotherap*.mp.
- 7 irradiation.mp.
- 8 radiation.mp.
- 9 4 or 5 or 6 or 7 or 8
- 10 exp Surgical Procedures, Operative/
- 11 surgery.fs.
- 12 lymphadenectom*.mp.
- 13 (lymph node* adj5 (excis* or dissect*)).mp.
- 14 surg*.mp.
- 15 10 or 11 or 12 or 13 or 14
- 16 3 and 9 and 15
- 17 limit 16 to yr="2006 - 2010"

key:

mp=title, original title, abstract, name of substance word, subject heading word, unique identifier

fs=floating subheading

Appendix 4. EMBASE search strategy

EMBASE Ovid 2006 to 2010 week 28

- 1 exp vulva tumor/
- 2 (vulva* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*)).mp.
- 3 1 or 2
- 4 radiotherapy/
- 5 rt.fs.
- 6 radiotherap*.mp.
- 7 irradiation.mp.
- 8 radiation.mp.
- 9 4 or 5 or 6 or 7 or 8
- 10 exp surgery/
- 11 su.fs.
- 12 lymphadenectom*.mp.
- 13 (lymph node* adj5 (excis* or dissect*)).mp.
- 14 surg*.mp.
- 15 10 or 11 or 12 or 13 or 14
- 16 3 and 9 and 15
- 17 limit 16 to yr="2006 - 2010"

key:

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

fs=floating subheading

Appendix 5. Methodology of the original review

Search Strategy

For the original review, The Cochrane Gynaecological Cancer Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using the criteria set by the Cochrane Gynaecological Cancer Group (The Cochrane Library Issue 4, 2006). A MEDLINE (1966 to 2006) and EMBASE (1988 to 2006) search using the Mesh Heading 'vulvar neoplasms' and text word 'vulva' was performed. Publications on the effectiveness of primary radiotherapy treatment of early squamous cell carcinoma of the vulva were selected.

Study Selection and Data extraction

Nine papers met the initial selection criteria (Daly 1974; Edsmyr 1961; Henderson 1984; Leiserowitz 1997; Manavi 1997; Perez 1998; Petereit 1993; Pirtoli 1982; Stehman 1992) with three being included in the original review (one RCT, one case-control and one observational study). All studies were assessed with the aid of a critical review form. We used three different critical review forms: one for RCTs, one for case control studies and studies with historic controls, and one for observational studies.

The critical review forms were filled out independently by both review authors. Differences were resolved by discussion. We included studies that met at least the following criteria:

1. All participants had clinical cT1-2N0,M0 vulvar cancer, or it was possible to analyse these participants separately.
2. Radiotherapeutic interventions are described adequately.
3. For studies with (non-randomised) controls, interventions should be the same in each group, apart from the experimental intervention.
4. Site of recurrence is mentioned precisely.
5. More than five patients meeting the above mentioned criteria are included in the study.

Six studies were excluded from further analysis for the following reasons:

1. Impossible to analyse incidence of groin recurrences in relation to initial stage of disease separately (Edsmyr 1961; Henderson 1984; Leiserowitz 1997;).
2. Site of recurrence not mentioned (Pirtoli 1982).
3. Incidence of groin recurrences cannot be analysed separately in relation to early stage of disease (Petereit 1993).
4. Insufficient numbers (Daly 1974).

Risk of bias associated with the NRSs

The quality of the five included studies is fair. Problems that remain after the selection process as described above are:

- (1) Three studies also include patients with non-squamous histology (Manavi 1997; Perez 1998; Hallak S 2007).
- (2) One study does not mention the duration of follow-up (Manavi 1997).
- (3) No study addresses the problems of sexuality (Katz 2003; Manavi 1997; Perez 1998; Stehman 1992; Hallak S 2007).
- (4) One study does not mention the stage of disease for patients in the surgery group (Hallak S 2007a)

Appendix 6. Differences between the updated and the original review

The original review included five studies: Hallak S 2007, Katz 2003; Manavi 1997; Perez 1998; Stehman 1992. For the updated review, these studies were reclassified to include only the RCT in the Included studies (Stehman 1992) and to exclude the formerly included case-control and observational studies (Excluded studies).

WHAT'S NEW

Date	Event	Description
11 February 2016	Review declared as stable	There are no additional trials to add to this review currently. Another review looking at sentinel node biopsy has been produced: 'Lawrie TA, Patel A, Martin-Hirsch PPL, Bryant A, Ratnavelu NDG, Naik R, Ralte A. Sentinel node assessment for diagnosis of groin lymph node involvement in vulval cancer. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD010409. DOI: 10.1002/14651858.CD010409.pub2.'

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 3, 2000

Date	Event	Description
29 March 2011	New search has been performed	The review has been extensively revised and updated to conform with updated Cochrane methodology. This involved excluding all non-randomised studies that were included in the original review. The searches were re-run in 2010 and new studies were identified but none included.
18 March 2011	New citation required but conclusions have not changed	Review updated but conclusions unchanged. New authors GF and TL have been added.
20 October 2008	Amended	Converted to new review format.
24 April 2007	Amended	Minor update: 25/04/07 New studies sought but none found: 01/11/06 Personal communication from Dr P Eiffel on the reviewed manuscript by Katz et al (International Journal of Radiation Oncology, Biology, Physics, 2003) is now included. This information entails detailed data on 14 T1/T2 patients with clinically negative groin lymph nodes who had primary radiation to the groins and no recurrence during follow-up.
1 November 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JV quality assessed papers, extracted data and wrote text; GF checked the updated review; TL assisted with the updating of the review and providing methodological support. AA compiled and carried out the original search strategy and reviewed text.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol and original review included case-control and observational studies. The updated review includes only the one RCT in data collection and analyses; however, findings of the NRSs are included in the discussion.

NOTES

There are no additional trials to add to this review currently. Another review on sentinel node biopsy has been produced: 'Lawrie TA, Patel A, Martin-Hirsch PPL, Bryant A, Ratnavelu NDG, Naik R, Ralte A. Sentinel node assessment for diagnosis of groin lymph node involvement in vulval cancer. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD010409. DOI: 10.1002/14651858.CD010409.pub2.'

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinoma, Squamous Cell [pathology] [*radiotherapy] [*surgery]; Inguinal Canal; Lymph Nodes; Neoplasm Recurrence, Local; Neoplasm Staging; Randomized Controlled Trials as Topic; Vulvar Neoplasms [pathology] [*radiotherapy] [*surgery]

MeSH check words

Female; Humans