MEDICAL PROTOCOL

ONCOLOGICAL MANAGEMENT OF VULVAR CANCER

These guidelines have been developed by members of the Gynaecological Oncology Guidelines Group, for approval by the Merseyside and Cheshire Gynaecological Cancer Network Group.

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1. Background

Vulval cancer is an uncommon illness with 943 cases registered in the UK in 2009. Hence most information about it comes from small personal series. In establishing these guidelines we have drawn upon previously published guideline texts, relevant published papers and chapters, and the RCOG publication, “Clinical Recommendations for the Management of Vulval Cancer”.

Ninety percent of all vulval cancers are squamous in origin, histological type being of importance because it is a variable affecting the likelihood of lymph node involvement. Survival is closely related to lymph node involvement. For those without any lymph node involvement 5-yr-survival is 80% but this falls to 50% if groin nodes are involved and to 10-15% if iliac or other pelvic nodes are involved. Overall 30% of patients presenting with vulvar cancer will be found to have nodal metastasis. Multifactorial analysis shows that nodal status and the diameters of the primary tumour are the only two variables which are associated with prognosis. These two variables, of course, simply represent advancing stage of disease.

There is no screening test available for vulval cancer although a number of precursor lesions are recognised. These include Vulval Intraepithelial Neoplasia (VIN), and Paget’s disease of the vulva and lichen sclerosus. Long term follow up of Paget’s disease is advisable, but in patients with previous VIN may be discharged after 2 years follow up if

- Asymptomatic
- No clinical recurrence
- Information given on signs and symptoms of recurrence to prompt re-referral

It should also be remembered that women who develop a vulval cancer are at an increased risk of developing other genital cancers, particularly cervix.

Surgery has been the treatment of choice for most women with vulval cancer. The standard approach is for radical local excision of the primary site, and separate groin incisions for the inguinal lymphadenectomy if necessary.
Combined modality therapy is also a potential approach, particularly in those patients with a locally advanced vulval tumour. This includes the use of radiotherapy with or without chemotherapy. Significant response can be achieved with well-planned radiotherapy, with or without chemotherapy. This may be of particular importance in advanced disease or where a tumour affects midline structures which are not amenable to surgical resection, or where presurgical downstaging can reduce the morbidity of any surgical treatment.

2. Histology

90% of all vulval cancers are squamous in origin, with all other types being much more uncommon. Melanoma (5%), sarcoma (2%) and basal cell carcinoma (1%) are the other main subtypes, with adenocarcinoma, adenosquamous and Bartholins gland tumours being exceedingly rare. All are treated in a similar manner, with the exception of vulval melanomas, which require involvement from the skin MDT and plastic surgeons, and basal cell carcinoma, which only requires local excision with clear margins.

3. Diagnosis and Referral

It is recommended that referral should be made if any of the following changes are detected:

- vulval pain, burning, pruritus or soreness
- swelling, polyp, lump or ulcer
- colour change; whitening or pigment deposition
- elevation and/or irregularity or surface contour
- clinical “wart” (a true condyloma is uncommon in elderly women and any warty lesion should be regarded as suspicious)
- irregular fungating mass
- ulcer with raised rolled edges
- enlarged groin nodes
If invasive disease is suspected then the patient should be referred to a clinician with an interest in vulval disease, with a view to onward referral to the network Gynaecological Oncology Centre if invasive cancer of any stage is confirmed. It is important that relevant histological material should be sent to the specialist gynaecological pathologist in the GOC.

Diagnosis should in most cases be confirmed by a biopsy prior to definitive surgery. Occasionally, where the clinical situation dictates, definitive surgery to the lesion may be performed, but in most instances all suspicious lesions should be biopsied prior to excisional surgery, especially if assessment for sentinel node biopsy is to be considered. In general, surgery to the groin nodes should not be performed prior to pathological confirmation of invasive disease. It is important to keep detailed notes regarding the site and size of the lesion in case further treatment is required. It may be helpful to take a clinical photograph prior to surgery in these circumstances, with the patient's express consent. On excision, all specimens should be pinned out and orientated prior to fixation in formalin to allow the histopathologist to accurately assess the excision margins.

3. Staging

Staging classification was updated by FIGO 2009 (Appendix1).

4. Prognostic factors

The main factors which are significantly associated with prognosis are tumour size, depth of invasion and nodal involvement².

5. Pre-treatment assessment

The most important investigation is a biopsy to confirm the diagnosis and assess depth of invasion. A representative biopsy should include an area of epithelium where there is a transition from normal to abnormal tissue. Biopsies should be sent for examination by a pathologist with a special interest in gynaecological oncology.

Other investigations may include:
- FBC
• Biochemical profile
• Chest X-ray
• Abdominal and pelvic CT if clinical suspicion of metastatic disease or primary surgery is likely to be excessively morbid or complex
• Biopsy or FNA of clinically suspicious nodes or other metastases where the result may alter management

6. Treatment

Although considerable change has taken place in the management of vulval cancer, the principles of management remain unchanged. All patients need assessment for:
1) appropriate treatment for the primary site of disease
2) appropriate treatment for potential lymph node metastases.

Treatment commonly requires an individual approach after MDT and patient discussion, as the presentation, comorbidities and involvement of surrounding tissues can vary significantly. A combined approach using surgery (with plastic surgical involvement), radiotherapy and chemotherapy may be an option in each case. This may lessen the surgical morbidity by allowing closure of tissues without undue tension and could reduce long-term psycho-sexual morbidity associated with the scarring that follows the standard radical approach. Many factors will influence decisions regarding management including the site and size of the primary tumour and its histological features, the presence or absence of nodal metastasis and the fitness of the patient.

7. Surgery

Early disease:
Disease that is limited on clinical examination to the vulva with no evidence of nodal metastasis.
Management of the primary tumour should involve a radical wide local excision. The main aim of the surgery is to remove the primary tumour with minimum 8-10mm histological margins of disease-free tissue in all directions. This equates clinically to an approximate 2cm clinical clearance at the time of surgery. This approach reflects
evidence demonstrating that the risk of local recurrence is related directly to the size of the surgical excision margins\textsuperscript{3,4}. Consideration should also be given to the removal of adjacent areas of abnormal epithelium (e.g. VIN or Lichen sclerosus) since it is possible that they could contain small, separate foci of invasion.

Surgery to assess the possibility of nodal metastasis is necessary in all cases except
1) Stage 1a disease\textsuperscript{5}.
2) Basal cell carcinoma and verrucous carcinoma - rarely associated with metastasis\textsuperscript{5,6}.
3) Malignant melanoma - no evidence of any nodal involvement\textsuperscript{7}. However, all cases of vulval melanoma should be assessed in conjunction with the skin MDT and plastic surgeons. Consideration may be given to assessment of sentinel nodes at Whiston Hospital.

In lateral tumours whose medial edge lies at least 2 cm from the midline, ipsilateral groin node dissection is performed. Bilateral groin node dissection is undertaken where the primary tumour is close to the midline. Surgery is carried out by the “triple incision” technique described by Hacker\textsuperscript{8} since the incidence of skin bridge recurrence in early-stage disease is very low. It is recommended that superficial groin nodes as well as deep femoral nodes are removed as the removal of superficial nodes alone is associated with a higher risk of groin node recurrence\textsuperscript{9}.

Recent research indicates that it is possible to accurately predict nodal metastasis using sentinel node biopsy in patients with early vulvar cancer (<4cm)\textsuperscript{10}. A. Van der Zee \textit{et al} performed sentinel node procedure on 623 groins, they found that recurrence rate was low (n=6) and survival excellent and treatment related morbidity minimal. The role of sentinel node biopsy needs to be actively explored within the Cancer Network; it is currently not available within this region.

Another method of follow up for patients who have declined groin dissection or been deemed unfit for surgery is a combination of ultrasonography and fine needle aspiration and cytology\textsuperscript{11}. At LWH over the last 4 years have assessed 40 patients
with a positive predictive rate of 100%, and one patient developed a groin recurrence 6 months after initial treatment.

**Vulvo-vaginal Melanoma**

The mainstay of treatment remains surgery, though there is limited evidence for radical surgery improving survival. The risk of recurrence and therefore survival in vulval melanomas is mostly related to the thickness of the melanoma at presentation (Breslow thickness). Breslow thickness is a better predictor of prognosis than Clark's levels, and the latter is now rarely used. The management of the groin nodes in melanoma is controversial and has little effect on survival but may provide local control of the groins. Thus, if nodes are palpable then they should be removed.

- **Stage 1A disease; Breslow thickness <0.76mm.** No indication for groin dissection as the risk of metastasis is almost zero.
- **Stage 1B or more: Breslow thickness >0.76mm.** For patients with a depth of invasion between 1mm and 4 mm but without palpable nodes, ultrasonography and fine needle aspiration can be offered. The role of sentinel node in this group has yet to be decided. In all cases greater than Stage 1A, the decision around treatment should be discussed in conjunction with the skin MDT. Joint treatment with the Plastic Surgeons should be considered.

**Surgery in advanced disease:**

Disease in with gross nodal involvement and/or where excision of the primary tumour would involve sacrifice of important midline structures.

The principles of surgery are unchanged in that wide excision of the disease with at least 1cm histological margins is the aim. Due to shrinkage during formalin fixation, a histological margin of 1cm equates approximately to a 2cm margin clinically at surgery. The surgery required will depend upon the size and site of disease and the involvement of any important midline structures. Primary radiotherapy or chemoradiation is advised when surgery might be significantly morbid, and in some patients may remove the need for surgery altogether if a complete response is achieved. Pre-operative chemoradiation can reduce the need for defunctioning
stomas\textsuperscript{12,13}. If radical surgery is considered, the procedure should be performed by the gynaecological oncologist in conjunction with plastic surgery colleagues. Groin node dissection is appropriate in all cases of late disease unless there are fixed and/or ulcerated groin nodes present. In these circumstances the involvement of the nodes can be confirmed by biopsy (open, trucut or FNA).
8. Radiotherapy

For early stage, surgery is the treatment of choice. Radiotherapy given alone or in conjunction with chemotherapy may be used in advanced stage to downstage the tumour prior to surgery or as a primary treatment if there is complete response. The use of radiotherapy prior to surgery will of course be determined by clinical factors relating to the extent and site of the disease.

I. Primary Radiotherapy

1) Small lesions in unfit patients - Radiotherapy can be limited to the vulva treating inguinal nodes at recurrence.

2) Patients with advanced disease where primary surgery is inappropriate - radical radiotherapy alone or in combination with concurrent chemotherapy may be considered.

II. Adjuvant Radiotherapy

Factors which will influence the need for radiotherapy in an adjuvant setting are related to the pathological findings from operative specimens. These include the surgical margins since the risk of local recurrence increases as the disease-free margin decreases (≥8mm = 0%; 8-4.8mm = 8%; <4.8mm = 54%)\(^4\). Adjuvant radiotherapy for patients with close or involved margins does improve local control.

In patients with positive nodes after radical surgery, adjuvant Radiotherapy significantly improves survival. A randomised GOG study\(^{14}\) showed 28% improvement in survival due to decreased incidence of groin recurrence.

*Adjuvant radiotherapy should be considered:*

1) **Two or more nodes positive nodes**

2) **Single positive node either completely replaced by tumour or with extra-capsular spread.**

3) **Excision margin < 8mm (surgical re-excision is an equally valid approach).**

*Surveillance with surgical salvage at recurrence is also valid in selected cases.*
III. Palliative Radiotherapy

In unfit patients with poor performance status and advanced tumours, a palliative approach is recommended to control symptoms such as pain and bleeding.

IV. Irradiation of Inguinal Nodes

Surgical dissection remains the treatment of choice, although it is not easy to draw conclusions about the efficacy of inguinal irradiation as primary treatment. A GOG study comparing groin dissection to groin radiotherapy was closed prematurely as an excess of groin failure was noted in the irradiated arm\textsuperscript{14}. There are limitations with this study, but this data shows that radiotherapy may be inferior to groin dissection and its use alone should be reserved for the less fit patients. 

\textit{We recommend surgery rather than radiotherapy for nodal disease for mobile groin node metastases.}

9. Chemoradiation

Chemoradiation has never been compared with radiation alone in the pre-operative setting in vulvar cancer. Several small single arm studies and a recent larger GOG phase II study have shown high response rates avoiding the need for exenteration in most patients\textsuperscript{15}. In the GOG study almost half the patients had no visible cancer at the time of surgery and the vast majority of these had complete pathological responses. This has lead to questioning the role of surgery in patients having complete response. Unlike in anal carcinoma treatment, there is currently insufficient evidence to advocate chemoradiation as the sole treatment of vulvar cancer. The morbidity of chemoradiation is the major issue and patients have to be carefully selected for this aggressive approach.

10. Chemotherapy

The role of chemotherapy is palliative for metastatic disease. Options include the use of 5-Fluorouracil, cisplatin and taxol.

11. Treatment at Relapse

Selected patients may be considered on an individual basis for more aggressive treatment. Some patients particularly those with local vulval relapse can be salvaged.
with further local surgery. Generally patients with nodal and/or distant failure have poor prognosis and palliative treatments are appropriate.

12. Hormone therapy

Hormonal therapy has no significant place in the management of vulval cancer. There are no contraindications to the prescription of hormone replacement therapy in women who have suffered from this disease.
13. Palliative Care and Nursing care

Palliative care input is appropriate to consider at all stages of the patient’s cancer journey. Please refer to the separate nursing and palliative care guidelines for detailed advice.

All women with a diagnosis of a Gynaecological cancer should be offered the support of and have access to a Clinical Nurse Specialist (CNS) in order to facilitate the woman’s needs throughout the cancer journey, including those of her partner and family. This CNS will be the keyworker for the patient and family. The skills of the CNS as a consultant, practitioner and educator can be drawn upon at all stages throughout their illness from pre-diagnosis to the terminal stage-incorporating the Specialist Palliative care services provided in the hospital and the community setting. Bereavement support will also be available, if appropriate.

The specifics of the role will include:

All women will be offered information about their disease including psychosocial and psychosexual issues that:

- Is available at the time they want it
- Includes the amount of detail that they want and are able to deal with
- Is in a suitable format, including written information

Ensure that the information is available about:

- The stage of the disease, treatment options and prognosis
- How to manage the side effects of both the disease and its treatments
- Sexuality including fertility and hormone treatment
- Symptoms and signs of disease recurrence
- Genetics referrals if appropriate
- Self help strategies to optimise independence and coping
- Where to go for support including local and national support groups
- How to deal with emotions
- Financial and social impacts and where to go for help with these issues

All patients are to be offered a Holistic needs assessment (HNA) at the milestones indicated in the Merseyside and Cheshire HNA and keyworker guidance.

The CNS will undertake a number of key responsibilities including:

- Linking with other professionals who can help the patients throughout the system
- A resource for information and support to the patient and carer and other HCP’s
- Liaison point for HCP’s in primary and secondary care
- Teacher and educator
- Be involved in research, audit, standards and guidelines
- Coordinate and develop care services
14. Follow-up

Standard: Four monthly for years 1 and 2, six monthly to 3 years. Discharge with open access to CNS in the event of new symptoms or concerns. CNS holistic assessment is carried out 6 weeks after the completion of primary treatment.

A careful examination of the vulva and examination of the pelvis and inguinal regions is required.

Patients who have associated VIN or Lichen sclerosus may be reviewed at intervals in a colposcopy or vulval clinic where vulvoscopy can be performed.

Longer term follow-up may be considered in patients treated with radiotherapy.

15. Maintenance of Quality

These guidelines conform to:


RCOG recommendations on specialists in gynaecological oncology, 1996.
# Appendix 1. FIGO Staging Description 2009

<table>
<thead>
<tr>
<th>FIGO 2009</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Tumour &lt;2cm, confined to vulva with &lt;1mm invasion,</td>
</tr>
<tr>
<td>1b</td>
<td>All lesions confined to vulva with diameter &gt;2cm or &gt;1mm invasion, with negative nodes</td>
</tr>
<tr>
<td>2</td>
<td>Tumour of any size with extension to adjacent perineal structures (lower 1/3rd urethra, lower 1/3rd vagina, anus) with negative nodes</td>
</tr>
<tr>
<td>3</td>
<td>Tumour of any size with or without extension to adjacent perineal structures with positive inguino-femoral lymph nodes</td>
</tr>
<tr>
<td>3a</td>
<td>1 lymph node metastases &gt;5mm or 1-2 nodal metastases &lt;5mm</td>
</tr>
<tr>
<td>3b</td>
<td>2 or more lymph node metastases &gt;5mm or 3 or more nodal metastases &lt;5mm</td>
</tr>
<tr>
<td>3c</td>
<td>Positive nodes with extracapsular spread</td>
</tr>
<tr>
<td>4</td>
<td>Further local invasion (Upper 2/3rd vagina, upper 2/3rd urethra) or distant disease</td>
</tr>
<tr>
<td>4a</td>
<td>Invasion of upper urethra, vaginal mucosa, bladder mucosa, rectal mucosa, fixed to pelvic bone</td>
</tr>
<tr>
<td></td>
<td>Fixed or ulcerated inguino-femoral nodes</td>
</tr>
<tr>
<td>4b</td>
<td>Distant metastases including pelvic lymph nodes</td>
</tr>
</tbody>
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Appendix 1

RADIOTHERAPY DETAILS

Radical Radiotherapy
- Radiotherapy dose of 60 Gy or equivalent.
- 45 Gy in 25 fractions over 5 weeks followed by phase II to gross disease, to equivalent dose of 60 Gy.
- Preoperative dose of 45 Gy in 25 fractions over 5 weeks with concurrent chemotherapy in selected cases.

Concurrent Chemoradiation
- 45 Gy in 25 fractions over 5 weeks with concurrent 5-fluorouracil infusion plus cisplatin on weeks 1 and 4, or weekly cisplatin for 5 weeks. Followed by small volume boost taking the dose to 60 Gy.
- 50.4 Gy in 28 fractions with concurrent 5-FU in 2 phases followed by boost (as above) to a total dose equivalent to 60 Gy.
- A split course is recommended in patients with severe acute skin reactions.

Palliative Radiotherapy dose schedules
30 Gy in 10 fractions over 2 weeks
20 Gy in 5 fractions over 1 week
8 Gy single fractions
References

13 Rotmensch J, Rubin SJ, Sutton HG, Javaheri G, Halpern HJ, Schwarz JL. Pre-operative radiotherapy followed by radical vulvectomy with inguinal
lymphadenectomy for advanced vulval carcinomas. Gynecol Oncol 1990. 36: 181-184
