South Wales Gynaecology
Clinical Guidelines

2011

<table>
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<th>Version</th>
<th>1.0</th>
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<tr>
<td>Release date</td>
<td>11/11/11</td>
</tr>
<tr>
<td>Editor</td>
<td>Mr Ken Lim</td>
</tr>
<tr>
<td>1. Review date</td>
<td>2. November 2014</td>
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South Wales Gynaecology Group (SWGOG)
South East Wales Gynaecology Centre
South West Wales Gynaecology Centre
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Foreword

The all Wales guidelines for gynaecological cancers were released in 2000, and have not been updated since then. In the interim, the North Wales Gynaecological Cancer Network has released their own guidelines, and the South West and South East Cancer Networks have merged into the South Wales Cancer Network. Coincidentally an educational group formed through membership from the gynaecology community was set up in 2009 and part of its brief was to rewrite the cancer guidelines for gynaecology. Each set of guidelines went through a draft cycle and a discussion at the South Wales Gynaecology Group (SWGOG) meeting before a final validation and release. This has consequently lead to a set of guidelines which has been widely discussed and agreed amongst the individuals involved in gynaecological cancer care in South Wales.

Each guideline is in its own a separate section, but does consist of a uniform structure throughout the document. The entire guideline will be reviewed in 3 years time, unless national guidelines are released and need to be incorporated in the interim. The sections are colour coded for ease of use. It is our hope that these guidelines will be widely referred to and adhered as much as possible so that the treatment for women with gynaecological cancer in South Wales can be as uniform as possible.

Finally I would like to thank all authors and co-authors of the following chapters on their diligence and perseverance in getting their contributions through in a timely fashion.

Ken Lim

On Behalf of the Guideline Group
## Guidelines for the Management of Vulval Cancer

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<tr>
<td>Author</td>
<td>Dr. Amanda Tristram</td>
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1. Background

1.1. Incidence, Age and Mortality

This is a rare carcinoma accounting for only 3-5% of all female genital tract carcinomas with 61 cases and 26 deaths in Wales in 2005\(^1\). Vulval cancer is commonest amongst women over 65 years old.

The five year survival in cases with no lymph node involvement is in excess of 80%. This falls to less than 50% if the inguinal nodes are involved and 10-15% if the iliac or other pelvic nodes are involved.

1.2. Aetiology

Lichen sclerosus and infection with high risk types of Human Papillomavirus are both conditions in which squamous neoplastic change can be seen. There may be an intraepithelial stage seen first (vulval intraepithelial neoplasia VIN) with either condition. Typically HPV-related disease is seen in younger women and may be multifocal. Either disease may also be present in the perianal region. Other pre-invasive conditions include Paget’s disease (adenocarcinoma in situ) and melanoma in situ.

1.3. Pathology

Most vulval carcinomas are of squamous cell type (SCC) (90%). Squamous cell carcinomas include the rare verrucous carcinoma which is relatively slow growing. Three percent are malignant melanomas and the remaining is made up of basal cell carcinoma, invasive adenocarcinoma, adenoid cystic carcinoma, sarcomas and others. Malignant melanoma should be separately reported and staged according to the system for cutaneous melanomas. Melanomas can be melanotic or amelanotic and are extremely aggressive.

Primary adenocarcinoma and adenoid cystic carcinoma most commonly arise from Bartholin’s glands. Such tumours represent 1-3% of all vulval carcinomas. They commonly involve groin and pelvic nodes with a correspondingly poor survival (52% at 5 years). Sarcoma of the vulva is rare and has a tendency to local blood borne spread. Basal cell carcinoma and verrucous carcinoma are squamous variants, rarely associated with lymph node metastases.
1.4. Symptoms and Signs

Most women present with vulval itching, irritation or pain. Women may also notice a lump, bleeding or discharge.
2. Staging

Staging of vulval cancer is according to FIGO staging system. Malignant melanomas are staged according Breslow’s depth of invasion.

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Features</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Tumour confined to the vulva</td>
</tr>
<tr>
<td>Ia</td>
<td>Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*, no nodal metastasis</td>
</tr>
<tr>
<td>Ib</td>
<td>Lesions &gt;2 cm in size or with stromal invasion &gt;1.0 mm*, confined to the vulva or perineum, with negative nodes</td>
</tr>
<tr>
<td>II</td>
<td>Tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes</td>
</tr>
<tr>
<td>III</td>
<td>Tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes</td>
</tr>
<tr>
<td>IIIA</td>
<td>(i) With 1 lymph node metastasis (≥5 mm), or</td>
</tr>
<tr>
<td></td>
<td>(ii) 1–2 lymph node metastasis(es) (&lt;5 mm)</td>
</tr>
<tr>
<td>IIIB</td>
<td>(i) With 2 or more lymph node metastases (≥5 mm), or</td>
</tr>
<tr>
<td></td>
<td>(ii) 3 or more lymph node metastases (&lt;5 mm)</td>
</tr>
<tr>
<td>IIIC</td>
<td>With positive nodes with extracapsular spread</td>
</tr>
<tr>
<td>IV</td>
<td>Tumour invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumour invades any of the following:</td>
</tr>
<tr>
<td></td>
<td>(i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or</td>
</tr>
<tr>
<td></td>
<td>(ii) fixed or ulcerated inguino-femoral lymph nodes</td>
</tr>
<tr>
<td>IVB</td>
<td>Any distant metastasis including pelvic lymph nodes</td>
</tr>
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</table>

*The depth of invasion is defined as the measurement of the tumour from the epithelial stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Table 1 Revised FIGO staging for carcinoma of the vulva 2009

3. Screening

There is no screening procedure for vulval cancer. Patients with carcinoma of the vulva are at an increased risk of developing other cancers of the genital tract. Cervical Screening Wales permit women with VIN to have annual cervical screening.
4. Referral Pathways/Networks

4.1. General Practitioner

If cancer of the vulva is suspected then referral should be to a Cancer Centre which has appropriately trained personnel. In this instance, referral will be to a gynaecologist who has additional training in oncology.

4.2. Non-oncological gynaecologists

If a patient with vulval cancer is seen by a gynaecologist who has had no additional training in oncology, then referral should be made to the Cancer Centre. The rarity of the cancer, the variety of possible management techniques and the additional skills required mandate that this cancer should be managed by specialist teams. Referral should include sending all relevant histopathological material to the specialist gynaecological pathologist in the gynaecological cancer centre.

4.3. Cancer Centre

The patient should be seen within two weeks of referral and definitive treatment should be undertaken within six weeks of diagnosis. All new cases of vulval cancer should be discussed at the cancer centre multidisciplinary team meeting and the histopathological material reviewed by a specialist gynaecological pathologist, prior to radical surgery.

5. Diagnosis

Clinical features strongly indicating vulval cancer include an irregular, fungating mass, an irregular ulcer or enlarged groin nodes. If vulval cancer is strongly suspected the patient should be referred urgently to a Cancer Centre.

Any change in vulval or vaginal epithelium in a post-menopausal woman warrants a biopsy. These changes include; a swelling, polyp or lump, an ulcer, colour change (whitening or pigment deposition), elevation or irregularity of the surface contour. Any “warts” in a post-menopausal woman or persistent “warts” in the pre-menopausal woman should be biopsied. In pre-menopausal women all other vulval signs and symptoms should be managed as for those in post-menopausal woman unless there is a confirmed infection. Lesions should be biopsied rather than excised. If cancer is confirmed, the patient should be referred to a gynaecological cancer centre.
All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy prior to definitive treatment.

6. Pre-invasive Disease

Colposcopy is useful for localisation but the signs are non-specific. Diagnosis is by biopsy. Multiple biopsies may be required to map the extent of disease and exclude invasion. Vulval Intraepithelial Neoplasia (VIN), Paget’s disease and melanoma-in-situ may be treated with local excision and groin node dissection is inappropriate. Women with VIN, Paget’s disease or melanoma-in-situ should be followed up by either specialist vulval clinics or gynaecological oncologists. Consideration should be given to enrolment in an appropriate trial.

7. Investigations

As patients often present in their 7th decade there may be appreciable medical problems and these must be corrected before major surgery is contemplated. However operability rates of 96% have been reported in large centres.

7.1. Pre-Operative Investigations for Women with Vulval Cancer

- Vulval biopsy
- Chest X-ray
- Cervical smear, if not up to date with national programme
- Full blood count, biochemical profile, liver function tests
- Abdominal and pelvic CT scan or MRI scan (for concurrent pelvic pathology and retroperitoneal nodes)
- Biopsy of any grossly involved nodes or other metastases
- Appropriate blood samples for cross matching blood
- MSU
- ECG if over 50 years
8. Treatment of Primary Disease

These cancers should be treated in the Cancer Centre. Each case should be considered individually and an agreed plan of management devised by the gynaecological cancer team. Factors such as tumour size, location, medical fitness and the wishes of the patient will all influence management.

8.1. Treatment of early vulval cancer

Surgery

Squamous Carcinoma Stage 1a

Small tumours with a depth of invasion of <1mm (Stage Ia) should usually be managed surgically. Surgery to the primary tumour should be radical to remove the tumour yet conservative to avoid unnecessary surgical and psychological morbidity. Wide radical local excision with a minimum margin of 1cm of disease free tissue is often sufficient. In these cases, it is not necessary to perform a groin node lymphadenectomy as the risk of involved nodes is negligible.

Squamous Carcinoma Stage 1b

When the tumour is Stage Ib or worse a groin node dissection is also undertaken with wide radical local excision or as part of a radical vulvectomy.

Radical vulvectomy involves removal of the vulva extending from the vaginal introitus to the outer borders of the labia majora and removal of the superficial and deep inguinal (groin) nodes either with a triple incision where the groin nodes are removed separately or en masse with the primary tumour as a ‘butterfly’ incision. The excision should have at least a 1.5cm disease free margin around the primary tumour in the fresh specimen, to allow for tumour shrinkage.

The triple incision approach is associated with significantly less operating time, less blood loss, shorter hospital stay and less wound morbidity. It also produces a less disfiguring scar. Patients with fungating groin nodes should have the groin dissection performed in continuity with the vulva.

Bilateral groin node dissection is usually required because of the cross-over of lymph channels. However in very lateral tumours (the medial edge of the tumour must be at least
2cm lateral to the midline of the vulva), only an ipsilateral groin node dissection need initially be performed [8]. If the ipsilateral nodes are subsequently shown to be positive for cancer, the contralateral nodes should also be excised or irradiated as the nodes are more likely to be positive.

It is recommended that the deep femoral nodes as well as the superficial groin nodes be removed. Superficial groin node dissection alone is associated with a higher risk of groin node recurrence 8. Preservation of the long saphenous vein is reported to reduce both groin wound and subsequent lower limb problems 9, 10, 11. Following inguinofemoral lymphadenectomy, sartorius muscle transposition may be of benefit in preventing subsequent femoral vessel damage, particularly in those women who are thin and in those in whom adjuvant groin radiation therapy is anticipated 12.

Pelvic node dissection is rarely performed as 15-20% of those with involved inguinal nodes will have involved pelvic nodes and surgery may only salvage 10% of these. Radiotherapy offers better prospect of sterilizing pelvic nodes with lower morbidity 13.

Morbidity after surgical treatment and groin node dissection is considerable. Primary radiotherapy to the groin is expected to result in less morbidity, however studies to date on the efficacy of primary radiotherapy to the groins in terms of groin recurrences and survival show conflicting results, surgery is still the cornerstone of therapy. Primary radiotherapy as should only be carried out as part of a clinical trial, unless there are specific clinical reasons and these are documented in the case notes.

Dye studies and lymphoscintigraphy may be of value in the detection of sentinel nodes 14-16, although the outcome of this type of intervention is awaiting the outcome of controlled clinical evaluation. Surgery confined to sentinel node dissection should only be undertaken as part of a clinical trial, unless there are specific clinical reasons and these are documented in the case notes.

**Complications of Surgery**

Wound disruption and infection

- Thromboembolic disease
- Secondary haemorrhage
- Leg oedema
- Femoral nerve damage
- Osteitis pubis
- Hernia
- Urinary infection
- Introital scarring and vaginal prolapse
- Sexual function and body image.

**Postoperative Radiotherapy**

**Postoperative radiotherapy to the primary site**

The incidence of vulval recurrence locally is related to the measured disease free surgical margin as measured in the histopathological specimen. The risk of recurrence increases as the disease free margin decreases (>8mm 0%; 8-4.8mm 8%; <4.8mm 54%)\(^6\). Postoperative radiotherapy to the primary site is therefore not recommended if the resection margin is greater than 8mm.

Although a reduction in local recurrence has been shown following adjuvant local therapy in patients with close surgical margins, this was not associated with an improvement in survival. Adjuvant treatment for positive margins was shown to improve survival compared with observation alone\(^{17}\).

**Postoperative radiotherapy to the nodes**

One randomised trial of patients who underwent radical vulvectomy and bilateral groin node dissection has shown a survival advantage to those given postoperative radiotherapy to the nodes compared with those given a pelvic node dissection particularly in those with two or more positive groin nodes\(^{13}\). Postoperative radiotherapy to the loco-regional nodes should be considered when two or more lymph nodes are involved with metastatic disease or when there is complete replacement or extra capsular spread in any node.
Although both lymphovascular invasion and infiltrative growth patterns are associated with a worse prognosis, currently, adjuvant radiotherapy is not recommended in these situations, in the absence of other risk factors.

8.2. Treatment of Advanced Vulval Cancer

This group includes all women with grossly involved nodes and those who have vulval lesions where there is an extensive vulval lesion necessitating functional disability for its removal.

Surgery

The size and location of the tumour will influence the surgical approach. Some tumours will require a radical ano-vulvectomy.

Groin node dissection should be undertaken when there are clinically suspicious groin nodes present. In cases with large primary lesions and clinically suspicious nodes, a radical vulvectomy with 'en bloc' groin node dissection may be warranted.

Reconstructive surgical techniques should be employed to enable primary surgical closure and reduce morbidity due to scarring.

Primary radiotherapy or chemoradiotherapy

These can be considered for selected patients with advanced disease such as those who are not suitable for surgery because of the extent of their disease or co-existing medical conditions. However, caution is needed when dealing with frail, often elderly, patients in view of the potential toxicity of treatment.
### Disease State

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Description</th>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>Early disease</strong></td>
<td>Small lesions with less than 1mm invasion (FIGO Stage Ia)</td>
<td>Wide local excision, groin node dissection unnecessary</td>
</tr>
<tr>
<td></td>
<td>Truly lateralised squamous lesions (FIGO Stage I and II)</td>
<td>Initially only require wide local excision and ipsilateral lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td>Centrally located tumours where excision is possible without sphincter compromise</td>
<td>Requires wide local excision and bilateral lymphadenectomy initially</td>
</tr>
<tr>
<td><strong>Advanced disease</strong></td>
<td>Extensive vulval involvement</td>
<td>Groin node dissection and either surgical excision (consider vulval reconstruction) or primary (chemo)radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Clinically advanced nodes</td>
<td>Excision and/or chemo radiation therapy</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td></td>
<td>Palliation may require surgical management of the primary tumour</td>
</tr>
</tbody>
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Table 2 Summary of Primary Treatment of Squamous Vulval Cancer

#### 8.3. Surgical Management of Non Squamous Vulval Cancer

**Carcinoma of the Bartholin’s gland**

This is rare and can be either a squamous carcinoma or adenocarcinoma histologically. The current evidence base is insufficient to suggest different management from squamous tumours.

**Basal Cell Carcinoma and Verrucous Carcinoma**

These squamous variants are rarely associated with lymph node metastases and can be managed by wide local excision. Basal cell carcinomas are also amenable to treatment by radiotherapy, which should be the preferred treatment if resection would compromise function (for example anal sphincter damage).

**Malignant Melanomas**

This group of tumours has not been shown to benefit from en-block dissection of the groin. Wide local excision is preferred. Relapse in this subgroup is high and closely correlates with the depth of invasion.
Sarcoma of the vulva

Sarcoma of the vulva is rare and has a tendency to local blood borne spread. Surgery is often combined with radiotherapy and chemotherapy.

9. Management of Recurrent Disease

Twenty six per cent of patients develop recurrent disease, which, is usually on the vulva.

9.1. Local Recurrence

Local recurrence is managed by repeat excision, especially if irradiation has already been given to maximum dose. If excision will impair sphincter function then radiotherapy should be considered. Plastic surgery with rotational skin and myocutaneous flaps may be necessary. The patient should be referred to the Cancer Centre for appropriate assessment by the multidisciplinary team.

9.2. Regional Recurrence

Groin recurrence is much more difficult to manage. In patients who have not received radiation, this should be performed first followed by resection, if the response to radiotherapy is not complete. Patients who have been irradiated should be offered palliative resection if possible. Survival after groin recurrence is poor. The palliative care team should be involved early.

9.3. Chemotherapy and radiotherapy for Recurrent Disease

For selected patients with loco-regional recurrences who have been treated with surgery alone, radiotherapy or chemoradiotherapy can be considered and may offer the prospect of disease control\(^\text{18}\). For patients with recurrent and progressive vulval cancer, palliative chemotherapy may be appropriate in some cases, although responses are often short-lived. Frequent complications from the cancer include infection, bleeding and lymphoedema, and chemotherapy should be given in the context of multi-disciplinary palliative care.

10. Follow up

Follow up intervals are currently arbitrary, but the following schedule is suggested:

- Three monthly first year.
11. **Lymphoedema**

All women undergoing groin node dissection should be referred to a specialist lymphoedema service. All women are seen by the GONS following surgery for management of lymphoedema, education and skincare management. They are then referred to their local lymphoedema service upon discharge.

12. **Gynaecological Oncology Nurse Specialist (GONS)**

All women with vulval cancer should be referred to a gynaecological specialist nurse and be provided with written information about the disease and its treatment.

All women with a suspected or confirmed vulval malignancy should be seen by the GONS for verbal and written information and psychological/psychosexual support prior to and following surgery. This is ongoing support for as long as patients require this service.
13. Flow Chart for Guidelines for the Management of Vulval Tumours
14. References


# Guidelines for the Management of Endometrial Cancer

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<th>Version</th>
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<tr>
<td>Author</td>
<td>Dr. TS Shylasree</td>
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</table>
1. Introduction

Endometrial cancer is the most common gynaecological malignancy in the United Kingdom. The lifetime risk of developing endometrial cancer among women in industrialised nations is 2-3%. There will be an increase in the incidence of endometrial cancer due to increasing life expectancy and obesity.

Seventy five percent of patients present with cancer confined to the uterus. The overall five-year survival is approximately 75% and is attributed to diagnosis at early stage.

Approximately 286 new cases are diagnosed annually in Wales, with 50 dying of their disease.

2. Background

Ninety percent of the cases occur in women older than 50 years of age, with a median age of 63 years.

The exact aetiology of endometrial cancer is unclear. Risk factors which predispose to developing endometrial cancer include: obesity, early menarche and late menopause, nulliparity, polycystic ovarian syndrome, diabetes, hypertension, exogenous drugs like oestrogen replacement therapy and tamoxifen and hereditary cancer syndromes.

3. Screening

Currently, there is no screening programme for endometrial cancer.

Atypical hyperplasia of the endometrium (WHO 1994 nomenclature) is considered to be a precancerous lesion. Endometrial intraepithelial neoplasia (EIN) is a parallel nomenclature used by some for complex atypical hyperplasia.

The natural history of atypical endometrial hyperplasia is not well understood. Loss of PTEN expression in endometrial cells may predict the development of endometrial cancer\(^1\).

Studies have shown that more than 30% of women with atypical hyperplasia of the endometrium at presentation harbour endometrial cancer. (GOG167A)
Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC) is associated with germline mutation in mismatch repair genes MLH1 MSH2, 6 and PM2.

Women with HNPCC syndrome have a 40-60% lifetime risk of developing endometrial cancer and a similar risk of developing colon cancer. They have also a smaller but significant risk of developing ovarian cancer.

Periodic scanning of asymptomatic women on tamoxifen is not routinely recommended. In symptomatic women on tamoxifen, diagnostic hysteroscopy is the preferred method of investigation.

4. Diagnosis and Workup

Over 90% of women with endometrial carcinoma present with postmenopausal bleeding (PMB) and a small proportion present with offensive vaginal discharge due to a draining pyometra. However only 15-20% of women with PMB will have cancer of which 50% will be due to endometrial cancer. 1-5% of women are asymptomatic and are detected by cervical screening.

Advanced disease can present with asymptomatic or symptomatic vaginal, distant lymph node, omental, and peritoneal, hepatic and pulmonary metastasis.

The initial triage of women with PMB is to perform a transvaginal scan to assess endometrial thickness. An endometrial thickness of more than 4 - 5mm is considered abnormal depending on local guidelines and should be seen and investigated by the rapid access team and which may require tissue diagnosis.

History taking, general, abdominal and pelvic examination should be done in all women at the time of diagnosis.

MRI (to cover upper abdomen to lower para-aortic nodes & pelvis) is recommended in all cases of endometrial cancer. Contrast enhanced MRI is recommended.

Along with preoperative histology, imaging will assist in preoperative staging of cancer \(^2,3\) (depth of myometrial invasion, lymphadenopathy & cervical involvement) along with preoperative histopathology. The information obtained will help and thus determine the patient referral criteria, extent of surgery and adjuvant treatment.
CA1-25 may be a helpful in monitoring women with extra uterine disease and in women with histological diagnosis of uterine serous papillary tumours.\textsuperscript{4, 5}

Pre-operative investigation should include:

FBC, U & E, liver function tests

chest x-ray

consider 2 units cross match.

Further specific investigations should be requested depending on the presence of co-morbidity.

5. Referral pathway

5.1. Pre-diagnosis:

Women with postmenopausal bleeding should be urgently referred to a rapid access postmenopausal clinic or a gynaecologist. They should be seen within 10 working days from the time of referral from the GP or any other source\textsuperscript{22}.

Women with other symptoms & signs suggestive of endometrial cancer should be referred to cancer unit or cancer centre.

Women with a family history conferring a risk of developing endometrial cancer, women with HNPCC gene mutation or women who develop endometrial cancer under the age of 40 should be referred to genetics department.

5.2. Post-diagnosis:

Women with confirmed diagnosis of endometrial cancer should be referred to a gynaecological centre or unit and active treatment should be commenced no later than 6 weeks following diagnosis.

All women with confirmed diagnosis of endometrial cancer should be given written information and should be seen by a cancer specialist nurse.
6. Pathology

The histological subtypes of endometrial carcinoma comprise endometrioid adenocarcinoma with or without squamous differentiation (80%), serous papillary carcinoma (10%), and others (clear cell, mucinous, carcinosarcoma, mixed types). FIGO grading of endometriot adenocarcinoma comprises three grades (grade 1, 2, 3). Serous papillary, clear cell and carcinosarcomas are graded as grade 3. Histopathology minimum dataset should be used for recording information.

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tumour confined to the corpus uteri</td>
</tr>
<tr>
<td>IA&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>Stage II&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tumour invades cervical stroma, but does not extend beyond the uterus&lt;sup&gt;ii&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage III&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Local and/or regional spread of the tumour</td>
</tr>
<tr>
<td>IIIA&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tumour invades the serosa of the corpus uteri and/or adnexae&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIB&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Vaginal and/or parametrical involvement&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td>IICC&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Metastases to pelvic and/or para-aortic lymph nodes&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td>IICC1&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IICC2&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>Stage IV&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tumour invades bladder and/or bowel mucosa, and/or distant metastases</td>
</tr>
<tr>
<td>IVA&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tumour invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Distant metastases, including intra-abdominal metastases and/or inguinal nodes</td>
</tr>
</tbody>
</table>

Table 3 FIGO (2009) Surgical pathological staging of carcinoma of endometrium

---

<sup>i</sup> Either G1, G2, or G3

<sup>ii</sup> Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II

<sup>iii</sup> Positive cytology has to be reported separately without changing the stage
6.1. Treatment

Early Stage disease (Stage 1)

Most women with endometrial cancer have stage I disease at presentation. Stage 1 endometrial cancer is classified into low, intermediate and high risk on the basis of risk of pelvic and distant recurrence.\textsuperscript{6, 7, 8}

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A</td>
<td>Low-risk</td>
<td>Low-risk</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>Intermediate-risk</td>
<td>Intermediate-risk</td>
</tr>
</tbody>
</table>

The recommended primary treatment for stage 1 endometrial cancer is complete surgical staging, which encompasses:

- Laparotomy or Laparoscopy with peritoneal lavage for cytology
- Careful inspection and or palpation of the abdomen & pelvis (diaphragm, liver, omentum, pelvic & para-aortic lymph nodes, pelvic and bowel peritoneal surfaces)
- Followed by total hysterectomy and bilateral salpingo-oopherectomy

The evidence so far suggests that there is no therapeutic role for regional lymphadenectomy in stage 1 disease.\textsuperscript{8}

The role of staging pelvic lymphadenectomy and or para-aortic lymphadenectomy in Stage 1 endometrial carcinoma

The incidence of pelvic lymph node metastasis in stage 1 is 9-11% \textsuperscript{8, 9}. This is subdivided into:-

- Low-risk group: 1-4%
- Intermediate risk group: 5-10%
- High-risk group: 18-20%
The study by the Gynaecological Oncology Group (GOG 33) revealed that in women with apparent stage 1 disease, 22% had occult extraperitoneal disease and found the rate of nodal metastasis to be 11% which is similar to ASTEC study which found 9% nodal metastasis. The overall survival drops from 90% to 50% with lymph node metastasis in stage 1 disease. Thus lymph node status is an independent important prognostic indicator in early stage disease. Since 1988, FIGO classification has required a full systemic pelvic and para-aortic lymphadenectomy for staging the disease.

**Reasons for performing staging lymphadenectomy:**

- Prognosis is stage dependent

- To identify the extent (para-aortic nodes) of adjuvant treatment in individual patient

- Prevents stage mix and hence helps in calculating accurate survival statistics

**Reasons for not performing staging lymphadenectomy:**

- Women at risk of harbouring lymph node metastasis can be identified in most cases with staging MRI and surgical-pathological findings and hence adjuvant treatment can be planned accordingly.

- Lymphadenectomy is associated with slightly increased morbidity

- There is no role for routine pelvic lymph node sampling. Enlarged nodes can be removed as a part of debulking procedure. There is no national consensus regarding the mean number of lymph nodes to be removed during systematic regional lymphadenectomy.

**Where should these women be treated**

Stage 1, low and intermediate risk endometrial cancer can be treated in cancer units with emphasis on adequate surgical staging. A thorough clinical assessment, radiological staging and attention to histopathology (grade and type of tumour) in the pre-operative period will aid in appropriate referral and prevents stage migration.

In keeping with the national guidelines, all women at high risk of extra uterine disease should be managed by trained gynaecological oncologists in cancer centres.

Women in whom surgery might be technically difficult due to body habitus should preferably be referred to cancer centre.
All patients with incomplete surgical staging should be discussed in the multidisciplinary team meeting and should have a staging CT scan performed prior to decision on further management.

**Role of Adjuvant treatment in Stage I disease**

A systematic review and meta-analysis of adjuvant radiotherapy for stage 1 cancer (PORTEC1, GOG, Aalders, Soderini, 1770 patients) showed that adjuvant external beam radiotherapy (EBRT) reduces locoregional recurrence by a relative risk reduction of 72% (RR 0.28), although this did not translate into a reduction in the risk of death from all causes, distant recurrence and endometrial cancer death.\(^{12}\)

The updated meta-analysis including (PORTEC1, GOG99 and ASTEC/EN.5) results show no benefit of EBRT on overall survival in stage I intermediate and high-risk group. EBRT does not seem to have a distant effect and it might be necessary to use systemic treatments in high-risk women to prevent distant metastases and death from endometrial cancer.\(^{8}\) A small reduction in the isolated local recurrence observed in the above mentioned trials following EBRT in intermediate and high-risk group can be achieved by the use of brachytherapy alone (reduction of isolated recurrence rate at 5 years to 6.1%)\(^{8}\)

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Proposed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>No further treatment</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Vaginal vault brachytherapy</td>
</tr>
<tr>
<td>High risk</td>
<td>EBRT + vaginal vault brachytherapy consider concurrent chemoradiation or adjuvant chemotherapy in context to PORTEC 3</td>
</tr>
</tbody>
</table>

Table 4 Adjuvant treatment options for Stage I endometrial cancer

**Treatment of Stage II cancer**

Women with clinical or radiological evidence of disease involving the cervix should have a radical hysterectomy with bilateral regional lymphadenectomy. Administration of adjuvant RT with or without concurrent chemotherapy should be decided following discussion in the MDM.
In women, who are not fit for surgery, radiation therapy has been demonstrated as a well-tolerated and effective treatment that can provide some measure of pelvic control and long-term progression-free survival.\(^\text{13}\)

Hormonal treatment in stage I & II cancer:

The use of hormonal therapy in early stage disease is unproven and not routinely recommended, however progestogen therapy has been used for young women with atypical endometrial hyperplasia or low-risk endometrial cancer who desire fertility preservation.

Progestogens are also used in women who are not fit for surgery or radiotherapy.\(^\text{14, 15}\)

**Treatment for advanced stage cancer**

There is no standard approach to management of women with advanced or recurrent disease. The median survival of women with advanced/recurrent disease is only approximately 1 year.\(^\text{16}\) Combination of debulking surgery, radiotherapy, and chemotherapy and hormone therapy has been used in these cases and tailored to the individual patient.

**Radiotherapy**

Radiotherapy may include intracavitary therapy with external beam pelvic radiotherapy or whole abdominal radiotherapy. There are no data to define a preferred option and treatment at present is individualised.

Radiotherapy may be given in either a radical or palliative setting depending on the stage of disease.

**Surgery**

Laparotomy and debulking surgery may be an option and should be considered on an individualised basis.

**Chemotherapy**

Combination chemotherapy including a platinum based agent may have benefit in such patients, but should be used judiciously due to associated toxicity.\(^\text{17}\).
**Hormone Therapy**

In advanced metastatic disease, progestational agents & aromatase inhibitors have been used. Response rates to hormonal therapy are approximately 30% and should be considered.\(^{18,19}\)

**6.2. Recurrent Disease**

Fifteen to twenty percent of women with no signs of locally advanced or metastatic disease at primary treatment recur, with limited response to systemic therapy.

Recurrent disease may be local (vault), regional or distant. In a review of postoperative surveillance in patients with stage 1 & II disease, 15% recurrence rate was noted, 58% of the patients had symptomatic recurrences. For most patients, disease recurred within 3 years of initial treatment\(^2^4\).

The strategy for treatment of recurrence depends upon the site and extent of the disease, fitness of the patient and also on whether adjuvant radiotherapy was used in the primary setting.

50% of recurrent disease is local and usually at the vaginal vault. Local recurrence may be amenable to radiotherapy or surgical intervention and referral to a cancer centre should be considered particularly if an exenterative procedure is appropriate\(^2^0\). Most of the remaining metastases occur in the lymphnodes, lung, liver or bone. Localised distant recurrences in bone or supraclavicular glands could be considered for radiotherapy.

Hormone therapy should be tried. The main predictors of response are well differentiated tumours, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases. For low-grade tumours, progestational agents has shown a good response for oestrogen and progesterone receptor-positive tumour\(^1^8\). Tamoxifen has a 20% response rate in those who do not respond to standard progestational therapy.\(^1^9\)

Chemotherapy may be considered for recurrent disease in women who are fit to tolerate treatment\(^2^1\). Carboplatin, doxorubicin (GOG 122) and paclitaxel (GOG 177) are the most active agents. Combination chemotherapy gives a higher response rate than single agent, but is more toxic.
Palliation:

Salvage therapy (chemotherapy or RT or surgical diversion procedures) along with supportive care is recommended to relieve symptoms in advanced disease.

Survival

Overall five year survival is approximately 68%

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>77%</td>
</tr>
<tr>
<td>Stage II</td>
<td>48%</td>
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<tr>
<td>Stage III</td>
<td>34%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7%</td>
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</table>

6.3. Hospital Follow-up

Currently all women diagnosed as having endometrial cancer are followed up by the treating gynaecologist or oncologist or the referral DGH. There is no evidence for hospital follow up. These women should be made aware of the earliest signs and symptoms of recurrence and should be appropriately investigated by trained personnel.

Follow up intervals are currently arbitrary and are as follows

- Three monthly first year.
- Six monthly second year.
- Annual review until five years.
- Discharge after five years if well.

*NB For some patients these intervals can be incorporated into a formal shared schedule between the index hospital and the treatment centres to avoid patients having to travel distances on a frequent basis. However this should be formally arranged within the networks.*
6.4. Summary

Women presenting with PMB should be urgently investigated.

Women with histological diagnosis of endometrial cancer should be seen and supported by a specialist nurse and information leaflet given.

Women with histological diagnosis of endometrial cancer should have a pre-operative MRI and should be discussed in the local MDT.

Women with stage I low risk cancer can be treated in cancer unit.

Women with high risk of metastasis and recurrence should be referred to cancer centre.

The primary modality of treatment for Stage I and II endometrial cancer is surgery. Adjuvant postoperative radiotherapy with or without chemotherapy is administered depending on the risk factors.

Advanced and recurrent endometrial cancer is treated with a combination of surgery, radiotherapy, chemotherapy and/or hormonal therapy.

All women are followed up for 5 years following treatment and discharged if disease free.

Women suitable for enrolling in national or regional trials should be given appropriate information.
7. Flowchart For The Management Of Endometrial Cancer
8. References


South Wales Guidelines for the Management of Ovarian Cancer

<table>
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| Author  | Mr Kerryn Lutchman Singh  
|         | Dr Gianfilippo Bertelli  
|         | Dr Rachel Jones |
1. Foreword

This guidance document is an update of “Guidelines for the management of ovarian cancer” published in 2001. The aim of this document is to help the decision making of clinicians in South Wales who treat women with gynaecological malignancy, as well as to clarify the patient pathway and processes, in an effort to improve outcomes. Guidance on the detection of ovarian cancer in primary care and its initial management have recently been published by NICE\(^1\).

This guideline is intended for clinicians in secondary care (i.e. cancer units and centres), however where applicable reference will be made to the NICE guidance as it applies to the secondary care setting.

To support this, an evidence base is provided and important practice points are highlighted.

Improving outcomes for women with ovarian cancer requires a concerted and coordinated effort by all health professionals involved in their care and throughout the document, the role of the gynaecological oncology multidisciplinary team is stressed as a vital component to the success of this strategy.

The authors would like to thank the following for their contributions: Mr. Ken Lim for the patient pathway in Appendix 2, Dr Sue Catling for her input into perioperative care and Dr Idris Baker for Appendix 3 – palliative care, and Dr’s Sue Williams and Nasima Tofazzal for Appendix 4 – pathology reporting.

Feedback is welcome and any questions or comments should be addressed to:

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2. **Introduction**

Ovarian cancer is the most common cause of gynaecological cancer death and is the fourth most common cause of cancer deaths of women in Europe\(^2\). It has the highest fatality-to-case ratio because almost 75% of patients have advanced disease at the time of diagnosis\(^3\). Incidence increases with age, with a median age at diagnosis of 63 years. In the 2007, there were 6,719 cases of ovarian cancer diagnosed in UK., with 4,373 patients dying from the disease in 2008\(^4\). In Wales there were 392 cases of ovarian cancer diagnosed in 2008, with 215 women dying from the disease\(^5\).

Survival figures have improved slightly in the UK over the past 30 years but appear to be inferior to the Nordic countries and the USA respectively\(^2\). In England, the 5-year survival rate for women diagnosed 2001-2006 was 39%. In Wales, there was an improvement in the 5-year survival, from 30% (1992-1996) to 35% (1997-2001)\(^2\). In the USA, five-year survival for ovarian cancer was 45% in 1996-2003\(^3\).

The management of ovarian cancer represents a major and complex challenge for healthcare professionals. Improved outcomes can be achieved by centralization of care and a multidisciplinary approach\(^6\).

3. **Background**

Approximately 30% of ovarian neoplasms in postmenopausal women are malignant, compared to 7% in premenopausal women. Up to 90% of all primary ovarian malignancies are epithelial. In addition, approximately 75-80% of epithelial cancers are of the serous histological type. Serous carcinomas are now believed to be related aetiologically to fallopian tube and peritoneal cancer\(^7\). As such, these cancers shall be discussed together while germ cell, non-epithelial and borderline cancers shall be discussed separately.
3.1. Screening and Risk Reduction

Formal guidance on these issues is outside the remit of this guideline. In summary, there is currently no established method of screening for ovarian cancer. There are three randomised controlled trials in progress addressing this issue, the results of which are awaited (8-10). With regards women at high risk for ovarian cancers: Familial predisposition accounts for approximately 10% of epithelial ovarian cancer. The UK Familial Ovarian Cancer Screening Study (UKFOCSS) is a national trial that aims to determine whether or not ovarian cancer can be detected early in women at high risk. It is due to close recruitment in March 2011 and the results are awaited with interest. In the interim, it is recommended that women who appear to be high risk should undergo genetic counselling, and offered genetic testing for BRCA 1 and BRCA 2 if appropriate. Women at high risk may be offered options for risk reduction including surgery in the form of a laparoscopic BSO. These issues can be quite complex and require careful counselling, which may be best achieved in a joint clinic comprising genetic and gynaecological input. Formal guidance on ovarian cancer screening and risk reduction shall be proposed in separate guidance to follow.

3.2. Symptoms, Signs and Diagnosis

Symptoms of ovarian cancer are often vague and non-specific. As the majority of patients with ovarian cancer have advanced disease at presentation, early symptom recognition has attracted much recent interest in an attempt to diagnose disease at an earlier stage (11). There does appear however to be a significant overlap in the duration and nature of symptoms for both early and advanced disease respectively however (12). This implies which that early and late stage disease are biologically distinct, thus limiting the prospect of diagnosing disease at an “earlier stage” based on symptoms alone. Nonetheless, early diagnosis is desirable (regardless of stage) as it can lead to prompt referral and specialist care, leading to improved cure rates.

Women may also present with an incidental finding of a pelvic mass detected clinically or at the time of imaging. The possibility of other primary tumours metastatic to the ovary should always be considered. As such, gastrointestinal symptoms should prompt consideration of upper and lower GIT investigations and a complaint of postmenopausal bleeding should prompt investigation of the endometrial cavity. A family history of cancer should be elicited in all cases (especially for breast, ovary and colon cancer). In addition,
patients may present acutely with symptoms and signs suggesting torsion/infarction or sub acute bowel obstruction.

Clinical examination should assess the patient’s performance and nutrition status as well as detecting signs of metastatic disease. Breast examination should be considered, especially in the setting of advanced disease. Abdominal and pelvic examination should be routinely performed. The finding of a pelvic mass on clinical examination raises significantly the possibility of an ovarian cancer, especially if found in association with ascites. Rectal examination should be performed to exclude a rectal mass and to help assess resectability.

For further information on detection of ovarian cancer in primary care, please refer to NICE guidance¹.

**CLINICAL PRACTICE POINT 1**

The finding of a pelvic mass either on clinical or radiological examination (especially in a postmenopausal patient) is a critical sign, and warrants immediate further investigation to exclude malignancy.

### 3.3. Investigations

- Full blood count (FBC) and differential, liver and renal function tests
- Tumour markers: CA125 and CEA routinely. A ratio of CA125: CEA of greater than 25 favours the diagnosis of ovarian cancer¹³. If there is a possibility of disseminated upper GI malignancy add CA19-9, and for disseminated breast malignancy add CA 15-3. In the younger patient (age < 40 years), add AFP, HCG and LDH.
- Chest x-ray
- If ascites or pleural effusion present consider diagnostic paracentesis or pleural tap respectively
- CT abdomen and pelvis (MRI may be considered in certain cases)
3.4. Differential Diagnosis

Ovarian cancers must be differentiated from benign neoplasms and functional cysts of the ovaries. CA 125 levels on their own are considered unreliable as it is elevated in only 50% of patients with stage 1 ovarian cancer and tends not to be elevated in mucinous carcinomas\textsuperscript{14}. Furthermore, interpretation in premenopausal patients is unreliable due to the high incidence of non-neoplastic conditions, which can cause an elevated CA 125. The risk of malignancy index (RMI), first described by Jacobs in 1990\textsuperscript{15} appears to be the best predictor of malignancy\textsuperscript{16}. Various modifications of this model have been proposed although it is not entirely clear the optimum cut-off score should be, as alterations of this can affect the sensitivity of the RMI relative to specificity\textsuperscript{17-19}. On one extreme, a low cut-off may potentially cause an overburdening of cancer centre resources. On the other, a patient with ovarian cancer might be missed. Most of the published data regarding RMI uses a cut-off of 200 however\textsuperscript{20} and a recent systematic review concluded that a score of 200 or greater gives a sensitivity of 78% and specificity of 87% for ovarian cancer\textsuperscript{21}. However, in the recent ovarian cancer guidance published by NICE, a cut-off of 250 has been recommended based on a health economics evaluation\textsuperscript{1}. Adoption of this cut-off should allow comparison with centres nationwide, and local audit of the referral pathway should be performed to ensure that a significant proportion of ovarian cancers are not being missed using this threshold.

The recommended cut-off for high-risk patients in this guideline is RMI $>$ 250.

The RMI is not the only consideration to be made however. Size of the lesion is also considered to be important, a factor not included in the RMI calculation\textsuperscript{22}. As such, it is recommended that asymptomatic, low-risk ovarian cysts $<$ 8cm in diameter is evaluated by the local MDT, where a conservative approach can be considered. The overall clinical picture should always be taken into account and it is the MDT’s role to consider this before recommending further management.

It is essential to determine preoperatively whether a patient is high risk for ovarian malignancy or not. This would allow the opportunity for the patient to undergo thorough surgical staging, which is a critical determinant of subsequent treatment and prognosis. Furthermore, optimal debulking at the time of initial surgery is an important determinant of the success of systemic chemotherapy.
3.5. Referral Pathways

The Calman Hine report, published in 1995 proposed a restructuring of cancer services in the United Kingdom\textsuperscript{23}. This led to publication of an important document: Guidance on commissioning cancer services: Improving outcomes in gynaecological cancers in 1999. This document set out the rationale and provided the details of how patient referral pathways should be established, which was based mainly on the interaction between cancer units and the cancer centre multidisciplinary team\textsuperscript{24}. Most of what is mentioned in that document is still relevant today. Following on from this pivotal document, the Welsh Assembly Government published National Standards for Gynaecological Services in 2005\textsuperscript{25}. These standards are still in place today and are monitored on a yearly basis. These three documents form the basis of gynaecological cancer care provision in Wales and clinicians treating these cancers should ensure that they are familiar with them. A suggested referral pathway for ovarian cancer is shown in appendix 2.

**CLINICAL PRACTICE POINT 2**

Any patient that is being considered for laparotomy to investigate a pelvic mass should have their risk of malignancy assessed pre-operatively under the guidance of the local gynaecological oncology MDT. This risk must take into account all clinical information, including the RMI.

**CLINICAL PRACTICE POINT 3**

An effective referral pathway between the local cancer unit and the cancer centre is essential to prevent delays in diagnosis and delivery of optimum treatment, which can result in poor outcomes. This process should be the subject of continuous audit.
3.6. Confirmation of Diagnosis (Pathology)

This is usually achieved either at laparotomy or, if primary chemotherapy is chosen for treatment, by radiologically guided percutaneous biopsy. The latter has been shown to be safe and has high diagnostic accuracy\(^26\). Occasionally, cytological examination can be used to make a diagnosis, but this shall be discussed in a later section.

Serous histology makes up 75% to 80% of epithelial cancers. Less common types are mucinous (10%), endometrioid (10%), clear cell, Brenner and undifferentiated carcinomas\(^27\). Borderline tumours (tumours of low malignant potential) tend to remain confined to the ovary for long periods of time and are associated with a very good prognosis. Metastatic implants can occur however, which can be divided into invasive and non-invasive. The former group has a higher likelihood of proliferating and progressing within the abdominal cavity, which can lead to intestinal obstruction and death\(^28\). Primary malignant transformation of the peritoneum is called peritoneal cancer. This has the appearance of “mullerian” cancer and simulates ovarian carcinoma clinically.

The use of perioperative frozen section analysis in apparent early stage disease has been shown to effectively guide surgical staging procedures and has been used in the USA for some time\(^29\). More recently, routine frozen section analysis has been performed in some centres in the UK with excellent results\(^30,31\). Sensitivity and specificity is reduced with borderline tumours, but this is not considered to have any significant clinical impact\(^32\).
FIGO Staging

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Growth limited to the ovaries.</td>
</tr>
<tr>
<td>Stage IA</td>
<td>Growth limited to one ovary; no ascites containing malignant cells. No tumour on the external surface, capsule intact.</td>
</tr>
<tr>
<td>Stage IB</td>
<td>Growth limited to both ovaries; no ascites containing malignant cells. No tumour on the external surface, capsule intact.</td>
</tr>
<tr>
<td>Stage IC</td>
<td>Tumour either stage 1A or 1B but with tumour on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Growth involving one or both ovaries with pelvic extension.</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Extension or metastases to the uterus or tubes</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Tumour either stage IIA or IIB but with tumour on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumour involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Tumour of one or both ovaries with histologically confirmed implants of peritoneal surfaces, none exceeding 2cm in diameter. Nodes negative.</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Abdominal implants &gt; 2cm in diameter or positive retroperitoneal or inguinal nodes.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytological test results to allot a case to stage IV. Parenchymal liver metastases equals stage IV.</td>
</tr>
</tbody>
</table>
4. Surgical Treatment

Initial surgery has historically been the standard for treatment of suspected or proven ovarian cancer. Indications for laparotomy include:

- establishment of diagnosis
- accurate staging
- optimal debulking/cytoreduction
- interval/secondary debulking
- palliation

In advanced disease, studies have consistently shown that the volume of residual disease remaining after debulking surgery inversely correlates with survival\(^{34,35}\). Compared to other intra-abdominal carcinomas, this aggressive approach to debulking is unique to ovarian cancer. Optimal debulking is most likely to be achieved under the care of a gynaecological oncologist as evidenced by studies, which have consistently shown that surgical treatment by non-gynaecological oncologists contributes to suboptimal surgical management and shorter median survival\(^{36-41}\). Furthermore, there is also the risk of underestimating the stage of disease, as earlier series have shown overall 5-year survival for apparent stage I disease was only 60\%\(^{42}\). Later studies have shown that with thorough surgical staging that the overall 5-year survival for stage IA or IB disease was reported at 90\%\(^{43}\).

**CLINICAL PRACTICE POINT 4**

The gynaecological oncology MDT should make an assessment of each case individually and ascribe a risk of malignancy. Low risk cases should be managed locally. Intermediate risk cases should be evaluated at the MDT and managed locally if appropriate. All patients deemed high risk should be referred immediately to the cancer centre for treatment.
4.1. Perioperative Issues

Patients with ovarian cancer are commonly in the elderly age group and have significant coexisting medical co morbidities. A designated anaesthetist for gynaecology often performs a thorough preoperative anaesthetic assessment at the earliest opportunity, and this will often involve the patient in a visit of several hours while clinical and notes review plus relevant investigations takes place. Patients should be warned to expect this, and ideally the timing should be negotiated to minimize inconvenience and travelling. In some cases, further expert review is required for example from cardiology, haematology and medicine in an effort to optimise the patient’s condition for major surgery, and there should be a rapid and robust mechanism to achieve this with minimal delay. In addition, patients with advanced disease have poor nutrition status and a significant percentage of patients require enteral and parenteral nutritional support both pre and postoperatively. Enhanced recovery programmes have attracted much recent interest in the UK, and are currently being evaluated with regard to its potential application. Preoperative bowel preparation should be undertaken where advanced disease is suspected, as the risk if bowel surgery is significant and the rate of infectious complications appears to be lower in patients who receive preoperative bowel preparation. Debilitated patients having bowel preparation are particularly susceptible to intravascular depletion and require careful immediate pre-operative fluid balance and rehydration. The risk of venous thromboembolism (VTE) is particularly high in these patients and VTE thromboprophylaxis is essential. Asymptomatic deep vein thrombosis (usually detected at the time of staging CT) sometimes necessitates placement of an inferior vena cava filter pre-op, which requires specialist interventional radiology expertise. Coexisting pleural effusions and/or ascites may need drainage at the time or just preceding laparotomy. Invasive monitoring is often needed and the laparotomy approach commonly utilizes extended midline incisions, which require epidurals/intrathecal opiates for adequate pain relief. The risk of intraoperative haemorrhage is high and in some cases, cell salvage is utilized. Cell salvage expertise can reduce the patients’ exposure to allogeneic blood transfusion and studies to date have suggested that the technique is safe and that tumour cells are reliably removed by the use of leukocyte depletion filtration. It is cost effective to set up the machine to collect operative blood loss and to only process and retransfuse if clinically indicated.
Postoperatively, fluid balance is a particularly challenging issue and patients with extensive co morbidities are cared for in a high dependency or intensive care setting usually for the first 24 to 48 hours. Adequate fluid and blood product replacement is important, particularly as these patients are likely to need chemotherapy postoperatively. Nursing and physiotherapy requirements can be extensive and specialized. Clinical nurse specialists provide support at the pre-operative phase, which continues throughout the patient journey. The pre-, peri and postoperative care provided to patients with advanced ovarian cancer is a major and complex undertaking, which requires optimal delivery of care to patients who are medically infirm, in an efficient and timely manner. Such a coordinated multidisciplinary effort is one of the main strengths of the cancer centre.

4.2. Low Risk Disease (Cancer Unit)

The procedures to be carried out at laparotomy include the following:

- Total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH+BSO) via a midline incision.
- Peritoneal washings.
- Consider omental and peritoneal biopsies if a suspicious lesion is suspected.
- If fertility preservation is a consideration, a unilateral salpingo-oophorectomy could replace TAH+BSO especially if the contralateral ovary appeared normal.

4.3. High Risk Disease (Cancer Centre)

This may be further subdivided into apparent early-stage disease and advanced disease.

Early Stage Disease

Early stage disease may be suspected preoperatively upon review of imaging at the MDM. As before, a midline approach is recommended.

Optimal surgical staging constitutes: midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum; and retroperitoneal lymph node assessment. The advantage of thoroughly staging these patients in addition to providing accurate prognostic
information, is the potential avoidance of chemotherapy in patients with histologically confirmed, well differentiated stage IA or IB disease. One approach is to remove the ovarian tumour intact, if possible and a frozen section histological section obtained as a guide to staging. This approach has been adopted in many centres worldwide and some centres in the U.K. The accuracy of frozen section has been analysed, with acceptable sensitivities and very good specificities respectively. Concerns have been raised regarding the accuracy of frozen section when large masses are assessed. Routine implementation of frozen section analysis of adnexal masses in South Wales is under review and is not currently considered standard practice.

**If disease appears to be confined to the pelvis, the following may be performed in addition to TAH+BSO:**

- Aspiration of any ascites for cytological examination.
- If no ascites, peritoneal washings should be performed with samples being taken from the pouch of Douglas, each paracolic gutter and from beneath each hemidiaphragm.
- Systematic exploration of all intra-abdominal surfaces and viscera.
- Biopsy of any suspicious peritoneal surfaces or adhesions. If no suspicious areas identified, peritoneal biopsies should be taken from 4 quadrants as for washings above.
- Diaphragmatic surface irregularities should either be biopsied or smeared for cytological evaluation.
- Infracolic omentectomy.
- Appendicectomy should be performed if a mucinous tumour is suspected.

**Assessment of pelvic and para-aortic nodes**

The role of pelvic and para-aortic lymph node sampling is controversial. As many as three in ten patients whose tumour appears confined to the pelvis have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes. The retroperitoneal spaces
should be assessed and suspicious nodes should be removed and sent for histological analysis. NICE have recommended that systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) should not be included as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease)(1). More recent evidence appears to be reassuring, in that in a retrospective review of 721 patients treated for epithelial ovarian cancer (EOC) with apparent early stage disease, no survival differences were noticed between EOC patients who had negative lymph nodes after surgical staging and did not receive chemotherapy, versus patients who did not have lymphadenectomy but did receive chemotherapy. It would appear therefore that the potential under staging of ovarian tumours could be compensated for by overtreatment of patients with chemotherapy (which historically is probably the case in many centres where lymphadenectomy is not routinely performed). In the absence of prospective randomised data to determine the therapeutic effect of systematic lymphadenectomy and until frozen section analysis becomes more widely available, this approach may be acceptable. However it is recommended that survival outcomes for stage 1 ovarian cancer are assessed locally, to ensure that the observations alluded to above are comparable.

Following complete surgical staging, these women may be further divided prognostically based on high-risk variables, which include: high grade disease, clear cell histological type, tumour growth through capsule, surface excrescences, ascites, malignant cells in fluid, preoperative rupture, dense adherence and aneuploidy50,51.

Fertility Preservation

There is retrospective data to suggest that fertility conserving procedures in patients with stage 1 epithelial cancer have excellent long-term survival and good pregnancy outcomes52. The uterus and contralateral ovary can be retained in women wishing to preserve fertility provided they have undergone a thorough staging laparotomy where it was confirmed that there was no disease outside the pelvis53. This applies as well to patients with borderline ovarian tumours54. Caution should be applied however to patients with grade 3 or higher stage disease, as there is a significantly higher recurrence rate and lower survival55. As such, completion hysterectomy plus removal of the contralateral ovary should be offered once childbearing is completed.
5. Advanced Disease (Cancer Centre)

There is evidence that survival of women with advanced ovarian cancer is improved when the surgeon is trained to perform cytoreductive surgery and when there is centralisation of care. The treatment aim of laparotomy for advanced disease is to achieve optimal cytoreduction. While there has been no prospective randomised trial to define the role of primary debulking surgery, there is a large body of retrospective evidence that supports the role of optimal cytoreduction prior to chemotherapy, both in terms of progression free survival and prolonged palliation. Older studies raised the question that platinum-based chemotherapy, not maximum cytoreduction, was the most important factor in determining prognosis. The benefit of maximal cytoreduction now seems clear and women with optimally debulked tumour have on average a 20-month improvement in median survival compared to those with suboptimal resection. There also appears to be benefit in optimal cytoreduction of stage IV disease. The Gynecologic Oncology Group (GOG) has the most widely accepted definition of optimal debulking, described as less than 1cm in maximum tumour diameter.

A growing body of evidence supports the role of cytoreduction to < 1mm or no visible disease with improved survival. So called ultra-radical surgery seems achievable in 22-25% of advanced stage III disease, with a lower cytoreduction rate in stage IV disease. These procedures include extensive peritonectomies, resection of subcapsular liver metastases, partial gastrectomy etc. Despite an increased incidence of postoperative morbidity, median survival for these patients is impressive enough to attract much interest in the UK, but this is not considered standard treatment at present.

Exceptions to initial surgical management include:

1. Patients with poor nutritional and performance status in addition to severe medical co morbidity. In these patients, the risk of perioperative morbidity and mortality may be unacceptably high.

2. Patients in whom an extra-ovarian primary tumour is a possibility and has not been excluded.

3. Preoperative assessment of resectability and optimal clearance: This relates to patients who appear to have such a high tumour burden that optimal cytoreduction does not appear to be feasible. In this scenario, location of disease appears to be paramount and
includes the presence of extensive disease on the diaphragm, liver parenchyma, along the base of the small bowel mesentery, the lesser omentum and the porta hepatis\textsuperscript{57}.

Predicting optimal cytoreduction is very difficult and may be related to the following\textsuperscript{66}: High preoperative CA125, strong expression of the p53 tumour suppression gene and imaging (CT, CT/PET and MRI). Preoperative CT has shown promise, but caution regarding its use has been advised in a validation study\textsuperscript{67}. Efforts to improve the prediction of optimal cytoreduction include the use of diagnostic laparoscopy, which has been shown to be very useful\textsuperscript{68,69}. There is concern however regarding the significant risk of port site metastases\textsuperscript{70}.

**Decision making of this nature is complex and the role of the MDT is crucial in this regard.**

The planning and implementation of an efficient cytoreductive surgery service requires advanced operating theatres with highly skilled theatre staff. Involvement of other oncological surgical subspecialists is often required and there is a significant impact on operating time. Such a high demand on specialist resources can only be readily achieved and maintained at the cancer centre.

**5.1. Procedure For Cytoreductive Surgery**

The aim is to remove the entire primary tumour and as much metastatic disease as possible. The Gynaecologic Oncology Group definition for optimal cytoreduction is proposed, which is less than 1cm in maximum tumour diameter.

As before, a vertical midline approach is recommended, this can be extended if necessary:

- TAH+BSO – this is very seldom straightforward and commonly requires a retroperitoneal approach depending on pelvic anatomy.
- Supracolic and infracolic (total) omentectomy.
- Sampling and drainage of ascites (or washings if no ascites).
- Resection of all macroscopic peritoneal deposits > 1cm in diameter.
The following should be considered especially if it allowed maximal cytoreduction to be achieved:

- Rectosigmoid excision (en bloc with uterus, ovarian masses and pelvic peritoneum - Hudson procedure\(^2\)) or intestinal resection: These procedures may also be considered in the setting of obstruction.
- Appendicectomy
- Splenectomy\(^2\)
- Partial hepatic resection\(^3\)
- Debulking of grossly suspicious lymph nodes

Factors limiting optimal cytoreduction at the time of surgery include:

- Diffuse encasement of small bowel mesenteric vessels – in this setting, multiple small bowel resections and/or a permanent ileostomy are not advised.
- Infiltration of porta hepatis.
- Diffuse infiltrative involvement of the right hemi-diaphragm including the suprahepatic inferior vena cava (IVC).

**Systemic Lymphadenectomy**

While resection of grossly suspicious lymph nodes is considered part of the surgical debulking procedure, systemic lymphadenectomy has not been shown to confer a significant survival advantage\(^4\) and as such is not currently part of UK standard practice.

**5.2. Interval Debulking Surgery (IDS)**

Previous studies supported the concept that primary chemotherapy rendered surgical debulking less morbid and technically easier\(^5,6\). The impact on survival however compared to primary surgery followed by chemotherapy remained unanswered. Neoadjuvant chemotherapy followed by surgery (NCAT-S) is the term applied to the strategy of primary chemotherapy in surgically resectable cases. The EORTC Randomised trial 55971 compared NACT-S with standard primary surgery followed by platinum-based chemotherapy\(^7\) while the MRC CHORUS study is similar but with less stringent entry
criteria\textsuperscript{78}. Results recently published by the EORTC group showed that IDS in this context was no less effective than primary debulking in terms of survival (29 versus 30 months), but was significantly less morbid\textsuperscript{79}. A major issue with the findings of this study relate to the inferior survival rates quoted, compared with American data from randomised studies on patients with advanced ovarian carcinoma undergoing primary debulking surgery followed by chemotherapy, which are now approaching 50\%\textsuperscript{80}. CHORUS closed recruitment recently and the results are awaited from the pooled analysis of both studies.

To ensure a consistent approach it is recommended that a protocol similar to the EORTC trial be adopted\textsuperscript{79}. Percutaneous biopsy should be done to confirm the diagnosis. If a biopsy specimen is not available, fine needle aspirate (FNA) showing adenocarcinoma cells may be acceptable under the following conditions:

- Presence of a pelvic mass
- Evidence of extra-pelvic spread > 2cm in size
- Regional lymph node metastases or stage IV disease
- CA 125/CEA ratio > 25. If < 25, consider GI endoscopy and mammography

The preferred standard is that primary treatment should begin within two weeks and no later than three weeks from the date of decision to treat. If primary chemotherapy is chosen, chemotherapy should be initiated no later than three weeks from the date of percutaneous biopsy or FNA.

In general, three cycles of chemotherapy are administered and a response to treatment is ascertained by clinical, radiological and biochemical means. If there is a response to chemotherapy (usually after 3 cycles), interval debulking should be offered followed by a further 3 cycles of chemotherapy. No response to chemotherapy is an indication for

\begin{center}
\textbf{CLINICAL PRACTICE POINT 5}
\end{center}

\textit{Until the data on interval debulking becomes clearer, its role at present is reserved for when primary optimal debulking is deemed unlikely, which should be based on the MDT’s assessment.}
experimental protocols and/or palliation. Following completion of 6 cycles, the MDT shall discuss the role of maintenance treatment or continued surveillance.

**CLINICAL PRACTICE POINT 6**

The goal standard remains optimal surgical cytoreduction, whether this is preceded by chemotherapy or not.

### 5.3. Management Following Suboptimal Cytoreduction

Prospective trials have been carried out to assess survival benefit of interval debulking after an initial surgical effort (maximal or suboptimal). The evidence is mixed, with one study suggesting improved survival\(^76\) while others have showed that a second attempt at cytoreduction for sub optimally debulked disease does not provide improved survival or long-term quality of life that is equivalent to that achieved by aggressive surgical debulking followed by combination chemotherapy\(^{81-83}\). As such it appears that the performance of a debulking operation as early as possible in the course of the patient’s treatment should be considered the standard of care\(^84\). There may still be some benefit to be derived by secondary surgical cytoreduction however. This is especially the case when the initial attempt at debulking was not carried out by a gynaecological oncologist\(^76\). Decisions of this nature are complex and should be made at the cancer centre MDT.

### 5.4. Second Look Laparotomy/Laparoscopy

The aim of this procedure was to assess response to chemotherapy. The evidence to date suggests that this procedure adds no survival advantage, although the information derived does correlate with subsequent outcome\(^85\). Furthermore, the value of tumour resection at the time of “second look” remains unclear. This procedure does not constitute standard practice in the UK.

### 5.5. Incompletely Staged Ovarian Cancer

This is a very undesirable situation that must be avoided. It can lead to inevitable delays in adequate staging and optimal debulking, which can have an adverse impact on treatment
and prognosis. One must also consider the significant morbid physical and psychological impact on the patient of having to undergo a second laparotomy.

A suggested approach to managing these patients is modified from the National Comprehensive Cancer Network (NCCN) guidelines:

1. A surgical staging procedure is recommended for all patients with suspected stage IA or IB, grade 1 tumours because, if this stage is confirmed, no further adjuvant therapy is indicated.

2. If potentially resectable residual disease is suspected, a completion surgical staging procedure with debulking is recommended for all stages.

3. For stages higher than stage IA or IB, grade 1, if no residual disease is suspected; chemotherapy or completion surgical staging may be considered. Observation after careful surgical staging is considered an option for stage IA or IB, grade 2 disease. For patients with stage II-IV disease, consider completion surgery after 3 cycles of chemotherapy followed by postoperative chemotherapy.

**CLINICAL PRACTICE POINT 7**

It is the responsibility of local MDT’s to ensure that all patients undergoing laparotomy for evaluation of a pelvic mass or suspected ovarian cancer are discussed preoperatively and referred promptly to the cancer centre if a high risk of ovarian cancer is suspected.
5.6. Role of Laparoscopy

Inappropriate treatment of malignant tumours by laparoscopic resection carries the risk of peritoneal dissemination of disease\textsuperscript{87}. There seems to be an increasing role for its use however in the following situations:

- Assessing resectability in advanced disease.
- Assessing possibility of recurrent disease.
- Staging of disease (especially in context of incomplete previous staging).
- Obtaining a diagnosis in primary disease when percutaneous biopsy is not feasible.

5.7. Secondary Cytoreduction

This may be defined as an attempt at cytoreductive surgery at some stage following completion of first line chemotherapy. It has been suggested that tumour resection under these circumstances should be limited to patients with a long natural history, with a disease-free interval of at least 12 months, with the possibility that all macroscopic disease can be resected\textsuperscript{88}. It is not known whether or not patients should be treated with chemotherapy alone in these circumstances or a combination of secondary cytoreductive surgery followed by chemotherapy. A recent Cochrane review on this issue was unable to arrive at a definitive conclusion due to a lack of good quality data\textsuperscript{89}.

5.8. Palliative Care

For patients for whom a palliative approach is appropriate, including those who need active treatment such as chemotherapy or surgery with palliative intent, the primary care team and the local MDT will lead on providing that approach. Sources of written guidance on symptom control for the non-specialist, and a summary referral guide, are included in Appendix 3 with reference to patients in South West Wales.
6. Chemotherapy

Inclusion in clinical trials, if available, is recommended for all patients with ovarian cancer who need chemotherapy. Outside clinical trials, the standard recommendations for chemotherapy are outlined here with regards to first-line (adjuvant or neoadjuvant) chemotherapy and treatments for relapsed disease.

6.1. First line chemotherapy

Early disease (FIGO I-IIa)

Completely debulked and optimally staged patients with FIGO Ia grade 1 tumours are at low risk of recurrence and can be managed by follow up only. Chemotherapy should however be considered in sub optimally staged patients.

Patients with risk factors for recurrence (grade >1; bilateral cancers; clear cell histology; capsule ruptured; presence of tumour on ovarian surface; malignant cells in ascites or peritoneal washings) should be offered adjuvant chemotherapy. NICE guidance states that platinum + taxol or platinum alone can be offered as alternatives to these patients; the use of single-agent carboplatin is supported by the ICON1 and ACTION studies\(^{46,47}\).

Advanced disease (FIGO IIb-IV)

Postoperative chemotherapy

NICE guidance states that platinum + taxol or platinum alone can be offered as alternatives to these patients; in practice, since all major international guidelines recommend combination therapy for patients with advanced disease, the carboplatin + paclitaxel regimen is usually considered the first choice:

Paclitaxel 175mg/m\(^2\) over 3 hours (give paclitaxel first)

Carboplatin AUC 5/6* over 30 minutes

Repeated every 21 days for 6 cycles

* Carboplatin doses are calculated with the Calvert formula:

Carboplatin dose in mg = (desired AUC) x (GFR+25)
AUC = 5 if GFR is measured by EDTA; AUC = 6 if GFR is calculated with the Cockroft-Gault formula:

$$1.05 \times (140 \text{- age}) \times \text{weight (kg)}$$

Serum creatinine (mmol/l)

Although EDTA clearance is the most accurate method for measuring GFR, the Cockroft-Gault formula can be used as a substitute in patients with stable renal function. Serum creatinine and weight should be rechecked before each cycle, but only in case of significant variations from baseline (GFR change >25%, or weight change >10%) the dose needs to be recalculated. Actual body weight should be used in the formula. In extremely obese patients (BMI>30) this can lead to overestimation of GFR, which should be rounded down to the upper limit of the normal range (125 ml/min). Round up to the lower limit of the normal range (40 mmol/l) when creatinine values are <40 mmol/l.

Weekly chemotherapy can be considered in frail patients who may not tolerate standard three-weekly carboplatin and paclitaxel:

Paclitaxel 60mg/m$^2$ over 1 hour (give paclitaxel first)

Carboplatin AUC 2 over 30 minutes

Days 1, 8, 15 every 21 days for 6 cycles

Single-agent carboplatin (weekly AUC 2 or three-weekly AUC 5-6) is an option for patients who are not suitable for the regimens listed above, or unwilling to accept hair loss.

Maintenance chemotherapy (beyond 6 cycles) may prolong progression free survival but there is no demonstration of overall survival benefit: in view of the additional toxicity, this is not a recommended strategy.

Bevacizumab given with first-line postoperative chemotherapy and as a maintenance therapy afterwards improves progression free survival. The effects on overall survival are not yet clear and this will determine whether or not this agent should become part of first-line management.
Postoperative chemotherapy should be preceded by a restaging CT scan of abdomen and pelvis. If this shows residual disease, another CT scan should be performed after completion of chemotherapy to document the overall results of primary treatment and serve as a new baseline if further scans are obtained during follow up.

Ca125 levels must be checked before starting postoperative chemotherapy and monitored during treatment. If CA125 fails to normalize by the end of chemotherapy, the nadir level will be used as baseline to assess biochemical progression during follow up.

**6.2. Intraperitoneal Chemotherapy (IPC)**

Studies have shown (including a systematic review) that IPC is associated with better outcomes than intravenous chemotherapy. This led to a National Cancer Institute announcement in 2006 recommending that women with optimally debulked Stage 3 ovarian cancer be considered for IPC. Serious concerns have been raised however regarding its associated morbidity and technical difficulties. As such it is not considered standard practice in the UK at present.

**6.3. Neoadjuvant chemotherapy**

Neoadjuvant chemotherapy with interval debulking surgery is an option when primary optimal debulking is considered unlikely by the MDT. The treatment protocol should emulate as much as possible the EORTC study, with an aim of starting chemotherapy within 3 weeks from biopsy. IDS should be performed after 3 cycles in all non-progressing patients; chemotherapy is restarted no later than 6 weeks after IDS and given for 3 more cycles.

**6.4. Chemotherapy for relapsed disease**

The choice of second- and further line chemotherapy traditionally depends on an evaluation of the likelihood of platinum sensitivity. Patients who relapse more than 6 months from completion of previous platinum-based chemotherapy are considered as potentially platinum-sensitive. Combination chemotherapy with carboplatin + paclitaxel is supported in this setting by the results of the ICON4/AGO/OVAR trials, suggesting survival improvement compared to single-agent platinum. However the combination of carboplatin + liposomal doxorubicin is an acceptable alternative, especially in patients where avoidance of paclitaxel is desired (e.g. persistent neuropathy, history of intolerance, desire to avoid alopecia):
Carboplatin AUC 5 over 30 minutes +

Liposomal doxorubicin 30 mg/m2 over 60 minutes

Repeated every 28 days

Platinum-refractory (progressing during platinum-based chemotherapy) and platinum-resistant patients (progressing within 6 months from completion of previous platinum-based chemotherapy) have a poor prognosis. Response rates to further chemotherapy with non-cross resistant agents are low, but a small proportion of patients maintains sensitivity to chemotherapy for prolonged periods and may benefit from multiple lines of chemotherapy. In these patients, active drugs are often given as single agent chemotherapy:

Liposomal doxorubicin 40 mg/m2 over 60 minutes every 28 days

Topotecan 1.25 mg/m2 day 1-5 every 21 days

Topotecan 4 mg/m2 days 1, 8, 15 every 28 days

Gemcitabine 1000 mg/m2 days 1, 8, 15 every 28 days

Paclitaxel 80 mg/m2 weekly

Oral etoposide 50 mg bd days 1-14 every 21 days

The value of endocrine therapy with tamoxifen or aromatase inhibitors is not fully defined, but it represents a low-toxicity option in patients with asymptomatic relapsed disease as alternative to watchful waiting.

6.5. Response Evaluation

This is usually achieved with a combination of CA 125 and CT scans. Women with an elevated CA125 pre-treatment should have their CA125 levels checked at regular intervals during chemotherapy as levels correlate with tumour response and overall survival. CT scans are useful as a baseline and usually do not need to be repeated until completion of six cycles of chemotherapy, or if there is suspicion of progression on treatment. Patients with normal baseline CA 125 should have a CT scan after 3 cycles to assess response, as should patients who are being considered for interval debulking.
6.6. Follow Up

Absence of symptoms does not indicate absence of disease as approximately 40% of asymptomatic women with no clinical evidence of recurrence can have disease at the time of second-look laparotomy. Elevated CA 125 can accurately predict tumour recurrence and often does so prior to symptoms developing. A recent randomised study however showed no difference in survival in patients treated with second-line chemotherapy at biochemical relapse compared to patients who delayed treatment until they became symptomatic. The authors suggested that on the basis of no increased survival benefit, that there was no value of performing routine CA 125 levels. This may be an oversimplification as there clearly must be some value in having a marker that predates symptomatic relapse, for example patients with a long natural history that might be candidates for secondary cytoreduction. It is recommended that until further data emerge patients are counselled at the time of follow up regarding the relative limitations and advantages of routine CA 125 measurement and a decision be made regarding its use on an individual basis.

Clinical follow up should take place on a three monthly basis for the first year, followed by six monthly intervals for two years, followed by annual review for a further 2 years. Consideration should be given to the establishment of nurse-led follow up clinics, with the combined oncology clinics reserved for patients at high risk or with suspected relapse.

7. Germ Cell And Other Non-Epithelial Cancers

These are a heterogeneous group of cancers which are rare but often curable. The management of these cancers should always be discussed in a multidisciplinary setting to ensure appropriate diagnosis, choice of surgical treatment and adjuvant treatment.

The following non-epithelial ovarian cancers will be discussed:

- Carcinosarcoma of the ovary
- Sex-cord and stromal tumours
- Germ cell tumours
- Small cell and NET tumours of the ovary
- Squamous carcinoma arising within a dermoid cyst
- Struma ovarii malignum
7.1. Carcinosarcoma of the ovary

These are rare tumours accounting for approximately 2-4% of all ovarian cancer tumours. Surgically these should be treated as EOCs and undergo compete surgical staging.

**Treatment**

This should be considered in all patients with carcinosarcoma as all should be considered as high grade even stage 1. There is still no consensus on the optimal chemotherapeutic regimen for these patients; carboplatin and paclitaxel or regimens including ananthracycline and ifosfamide can be considered. Small series have reported similar response rates between these regimens: **the local preference is for carboplatin and paclitaxel as per EOC as first line treatment.** Patients with poor performance status can be offered single agent carboplatin in this setting. In patients with advanced disease or recurrence ifosfamide has shown activity but these patients are often treated using recommendations for EOC.

Follow-up should follow protocol as for EOCs.

7.2. Sex-cord and ovarian stromal tumours

These tumours account for approximately 7% of malignant ovarian cancers and derive from the sex cords and ovarian stroma or mesenchyme. These tumours can present with a combination of various elements including the female cells (granulosa cells, theca cells and their luteinized derivatives), male cells (Sertoli and Leydig cells) and fibroblasts of gonadal stromal origin as well as morphologically indifferent cells. This classification includes:

- Granulosa cell tumours, adult and juvenile forms

Granulosa cell tumours (GCT) are the commonest tumour in this group accounting for 70% of all malignant sex-cord stromal tumours and 3-5% of all ovarian cancers. The adult type account for 95% GCT’s and usually occurs in perimenopausal women. It often presents with symptoms of excess oestrogen with endometrial hyperplasia, post-menopausal bleeding and pain and rarely a virilisation syndrome. Serum marker CA 125 is often not helpful and other markers can be helpful in diagnosis and monitoring disease e.g. oestradiol and inhibins. More than 95% of these tumours are unilateral and 78-91%
are diagnosed at stage 1. This tumour has good long-term prognosis but can relapse very late and long-term follow-up is necessary.

Juvenile GCT tends to occur in prepubertal girls and often presents with unilateral, early stage disease. The majority present with isosexual precocious pseudo puberty, although rarely a virilisation syndrome can occur due to an androgen-secreting tumour.

- Fibromas, thecomas and fibrothecomas
- Sertoli cell, Leydig cell and Sertoli-Leydig cell tumours

These tumours most commonly occur in women <75 years and are rare accounting for <0.2% of ovarian cancer. These tumours are often stage 1 at presentation and low-grade with <20% becoming clinically malignant. Overall 5 year survival is 70-90% with recurrences usually occurring early. Again CA 125 is not helpful but testosterone can be a helpful marker

- Gynandroblastomas
- Sterol cell tumours
- Sex –cord tumour with annular tubules
- Associated with Peutz-Jegher syndrome
- Unclassified

**Treatment**

Cytoreductive surgery is the mainstay of treatment and is necessary to establish a diagnosis. The surgical principles are the same as in EOC although in apparent localized disease fertility-sparing surgery can be considered.

The only prognostic factor consistently significant in these cancers is the stage of disease. For Sertoli-Leydig cell tumours stage, histological differentiation, presence of heterologous elements and tumour rupture appear to have prognostic significance.
7.3. **Granulosa cell tumours:**

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<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A</td>
<td>Adjuvant treatment not indicated</td>
</tr>
<tr>
<td>Stage 1C with pre-operative rupture, malignant ascites and high mitotic activity Stage&gt;1</td>
<td>Adjuvant platinum-based therapy (BEP or platinum-taxane)</td>
</tr>
</tbody>
</table>
| Recurrent disease pelvic/intra-abdominal | Consider secondary debulking
Consider platinum-based therapy as guided by previous treatments
Consider RT for localised disease |
| Recurrent disease distant | Consider platinum-based therapy as guided by previous treatments
Hormonal treatment in selected patients |

7.4. **Sertoli-Leydig tumours:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (no high risk factors)</td>
<td>Adjuvant treatment not indicated</td>
</tr>
<tr>
<td>Stage 1, poorly differentiated with retiform component and mesenchymal heterologous elements</td>
<td>Adjuvant platinum-based therapy (BEP or platinum-taxane)</td>
</tr>
<tr>
<td>Stage &gt;1</td>
<td>Adjuvant platinum-based therapy (BEP or platinum-taxane)</td>
</tr>
</tbody>
</table>
| Recurrent disease | Consider salvage surgery
Platinum-based chemotherapy (BEP or platinum-taxane) |

Long-term follow-up is recommended as recurrences can occur very late.

7.5. **Germ-cell tumours**

These tumours account for approximately 5% of ovarian tumours but with a high incidence in young women or adolescent girls\(^{100}\).

This classification includes:

- Dysgerminoma
- Endodermal sinus tumour
- Embryonal carcinoma
South Wales Guidelines for the Management of Ovarian Cancer - Version 1.0 – 11/11/11

- Polyembryoma
- Choriocarcinoma
- Teratoma: immature
- Teratoma: mature
- Solid cystic: dermoid cyst (mature cystic teratoma) or dermoid cyst with malignant transformation
- Monodermal and highly specialized: struma ovarii carcinoid, struma ovarii and carcinoid
- Mixed forms

These tumours often present with abdominal pain with rapid progression. Ascites or peritonitis secondary to torsion, infection or rupture of the tumour is also possible. Other less common symptoms are abdominal distension and vaginal bleeding. Approximately 60-70% of women present with FIGO stage 1 or 2 disease, 20-30% stage 3 and stage 4 is infrequent. These tumours are often unilateral except for dysgerminomas which can present with bilateral disease in 10-15% cases. Tumour markers (AFP, β-hCG and LDH) can be helpful in diagnosis and should be considered in any young women presenting with a pelvic mass.

**Treatment**

Initial management should be cytoreductive surgery. As a high number of cases are stage I fertility-sparing surgery can be considered.

<table>
<thead>
<tr>
<th>Stage I dysgerminoma</th>
<th>Observe with markers if initially elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, grade 1 immature teratoma</td>
<td></td>
</tr>
<tr>
<td>Embryonal tumour</td>
<td>BEP chemotherapy</td>
</tr>
<tr>
<td>Endodermal sinus tumour</td>
<td>3 -4 cycles</td>
</tr>
<tr>
<td>Stage II-IV dysgerminomas</td>
<td>Recommend pulmonary function tests if considering bleomycin</td>
</tr>
<tr>
<td>Stage I, grade 2 or 3 or stage II-IV immature teratoma</td>
<td></td>
</tr>
</tbody>
</table>
Patients who achieve complete clinical response after chemotherapy require clinical follow-up with tumour markers every 3 months. Regular CT scanning has been recommended but MRI may provide a safer option in these patients by reducing radiation exposure. Treatment options for recurrent disease include surgical resection, chemotherapy e.g. TIP (paclitaxel, ifosfamide and cisplatin) or radiotherapy.

7.6. Struma ovarii malignum

These strumal carcinoids or malignant struma ovarii are very uncommon and are of endodermal origin with evidence of thyroid or C-cell differentiation arising from within a teratoma. Struma ovarii are a variant with >50% thyroid tissue within a teratoma.

Current treatment options include cytoreductive surgery and then discussion for total thyroidectomy and management as for differentiated thyroid carcinoma with radio-iodine imaging and ablation.

7.7. Squamous cell carcinoma arising within dermoid cyst/teratoma

Malignant transformation within a dermoid cyst occurs in approximately 1-2% of cases and in over 80% cases is a squamous cell carcinoma. These tend to occur in older women with late symptoms due to pressure or torsion.

The initial treatment option is for surgical cytoreduction. If the disease is confined to the ovary without rupture then adjuvant treatment is not necessary but in more advanced cases chemotherapy is advised. There is still considerable debate about which chemotherapy regimen to use. The options include BEP, cisplatin and 5-fluorouracil regimens or carboplatin and paclitaxel. RT can be considered as local treatment for palliation.

7.8. Small cell and neuro-endocrine cancers

These are rare and account for approximately 1% of ovarian cancers. This classification includes:

- Small cell carcinoma of ovary of pulmonary type
- Small cell carcinoma of ovary of hypercalcaemic type
- Non-small cell neuro-endocrine carcinoma (large cell variant)
- Classical primary carcinoid (well differentiated neuroendocrine cancer)
- Classical carcinoid metastatic from primary gastrointestinal type
These tumours, except for carcinoids, are often very aggressive with high mortality beyond stage 1.

**Treatment**

Standard surgical cytoreduction should be considered. Evidence is limited but suggests that adjuvant chemotherapy should be considered with platinum and etoposide similar to regimens for small cell lung cancer. Pelvic radiation may also improve survival and should be discussed.
8. Metastatic Tumours

It must be remembered that 5-6% of ovarian tumours represent metastases from other organs, which include the female genital tract, breast or gastrointestinal tract (GIT). Krukenberg tumours can account for 30-40% of metastatic tumours to the ovaries, arises in the ovarian stroma and are most frequently associated with the stomach or colon and usually not until the primary disease is advanced. Metastatic colon cancer can mimic a mucinous cystadenocarcinoma of the ovary. Metastatic lesions from the appendix are particularly difficult to differentiate, especially when associated with pseudomyxoma peritonei. It is important to remember the possibility of metastatic lesions to the ovary and appendicectomy should be performed if a mucinous tumour of the ovary is suspected. In addition, the presence of GI symptoms pre-operatively, should prompt consideration of further investigation of the GI tract before subjecting the patient to laparotomy.

9. Borderline Ovarian Tumours

Tumours of low malignant potential (borderline tumours) are a heterogeneous group of lesions that are defined histologically by atypical epithelial proliferation without stromal invasion. They account for 10-15% of all ovarian tumours and occur predominantly in premenopausal women, whereas invasive carcinomas are more commonly found in an older age group. Prognosis is generally good however there is a mortality risk in a small group of patients who develop invasive, proliferative peritoneal disease.

9.1. Background

The majority of tumours are serous, with up to 25-50% being bilateral. Most patients present as stage 1 disease, but 25-30% of women with serous tumours will have extra-ovarian disease at the time of presentation. Micropapillary features increases the risk of both invasive peritoneal implants and recurrence. Mucinous tumours make up the other common histological type. Pseudomyxoma peritonei is associated in 10% of ovarian mucinous tumours. In these cases, the tumour is potentially of appendiceal origin and therefore is not classified as a borderline ovarian tumour.

9.2. Diagnosis

Most patients usually present with an asymptomatic pelvic mass, however symptoms can present in keeping with any adnexal mass e.g. due to torsion/infarction, pressure
symptoms etc. CA 125 is not a good discriminator\textsuperscript{106}. Sonographic appearances vary widely. Use of CT, MRI and TVS doppler have been shown to predict likelihood but are not specific enough\textsuperscript{108}. Diagnosis is made at histology.

**9.3. Surgery**

Borderline ovarian tumours are staged surgically using the same FIGO criteria as for other ovarian tumours. The main advantages of complete surgical staging are that prognostic information is improved, in addition to discovering areas of occult invasive disease. Frozen section can be performed at the time of operation, which can help determine the extent of the staging procedure. The diagnostic accuracy of frozen section results of ovarian pathology has been reported to have a sensitivity of 65-100\% and specificity of >99\% when compared with the final pathological diagnosis\textsuperscript{47}. There are factors that lower sensitivity however, particularly size (>10cm)\textsuperscript{48}.

Furthermore, it has been estimated that 6-27\% of patients with a frozen section diagnosis of borderline tumour will be upgraded to invasive cancer on final histological examination\textsuperscript{103}.

**CLINICAL PRACTICE POINT 8:**

It is recommended that all cases of borderline ovarian tumours (diagnosed post-operatively) are referred to the cancer centre for pathological review.

Staging laparotomy may be radical or conservative, depending on whether or not fertility sparing is a consideration. Laparotomy is preferred to laparoscopy, due to concerns regarding cyst rupture and recurrence, especially if the cyst is > 5cm diameter\textsuperscript{109}. A French multicentre study showed that following surgical restaging; only 50\% of patients were properly staged originally. Peritoneal deposits were present in 58\%(pelvic) and 48\%(abdominal), with the omentum being involved in 39\%, of which 9\% had invasive implants\textsuperscript{109}. On the other hand, systemic lymphadenectomy can be omitted as it appears to offer low prognostic value\textsuperscript{110,111}. In the presence of mucinous tumours, appendicectomy and close inspection of the gastro-intestinal tract should be considered\textsuperscript{112}. 
Recommended staging procedure (radical):

- Midline laparotomy
- TAH+BSO
- Omentectomy
- Peritoneal biopsies and resection of macroscopic deposits
- Appendicectomy if mucinous tumour suspected

**9.4. Fertility Sparing Surgery**

Conservative surgery should be considered given the fact that many of these patients fall into the reproductive age-group and the overall prognosis is good. Unilateral salpingo-oophorectomy is preferred to cystectomy due to the higher rate of recurrence with cystectomy alone\(^{113}\), especially in advanced stage disease\(^{114}\). The risk of recurrence overall ranges from 7 to 30% and can occur very late\(^{115}\), however recurrences are typically non-invasive\(^{116}\). There appears overall to be no effect on survival\(^{117}\) and although recurrence rates are higher in advanced disease, it would seem appropriate to consider fertility sparing surgery in all cases\(^{118}\). Pregnancy rates have been reported in excess of 30%\(^{119}\) and there is no evidence that these patients are at increased risk of mortality, nor does there appear to be a detrimental effect as a result of ovulation induction\(^{120,121}\).

It is recommended that the contralateral ovary is removed upon completion of family due to the higher rate of recurrence (15.2% vs. 2.5% for radical surgery)\(^{102}\).

**9.5. Restaging**

Upstaging of borderline malignancy can occur in 12-47% of presumed stage 1 serous tumours following a comprehensive surgical staging procedure\(^{109}\). Reasons for upstaging include positive peritoneal cytology, non-invasive implants and microscopic invasive implants. Studies however have shown that restaging has no impact on survival in that it remains high regardless of stage\(^{103,110}\). It is recommended that surgical restaging be considered when there is no description of the abdominal cavity and peritoneal surface, or where there is a suspicion of extraovarian disease\(^{122}\).
9.6. **Chemotherapy**

There appears to be no benefit to the use of adjuvant chemotherapy in women with early stage disease, although it may be considered in the presence of invasive implants\(^\text{124}\).

9.7. **Follow Up**

The role and method of follow up is not clear. It has been suggested that true recurrence and survival rates can only be achieved with 10 year and 20 year follow-up respectively\(^\text{124}\). Recurrence appears to be related to the use of chemotherapy, time from treatment and\(^\text{125}\) as well as a micropapillary/cribriform histological pattern\(^\text{124}\).

The patients at most risk are those who develop invasive serous carcinoma, but there is no evidence that follow up effectively detects recurrence nor made any difference to survival\(^\text{107,118}\). Several centres use a combination of clinical follow up, CA 125 and ultrasound. Radiological examination appears not to be important unless conservative surgery is adopted.

A suggested protocol is as follows:

CA 125 (if initially elevated) and clinical examination every 6 months for up to 5 years, then consider annual review for 10 years

If conservative surgery performed then add USS

Consider CT if recurrence suspected.

9.8. **Management Of Recurrence**

Surgical cytoreduction appears to be the best option, with some evidence of improved survival\(^\text{126}\). The presence of invasive disease may represent malignant transformation or de novo development of ovarian or primary peritoneal cancer, for which chemotherapy may be considered.
10. Appendix 1

The Risk of Malignancy Index gives an estimate of the risk of Ovarian Cancer for women with adnexal masses.

The RMI is calculated using ultrasound findings (U), menopausal status (M) and CA125 value (serum levels >35U/ml abnormal).

\[
RMI = U \times M \times CA125
\]

Ultrasound findings are scored with one point for each of the following:

- Multi-locular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 0 (ultrasound score of 0)
U = 1 (ultrasound score of 1)
U = 3 (ultrasound score of 2 – 5)

Menopausal status is defined as women who have had no period for more than one year or women over the age of 50 years who have had a hysterectomy and is scored as follows:

Postmenopausal status is graded M = 3,
Pre-menopausal status is graded M = 1

MANAGEMENT GUIDE:

<table>
<thead>
<tr>
<th>RMI SCORE</th>
<th>RISK</th>
<th>PLAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>LOW</td>
<td>Manage locally</td>
</tr>
<tr>
<td>25-250</td>
<td>INTERMEDIATE</td>
<td>Discuss at MDT and manage locally if appropriate</td>
</tr>
<tr>
<td>&gt;250</td>
<td>HIGH</td>
<td>Arrange further investigations and refer immediately to cancer centre</td>
</tr>
</tbody>
</table>
11. Appendix 2 PATIENT PATHWAY

**SUSPECTED OVARIAN CANCER**

1. **Clinical/Markers/USS**
2. **Calculate RMI**
3. **Local MDT**
   - **Risk assessment**
   - **Decision to treat**
4. **Further imaging CT/CXR**
5. **Cancer Centre**
   - **Rapid Access clinic (RAC)**
   - **Decision to treat/ Supportive care**
7. **Cancer Network MDT**
   - **Further treatment**
8. **Cancer Centre**
   - **Primary or Interval Surgery**
9. **Cancer Network MDT**
   - **Neoadjuvant Chemotherapy**
   - **Palliative Care**
   - **Adjuvant Chemotherapy**
10. **Palliative Care**
11. **Downgrade and/or Discharge**

**Intermediate or low risk**

**Advanced disease**
- ascites/omentum cake/pleural effusion
- tap ascites/effusion for cytology

**REFER**

**RMI<250**

**RMI>250**

**Low risk**

**High risk**

**7 days**

**14 days**

**21 days**

**31 days**

**62 days**
11.1. PATHWAY OVERVIEW:

Most patients will enter the USC (urgent suspected cancer) pathway having been referred by their general practitioner. The risk of malignancy index (RMI) is calculated and if deemed high-risk, the patient will likely undergo further imaging prior to being referred directly to the cancer centre rapid access clinic (RAC). Patients at intermediate or low risk will be managed according to local MDT policy, using guidance established at a cancer network level. The local MDT may consider a patient to have high-risk features (regardless of the RMI) and can refer such a patient directly to the cancer centre.

Patients may present initially with advanced disease – suspicious of ovarian or peritoneal origin. In such cases, a diagnostic cytology tap (pleural and/or ascitic) should be performed and the case discussed at the cancer centre MDT.

Please note that there will be some overlap between diagnostic and supportive services provided at the cancer centre and cancer unit. For example, image – guided biopsies for the purpose of histological diagnosis may be performed in the cancer unit however the decision to proceed to image-guided biopsy with a view to neoadjuvant chemotherapy would be made at the cancer network MDT. It is envisaged that all diagnostic procedures will be carried out at the cancer unit, using standardised protocols and reporting procedures.
12. Appendix 3: Palliative Care

12.1. Palliative Treatment

Many patients who are treated for potentially life-limiting illness will be cured or may achieve useful and prolonged control or remission. However, many will die of that life-limiting illness. For patients who present with advanced disease palliative treatment may be the only option. Disease progression also necessitates a change in management, palliation becoming the main objective.

12.2. Palliative Care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. These cares involves the use of palliative interventions, a palliative approach and where appropriate the involvement of Specialist Palliative Care services.

12.3. The Palliative Care Approach

The Palliative Care Approach aims to provide both physical and psychosocial well-being. It is a vital and integral part of all clinical practice, whatever the illness or its stage, informed by a knowledge and practice of palliative care principles and supported by specialist palliative care. The goal of palliative care is the best possible quality of life for patients and their families. Palliative care embraces palliative interventions and includes rehabilitation, continuity of care and also terminal care of patients dying in any setting.

The key principles underpinning palliative care which should be practiced by all health professionals in primary care, hospital and other settings are:-

- focus on quality of life, which includes good symptom control
- whole-person approach, taking into account the person’s past life experiences and current situation
- care which encompasses both the person with life-threatening disease and those who matter to that person
- respect for patient autonomy and choice (e.g. over place of care, treatment options, access to specialist palliative care)
• emphasis on open and sensitive communication, which extends to patient, informal carers and professional colleagues.

Many aspects of palliative care are applicable from diagnosis onwards, in conjunction with specific treatments. The spectrum of services that may be needed will overlap with support services to other patients not in a palliative phase.

12.4. **Palliative interventions**

Palliative interventions are non-curative treatments given by specialists in disciplines other than specialist palliative care, aimed at controlling symptoms and improving a patient’s quality of life, *e.g.* the use of disease-specific treatments such palliative radiotherapy, chemotherapy, surgical procedures and anaesthetic techniques for pain relief.

12.5. **Symptom control**

Guidance on this is widely available, for instance from local specialist palliative care teams or from the text of the Palliative Medicine Handbook at [http://book.pallcare.info/](http://book.pallcare.info/).
12.6. **Referrals to specialist palliative care services in South West Wales**

Refer if the patient

<table>
<thead>
<tr>
<th>has progressive disease with an appropriate diagnosis (local variation; for non-cancer diagnoses discuss with local team)</th>
</tr>
</thead>
</table>

AND

<table>
<thead>
<tr>
<th>lives within the area covered by the service OR is registered with a GP within the area covered by the service OR is a hospital inpatient</th>
</tr>
</thead>
</table>

AND

<table>
<thead>
<tr>
<th>is willing to see the palliative care team (if able to discuss), OR if patient is not able to discuss then relevant carer is aware of the referral to the team unless there is clear reason not to inform them</th>
</tr>
</thead>
</table>

AND

<table>
<thead>
<tr>
<th>has one or more of the following:-</th>
</tr>
</thead>
</table>

- pain related to progressive disease uncontrolled by simple analgesia &/or first line strong opioid &/or 1st line adjuvant
- other physical symptom(s) uncontrolled by 1st line of drug treatment
- any severe related symptom uncontrolled within 48 hours of starting treatment of it
- symptoms uncontrolled after 48 hours in rapidly progressive disease
- psychosocial distress in patient or family concerning progressive illness, dying or related issues
- need for support and additional opinion on decisions such as whether treatments including artificial nutrition and hydration should be withheld or withdrawn
- need for further assessment of complex symptoms or other problems, or ongoing specialist support at home, following hospital discharge
- dying complicated by physical symptoms, psychological, social or spiritual distress in patient or family, complex care needs or other aspects of care for which specialist palliative care support or advice would be helpful |
### APPENDIX 4: PATHOLOGY REPORTING

**REPORTING PROFORMA FOR OVARIAN CANCER TO BE USED FOR PRIMARY OVARIAN CARCINOMA, BORDERLINE TUMOURS AND MMMT**

<table>
<thead>
<tr>
<th><strong>OVARIAN MASS</strong></th>
<th>LEFT / RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEIGHT OF OVARIAN MASS</strong></td>
<td>gm</td>
</tr>
<tr>
<td><strong>SIZE OF MASS</strong></td>
<td>x x cm</td>
</tr>
<tr>
<td><strong>CAPSULE</strong></td>
<td>INTACT / BREACHED</td>
</tr>
<tr>
<td><strong>MACROSCOPIC SURFACE TUMOUR</strong></td>
<td>YES / NO</td>
</tr>
<tr>
<td><strong>FALLOPIAN TUBE ATTACHED</strong></td>
<td>YES / NO</td>
</tr>
<tr>
<td><strong>TUMOUR TYPE PLEASE STATE HISTOLOGICAL TYPE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>GRADE OF TUMOUR (SEE RCPATH DATASET NOV 2010 FOR GUIDANCE)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MICROINVASION</strong> (FOR BORDERLINE TUMOURS ONLY)</td>
<td>PRESENT / ABSENT</td>
</tr>
<tr>
<td><strong>LYMPH NODES</strong></td>
<td>SUBMITTED / NOT SUBMITTED</td>
</tr>
<tr>
<td><strong>NUMBER OF NODES EXAMINED FROM EACH SITE</strong></td>
<td>N/A NO. SITE NO. SITE NO. SITE</td>
</tr>
<tr>
<td><strong>NUMBER OF NODES INVOLVED FROM EACH SITE</strong></td>
<td>N/A NO. SITE NO. SITE NO. SITE</td>
</tr>
<tr>
<td><strong>NODAL EXTRACAPSULAR SPREAD</strong></td>
<td>PRESENT / ABSENT N / A</td>
</tr>
<tr>
<td><strong>PERITONEAL BIOPSIES</strong></td>
<td>SUBMITTED / NOT SUBMITTED</td>
</tr>
<tr>
<td><strong>PERITONEAL BIOPSIES INVOLVED</strong></td>
<td>YES / NO SITE INVOLVED N / A</td>
</tr>
<tr>
<td>OMENTUM</td>
<td>SUBMITTED / NOT SUBMITTED</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>OMENTUM INVOLVED</td>
<td>YES / NO</td>
</tr>
<tr>
<td>IF Y SIZE OF LARGEST DEPOSIT</td>
<td></td>
</tr>
<tr>
<td>PERITONEAL WASHING SUBMITTED</td>
<td>YES / NO</td>
</tr>
<tr>
<td>PERITONEAL WASHING CONTAINS TUMOUR CELLS</td>
<td>YES / NO</td>
</tr>
<tr>
<td></td>
<td>N / A</td>
</tr>
<tr>
<td>FALLOPIAN TUBE INVOLVED</td>
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<tr>
<td>OVARIAN SURFACE INVOLVED</td>
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<td>LYMPHOVASCULAR SPACE INVASION</td>
<td>PRESENT / ABSENT</td>
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<tr>
<td>CONTRALATERAL OVARY - TUMOUR</td>
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</tr>
<tr>
<td></td>
<td>IF PRESENT SIZE</td>
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<tr>
<td></td>
<td>SURFACE INVOLVED</td>
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<td>YES / NO</td>
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<tr>
<td>ADDITIONAL COMMENTS</td>
<td></td>
</tr>
<tr>
<td>FIGO STAGE</td>
<td></td>
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</tbody>
</table>

PLEASE NOTE:
It is recommended that a full macroscopic description the specimen (uterus, omentum etc) is documented at the end of the report including any significant pathology.

IMMUNOHISTOCHEMISTRY:

If a percutaneous/laparoscopic/open biopsy is performed the minimum requirement for immunostaining is CK7 and CK20.
14. REFERENCES


5  Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence in Wales. 2010.


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56 Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 Trial. J Clin Oncol 2005 Dec 1;23(34):8802-11.


76 EORTC 55971: A Randomized phase III study comparing upfront debulking surgery vs neo-adjuvant chemotherapy in patients with Stage IIIc or IV epithelial ovarian carcinoma. [http://groups.eortc.be/gcg/studyprotocols.htm](http://groups.eortc.be/gcg/studyprotocols.htm) 2010


95 Rustin GJ, van der Burg ME, on behalf of MRC and EORTC collaborators. A randomized trial in ovarian cancer (OC) of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials). J Clin Oncol 27:18s, 2009 (suppl; abstr 1) 2010


### Guidelines for the Management of Cervical Cancer

<table>
<thead>
<tr>
<th>Version</th>
<th>1.0</th>
</tr>
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<tbody>
<tr>
<td>Author</td>
<td>Mr R Howells</td>
</tr>
<tr>
<td></td>
<td>Dr L Hanna</td>
</tr>
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</table>
1. Introduction

Cervical carcinoma is the third commonest cancer of the female genital tract in the UK. Approximately 3000 new cases were diagnosed in 2008 in the UK and there were around 1000 deaths\(^1\). Both the incidence and death rate for cervical carcinoma has declined in recent times, which may reflect the apparent success of the national cervical screening programme. This is despite an increased incidence of CIN. Risk factors for cervical cancer include; sexually transmitted high risk (HR) HPV infection, early onset of sexual activity, multiple sexual partners, the combined contraceptive pill and smoking.

1.1. Background

1.2. Pathology

- Most cancers are squamous (60-90%), the remainder are adenocarcinoma (10%), adenosquamous (<3-4%), sarcomas and others including adenoid cystic carcinoma and adenoma malignum.

- The primary tumour may spread by direct extension into adjacent structures, permeate lymphatics and at a late stage, spread into blood vessels.

- Direct spread to the vagina, cardinal ligaments and pelvic sidewall may occur and at a late stage may involve the ureters, bladder or rectum.

- Lymph nodes are initially involved close to the parametrium. Then spread is to pelvic nodes around the obturator, internal iliac external iliac and common iliac vessels. Para-aortic lymphadenopathy and blood borne distant metastases are generally believed to be late developments of the disease.

- 50% of women present at an early stage appropriate for a surgical cure.

- Symptoms may include; postcoital bleeding (PCB), intermenstrual bleeding (IMB), vaginal discharge, pelvic, back or leg pain, the sensation of a pelvic mass, or involvement of other structures giving rise to bowel or urological symptoms. However, the patient may be completely asymptomatic and a cancer may even be detected by cervical cytology.
1.3. Screening

In the Wales there is in operation a computerised system of call and recall for cervical cytology for all women between the ages of 20-64 years. Currently smears are performed every three years. Cervical screening has led to a reduction in the number of invasive cancers of the cervix as the rate of coverage has increased from 22% in 1988 to 83% in 1993 and 76.5% in 2009/10.

1.4. Diagnosis and Referral

Referral Pathways

1. **For GP:** If cancer of the cervix is suspected then referral should be to the Cancer Unit lead clinician or to the Cancer Centre MDT. Referral will be to a gynaecologist who has additional training in oncology.

2. **For non-oncological gynaecologists:** If the patient is referred to a gynaecologist, then referral to the lead clinician in gynaecological oncology in the Cancer Unit or the MDT in the Cancer Centre. If the woman presents with advanced disease, such as ureteric obstruction or bowel complications she may be seen initially by the urologists or the general surgeons. These patients should be referred to the gynaecological MDT in the Cancer Centre for consideration of further management.

3. The patient should be seen within 10 working days of the initial referral from the GP.

1.5. Investigations and staging

Initial cervical assessment (Cancer Unit or Cancer Centre)

- Any woman who has symptoms of PCB, IMB, persistent vaginal discharge, a suspicious looking cervix or invasion suspected either clinically or cytologically should be referred to a gynaecologist. If the suspicion of cancer is high, the woman should be referred for urgent assessment in the Cancer Unit.

- All urgent referrals with a suspected diagnosis of cervical cancer should be seen within 10 working days of receipt by the hospital of the referral.
• Formal assessment should include an assessment of disease extent and spread, and tissue should be obtained for histological diagnosis.

• Colposcopic assessment may be undertaken where features of invasion (abnormal vasculature, ulceration) may be present. Diagnosis depends on a suitably-sized biopsy (loop, cone or wedge biopsy).

• Initial pelvic examination and rectal examination because more advanced cancers present with a mass detectable at digital examination.

Investigations

These are performed in the Cancer Unit, Cancer Centre or Regional Imaging Centre

• Hb, U+E, liver function tests, 2 unit cross match

• MRI scan abdomen/ pelvis for: - primary tumour size, presence of lymphadenopathy (>1cm diameter), ureteric involvement and parametrial spread. (This is probably the most important investigation to perform in the pre-op work up for carcinoma of the cervix and is considered mandatory). This should be arranged locally with the aim that this is performed within 2 weeks of request. The scan needs to include upper abdominal imaging for lymph nodes. Cervical biopsy/loop/cone will cause some artifact and MRI should either be performed prior to this or after at least 1 week. IV gadolinium is not routinely required. IV buscopan may reduce artifact from bowel peristalsis if problematic. Parametrial spread is best assessed on high resolution small FOV T2 axial oblique imaging (i.e. perpendicular to the cervix). The following Royal College of Radiologists recommendations (2006) are considered the minimum standard within the Network:
Protocol for imaging of carcinoma of cervix

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Plane</th>
<th>Slice thickness</th>
<th>Field of view</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1W</td>
<td>Axial</td>
<td>6 ± 2mm</td>
<td>Whole pelvis</td>
<td>To localise primary lesions or identify pelvic nodes</td>
</tr>
<tr>
<td>T2W</td>
<td>Axial</td>
<td>6 ± 2mm</td>
<td>Whole pelvis</td>
<td></td>
</tr>
<tr>
<td>T2W</td>
<td>Sagittal</td>
<td>6 ± 2mm</td>
<td>Small</td>
<td></td>
</tr>
<tr>
<td>T2W Perpendicular to cervix</td>
<td>Oblique *</td>
<td>5 ± 2mm</td>
<td>Small</td>
<td>To assess parametrial spread</td>
</tr>
<tr>
<td>T1W/T2W</td>
<td>Coronal</td>
<td>6 ± 2mm</td>
<td>Large</td>
<td>Abdominal lymphnodes and kidneys</td>
</tr>
<tr>
<td>T1W**</td>
<td>Axial</td>
<td>6 ± 2mm</td>
<td>Medium/large</td>
<td>(abdomen)</td>
</tr>
</tbody>
</table>

* Perpendicular to plane of cervix and tumour

** Optional: Performed if pelvic lymph node enlargement is identified in the pelvis

- Chest X-ray (CXR will identify chest metastases or other disease).

- PET-CT scan for patients with stage IB2 to IVA or those with suspicious findings on conventional imaging, such as abnormal pelvic nodes on MRI.4

### 1.6. Staging

**Staging may be performed in the Cancer Unit or Cancer Centre**

- The patient requires an examination under anaesthesia to determine suitability for operative treatment. This determines the degree of encroachment of tumour into the vagina, to the pelvic sidewall and mobility of any mass.

- Staging should be undertaken by a suitably trained individual or under their direct supervision.

- Staging should include: EUA, with biopsies of suspicious areas, cystoscopy, and consider sigmoidoscopy if a high index of local invasion.
Cystoscopy follows with the initial drained urine sent for cytological examination.

Rectal examination is the most accurate clinical method to assess parametrial involvement and spread of tumour toward the pelvic sidewall.

Clinical staging will be used in conjunction with information from the MRI to provide an accurate pre-op assessment of stage and therefore suitability for surgical treatment.

*All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0mm and a horizontal extension of not >7.0mm. Depth of invasion should not be >5.0mm taken from the base of the epithelium of the original tissue – superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with ‘early (minimal) stromal invasion’ (approximately 1.0mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause (FIGO, 2010)*

### 1.7 Management

Patients are treated with primary surgery if the stage is IB1 or less, or occasionally for selected patients with stage IIA cancers that are no greater than 4cm. It is
recommended that the surgical management of all cases of invasive cervical cancer should be undertaken in the Cancer Centre\textsuperscript{6}. The only exceptions are highly selective patients (such as those with Stage IA1) who may be managed in the Cancer Unit. Patients who are unfit for surgery may be treated with radical radiotherapy.

- Primary radical chemoradiotherapy is the treatment of choice in patients if the clinical stage is IB2 to IIIB. An exception is highly selected patients with stage IIA disease which is no greater than 4cm, in whom it is felt adequate resection margins will be obtained and in whom radical surgery is the preferred treatment. In all patients with cancers of stage IB2 or above, immediate referral to a Cancer Centre should be made.

- Some patients with stage IV disease may be suitable for radical treatment. For those with stage IVA cancers, radical radiotherapy or occasionally primary exenteration may be indicated. For patients with stage IVB whose metastatic disease is confined to para-aortic nodes, radical radiotherapy may also be indicated.

- The second outpatient visit should be within two weeks of the staging procedure. At this visit, a management plan can be agreed between the doctor and the patient. The results of biopsies, X-rays and other imaging procedures should be available at this visit.

- The following refers to management of cervical carcinoma. For other rarer tumour types such as lymphoma, sarcoma or melanoma, the patient should be referred to the Cancer Centre MDT for an individualized treatment decision.

\textbf{Treatment of stage IA disease}

\textit{Radical surgery should be undertaken in the Cancer Centre}

- Loop or cone biopsy is suitable treatment for stage IA1 disease $\leq 3$mm stromal invasion\textsuperscript{7}, non confluence, no lymph-vascular space invasion and where excision is complete. This would be acceptable in an individual who wishes to retain her fertility. A suitably planned loop or cone biopsy may be both diagnostic and
therapeutic. The entire abnormality must be included in the pathological specimen and the diagnosis of microinvasion requires a 2cm deep loop or cone biopsy.

- For women wishing to retain their fertility a simple trachelectomy could appropriate if the stage is IA1 or IA2 without risk factors. The women must express a strong desire to maintain fertility. They will need to be fully counselled.

- Stage IA1 can also be managed by simple hysterectomy. The risk of distant nodal metastases is <1% in stage IA1.

- Lymph node metastases are seen in lesions extending deeper than 3mm with <5% risk of distant spread in stage 1A2 disease. For these tumours a more aggressive surgical procedure with pelvic node dissection and a modified radical hysterectomy (Level II) may be undertaken. This procedure may also be employed when there is a larger volume disease.

- Lymph-vascular space involvement (LVI) is a marker for more aggressive disease as does incompletely excised microinvasive disease. Both require more radical hysterectomy.

- If a patient wishes to preserve her fertility, a radical vaginal or abdominal trachelectomy could be considered.

- Cancers that invade beyond 5 mm in depth are at least stage IB and should be treated with radical surgery or radiotherapy.

- Adenocarcinomas have no direct equivalent to early invasive squamous lesions. Adenocarcinoma in-situ is known to have skip lesions in separate crypts and multifocal disease in approximately 15% of cases. CGIN also has a recurrence rate of 15% over four years. Care must be taken if they are to be treated in a similar conservative manner to squamous lesions, but there is a move to be more conservative in their management nowadays.

**Treatment of stage IB1 and selected stage IIA disease**

**Surgery**
• The optimal therapy is that which has the highest cure rates with the least associated morbidity.

• A radical vaginal or abdominal trachelectomy\textsuperscript{11} may be considered if: -
  1. There is a strong desire to maintain fertility.
  2. The tumour should ideally be less than 2cms in diameter.
  3. Ideally there should be no other risk factors such as LVI or poorly differentiated tumour.
  4. Their case need to be discussed in the Gynaecological MDM where the previous imaging and histopathology is reviewed prior to undertaking a decision whether or not a trachelectomy is feasible.

• They will also need to be fully counselled regarding the cure and failure rates (compared to radical hysterectomy – which is the ‘Gold Standard’ treatment). They should also be counselled regarding future fertility and pregnancy issues. A cervical cerclage should be considered at the time of trachelectomy.

• Wertheim hysterectomy is the surgical treatment in women with early stage disease (stage IB1 and IIA) fit for surgery. It involves a ureteric fistula rate of $<2\%$ in centres specialising in radical pelvic surgery.

• The operation involves a radical hysterectomy, removing parametrium, the upper third of vagina and a formal bilateral lymphadenectomy, removing the common iliac, internal and external iliac and obturator lymph nodes.

• The ovaries are only removed if there is coincident ovarian pathology or if the patient is approaching or beyond her menopause. This procedure involves close dissection to and mobilisation of the ureters explaining its association with urological morbidity, but careful surgical technique, five days of continuous bladder drainage, antibiotics and drainage of the lateral pelvic sidewalls, serve to limit complications. Attention to blood transfusion and thromboprophylaxis is important.

• For young women surgery also offers the opportunity to preserve the ovaries, it reduces the risk of sexual dysfunction and is not associated with the late sequelae
seen with radiotherapy. The nodal status influences long-term survival - the five year survival rate is approximately twice as good in node negative patients (90%) as in node positive patients (46%). There is no apparent difference in cure rates between the two modalities. For those offered surgical treatment this should be undertaken by appropriately trained doctors in the context of full support services.

- In highly selected cases, for example women with stage IVA cancers, primary exenterative surgery may be considered. Preoperative PET-CT scanning is indicated in these situations.  

**Postoperative radiotherapy**

Patients who have undergone surgery for cervical cancer may have histological findings that indicate further treatment with postoperative radiotherapy should be offered. If patients are fit enough, concurrent cisplatin chemotherapy should be added to radiotherapy.

Postoperative radiotherapy is indicated in the following situations:

- Positive pelvic lymph nodes
- Parametrial invasion
- Positive or close resection margin

**Definitive radiotherapy**

Radiotherapy may be preferable to surgery in patients with early disease (IA, IB1 and IIA disease) where a patient is unfit for surgery or in cases where nodal involvement has been detected on pre-operative staging. Very rarely, patients will decline surgery. It should also be used for Stage IB2 disease where the surgeon may be unsure of obtaining clear margins of excision.

**Treatment of stage IB2-IV disease**

- Radical radiotherapy is the treatment of choice in stage IB2 to IVA disease and may be considered in patients with stage IVB cancers whose disease is confined to the pelvis and para-aortic lymph nodes. Selected patients with stage IIA cancers that are no greater than 4cm in size may be treated with surgery as described earlier. Patients undergoing radical radiotherapy should be treated by external
beam therapy followed by an intracavitary insertion if possible depending on the response to therapy. A dose of 45 Gy in 25 fractions followed by an intracavitary dose of 21.3 Gy in four fractions to point A is recommended usually given as high dose rate (HDR).

- Five randomized-controlled trials from the USA compared radiotherapy with platinum based chemo-radiation in women with advanced cervical cancer. The results of these studies are consistent and demonstrate a significantly improved survival and progression free survival in women in the chemoradiotherapy group. Rates of both loco-regional and distant relapse were also significantly lower in the combined therapy group.

- It is now standard practice to use chemoradiotherapy in the management of women with locally advanced cervical cancer in women who are well enough to tolerate it. Cisplatin 40mg/m² is administered weekly for four weeks during the external beam therapy.

- In some cases (especially stages III and IVA), the volume of residual disease is too large for intracavitary treatment and further external beam therapy to a reduced volume may be required. In patients who are elderly with poor performance status and stage IVA disease radical radiotherapy may not be appropriate.

- Radical radiotherapy and radical chemoradiotherapy for cervical cancer should be undertaken by an oncologist with a site-specialist interest in gynaecological cancers.

- Patients with stage IVB cervical cancer whose disease is confined to the pelvis and para-aortic lymph nodes should be considered for radical radiotherapy or chemoradiotherapy. Patients with stage IVB cervical cancer whose disease extends outside of a radical radiotherapy treatment volume are treated with palliative intent.

**Management of recurrent cervical cancer and palliative treatment**

- The patient should be referred to the gynaecological, radiation or medical oncologist or to the MDT in the Cancer Centre. If radical treatment is planned it
should be conducted in a centre suitably equipped and with the appropriate support facilities including an intensive care unit.

- Cases of pelvic recurrence after surgery in patients who have not already received radical radiotherapy are generally treated with radiotherapy or with chemoradiotherapy.

- Cases of recurrence following radiation, where the disease is confined to the pelvis can be managed with exenterative surgery in women who are fit.

- PET-CT imaging should be considered in all cases of recurrence when further radical treatment is being considered\textsuperscript{4}.

- No single treatment protocol exists for recurrent disease beyond the pelvis, or in those women who have failed radiotherapy and are not candidates for further surgery.

- Platinum based chemotherapy may be given as a palliative measure. Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin\textsuperscript{18}.

- Women with advanced recurrent disease may also be recruited into clinical trials for novel treatment.

**Cervical cancer in pregnancy**

- This relatively rare, with an incidence of approximately 0.05%.

- Women with cervical cancer in pregnancy should be referred to the MDT in the Cancer Centre.

- Most women present with abnormal bleeding, although 20% of women who present are asymptomatic. The survival figures stage for stage are the same as those for women who are not pregnant. It is now believed that the route of delivery of the child does not affect the overall five year survival.

- Cone biopsy can result in excessive bleeding and spontaneous abortion. The absolute indications for cone biopsy include a cervical smear suspicious of
invasive cancer with no colposcopic proof, and colposcopic suspicion or directed biopsy indicating invasion.

**Cervical stump cancer**

The incidence is approximately 0.1-0.5%. Women carcinoma of the stump should be referred to the Cancer Centre. Treatment is with further surgery or radiotherapy.

**1.8. Survival**

Overall five year survival is 69.6%\(^{19}\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>95-98%</td>
</tr>
<tr>
<td>IB</td>
<td>76-89%</td>
</tr>
<tr>
<td>IIA</td>
<td>73%</td>
</tr>
<tr>
<td>IIB</td>
<td>66%</td>
</tr>
<tr>
<td>III</td>
<td>40-42%</td>
</tr>
<tr>
<td>IV</td>
<td>9-22%</td>
</tr>
</tbody>
</table>

Survival drops by nearly half if lymph nodes are involved.

**1.9. Hospital follow-up**

As patients who relapse locally have a good chance of cure and/or prolonged remission with prompt treatment, the patient should be followed up by trained personnel when the earliest signs and symptoms of recurrence will be recognised. However, this should be taken in context as follow-up is not universally accepted to influences outcome or is successful in detecting recurrence\(^{20}\). For patients treated in the Cancer Centre, follow up will ordinarily take place in the Cancer Centre, although could be in the Cancer Unit if follow up closer to home is considered important for the patient.

Patients who have previously received radiotherapy to the cervix should not be followed up with cervical or vault smears. Similarly, vault smears are not indicated after hysterectomy for cervical cancer.

PET-CT is indicated in selected patients to assess response to chemoradiotherapy who have a residual mass following treatment\(^{4}\).
Follow up intervals are currently arbitrary and would be subject to audit and review. The following schedule is recommended:

History and clinical examination:

- Three monthly the first year
- Six monthly the second years.
- Annually until five years.
2. Appendix 1 Cervical patient pathway

- Cervix Colp/GP
  - OPD/Ward - Cervical biopsy
    - Imaging Pelvic/abdo MRI/CXR
    - 14 days
  - Cancer Centre OPD - +/- Cervical biopsy +/- decision to treat
    - EUA/Cystoscopy +/- biopsy
    - Further imaging CT/MRI
    - 14 days
    - Stage 1a1
    - 14 days
  - OPD/Diagnostic MDT decision to treat
    - Surgery
      - 14 days
    - Chemoradiotherapy /radiotherapy
      - 14 days
  - Cancer MDT
    - 14 days
    - Clinical FU
  - 31 days

References

1. http://info.cancerresearchuk.org


4. Indications for PET-CT. Guidance from the Royal College of Radiologists Board of the Faculty of Clinical Radiology. The Royal College of Radiologists 2010.


