Greater Manchester Cancer Alliance

Gynaecology Pathway board

Guidelines for the management of gynaecological cancers

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INTRODUCTION

One of the principal goals of the pathway board is to improve outcomes in cancer by achieving the evidence-based standards set out in the COG Guidance (NHS Executive). A key objective in reaching this aim is the establishment and maintenance of up-to-date clinical practice guidelines. Such guidelines are intended to raise standards and ensure consistency in the quality of care that patients receive. “Improving Outcomes in Gynaecological Cancer” provides a model framework for multidisciplinary care by expert teams at the Centre and in the Units. The term ‘Centre’ refers to two sites: Central Manchester NHS FT and the Christie NHS FT.

This document has been circulated to and approved by the pathway board. It is envisaged that the contents will be reviewed on an annual basis to ensure that management is current and where possible, evidence-based.

These guidelines are based on the best evidence currently available, and include diagnosis, staging and treatment. There are several fundamental principles on which the guidance is built: accurate pathological diagnosis and staging, multidisciplinary team decision making, appropriate referral to the Centre, and access to clinical nurse specialists.

It is important that eligible women are offered entry into international, national, regional and local cancer trials. Continual improvements in data collection are required in order to comply with NHS standards. Where relevant trials exist for each cancer site, these are described.

The Guidelines are set out by primary tumour site and include investigation and staging, primary treatment, rarer histo-types, follow up and management of recurrent disease. There is also a section on Supportive and Palliative care.

Summary of Service Provision by Trusts

There is one gynaecology SMDT with 2 arms (Manchester University NHS Foundation Trust and the Christie NHS Foundation Trust) in Greater Manchester and East Cheshire. The population has been geographically organised into the following organisational sectors.

Manchester University NHS Foundation Trust covering the North-East Sector:

- Northern Care Alliance NHS Foundation Trust (Bury, Oldham, Rochdale)
- Manchester University NHS Foundation Trust (including North Manchester General Hospital)
- Tameside Acute NHS Foundation Trust

The Christie NHS Foundation Trust covering the North-West/South Sector:

- Wrightington Wigan and Leigh NHS Trust
- Royal Bolton Hospital NHS Foundation Trust
- Northern Care Alliance NHS Foundation Trust (Salford)
- East Cheshire NHS Trust
- Mid Cheshire NHS Trust
- Stockport Foundation NHS Trust
- Manchester University NHS Foundation Trust (Wythenshawe)
- Christie Hospital NHS Foundation Trust

The named local diagnostic gynaecology teams carry out the diagnostic process for patients from their own catchment, referring patients to the specialist gynaecology cancer teams for specialist care.

Low risk endometrial cancer and stage 1a1 cervical cancer may be managed by individual surgeons from the diagnostic teams provided that they are named as a member of the diagnostic service, and they attend the specialist MDT as a core member.

The Christie Hospital is the Tertiary Referral Centre for treatment with radiotherapy delivered at The Christie Hospital and the satellite radiotherapy units based at Royal Oldham Hospital and Salford Royal.

Chemotherapy and clinical trials for gynaecology are predominantly delivered at The Christie Hospital. Although chemotherapy for other tumour sites is currently available at a number of local trusts across the area, this pathway is not yet established for gynaecological cancers.

Contents

1. CANCER OF THE CERVIX [1,-5]

1.1 Epidemiology

The incidence of cervical cancer has fallen significantly in the UK due to the success of the Cervical Screening Programme. Primary HPV screening is now adopted across Greater Manchester. There are now approximately 3256new cases in the UK and approximately 856 deaths per year. Squamous carcinoma and adenocarcinoma carry the same prognosis, which is stage dependent. The increasing cure rate partly reflects down staging achieved through screening and increased health awareness by women.

Around a third of women with cervical cancer are identified via the screening programme. One quarter are referred on the suspected cancer pathway and a further quarter are referred via the general outpatients service. Those not identified via screening often present with abnormal bleeding (postcoital bleeding, intermenstrual or menorrhagia), discharge or pain (pelvic or back pain). As postcoital bleeding is common, the GMCA postcoital bleeding algorithm recommends initial management.

1.2 Diagnosis and management of micro-invasive disease (FIGO $1A_1$ +$1A_2$)

This is currently defined as disease with stromal invasion measuring no more than 5 mm. Stage 1A1 is < 3 mm invasion and 1A2 is 3 - 5 mm invasion. Lymphatic/vascular channel involvement does not influence the stage but may influence the management.

In women who may wish further children, an excisional biopsy (cone / LLETZ / NETZ) with clear margins both ecto-and endo-cervically is adequate treatment for stage 1A1 disease (Grade C). If the margins are uncertain or involved with CIN or CGIN, further surgery is required to exclude multifocal invasive disease. For women wishing to have further children, a second excisional treatment is preferable as further surgery. Cone biopsy/ LLETZ/ NETZ and lymphadenectomy is sufficient treatment for women with stage 1A2 disease (disease >3mm and <5mm in depth) (Grade C). In terms of fertility preservation, conservative management of stage 1A2 is feasible and should be discussed by the SMDT. In women for whom fertility is not

an issue, hysterectomy with ovarian conservation (if <45 years) may be the preferred option.

It is imperative that all cases of cervical cancer are discussed at the SMDT and are available for review by a specialist team, core member histo-pathologist.

1.3 Diagnosis and staging of frankly Invasive Disease (≥FIGO 1B)

1.3.1 Investigations and Staging

Clinical assessment should include a full history, general examination, examination with biopsy and radiological staging. Bimanual vaginal and rectal examination will usually reveal whether the tumour is confined to the cervix or not. If possible, an outpatient biopsy could be obtained. An examination under general anaesthesia may be performed to stage the disease. Cystoscopy +/- sigmoidoscopy may also be required where bladder or rectal involvement is a possibility, but routine cystoscopy/sigmoidoscopy is not indicated. Full blood count and serum biochemistry should be carried out paying particular attention to anaemia and renal function.

Where renal obstructive uropathy is present, there should be discussion with the clinical oncologist with consideration given to correction of the Uropathy before transfer of the patient e.g. nephrostomy. Also, any significant anaemia should be corrected after diagnosis considering blood transfusion if clinically indicated.

1.4 Radiological Investigations

Radiological investigation of tumours clinically stage 1B or greater and those considered suitable for primary surgical treatment should include CXR, and MRI of the pelvis to assess tumour volume and lymphadenopathy. PET-CT is better than MRI for evaluating extra-pelvic disease in patients with advanced or metastatic disease. PET-CT is indicated if there is high clinical suspicion of advanced cervical cancer on examination or ≥Stage 1B2 cervical cancer on MRI. PET-CT is also indicated in atypical histological types of cervical cancer, such as small cell or neuroendocrine malignancies. A non-diagnostic CT scan of the pelvis and abdomen will be performed at The Christie for radiotherapy planning.

MRI +/- PET CT scans will be performed after radical radiotherapy to assess

response at 3 monthly intervals, until there is complete radiological response. Thereafter in the follow-up of asymptomatic women, routine radiological surveillance by MRI or CT scans could be considered at 1- and 2-years post treatment completion. Patients with signs of recurrent tumour should be imaged using CT or MRI, depending on the potential treatment options. Cases of incomplete response post radical radiotherapy will be discussed at the SMDT and referred for PET CT, EUA and biopsy to consider suitability for exenterative salvage surgery.

1.4.1 Radiological Guidelines

FIGO Stage	**Imaging**
1a1 & 1a2	Not indicated
Clinical 1B1 Patient fit/suitable for surgery	MRI pelvis CT abdomen and pelvis if MR contraindicated CXR
Clinical ≥1B2	PET-CT / MRI – tumour and nodes (inc. para-aortics) CT – if MRI contra-indicated RT planning
Clinical advanced/metastatic	CT – chest, abdomen, pelvis or PET CT
Small cell or other atypical histology	CT – chest, abdomen, pelvis
Follow-up	MRI post radiotherapy until complete response or residual disease established Consider annual CT or MR to assess for oligometastatic disease CT if MR not possible
Suspected recurrence	CT/MR/PET CT to assess feasibility of further treatment

1.5 Primary Treatment

Women with frankly invasive cervical cancer should be managed in consultation with the MDT and referred to the Centre. MDT management plan needs to take account of patient choice once the patient is informed of the possible clinical management options, taking into account reproductive and psycho-sexual needs.

1.5.1 FIGO 1b1/IIa

Low volume early stage disease (IB1/IIA1) can be managed equally effectively by

radical surgery or chemo-radiotherapy and brachytherapy (Grade A). Surgery is generally preferred because of ovarian preservation, length of treatment and avoidance of radiation effects; however, patient preference may influence management. Extensive LVSI may influence the treatment choice, favouring radical chemo-radiation.

Bulky (>4cm) early stage disease is better managed by radical chemo-radiation (Grade A) and to avoid both radical surgery combined with radiotherapy, which may result in increased morbidity. Strong radiological evidence of lymphadenopathy is a contraindication to surgical treatment.

Surgery for cervical cancer should, be undertaken by a gynaecological oncologist at the Centre and decisions regarding adjuvant or primary radiotherapy should be made in discussion with the clinical oncologist in the gynaecological team (Grade C). In women with small volume stage IB1 disease (<2cm diameter) and IB2 (2-4 cm diameter) who wish to have further children, consideration can be given to radical trachelectomy with lymphadenectomy, which should be undertaken by a gynaecological oncologist trained in the procedure (Grade C). Patients should be appropriately counselled about the risks of pre-term labour, the need for specialist feto-maternal care in subsequent pregnancy and the need for Caesarean delivery (Grade B).

Radical surgery, if performed, would normally comprise a Piver-Rutledge type II or III procedure dependent on tumour size; full iliac and obturator node dissection to 2cms above the bifurcation of the common iliac arteries is required. Para-aortic nodes are removed if enlarged or if pelvic nodes are suspicious, but not routinely. Hysterectomy is performed with a 2 cm vaginal cuff. Suction drainage to the pelvis may be used according to an individual surgeon’s practice but is not essential (Grade A) and indwelling catheterisation for at least five days with a urethral or supra-pubic catheter is usually required. Residual urine volume should be <150 ml, before permanent removal of the catheter. As with all major pelvic surgery, thrombo-prophylaxis and prophylactic IV antibiotics should be administered.

1.5.2 FIGO IB3/IIB-IV

Primary surgery is not indicated for bulky stage IB disease or above. Those patients with bulky IB (>4cms) and locally advanced disease stages IIA2, IIB and III

and some stage IV should be offered chemo-radiation if fit (Grade A). Patients must have good performance status 0 or 1 and have adequate renal function (isotope GFR>50ml/min) and adequate marrow reserves if they are to receive concurrent cisplatin weekly during their external beam radiotherapy. Correction of anaemia, including the option of blood transfusion, should be considered in patients with Hb < 11g/dl.

External beam pelvic radiotherapy is administered to the pelvis using IMRT (delivered with VMAT technique at The Christie), dose of 45Gy in 25 fractions over 5 weeks with weekly concomitant cisplatin. The field includes the cervix, uterus, parametrium, upper vagina and loco-regional nodes including obturator, external, internal and common iliac +/- para-aortic nodal chain depending on presence and extent of nodal disease on diagnostic imaging. For node negative disease or 1-2 pelvic nodes only, the superior border is at the level of the aortic bifurcation. This is extended superiorly to the renal vessels if ≥3 pelvic nodes or PA nodes are involved. Involved nodes are treated with a simultaneous radiation boost to 55-57.5Gy/25 fractions. It is acknowledged that this is associated with higher toxicity. Patients are supported accordingly.

External beam radiotherapy is followed by image guided and adaptive intra-cavitary brachytherapy, generally during the 2 weeks following completion of pelvic radiotherapy. Gaps between intra-cavitary and external beam therapy should be kept to a minimum compatible with the patient's medical condition (RCR document "The Avoidance of Gaps in Radiotherapy"). The overall treatment time should be ≤7-8 weeks. An external beam boost to the cervix tumour may be given over 8-10 fractions in patients where cannulation of the uterus is not possible, if the pelvic disease is too extensive for brachytherapy or medical reasons prohibit a general anaesthetic.

Patients should be given written information and advice about radiotherapy reactions, both early and late. Written consent relating to treatment and morbidity should be recorded by a member of the treating medical team and the patient prior to the start of treatment.

1.5.3 Adjuvant Radiotherapy

Radiotherapy after radical hysterectomy should be considered if central tumour

margins are doubtful (i.e. <5mm), if there are positive nodes, if the primary tumour is of poor prognostic type (grade C). Concurrent Cisplatin is offered during external beam radiotherapy provided the patient has adequate renal function and marrow reserve.

The radiotherapy to the pelvis is given as for radical radiotherapy described in section 1.5.2. Brachytherapy may be combined with external beam in these patients if there is any doubt about adequacy of surgical margins in the vagina or if there has been recurrence centrally after primary surgery.

1.6 Management Algorithm

FIGO stage	Treatment
Stage IA1	Cone biopsy or “simple” hysterectomy
Stage IA2	Cone biopsy or “simple” hysterectomy plus pelvic lymphadenectomy
Stage IB1/IB2/IIA1	Radical hysterectomy and lymphadenectomy or radical Radiotherapy. Consider trachelectomy if fertility preservation desired
Stage IB3 or IIA2(> 4cm)	Radical radiotherapy with concomitant Cisplatin chemotherapy and brachytherapy
Stage IIB, III, IV	

1.7 Rare Histo-types

Squamous carcinoma, adenosquamous carcinoma and adenocarcinoma tend to be managed along the above lines. Rare small cell tumours and neuroendocrine tumours require treatment with chemotherapy, recognising the poor prognosis. Aggressive surgery is probably not indicated initially as the principal risk for these women is blood born metastases. These women will normally be referred to the medical oncology lung cancer team for chemotherapy.

1.8 Follow-up

Patients should be followed up at 3-6 monthly intervals for the first 2 years (90% of recurrences will occur by 2 years with 80% of recurrences occurring in the first year after treatment). Thereafter patients will be seen at 6 monthly intervals for 5 years. Follow-up will be to manage any potentially curable recurrence. It is always good practice to discuss continuation or discontinuation of follow-up with individual patients so that their views can be taken into consideration.

Routine vault smears either post radiotherapy or post radical surgery is not indicated. Cytology following radiotherapy is very unreliable and difficult to interpret.

Table 1: follow up cytology post cervical cancer treatment (NHSCSP 20, 3rd edition, March 2016, Public Health England)

treatment	Cytology on Follow up	Where?
LLETZ / NETZ / Knife cone	Smear 6 and 12 months after treatment then annually for the next 9 years.	Local colposcopy clinic NHSCSP recall
Trachelectomy	Colposcopy + smear	Gynae Oncology surgeon
Total (simple) hysterectomy Or Radical Hysterectomy	If residual CIN • completely excised CIN1/2/3, then vaginal vault cytology 6 and 18 months post-surgery • incompletely excised CIN 1, then vault cytology at 6, 12 and 24 months • incompletely excised CIN 2/3, then vault cytology at 6, 18 and 24 months post-surgery and annually for the next 9 years	GP Local colposcopy clinic
	If no CIN, on surgical specimen (cancer only) • No cytology on follow up	n/a
Radiotherapy + / - chemotherapy	No cytology on follow up	n/a

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/515817/NHSCSP_colposcopy_management.pdf

Routine follow-up MRI or CT imaging could be considered at 1 and 2 years after treatment in the absence of symptoms or abnormalities detected on clinical examination. For those patients with bulky tumours treated with radiotherapy +/-

chemotherapy, MRI and PET-CT scans are performed at three months following completion of treatment to check that there has been resolution of disease. Follow-up interval scans may be performed if residual disease is identified at three months when discussed at the multidisciplinary meeting at the cancer centre or when clinically indicated.

Alternate follow-up between the referring surgeon and the oncologist is desirable if this is in accordance with the patient's wishes. Patients with treatment effects that require surgical intervention may require indefinite and individualised follow-up, as per their need. It is acknowledged that it is relatively unusual to detect asymptomatic recurrence in a well patient at routine follow-up. Once complete response is established then phone consultation during FU can be offered. It should be emphasized that patient-initiated attendance with symptoms between routine follow-up visits is more important in the detection of recurrence.

1.8.1 Suggested Follow-up intervals

Surgery Only

Year 1: three monthly

Year 2, 3, 4 and 5: six monthly

Radiotherapy (Primary mostly remain solely under the Christie clinical oncologists & Adjuvant mostly referred back to gynaecological oncologists)

3 months: Christie/MFT

6 months: Gynaecologist

9 months: Christie/MFT

12 months: Gynaecologist

18 months: Christie/MFT

24 months: Gynaecologist

30 months: Christie/MFT

36 months: Gynaecologist

42 months: Christie/MFT

48 months: Gynaecologist

54 months: Christie/MFT

60 months: Gynaecologist

1.9 Recurrent disease

Patients who develop symptoms/signs suspicious of recurrence should be referred to the multi-disciplinary team at the centre. Those patients who have received prior pelvic radiotherapy should be assessed with a view to surgical salvage, which normally means pelvic exenteration.

Exenteration is used in highly selected cases of recurrent pelvic cancer when the aim is to salvage recurrence with curative intent. It is generally employed for central recurrence of cervical cancer when radiotherapy had already been used. Under optimal circumstances it is associated with a 5-year survival rate of 50% (Grade C), so case selection is paramount.

Assessment of women for exenteration and exenterative procedures are the responsibility of a multidisciplinary surgical team comprising a gynaecological oncologist and a urological oncology surgeon and /or a colorectal cancer surgeon, as appropriate. These women require careful assessment. The prognosis is extremely poor in the presence of any sidewall disease, in which case exenteration should not be performed.

Recurrences in radiation naïve women are usually best treated with chemo-radiation; central recurrence carries a far better prognosis than side wall recurrence.

Those patients who are inoperable or who have metastatic disease outside the pelvis should be considered for palliative radiotherapy or chemotherapy.

1.10 Fistulae

Fistulae may arise as a consequence of advanced pelvic disease but are also late problems following pelvic radiotherapy for locally advanced tumour, usually where there is invasion of adjacent bladder and bowel.

In the absence of clinical evidence of active disease, a MR scan should be performed to assess with a view to surgical management.

Those patients with fistulae associated with progressive malignancy should have surgical assessment to consider palliative bowel or urinary diversions.

Uncontrolled loss of small bowel contents leads to skin excoriation. Palliative care measures include a trial of Ocreotide by subcutaneous infusion (300-600mgs/24 hours) and attempts to solidify/bulk the stool using Loperamide and Fybogel. Intensive skin care with use of barrier creams (e.g. Cavilon) is important.

1.11 Sexual Rehabilitation Clinic

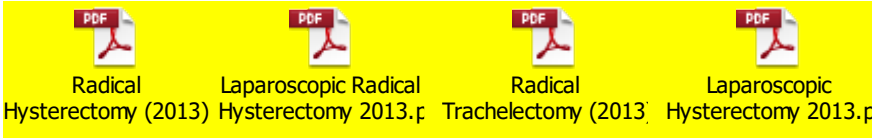
Women who undergo treatments for any gynaecological cancer may experience physical and/or psychological sexual issues afterwards, which may affect their own sexuality, body image and fertility or their intimate relationships with their partners. Women require information prior to treatment about possible sexual dysfunction afterwards. Assessment of sexual function/dysfunction should be routine follow-up post-surgery, radiotherapy and/or chemotherapy. Following radiotherapy, to the vagina, patients are advised and educated in the use of vaginal dilators in order to prevent/minimise vaginal stenosis. They are also given information when appropriate about returning to sexual activity.

If women have sexual dysfunction/sexuality problems beyond the scope of the team providing follow-up they should be referred to the appropriate specialist. The Sexual Rehabilitation Clinic at St. Mary's Hospital offers a service to any woman post gynaecological cancer treatment, with either physical or psychosexual problems by an appropriately trained nurse specialist, psychosexual therapist and gynaecologist.

1.12 Patient Information

Following confirmation of the diagnosis and recommended treatment plan at the MDT the Unit Lead and CNS should relay the information to the patient together with the information booklet 'cervical cancer'.

The information on the mode of treatment can also be given at this stage.



If the patient is treated at the cancer centre a check should be made to ascertain the patient has received the relevant patient information and if found to be missing, given at this stage. If the mode of the treatment is changed at upon review of the patient then the relevant information should be given.

2. VAGINAL CANCER

2.1 Investigations/Staging

Imaging is not routinely indicated for micro-invasive or clinical stage I tumours. MRI may be helpful for surgical treatment or radiotherapy planning in more extensive disease, and to assess the lymph nodes. CT will be required for radiotherapy treatment planning.

2.2 Diagnosis and Treatment

Vaginal cancer is almost always squamous carcinoma and is rare (occurs in 250 women/ year in the UK- CRUK 2017-2019) It should be diagnosed only in the following circumstances:

(i) In the presence of a normal cervix.

(ii) Following documented total hysterectomy.

(iii) More than 10 years following cure of cervical cancer.

The principles of management are similar to cervical cancer. A superficial lesion at the vault (post hysterectomy) or posterior fornix may be resectable and curable by means of vaginectomy. More deeply infiltrative tumours are generally best treated by radiotherapy +/- concurrent Cisplatin chemotherapy +/- brachytherapy, which offers vaginal preservation. All cases of vaginal cancer should be referred to the Centre for management decisions, allowing treatment options and side effects of treatment to be fully explained to the patient so they can be involved in the decision making process. [4]

2.3 Patient Information

Following confirmation of the diagnosis and recommended treatment plan at the MDT, the Unit Lead and CNS should relay the information to the patient together with the information booklet regarding radiotherapy which will be the mode of treatment in the majority of cases. If an examination under anaesthetic is required to confirm diagnosis and plan treatment this information leaflet should be given.

1024 Examination under anaesthesia.dc

When the patient is treated at the cancer centre a check should be made to ascertain the patient has received the relevant patient information and if found to be missing, then given at this stage. If the mode of the treatment is changed at upon review of the patient, then the relevant information should be given.

3. ENDOMETRIAL CANCER [7-22]

Most uterine cancers are endometrial. Uterine sarcomas are rare and are covered separately in section 3.18.

3.1 Epidemiology

The incidence of endometrial cancer is rising alongside life expectancy and the prevalence of obesity. Endometrial cancer is now the commonest gynaecological malignancy and the 4th most common female cancer, with 10,000 new cases every year (CRUK 2017-19). The majority of patients have early disease, survival being 90% in Stage I. The overall 5-year survival rate of 70% reflects the poor prognosis in more advanced disease. A significant proportion of women with endometrial cancer have substantial (sometimes life-limiting) co-morbidities, particularly obesity. There are increased peri-operative requirements for this group of women and a need for High Dependency Unit support. Pelvic surgery in women living with obesity can be particularly challenging. This, together with the need for a high degree of peri-operative support is likely to lead to an increased trend towards centralisation of even 'low risk' cases in the future.

3.2 Prevention and Screening

There is no evidence that screening asymptomatic women in the general population with TVUS or endometrial sampling reduces mortality from endometrial cancer (level 2+).

Women with Lynch syndrome and their first degree relatives could be offered annual screening with TVUS and endometrial biopsy from the age of 35 years after counselling about the risks, benefits and limitations of screening. There is no formalised programme in place and provision for these patients varies between institutions (Grade C, level 4, expert evidence). BGCS suggests offering hysterectomy and BSO in known Lynch syndrome carriers who have completed their families, from age 40 years.

Routine screening with TVUS, endometrial biopsy or both has not been shown to be effective in women who are on tamoxifen therapy. Tamoxifen increases the risk of

endometrial cancer four-fold. Postmenopausal women taking tamoxifen should be routinely questioned at breast cancer follow up visits about symptoms of vaginal bleeding /discharge and made aware of the risks. Symptoms in these women should be investigated with hysteroscopy as well as biopsy and ultrasound, since ultrasound appearances are not discriminatory. Tamoxifen use should be reassessed if hyperplasia is identified (level 2+).

There is no evidence to support a screening programme in PCOS or obesity.

3.3 Investigations

Postmenopausal bleeding triggers urgent referral on the suspected cancer pathway in women >55 years of age. Abnormal perimenopausal (45-55years) bleeding that lasts for 3+ months or is not responsive to first line treatments should also be referred on the suspected cancer pathway. Recurrent PMB should be investigated in line with the GMCA Postmenopausal Bleeding algorithm. Unscheduled bleeding on HRT is investigated according to the joint BMS-BGCS guideline (April 2024).

Pelvic examination and transvaginal scan are the first line assessments. Trans-vaginal scan (TVS) with measurement of endometrial thickness should be employed as initial investigation for women presenting with PMB (Level 2++, Grade B). Double layer endometrial thickness measurements on TVS with a cut off of ≥ 4 mm require further investigation. No further investigations are required where the endometrial thickness is < 4mm, unless there are irregularities of the endometrial cavity (e.g. fluid) or there is recurrent PMB (Level 2++, Grade B).

In patients with PMB and a TVS endometrial thickness measurement of ≥ 4 mm, an outpatient endometrial biopsy should be carried out (Level 2++, Grade B).

In asymptomatic postmenopausal women, endometrial biopsy is recommended in those who are at high risk of endometrial cancer if the endometrial thickness is $\underline{\geq}$ 6mm, and in those who are at low risk of endometrial cancer, if the endometrial thickness is $\underline{\geq}$ 11mm.

Hysteroscopy should only be carried out if outpatient endometrial biopsy is not feasible, there are focal endometrial irregularities on ultrasound scan or women are at high risk of endometrial cancer (Level 2++, Grade B). Hysteroscopy should also be considered in women with recurrent PMB 3-6 months after negative endometrial

biopsy. Hysteroscopy should be preferably carried out as an outpatient procedure (Level 2++, Grade C).

Hysterectomy may be considered in cases of unexplained recurrent PMB or when endometrial biopsy is recommended but is not possible due to cervical stenosis (Level 4, Grade D). This will usually be considered after pelvic MRI assessment confirms an endometrial abnormality.

3.3.1 Imaging guidelines in endometrial carcinoma

Imaging of the pelvis should be performed in all women with endometrial cancer (Grade D).

Women at high risk of potential metastases (high grade histological subtypes, p53 abnormal tumours) should have a CT of the chest, abdomen and pelvis preoperatively to help plan surgery or potentially avoid upfront surgery if metastatic disease is found. The yield from CT scanning in low-risk disease is very small, is very unlikely to alter the ultimate outcome and is not mandatory (Grade D). In these patients, a preoperative chest X-ray is recommended.

MRI of the pelvis is useful to assess tumour extent and identify lymph node metastases and may be useful to stratify patients into pathways of care (Grade D).

PET is not recommended for routine preoperative staging in the NHS outside of a clinical trial (Grade D).

3.4 Histological Types of Endometrial Cancers

Endometrial cancers are classified according to the 2020 WHO Classification (Tables 3.1 & 3.2). Bokhman first described two main pathogenetic types based on epidemiological studies. Type I carcinomas are generally low grade, oestrogen-related, clinically indolent and histologically of endometrioid type. Type II carcinomas are high grade, aggressive carcinomas, unrelated to oestrogen and histologically serous, clear cell and sometimes high grade endometrioid type.

Table 3.1: Histological Types of endometrial Carcinomas according to WHO (2020

Tumour type	Subtype
Endometrioid carcinoma	
Serous carcinoma	
Clear cell carcinoma	
Undifferentiated carcinoma	
Mixed carcinoma	Carcinoma composed of more than one type, with at least 10% of each component
Other endometrial carcinomas	Mesonephric adenocarcinoma Squamous cell carcinoma Mucinous carcinoma Intestinal type Mesonephric-like adenocarcinoma
Carcinosarcoma	
Neuroendocrine carcinomas	

Table 3.2: Grade of Endometrial Carcinomas according to WHO (2020)

Grade	Differentiation	Description
GX	Grade not assessed	Not assessed
G1	Well differentiated	Less than 5% of a nonsquamous or nonmorular growth pattern
G2	Moderately differentiated	6-50% of a nonsquamous or nonmorular growth pattern
G3	Poorly or undifferentiated	Greater than 50 % nonsquamous or nonmorular growth pattern; includes serous, clear cell and carcinosarcoma by definition

3.5 Molecular classification of endometrial cancers

It is increasingly understood that Bokhman's dualistic classification of endometrial cancers is too simplistic and there are overlapping features at clinical, pathological, and molecular levels. A new method of categorising endometrial tumours according to their molecular profile is now in widespread use. Molecular classification is both prognostic and predictive of chemotherapy response, and can be used to guide personalised treatment and follow up decisions. Molecular classification requires immunohistochemistry for mismatch repair (MMR) proteins and p53 status, and next generation sequencing of the tumour for *POLE* mutations.

The four molecular groups are:

- p53mut – p53 abnormal
- MMR deficient– mismatch repair deficient
- NSMP – no specific molecular profile

- *POLE* mutant– polymerase epsilon mutated

p53 abnormal tumours are the most biologically aggressive and have the poorest outcomes. These tumours tend to be serous or clear cell tumours, but p53 abnormal tumours can also be of endometrioid histology. *POLE* mutant tumours have an excellent prognosis despite often having high grade histological features. MMR deficient and NSMP tumours have intermediate outcomes. Those that are MMR deficient are usually sporadic tumours caused by *MLH1* hypermethylation, but around 10% of MMR deficient tumours are caused by Lynch syndrome. Molecular classification is now routinely performed on endometrial cancer diagnostic specimens without needing explicit patient consent (Figure 3.1).

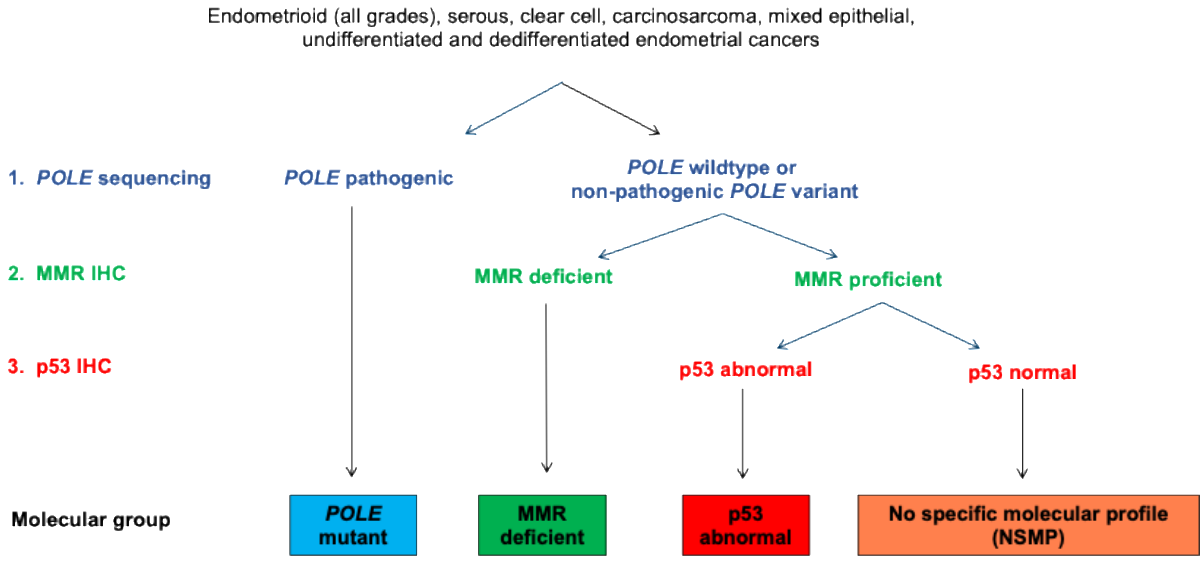


Figure 3.1. Molecular classification of endometrial cancer

3.6 Lynch syndrome testing

All endometrial cancers are screened for Lynch syndrome by MMR immunohistochemistry. If the tumour is MMR proficient (no MMR loss, approx. 75% of tumours) then the tumour is extremely unlikely to be caused by Lynch syndrome. If the tumour is MMR deficient (approx. 25% tumours), it may show loss of MLH1/ PMS2 or MSH2/ MSH6. If there is loss of MLH1/ PMS2, the tumour should be sent to genetics for *MLH1* methylation testing, to rule out Lynch syndrome. If the tumour is *MLH1* hypermethylated it is extremely unlikely to be caused by Lynch syndrome. All other tumours, i.e those that show MSH2/ MSH6 loss or MLH1/ PMS2 that do not show *MLH1* hypermethylation, could be caused by Lynch syndrome. Patients should

be counselled about their risk of Lynch syndrome and consented for germline Lynch syndrome testing, which requires a blood sample to be sent for genetic analysis to the North West Genomic Laboratory Hub at St Mary's Hospital and referral to genetic counselling (Figure 3.2). It is good practice to send blood and a referral to genetics at the same time, since if the patient tests positive, their genetics appointment will be expedited, and if they test negative, they may not need to be seen in genetics at all. Approximately 3% of endometrial cancer patients have Lynch syndrome and its diagnosis can prevent future cancer in themselves or their family members through colonoscopic surveillance, aspirin chemoprevention, risk reducing hysterectomy and cascade family testing.

Figure 3.2. Lynch syndrome testing pathway

Note: All endometrial tumours are tested for MMR deficiency by IHC. Patients undergo definitive germline testing for Lynch syndrome (via a blood test) if their MMR deficient tumour cannot be explained by *MLH1* hypermethylation (red box shows where patient consent is requested).

3.7 Surgical Treatment of presumed early disease

Surgery may be limited to hysterectomy and bilateral salpingo-oophorectomy in those patients with grade I or II endometrioid adenocarcinoma which appears confined to the uterus (Figure 3.3). However, there will be a proportion of women who may require further surgery or adjuvant treatment using this approach due to underestimation of histological grade on pre-operative biopsy or the presence of other risk factors on final histological examination (Grade D).

Ovarian conservation should be considered in premenopausal women with low-risk tumours to avoid the harms caused by iatrogenic menopause, especially those <40 years of age. Removing ovaries in such cases has not been shown to reduce the risk of recurrence and does not improve survival outcomes.

Pelvic and para-aortic lymphadenectomy does not reduce the risk of recurrence or improve survival outcomes but can be considered for complete surgical staging in selected cases (Grade A).

Sentinel lymph node biopsy has good diagnostic performance and is an alternative to lymphadenectomy for most cases. It reduces the harms associated with lymphadenectomy and the duration of surgery (Grade B).

Surgery should be performed laparoscopically, wherever possible, as it is associated with a lower rate of severe post-operative morbidity and shorter hospital stays compared with laparotomy. It is, therefore, a more cost-effective approach (Grade A).

Laparoscopic surgery is not associated with a significant adverse impact on disease recurrence and overall survival (Grade A). Robotic surgery appears to be non-inferior to laparoscopy for the treatment of endometrial cancer, but has a higher cost association (Grade C).

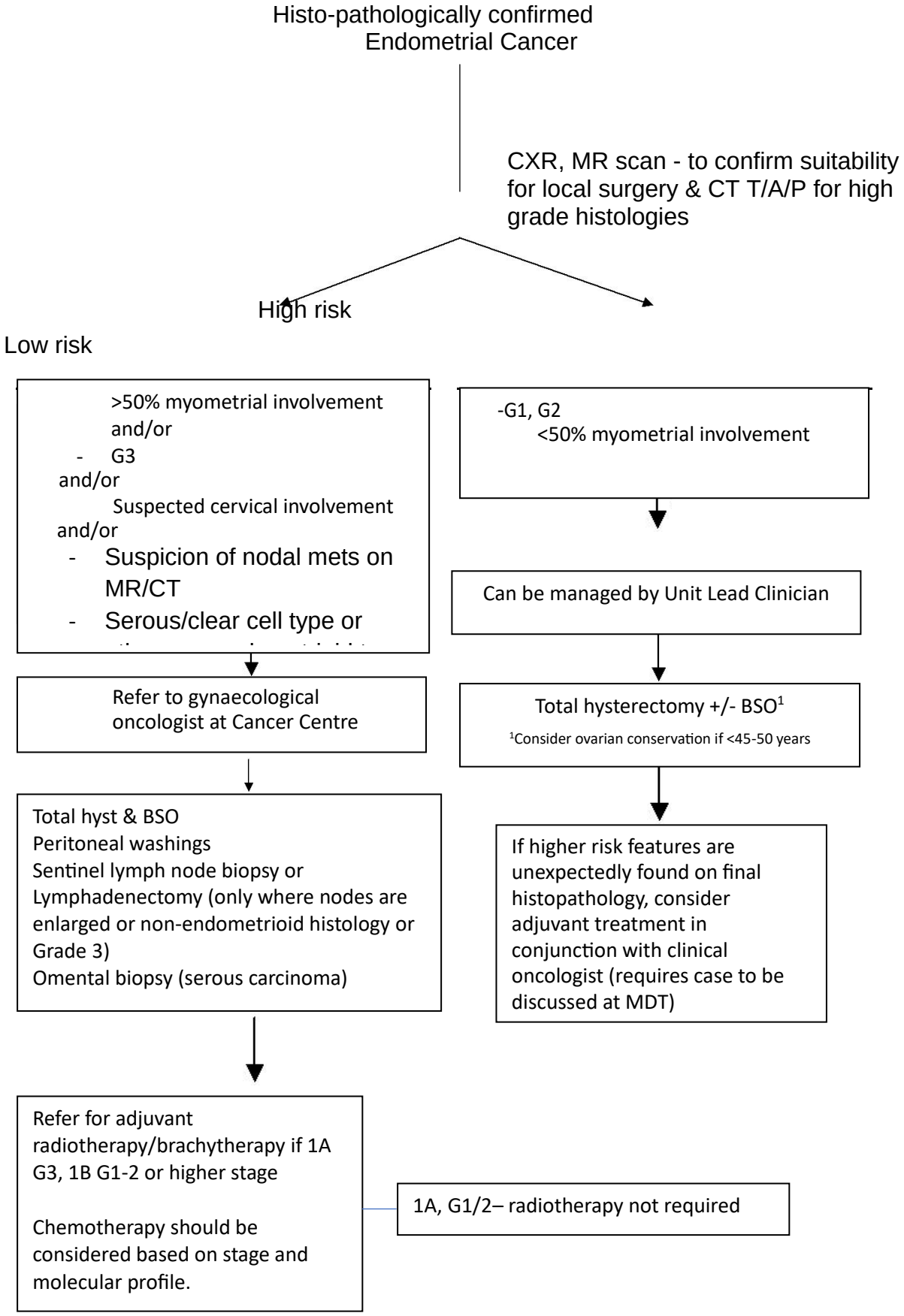
Robotic hysterectomy is associated with improved operative outcome and a lower complication rate compared with laparoscopic hysterectomy in women living with obesity (Grade C). Referral for robotic hysterectomy is recommended for women with BMI >45-50kg/m^2.

Surgery for presumed low risk endometrial cancer can be performed in a cancer unit as this does not appear to affect disease specific survival (Grade D).

Complete surgical staging including sentinel lymph node biopsy +/- pelvic and para-aortic lymphadenectomy and omental biopsy is appropriate for high risk endometrial cancers. These cases should be operated on in a cancer centre.

Radical hysterectomy is an alternative to simple hysterectomy and adjuvant radiotherapy for patients with stage II disease (Grade B).

Figure 3.3. Treatment Algorithm for Endometrial Cancer



3.8 Surgical management of advanced disease (stage III, IV)

Patients with advanced disease should be operated on in a cancer centre by gynaecological oncologists as this improves survival (Figure 3.3) (Grade C).

The aim of surgery in the management of advanced stage endometrial cancer should be complete surgical resection of all visible disease as this significantly prolongs survival (Grade C).

Complete resection of macroscopic nodal disease improves disease specific survival (Grade B).

Systematic lymphadenectomy should be performed in preference to palpation and removal of clinically enlarged nodes only as the latter is inaccurate (Grade B).

Surgery may be used to treat localised recurrent disease and can be curative (Grade C).

Surgery may be appropriate for patients with advanced disease at presentation who have responded to neoadjuvant chemotherapy or radiotherapy (Grade D).

The use of neoadjuvant chemotherapy in the context of treating advanced endometrial cancer has not been formally assessed in randomised controlled trials. However, it would seem reasonable, based upon available data from the management of epithelial ovarian tumours, to offer neoadjuvant chemotherapy to women with advanced disease where complete resection is unlikely to be achievable at primary surgery. Such cases should be discussed at the MDT and surgery could then be offered to those women who have responded to initial chemotherapy.

Debulking palliative surgery has a role in providing symptom relief (Grade C).

3.9 Management of patients wishing to preserve fertility

Current evidence suggests that conservative management of endometrial cancer is safe in the short term in selected women with low risk endometrial cancers, specifically

Grade 1 or 2 Stage IA endometrioid endometrial cancers without definite myometrial invasion.

Women with endometrial cancer desiring fertility-sparing management should be counselled carefully with respect to their fertility expectations, progestin response rates, recurrence rates and progression risk. Progestin treatment takes 12-18 months to be effective and is judged to be successful when two endometrial biopsies 6 weeks-3 months apart show no evidence of hyperplasia or cancer and there is no radiological evidence of pathology.

Mandatory baseline assessments include an MRI scan to confirm stage, and molecular phenotyping of the tumour to exclude p53 abnormal immunohistochemistry, which is a contraindication to conservative management.

First line treatment is oral and/or intrauterine progestin (Mirena intrauterine system). The Mirena IUS is a good option because of the high intrauterine and low systemic concentration of progestin associated with its use. The recommended oral progestins are Megestrol 160mg daily or Medroxyprogesterone acetate (MPA) 200mg or 400mg daily. The Mirena IUS is recommended for women living with obesity because oral progestins cause weight gain.

MDT should involve specialist gynae-pathology review, imaging and follow-up with regular endometrial sampling (3-6 monthly), preferably within a specialist clinic. The first on-treatment biopsy should confirm progestin treatment response but residual disease is expected. Successive biopsies show a gradual improvement in histological appearances until progestin effect only is seen. Response rates of 50-65% are typical. Progressive disease is usually observed on the first on-treatment biopsy and confirmed on repeat MRI scan. Progressive disease is uncommon (<10% patients) if patients have been selected carefully, and warrants urgent review, MDT discussion and re-discussion about hysterectomy. Young patients may be more receptive to undergoing hysterectomy if they have tried (albeit unsuccessful) fertility-sparing management first.

Weight loss should be encouraged during the progestin treatment window for women living with obesity as this may help response rates, improve fertility chances and

facilitate surgery if conservative management fails. Endometrial cancer is an indication for expedited bariatric surgery in those with BMI >35kg/m^2. Around 1 in 3 women will accept a referral for gastric bypass or sleeve gastrectomy as part of their endometrial cancer management. These surgical weight loss strategies are highly effective, achieving up to 50kg of weight loss during the 12-month progestin treatment window and improving the chances of disease remission. Those who do not accept bariatric surgery referral should be encouraged to lose weight through lifestyle changes and pharmacological means.

Women who respond to progestin treatment may keep their Mirena IUS in situ until they wish to conceive, while fertility referral and investigations take place, and for contraception/ menstruation control. Once removed, there is a high risk of recurrent endometrial pathology (25-35%), particularly if risk factors have not been addressed during the progestin treatment window (especially obesity). It is therefore sensible to keep the Mirena IUS in place unless the patient is actively trying to conceive. Endometrial surveillance, in terms of two 6-monthly biopsies, then annual biopsies for a total of 5 years, is recommended. At 4-5 years, the Mirena should be replaced. The patient can be discharged if they are 3-5 years in remission and advised to return in the event of symptoms.

The live birth rate following conservative management with a Mirena is 5-15%. It is at the lower end of these estimates if the patient had fertility problems before their endometrial cancer diagnosis and at advancing ages (>37 years). For patients embarking on fertility-sparing management in their late 30’s, particularly those with pre-existing fertility issues, on-treatment ovarian hyperstimulation and egg harvesting for cryopreservation should be considered once endometrial biopsies confirm a treatment response.

Recurrence can be managed with repeat progestin treatment. Hysterectomy is recommended once childbearing is complete if there is concern about ongoing endometrial cancer risk (ie in the context of obesity).

3.10. Patients considered unfit for definitive surgical management

Those women who are unfit for hysterectomy and bilateral salpingo-oophorectomy under general anaesthesia due to inter-current medical conditions or obesity may be considered for simple vaginal hysterectomy, definitive pelvic radiotherapy +/- intra-cavitary brachytherapy or conservative management with progestin/aromatase inhibitors. Ideally, patients should be referred to a dedicated clinic to discuss and consider appropriate options including recruitment into relevant clinical trials wherever possible.

Radiotherapy as primary treatment of endometrial cancer is only considered if medically inoperable. 5-year local control ranges from 78-94% with external beam radiotherapy and brachytherapy depending on stage.

Vaginal hysterectomy is likely to offer good palliation in women with high risk endometrial cancer who are less likely to respond to hormone treatments (Grade C).

The recommended oral progestins are Megestrol 160mg daily or Medroxyprogesterone acetate (MPA) 200mg or 400mg daily. However, a lower dose may be effective and in patients with a history of cardiac failure less problematic with respect to fluid retention. The Mirena IUS is recommended for women living with obesity because oral progestins cause weight gain. Aromatase inhibitors may be an alternative option for postmenopausal women. The comparative efficacy of progestin and aromatase inhibitors has not been investigated in a randomised controlled trial.

Monitoring of patients managed with progestin should be by 3-6 monthly biopsy, repeat MRI scans where indicated, expedited bariatric surgery and careful follow up (see section 3.9).

3.11 Adjuvant radiotherapy

Radiotherapy may be used as post-operative adjuvant treatment in women at high risk of developing recurrent disease according to the following guidance (Table 3.3):

- Patients with no or <50% myometrial invasion, G1-2 are at low risk of recurrence and are not given adjuvant radiotherapy (Grade A).

- Post-operative adjuvant radiotherapy improves survival and also reduces the risk of loco-regional recurrence from 15% to 6% in women with stage I disease with at least two risk factors of: grade 3 tumours, > 50% myometrial invasion and >60 years of age (Grade A).
- Brachytherapy to the vault has equivalent local control to external beam radiotherapy to the pelvis (<2%) for G1-2, >50% myometrial invasion (stage IB). Pelvic side wall recurrence is slightly higher with vault brachytherapy alone (5% vs 2%) however survival is the same as the rate of distant metastases is equivalent. Therefore, vault brachytherapy rather than external beam radiotherapy is recommended for this group of patients.
- Vault brachytherapy may also be used for G3 disease with <50% myometrial invasion (Grade A) with MMR G3/NSMP G3/p53mut and sentinel lymph node assessment/ lymphadenectomy. External beam RT is recommended for this group if no sentinel lymph node assessment/ lymphadenectomy has been performed.
- Pelvic external beam radiotherapy is indicated in stage II/ III disease. A combination of pelvic external beam radiotherapy plus vault brachytherapy is recommended in stage II disease or stage III disease with cervical involvement.
- Vaginal vault brachytherapy alone is recommended in stage II MMR/NSMP G1-2 disease irrespective of pelvic lymph node assessment.

Vaginal vault brachytherapy is given with pulsed dose rate or high dose rate iridium. External beam radiotherapy is delivered using VMAT, 46Gy in 23 fractions over 4.5 weeks.

3.12 Adjuvant chemotherapy

After the recent publication of results from 3 large randomised trials, PORTEC-3, GOG249 and GOG258, the role of adjuvant chemotherapy has become better defined. Postoperative carboplatin-paclitaxel chemotherapy is associated with a FIGO stage and histological/ molecular subtype dependent improvement in recurrence-free survival and overall survival irrespective of radiotherapy treatment (Table 3.3). (Grade A)

There is evidence that chemotherapy does not prevent pelvic recurrence so most patients receiving adjuvant systemic therapy should also receive adjuvant pelvic radiotherapy. In most cases, this should follow completion of chemotherapy. However, in patients at very high risk of local pelvic relapse e.g. involved para-cervical or parametrial resection margins or where wound-healing complications will delay chemotherapy administration, it may be appropriate to deliver pelvic irradiation first.

Table 3.3. Selection of patients for adjuvant chemotherapy and radiotherapy

Stage	**Tumour**	**Chemotherapy**	**Radiotherapy**
1A no myoinvasion	All	None	None
1A myoinvasion	*POLE* (any grade)[1]	None	None[2]
1A myoinvasion	MMR/NSMP G1/2	None	None
1A myoinvasion[4]	MMR/NSMP G3	None	Brachy
1A myoinvasion	P53mut	Chemo	Brachy

		With lymph node assessment		**Without lymph node assessment**	
Stage	**Tumour**	**Chemotherapy**	**Radiotherapy**	**Chemotherapy**	**Radiotherapy**
1B	*POLE* (any grade) [1]	None	None[2]	None	None[2]
1B	MMR/NSMP G1/2	None	Brachy	None	Brachy
1B	MMR G3	None	Brachy[4]	None	EBRT

1B	NSMP G3	Consider chemo	Brachy[4]	Consider chemo	EBRT
1B	P53mut	Chemo	EBRT	Chemo	EBRT
2	*POLE* (any grade) [1]	None	None[2]	None	None[2]
2	MMR/NSMP G1/2	None	Brachy	None	EBRT + Brachy[5]
2	MMR G3	None	EBRT+brachy[6]	None	EBRT+brachy
2	NSMP G3	Consider chemo	EBRT+brachy[6]	Consider chemo	EBRT+brachy
2	P53mut	Chemo	EBRT+brachy	Chemo	EBRT+brachy
3	*POLE* (any grade) [1]	Consider none	EBRT+/-Brachy	Consider none	EBRT+/-Brachy
3	MMR	Consider none	EBRT+/-Brachy	Consider none	EBRT+/-Brachy
3	NSMP	Chemo	EBRT+/-Brachy	Chemo	EBRT+/-Brachy
3	P53mut	Chemo	EBRT+/-Brachy	Chemo	EBRT+/-Brachy

Footnotes

1. POLE testing is available for cases where knowing its status will impact clinical care
2. Omission of adjuvant therapy for *POLE* tumours has not yet been established in prospective randomised trials
3. EBRT only if margins positive
4. Consider EBRT if extensive LVSI
5. Consider brachy alone if no LVSI
6. Consider brachy alone if otherwise low risk ie LVSI negative, <50% MI, clear margins

3.13 Adjuvant progestogen treatment

Progestogens offer no survival benefit in the adjuvant setting and should not be prescribed for this purpose (Grade A).

3.14 Primary Radiotherapy

Where a woman is considered unfit for surgery, radiotherapy may be used as primary treatment although this is not as effective as surgery (Grade B). The patient should be scanned to assess extent of disease, preferably with MR. Intra-cavitary brachytherapy may be considered although generally the reasons that exclude the patient from surgery also make brachytherapy challenging as it involves a light anaesthetic usually with sedation/total intravenous anaesthesia rather than a GA followed by a period of immobility (at least 3-4 hours) and lying flat. External beam radiotherapy may be given over 10-25 fractions.

3.15 Follow-up

The role of routine follow-up for women with completely resected early stage endometrial carcinoma is not well evidenced. Trials addressing the value (or otherwise) of routine follow-up are needed. A suggested follow-up schedule is given below although timing of follow-up visits may be modified according to individual patient circumstances.

For patients who have only received adjuvant chemotherapy, follow-up should be conducted at the surgical centre so that direct inspection of the vaginal vault can take place if required.

Patients' views need to be taken into account and it is good practice to discuss discontinuation or continuation of follow-up with individual patients where appropriate. It is acknowledged that it is relatively unusual to detect asymptomatic recurrence in a well patient at routine follow-up. It should be emphasized that patient-initiated attendance with symptoms between routine follow-up visits is more important for the detection of recurrence.

Some patients will be suitable for Patient Initiated Follow up (PIFU) – see BGCS guidance on PIFU. [14]

3.15.1 Suggested follow-up intervals

Surgery Only

Year 1:	3 – 4 monthly
Year 2, 3, 4, 5:	6 - 12 monthly

Radiotherapy (Primary & Adjuvant)

Year 1:	3 monthly	shared care, alternating between Christie / MFT
Year 2, 3, 4, 5:	6 monthly	shared care, alternating between Christie / MFT

3.16 Treatment of Recurrent Endometrial Carcinoma

For patients who develop pelvic recurrence following surgery, radiotherapy may be given with curative intent. Imaging of the chest, abdomen and pelvis should be carried out to assess disease extent. The prognosis is far more favourable for central mucosal disease. Patients are offered pelvic radiotherapy followed by vault brachytherapy.

Extra-pelvic recurrence or recurrence following adjuvant radiotherapy should be considered for chemotherapy which will usually be carboplatin/paclitaxel or single agent carboplatin. Response rates of 50% and median survival of 18-24 months have been reported with this doublet regimen which is now established as the international standard-of-care after the phase III GOG 0209 trial.

No standard-of –care second-line chemotherapy regimen has been established but women whose disease responds well to first-line treatment may gain benefit from additional chemotherapy and should be actively considered for clinical trials.

Endocrine therapy is an alternative treatment option for women with advanced/ recurrent low grade, hormone receptor-positive endometrioid endometrial cancer, as it

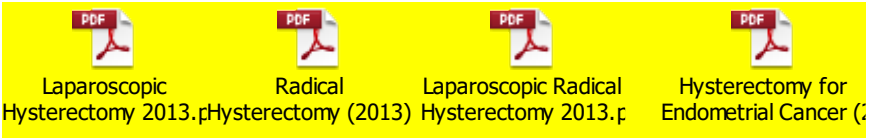
has a well-tolerated toxicity profile. It may be particularly useful in older women with multiple comorbidities and a limited disease burden. A recent meta-analysis included 1837 women, treated across 39 studies, using multiple endocrine therapies reported a response rate of 21.6% and clinical benefit rate on 36.7%. The likelihood of response was higher in women with oestrogen or progesterone receptor-positive disease. While the overall survival was less than one year, some women will get long-lasting disease control with endocrine therapy. Progestin treatment (eg medroxyprogesterone acetate 200 mg once daily) is considered the most appropriate first-line endocrine therapy although alternatives, such as tamoxifen or aromatase inhibitors can be considered, particularly in patients at high risk of vascular complications with progestin treatment.

Immunotherapy with monoclonal antibodies that inhibit the PD-1/PDL-1 checkpoint have shown very promising activity in recurrent mismatch repair-deficient endometrial cancer and their potential use in NHS practice is currently being appraised by NICE.

3.17 Patient Information

Following confirmation of the diagnosis and recommended treatment plan at the MDT the Unit Lead and CNS should relay the information to the patient together with the information booklet ‘endometrial cancer’.

The information on the mode of treatment can also be given at this stage.



If the patient is treated at the cancer centre a check should be made to ascertain the patient has received the relevant patient information and if found to be missing, given at this stage. If the mode of the treatment is changed upon review of the patient, then the relevant information must be given. Signpost the patient to relevant charities and patient support groups, including Peaches Womb Cancer Trust and Womb Cancer Support UK.

3.18 Uterine sarcoma

Uterine sarcomas include leiomyosarcoma, endometrial stromal sarcoma and uterine adenosarcoma. Leiomyosarcoma account for 1% of all uterine cancers and around 40% of gynaecological sarcomas (see Section 6).

3.18.1 Leiomyosarcoma

Recommendations (all Grade C)-

- The cornerstone of management of early leiomyosarcoma is total hysterectomy
- Salpingo-oophorectomy in young women is not mandatory
- Routine pelvic lymphadenectomy is not recommended
- Morcellation of fibroids should be avoided in postmenopausal women
- There is no data on the benefit of adjuvant chemotherapy or radiotherapy

In cases with suspected leiomyosarcoma restricted to the uterus, total hysterectomy could be carried out in local units by a consultant of the gynaecological oncology MDT.

Patients with advanced or recurrent leiomyosarcoma are usually challenged with chemotherapy unless complete surgical resection is possible.

Management of patients with primary or recurrent Leiomyosarcoma requires a multidisciplinary team approach preferably with the participation of the regional sarcoma team. Referral to the sarcoma MDT can be made by the local diagnosing unit or the regional SMDT. Completion of the Sarcoma referral form should be emailed to sarcoma.mdt@mft.nhs.uk

3.18.2 Early stage endometrial stromal sarcoma

Surgical treatment with total abdominal hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of the treatment, even in pre-menopausal women (Grade C).

3.18.3 Advanced or recurrent endometrial stromal sarcoma

Surgical resection can be considered in resectable cases.

3.18.4 Early stage undifferentiated endometrial sarcoma

Total abdominal hysterectomy with bilateral salpingo-oophorectomy remains the standard treatment for patients with undifferentiated endometrial sarcoma confined to the uterus.

3.18.5 Advanced or recurrent undifferentiated endometrial sarcoma

The role of debulking of extra-uterine disease is unclear. Retrospective studies showed that optimal cyto-reduction can be associated with better survival when compared with suboptimal debulking. Patients with advanced disease should be referred to sarcoma medical oncology team for considered for palliative chemotherapy. (See section 6 Gynaecological Sarcomas).

4. OVARIAN CANCER

The term ovarian cancer represents a heterogeneous set of diseases of diverse cellular and molecular origin. Until recently, most clinical trials have included a wide spectrum of subtypes and therefore evidence is often generic. This is now changing as knowledge of the individual subtypes increases and molecularly-targeted treatments are evaluated.

High Grade serous cancer (HGSC) of the ovary, fallopian tube and peritoneum are essentially variants of the same disease and appear to share the same progenitor lesion [(20)]. They are characterised by p53 mutation [(21)]. Up to 25% of HGSCs are associated with a pathogenic germline or somatic BRCA1 or BRCA2 mutation and nearly 50% have functional deficiencies in Homologous recombination DNA repair (HRD) leading to genomic instability and high copy number change. They are however, relatively chemo sensitive, particularly in the primary setting and management of the three conditions is similar.

In contrast, low grade serous cancer (LGSC) appears to arise on a background of borderline disease and is almost certainly a true ovarian cancer. Activating mutations in members of the RAS/RAF/MEK/ERK signalling pathway are seen in up to 70% of LGSC. Progression from low grade to high grade serous cancer appears to be extremely rare. Low grade serous cancer is chemo resistant (approx. 4% response to chemo in the primary setting) but has an indolent clinical behaviour and therefore warrants a different surgical approach in comparison to high grade serous cancer. [(22)]

Endometrioid cancer is uncommon and current thinking suggests that it usually arises on a background of endometriosis [(23)]. Endometriosis also has a clear association with clear cell cancer.

Mucinous cancer of the ovary is rarer than previously thought and is often secondary to a bowel or appendiceal primary. Non epithelial tumours have a very different biology, behaviour and therefore treatment. Their management is discussed separately below

4.1 Epidemiology

Ovarian cancer is the second commonest gynaecological cancer after uterine cancer and is the 6th most common female cancer in UK (Cancer Research UK-2017 data) accounting for 4% female cancer. Women born after 1960 have a 1 in 50 lifetime risk of ovarian cancer.

Overall survival from ovarian cancer has changed little over the last three decades with a 5-year overall survival of 41%, although median survival has increased significantly suggesting that treatment regimens have improved [24,25].

It usually presents at an advanced stage when cure is uncommon. It is a chemo responsive tumour and the best prospects for survival occur with a protocol of maximal surgical cyto-reduction to a zero residue followed by optimal chemotherapy and maintenance treatments. This requires expert multidisciplinary teams working to protocol obtain optimal survival.

4.2 Diagnosis and prevention

4.2.1 Screening

No survival benefit from whole population screening has as yet been demonstrated. [26] The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial randomised 200,000 women to observation alone, testing with an algorithm based on serial values of CA125 and multimodal testing or serial ultrasound. After a median follow-up of 16 years, no reduction in ovarian cancer deaths were observed in either screening group despite a significant stage shift towards stage I-II disease in the multimodal screening group.[27] Screening cannot therefore be recommended for women deemed to be at low risk of ovarian cancer.

Screening may have a role for women who carry germ line mutations of BRCA1 or BRCA2 and who wish to delay risk reducing surgery but requires careful adherence to screening protocols and should be managed within dedicated clinics.[28]

4.2.2 Symptom awareness and initial testing in primary care

The NICE document “The recognition and initial management of ovarian cancer” issued in April 2011 recommends that General Practitioners become more aware of symptoms and signs in women (especially over the age of 50) [29]. GPs should carry out appropriate tests should any of the following symptoms persist or happen more than 12 times a month.

- Bloating /Persistent abdominal distension
- Feeling full (early satiety) and/or loss of appetite
- Heartburn/ indigestion – new onset
- Increased urinary urgency and/or frequency

Initial investigations initiated in primary care should be CA125. An abnormal result should trigger referral for trans-vaginal ultrasound.

No guidance currently exists on the management of an elevated CA125 in the presence of a normal ultrasound scan other than other causes of an elevated CA125 should be sought. It has been estimated that the rate of false positives to true positive elevated CA125 will be in the order of 200:1 [30] and therefore these cases should not be referred to a central MDT for discussion, rather GPs should be encouraged to repeat CA125 at no less than 3 month intervals and only re refer if the CA125 has significantly increased.

4.3 Investigation and Staging

Women with a pelvic mass should have a reasonable effort made to try to establish a pre-operative diagnosis. In addition to the mandatory CA125, CA19-9, CEA (also AFP, beta HCG, LDH in those <40 years) could be measured and an ultrasound examination performed.

Measurement of tumour markers associated with other malignancies (e.g. Ca15-3)

may be of occasional benefit but is not advocated as routine practice.

NICE recommends that a risk of malignancy index (see appendix) should be calculated

based on the patients' menopausal status, ultrasound characteristics of the ovarian mass and serum CA-125 level. PWB recommends the use of the International Ovarian Tumour Analysis (IOTA) system for reporting ovarian cysts as it has a validated tool with 95% sensitivity and 91%specificity for ovarian cancers. (Ref) This describe cyst features as benign , malignant or inconclusive. Therefore women should be referred on a suspected cancer referral to secondary care if they have benign looking cysts on scan with a RMI >250 or those with inconclusive or malignant IOTA features on scan even if Ca125/ RMI is low. This can be used to guide the need for central referral (Grade B). All cases in which the RMI score is calculated at 250 or more should bereferred to a specialist multidisciplinary team. Women with a pelvic mass and calculated risk of malignancy index (RMI)< 250 but where the review of the imaging by the clinical team at the local diagnostic units strongly suggest malignancy should also be referred to a specialist multidisciplinary team.

Where ovarian malignancy is likely, a gynaecological oncologist should undertake the operation (Grade B). If bowel symptoms exist, efforts should be made to exclude bowel cancer so that the patient can be directed to an appropriate surgeon. It is recognised that a number of ovarian tumours thought likely not to be malignant will be operated on by unit leads.

It is undesirable for specialist teams to operate on benign pelvic masses unless for strong clinical reasons. Pre-operative Investigations should include CXR, full blood count, liver function tests, urea and electrolytes and CA125.

If a complex ovarian mass is thought to represent a borderline ovarian tumour or a possible ovarian malignancy then a CT scan of the abdomen and pelvis should be arranged to exclude upper abdominal disease and help planning any operation. Chest imaging is not mandatory in those patients where the mass is thought to represent a borderline ovarian tumour or early stage ovarian malignancy.

CT of the abdomen and pelvis can help with surgical planning if there are clinical signs of complicating factors such as bowel involvement. CT may also be helpful to assess areas that may be inaccessible to effective debulking e.g. coeliac axis / mesentery

(see section 4.5.3)

If primary chemotherapy is considered, NICE recommends that a diagnosis of ovarian cancer should be confirmed by histological evaluation of a core tumour biopsy in all but exceptional cases prior to treatment with cytotoxic chemotherapy.

This should be further supported by an appropriate immune profile to determine the histological subtype. Further guidance on this can be found in the Pathology guidelines available here on the Manchester Cancer website.

https://gmcancer.org.uk/wp-content/uploads/2021/10/2019-histopathology-mdt-guidelines-for-gynae-cancers-manchester-final.pdf

If FIGO stage III/IV HGSC or high grade endometrioid cancer is confirmed, tissue should be sent to Genetics for tumour BRCA mutation/ HRD testing after patient consent. A blood sample for germline BRCA mutation testing should also be obtained.

CT chest, abdomen and pelvis are required to document the extent of disease prior to chemotherapy.

Histological diagnosis can be obtained by either an ultrasound or CT scan guided percutaneous biopsy. Alternatively, a laparoscopically guided biopsy can be considered.

If a pleural effusion is detected radiologically, consideration should be given to obtaining a sample for cytological analysis as confirmation of stage IVa disease will allow the use of Bevacizumab as part of that individual's systemic treatment.

4.4 Imaging

Diagnosis

- US for initial assessment
- CT CAP if suspected advanced disease, but in cases with isolated ovarian malignancy CT abdomen & pelvic and CXR, for staging
- MRI if US/clinical diagnosis uncertain

Staging

Clinical / US Stage I

- RMI calculated on basis of USS features, Ca125 and menopausal status.
- Malignant IOTA features
- Refer to centre if RMI>250* or radiological suspicion of malignancy

Clinical Stage >1

Suspected bowel involvement

- CT chest, abdomen and pelvis

Gross intraperitoneal disease

- CT chest, abdomen and pelvis: to assess feasibility of optimal debulking

Patient not fit for surgery

- CT chest, abdomen and pelvis
- Image guided biopsy to confirm diagnosis
- Baseline prior to chemotherapy

<u>Follow-up imaging</u>

- Post-op not routinely indicated
- During chemotherapy CT assessment of response in all patients with measurable disease at the start of chemotherapy
- During neo-adjuvant chemotherapy CT assessment of response after 3 cycles chemotherapy to assess suitability for interval debulking surgery
- After completion of chemotherapy CT abdomen and pelvis
- Recurrence CT chest, abdomen and pelvis

**NB: where imaging highly suggestive of malignant mass, referral to centre should be made even if RMI <250.*

4.5 Primary Treatment of suspected or proven epithelial ovarian cancer

4.5.1 Surgical Treatment [37]

4.5.1.1 Surgical treatment of patients with apparent low stage disease

Laparotomy is the accepted standard primary management, with the purpose of establishing the diagnosis, staging the disease and undertaking complete resection of the disease.

Although there are several small series advocating the use of laparoscopy for the management of presumed early stage disease [31-33] there are no randomised controlled trials and a recent Cochrane review therefore concludes there is insufficient evidence to support the use of laparoscopy in this setting [34]. However, a laparoscopic approach may be appropriate in carefully selected patients

Laparotomy should be carried out through a vertical incision to enable whatever surgery may be required.

In early stage disease when the tumour is confined to one or both ovaries, surgery can be curative. It is important however that an adequate procedure has been performed to avoid under staging. Washings, biopsy of any adhesions, careful inspection and palpation of the whole abdominal cavity, and omental biopsy/ omentectomy should be performed. Biopsy of the pelvic and abdominal peritoneum should be done with a retroperitoneal lymph node assessment which consists of palpation of the pelvic and para-aortic areas with sampling of any enlarged lymph nodes or random sampling if the nodes are not enlarged[31] .

Frozen section can be of use in the diagnosis of malignancy peri-operatively. Whilst this can be of help to the surgeon, there must be sufficient throughput to ensure that the reporting pathologist has sufficient experience and exposure to cases to ensure a robust service and any such service must be subject to regular audit [35]. A robust protocol for its use should also be agreed with clinical users before commencing.

In women who wish for further children and where the tumour appears to be confined to one ovary, then an individual management plan needs to be drawn up in conjunction with the patient explaining the benefits and risk of removing the one ovary and possible biopsy of the contralateral ovary. Oophorectomy together with optimal staging may suffice.

A normal looking contralateral ovary need not be biopsied. Several retrospective cohort studies have been published reporting experience of fertility-sparing surgery in a total of 210 patients (grade B). These have confirmed the safety of this approach in stage I disease with an overall relapse rate of 11% (9% in the contralateral ovary).

4.5.1.2 Management of patients with advanced disease

Laparotomy is the accepted standard primary management, with the purpose of undertaking maximal debulking. The sites and volume of residual disease at the end of surgery should be clearly documented as these will impact on both prognosis and selection of adjuvant systemic therapy. A final assessment of cyto-reduction status should be given;

- complete macroscopic cyto-reduction (no visible residual disease)
- optimal cyto-reduction (visible residual disease <1cm diameter)
- suboptimal cyto-reduction (visible residual disease >1cm diameter)

Greatest survival benefit is associated with resection of all visible disease, although in the primary surgery setting there is also a smaller survival advantage associated with resection to less than 1cm [36]. No survival advantage has ever been demonstrated to be associated with suboptimal cyto-reduction [37].The aim of primary surgery should therefore be to leave no visible residual tumour, if this is feasible or residual disease less than 1cm if complete cyto-reduction is not possible (Grade B).

Primary debulking surgery is the standard of care where complete or optimal cytoreduction seems achievable in patients with good performance status. Where this is not achievable 3 randomized trials have showed non inferiority of the neoadjuvant chemotherapy approach followed by interval debulking surgery. Both trials demonstrated

reduction in morbidity with neoadjuvant chemotherapy and equal quality of life in both arms (Level I Grade A). (38) There is currently no validated algorithm to predict outcome of surgery and therefore to guide decision making regarding primary or delayed primary surgery [39,40].

4.5.1.3 Fertility preserving surgery

Any patient wishing to preserve her fertility in the context of possible invasive epithelial ovarian cancer should be discussed within the gynaecological MDT. Initial surgery should comprise of a unilateral salpingo-oophorectomy + peritoneal washings + / - omental biopsy, aiming to keep the ovarian capsule intact and obtain definitive histopathological diagnosis. Further surgery in the form of an omentectomy, pelvic and para-aortic lymph node sampling and peritoneal biopsies + biopsy of any suspicious lesions would then be performed as completion staging surgery. Fertility-sparing surgery can be considered in young patients with stages IA–C and grades I–II EOCs who desire to preserve their fertility.

4.5.2 Chemotherapy

Following histo-pathological confirmation of ovarian cancer, the patient's management should be discussed with and led by a medical oncologist with an interest in ovarian cancer. All cases should be discussed at a specialist multi-disciplinary team meeting.

Baseline investigations should include FBC, U/E, LFTs, CA125, GFR, CXR and nutritional status. CT of the abdomen and pelvis should be undertaken 4-6 weeks after surgery**.**

4.5.3 Neoadjuvant Chemotherapy

Primary debulking surgery is the standard-of-care for patients of good performance status when complete or optimal cyto-reduction seems achievable.

However, the EORTC 55791 [38] and CHORUS (41) Trials comparing primary surgery and neo-adjuvant chemotherapy in advanced staged disease reported equivalent overall survival in both treatment arms. There was however an improvement in the quality of life for those women randomised to neo-adjuvant chemotherapy.

Therefore, in women with significant medical co-morbidity or whose performance status is poor, consideration should be given at the MDT to recommending initial chemotherapy in place of primary surgery.

Neoadjuvant chemotherapy should also be considered if the prospects for optimal debulking at laparotomy are remote. Patients undergoing NACT should be tracked by the CNS team to allow timely discussion at the MDT and listing for surgery. Surgery should be considered after 3 cycles of chemotherapy and a discussion at the MDT meeting should be arranged for this purpose.

The default position should be to offer surgery after 3-4 cycles of chemotherapy though each case should be considered on an individual basis. Women who fail to respond adequately to chemotherapy or are considered to have irresectable disease may benefit from continuing chemotherapy.

Deferral of cyto-reductive surgery until after 6 cycles of chemotherapy should only occur

in exceptional circumstances, generally when reversible patient-related factors prevent surgery being performed in an interval fashion.

Important factors to consider that may preclude debulking are, bulky extra-abdominal disease sites, extensive mesenteric involvement and coeliac axis disease. It should be noted however, that CT appearances have not proven to be a reliable predictor of the feasibility of optimal debulking in several prospective studies (Grade B).

There are no absolute indications for neo-adjuvant chemotherapy but this may be considered where:

1. The patient considered medically unfit for surgery (NB: pleural effusion does not in isolation necessarily render a patient unfit for surgery and can be drained preoperatively if large/symptomatic).
2. There is extensive mesenteric involvement.
3. Disease at coeliac axis.
4. Fixed, bulky extra-abdominal disease (NB: omental caking may be operable/amenable to debulking).

It should be emphasised that primary debulking surgery remains the management strategy of choice for many women with suspected ovarian/ primary peritoneal cancer.

4.5.4 Adjuvant Treatment for Stage I disease

ICON 1 [34] showed a 9% improvement in 10-year survival in patients with early ovarian cancer who are treated with platinum-based chemotherapy (Grade A). A retrospective subset analysis of data from the ICON-1 trial has indicated that patients with intermediate risk stage I disease (IA moderately differentiated, IB well and moderately differentiated, IC well differentiated) do not benefit substantially from adjuvant chemotherapy.

In the ACTION trial , adjuvant chemotherapy was beneficial in women with stage 1 disease who had not undergone full surgical staging but in those who had been adequately staged (including full lymph node sampling), this effect was lost. This subset analysis however was based on small numbers of patients and should therefore not

prevent a discussion on adjuvant chemotherapy with individuals who have high risk stage I disease.

Current European guidelines recommend that women with optimally staged low-risk disease (Low grade Serous or endometrioid stage IA and expansile mucinous stage IA-B), should not be offered adjuvant chemotherapy. All optimally staged patients with high risk disease (all High Grade Serous cancers, Clear cell stage IC2 and IC3 and infiltrative mucinous cancers stage IB-IC) should be considered for adjuvant chemotherapy with 6 cycles of carboplatin. For those cases with intermediate risk of recurrence, the benefit of adjuvant chemotherapy is either small or poorly defined and in these adjuvant chemotherapy is optional and can be discussed on a case-by-case basis.

Women who have had incomplete surgery for apparent stage I disease should be considered for restaging or seen by a medical oncologist to discuss the possible benefits and side effects of adjuvant chemotherapy.

4.5.5 Adjuvant treatment for stage II-IV disease

Patients with more advanced disease (Stage II-IV) will normally all receive post-operative chemotherapy. Currently optimal first-line chemotherapy is platinum based and patients should be offered carboplatin and paclitaxel doublet chemotherapy which can be administered once every three weeks or weekly dependent on comorbidities and performance status [43-45] or single agent carboplatin (Grade A).

4.5.6 First-line maintenance therapy for stage III-IV disease

Both bevacizumab (an anti-angiogenic monoclonal antibody directed against VEGF-A) and oral PARP inhibitors improve survival in phase III trials when used as maintenance therapy after platinum-based chemotherapy for women with stage III and IV ovarian cancer.

In order to choose the best maintenance strategy for each patient it is important to determine germline and tumour BRCA mutation status as well as tumour HRD. Germline BRCA and HRD (incorporating tBRCA) testing are available through the NW Genomics Laboratory Hub based at St Mary's Hospital and should be requested as soon as possible in the patient's diagnostic pathway. For patients receiving neoadjuvant chemotherapy, tumour HRD (homologous recombination deficiency) testing should be requested on the initial core biopsy provided sufficient tumour tissue is available. If HRD testing fails on the biopsy specimen, this should be repeated on the interval surgical resection specimen.

For patients with high-risk advanced disease of all histological subtypes (stage III with sub-optimally debulked disease at primary surgery (>1cm diameter residual disease) or stage IV), the ICON7 trial demonstrated 5.5 month and 7.8 month improvements in progression-free survival and overall survival respectively with the addition of bevacizumab to carboplatin-paclitaxel chemotherapy. [46] Bevacizumab is administered as concurrent and maintenance therapy and is currently funded for a total duration of twelve months therapy.

Olaparib monotherapy maintenance for up to 2 years duration is approved for adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy on the basis of the SOLO-1 trial which showed a 42.2 month increase in progression-free survival and 20% increase in 7-year overall survival (67% compared to 47%) with maintenance olaparib compared to placebo. [47]

Combined olaparib and bevacizumab maintenance treatment is approved for adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy and whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability after the PAOLA-1 trial demonstrated an significant 19.5 month improvement in progression-free survival for combined therapy versus bevacizumab alone in women

whose cancer was HRD positive. Subsequent follow-up has shown an increase in 5 year overall survival from 48% to 65% with maintenance olaparib in this patient group. Combined therapy did not improve progression-free survival in women whose cancer was HRD negative. [48]

Niraparib monotherapy for up to 3 years duration is approved for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer unselected by BRCA mutation or HRD status who are in response (complete or partial) following completion of first-line platinum-based chemotherapy on the basis of the PRIMA trial. The magnitude of progression-free survival benefit associated with niraparib maintenance is associated with the cancer's HRD status and is lowest in HRD negative cancer [49]

The appropriate maintenance approach for each individual patient will be determined by the treating medical oncology team taking into account tumour stage, histology, BRCA mutation/HRD status, response to first-line chemotherapy and patient-related factors.

Women with stage III/IV Low grade serous cancer may benefit for adjuvant endocrine therapy in addition to or instead of platinum-based chemotherapy as this approach has shown promising efficacy in retrospectively reported patient cohorts. [22]

All patients should be offered the opportunity to participate in clinical trials if they meet the eligibility criteria.

4.6 Follow-up

At the completion of chemotherapy, a full re-staging evaluation is required. This will take account of performance status, current symptoms, findings on physical examination and the results of full blood count, serum biochemical profile, CA125 level and abdomen and pelvic CT scan.

On the basis of this, remission status (complete remission, partial remission, stable disease, progressive disease) should be assigned. Eligibility for maintenance treatment should be considered and commenced if appropriate.

If maintenance therapy is not recommended, patients should be followed up off treatment. Visits should occur every three months in years 1 and 2, six monthly in years 3-5 (Grade C). No benefit in survival has been demonstrated by the use of regular CA125 in follow up (Grade A) [37]. However, CA15 monitoring may allow the early identification of surgically resectable recurrence and trigger imaging that will allow decision making regarding the timing of chemotherapy treatment for many others. It is therefore considered an appropriate component of patient follow-up. It should be emphasized that patient-initiated attendance with symptoms between routine follow-up visits is important in the detection of recurrence.

For patients with complete remission at the end of first-line treatment, telephone FU using a structured symptom-based questionnaire in conjunction with a serum CA125 is an alternative to OP attendance.

Patients who have received adjuvant chemotherapy for stage I and II ovarian cancer will be referred back to their Cancer Units for follow-up after completion of chemotherapy. Patients with stage III and IV disease will remain under the care of their Medical Oncology team.

4.6.1 Suggested Follow-up intervals

Treatment type	Surgery only	Surgery / chemo	Chemo only	Surgery chemo maintenance treatment
Time interval	Years 1 & 2: 3monthly with Ca125 Years 3, 4 & 5: 6monthly with Ca125	Years 1 & 2: 3monthly with Ca125 Years 3, 4 & 5: 6monthly with Ca125	Years 1 & 2: 3monthly with Ca125 Years 3, 4 & 5: 6monthly with Ca125	Monthly with Ca125 and 3monthly CT TAP
who	gynaecologist	Alternating m. oncologist & gynaecologist	Medical oncologist	Medical oncologist

4.7 Management of recurrence

Although recurrent ovarian cancer is incurable improvements in median survival can be made with the judicious use of secondary surgical cytoreduction, further chemotherapy and maintenance treatments. A priority of management in the recurrent setting is to maintain quality of life.

4.7.1 Surgery for recurrent ovarian cancer

For patients who previously underwent complete cyto-reduction at initial surgery consideration should be given to MDT discussion at the time of first relapse in order to evaluate the role of surgery, if the criteria listed below are met. These are based on the eligibility criteria for the phase III DESKTOP III trial which reported a 7.7month improvement in overall survival in patients randomised to cytoreductive surgery prior to platinum-based chemotherapy compared to those who received chemotherapy alone. (50)

Surgery should be considered if the patient has a good ECOG performance status and the recurrence

- occurs more than 6 months after completion of primary chemotherapy
- in the absence of significant ascites,
- and previous surgery resulted in complete cyto-reduction
- or if it is thought necessary to relieve symptoms

4.7.2 Systemic Therapy for Recurrent Ovarian cancer

4.7.2.1 When Platinum might be the best option

Chemotherapy is the mainstay of treatment for recurrent ovarian cancer. The choice of regimen is dependent on the likelihood of benefit from further platinum-based chemotherapy and the time since last chemotherapy represents a continuum of probability of response to further platinum treatment. The use of a strict 6-month

platinum-free interval to define eligibility for further platinum-based chemotherapy is no longer recommended in current European Consensus Guidelines. [51]

For many women with recurrent ovarian cancer, rechallenge with further platinum-based chemotherapy is appropriate. Two phase III studies (grade A) have demonstrated a survival advantage for combination chemotherapy (carboplatin-paclitaxel OR carboplatin-gemcitabine) over single agent carboplatin in patients with potentially platinum-sensitive ovarian cancer. Carboplatin-Caelyx® also has proven phase III efficacy in this setting and a platinum-doublet should be considered as standard in this patient group.

In those women with recurrent high grade ovarian cancer where a radiological response to platinum-based chemotherapy is seen, PARP inhibitor maintenance treatment has been shown to improve progression-free survival irrespective of BRCA mutation or HRD status and should be considered if these drugs were not used in first-line maintenance. Rucaparib, niraparib and olaparib are all approved by the Cancer Drugs Fund in this indication although precise eligibility criteria are slightly different for each drug. [52,53] The appropriate PARP inhibitor for an individual patient will be determined by the treating medical oncology team.

4.7.2.2 When Further Platinum is not recommended

For many women with recurrent ovarian cancer, a point in their illness will be reached where the use of further conventionally-dosed platinum chemotherapy is not recommended. This includes cases where the cancer has progressed during or very shortly after platinum treatment or where platinum hypersensitivity prevents rechallenge. In these circumstances non-cross resistant chemotherapy regimens should be used. NICE has approved Pegylated liposomal doxorubicin (Caelyx®) for the treatment of platinum-resistant recurrent ovarian cancer (grade A). This drug and weekly paclitaxel are recommended treatment options in this setting. These should be administered under the supervision of a specialist ovarian cancer medical oncologist. In selected cases, the use of dose-intense platinum-based regimens may be considered as these

have demonstrated higher response rates, albeit at the expense of greater toxicity in the phase II setting (grade B).

The choice of treatment regimen should be made in conjunction with the patient and take into account co-morbid factors, prior chemotherapy side-effects and the patient's wishes. It should be noted that patients will often derive benefit from receiving multiple lines of chemotherapy after disease relapse.

In women with recurrent low grade ovarian cancer the use of endocrine therapy or oral MEK inhibitors is often more efficacious than further cytotoxic chemotherapy. In the phase III LOGS trial, trametinib improved PFS by almost 6 months (HR 0.48; 7.2 to 13 months) compared to either investigators-choice chemotherapy or endocrine therapy in patients with recurrent low grade serous cancer who had received prior platinum chemotherapy.

A substantial portfolio of clinical trials evaluating novel treatment strategies in relapsed ovarian cancer is available at The Christie. The suitability of patients for clinical trial participation should be actively considered at each disease relapse and relevant trials discussed with the patient if appropriate.

Radiotherapy should be considered for localised deposits of disease that are painful, ulcerating or bleeding. Psychological support is particularly important at this stage and the palliative care team should be involved earlier rather than later. Appropriate nursing care and other facilities can be arranged at home and if necessary, referral to a local hospice can be made.

4.8 Bowel Obstruction in Association with Recurrent/Progressing Ovarian Cancer

Bowel obstruction secondary to disseminated intra-peritoneal tumour is a common development in advanced ovarian cancer. Where symptoms are thought to be due to a single anatomical site of obstruction on imaging, review by the surgical team should be

requested although only selected patients may be suitable for palliative procedures to relieve or bypass the obstruction.

When surgery is not an option, it is important to achieve optimal control of nausea, colic and other abdominal pain. This is achieved through continuous subcutaneous infusions of anti-emetics, antispasmodics, anti-secretory agents and analgesics in a Graseby MS26 syringe driver.
Commonly used drugs include:

- Cyclizine 150 mg/24 hours + haloperidol 2.5-5 mg/24 hours
- Hyoscine butyl bromide 60-240 mg/24 hours (if colic)
- Octreotide (anti-secretory if high volume output persists)
- Diamorphine/ Oxycodone as titrated

A transdermal fentanyl patch is a useful option for those who require regular strong opioid analgesia, provided that analgesia requirements are stable.

All stimulant laxatives should be avoided; softeners (docusate) may be given by mouth if tolerated. Pro-kinetic anti-emetics (e.g. Metoclopramide) should be used with caution and discontinued if they exacerbate pain. A trial of dexamethasone may also be helpful and in some cases can improve symptoms and allow oral intake to resume. If the patient has subacute bowel obstruction, the use of a low fibre diet is recommended to reduce symptoms.

Note: It is possible to manage bowel obstruction in the terminal phase without IV fluids and nasogastric drainage for many patients. However, high small bowel obstruction will cause more frequent vomits. A trial of Hyoscine butylbromide (start at 60mg/24hours and increase in 60mg increments every 24 hours if symptoms still poorly controlled) or Octreotide (300- 600gs/24 hours) may reduce these to a tolerable level.

If not, a nasogastric tube should be offered and consideration of a venting gastrostomy to manage the problem if anticipated survival is still some weeks. Chemotherapy may be considered in patients who develop bowel obstruction during their initial presentation and assessment as there is a reasonable chance of inducing sufficient tumour

shrinkage to relieve obstruction. When bowel obstruction occurs in the context of relapsed disease, the utility of chemotherapy is unclear.

The role of parenteral feeding in patients with bowel obstruction is increasingly recognised although the absolute survival and quality-of-life benefit of this approach are not fully defined. It may be initiated alongside chemotherapy when this is a treatment option; individual patients may ask to continue supported feeding even if active treatment is discontinued. The use palliative home PN may be appropriate in careful assessed individuals of good performance status whose symptoms are well-controlled and who have no ascites or other disease-related problems.

The CAReGO (Complex and Recurrent Gynecological Oncology) Medical Oncology Service at The Christie (Clinical Lead –Dr Zena Salih) has recently been established to provide an integrated service for patients with inoperable bowel obstruction and other complex symptoms secondary to recurrent gynaecological cancers. Please contact the CAReGO Clinical Coordinator to discuss potential referrals.

4.9 Genetic Counselling/Testing

The current criteria for genetic testing in ovarian cancer are mandated by the national genomic test directory, which is updated regularly and takes into account international guidelines (ASCO/ESMO guideline references-see below). [51,54] This can be accessed at: https://www.england.nhs.uk/publication/national-genomic-test-directories/

The recently published NICE guideline NG 241-'Ovarian cancer- Identifying and managing familial and genetic risk' now recommends that germline testing for the detection of pathogenic variants (PVs) in a panel of ovarian cancer predisposition genes (most commonly panel R207 on the genomic test directory) is offered to all women with a diagnosis of invasive epithelial ovarian cancer. Although the prevalence of PVs in the BRCA 1 and 2 genes are most commonly seen in High Grade Serous cancers, they are found less frequently in other histological subtypes and PVs in other ovarian cancer predisposition genes such as the mismatch repair genes can be seen in other histological subtypes such as mucinous carcinomas.

Knowledge of both germline and tumour BRCA mutation (and HRD) status provides key information to direct management of the affected patient. Reflex tumour BRCA and HRD testing should be undertaken on diagnostic biopsies where possible and does not require specific patient consent. Germline and tumour genetic testing will inform decisions regarding risk-reducing mastectomy (germline BRCA mutation positive only) but importantly also determines the patient's eligibility for and the degree of benefit they may gain from PARP inhibitor maintenance therapy. In addition, knowledge of germline BRCA and other ovarian cancer predisposition gene PV status is of key importance for cascade testing of close relatives. [55,56]

Oncologist-directed counselling and consent for germline ovarian cancer predisposition gene PV testing for all patients with invasive epithelial ovarian cancer has now been adopted across the Network to allow timely access to testing.

All patients found to carry a germline PV in an ovarian cancer predisposition gene should be referred as a priority to the Regional Genetics Service for further management and advice on cascade testing for first-degree relatives. Where a VUS (variant of unknown significance) is found on testing, advice should also be sought for the Genetics Service in order that these patients can be tracked if the significance of the variant is upgraded. For clarity, in patients with High Grade Serous/ Endometrioid carcinoma the following genetic testing is required;

- Germline ovarian cancer predisposition gene panel (including BRCA) testing for all patients
- Reflex tumour BRCA/HRD testing for patients with stage III and IV disease at initial presentation
- Germline ovarian cancer predisposition panel and Tumour BRCA testing for patients with recurrent disease if no prior testing has been performed.

Non-epithelial Ovarian Tumours [57]

4.10.1 Sex-cord Stromal Tumours

These tumours vary in their degree of malignancy from relatively benign with a low risk of recurrence after removal to highly malignant with a high risk of recurrence.

- Laparotomy and surgery as for epithelial tumours
- Consider chemotherapy (carboplatin-paclitaxel) or endocrine therapy (letrozole) for any residual or inoperable recurrent disease.
- Serum Inhibins should be used as a tumour marker.

4.10.2 Germ Cell Tumours

Germ cell tumours are remarkably chemo-sensitive. These tumours often occur in younger women and the most important consideration is often preservation of reproductive function. These cases require expert care.

- Tumour markers are CA125, AFP, beta HCG, LDH
- Diagnostic laparotomy EXCEPT in paediatric cases who should be referred to Paediatric oncology for radiological guided biopsy
- In selected cases with bilateral ovarian involvement consider unilateral salpingo-oophorectomy (fertility sparing surgery)
- Post-operative chemotherapy: Platinum, Etoposide, Bleomycin for 4 cycles or until tumour marker negative

They should be discussed at the MDT for an individualised management decision. Following any surgical treatment provided patients with germ cell tumours should be referred to the germ cell team (Dr Alex Lee) at the Christie Hospital for treatment/ follow-up.

Girls under 16 years are treated by Dr Bernadette Brennan, Consultant Paediatric Oncologist at Manchester Children’s Hospital.

4.11 Borderline ovarian tumours

Borderline ovarian tumours (BOTs) are a heterogeneous group of tumours ranging from tumours with a benign natural history to premalignant lesions capable of malignant transformation.

These tumours account for up to 15% of all epithelial ovarian tumours. They generally present at a younger age than carcinomas and nearly 75% are stage I at presentation.

Adequate surgical staging, tumour sampling and expert histo-pathological review are crucial in making the diagnosis.

If the diagnosis of BOT is made as an incidental finding following surgery then the case (but not the patient) should be referred to the centre MDT for histological review and discussion. Referral should include the operation note in addition to the histology.

MDT review and discussion should include a discussion of the role of further surgery dependent upon the histology, fertility desires and completeness of the primary surgery. If the patient is to be considered for further surgery then this should be carried out at the centre.

Patients should be followed up for 5 years. This should include the use of ultrasound where the contralateral ovary remains in situ, and consideration of tumour markers where these were raised at primary diagnosis [58]. The diagnosis of recurrent disease should always include histological confirmation.

In young patients with stage I disease, fertility-sparing surgery can be considered. In mucinous borderline tumours, particularly those associated with mucinous ascites (pseudomyxoma peritonei) or extension outside of the ovary, appendectomy should be performed.

If true PMP is diagnosed, further management should be discussed with the PMP multidisciplinary team at the Christie. 5-year disease-specific survival for true stage I borderline disease is close to 100%. As with all gynaecological cancers the value of routine follow-up is not known.

Relapsed disease should be managed surgically and the low risk of malignant transformation excluded at histo-pathological review. In the absence of malignant change, the role of chemotherapy is unclear and there is little evidence to suggest that it alters the course of advanced recurrent disease in any beneficial way.

4.12 Management of emergency admissions with ovarian cancer

A significant number of women with undiagnosed ovarian cancer can present to general surgeons as an emergency with bowel obstruction requiring surgery. Where ovarian cancer is suspected either following clinical assessment or at emergency laparotomy a gynaecological opinion should be sought. Each unit or centre should have an agreed plan for responding to this situation and this should be agreed locally. In the cancer unit or centre, the lead gynaecological cancer clinician or a gynaecological oncologist respectively, should be involved as soon as is practicable.

4.13 Patient Information

Following confirmation of the diagnosis of an ovarian mass and recommended treatment plan for surgery at the MDT the Unit Lead and CNS should relay the information to the patient together with the information booklet.

Surgery for Ovarian Mass.pdf

If a diagnosis of ovarian cancer has been made by histopathological or cytological review and the patient is to receive systemic anti-cancer treatment or neo-adjuvant chemotherapy then the Unit Lead and CNS should supply the ‘chemotherapy’ booklet.

If the patient is treated at the cancer centre a check should be made to ascertain the patient has received the relevant patient information and if found to be missing, given at this stage. If the mode of the treatment is changed, at review of the patient

then the relevant information given. Information regarding specific types of chemotherapy should be given by the medical oncologist and CNS at the Christie.

If a diagnosis of borderline ovarian tumour is made the clinician and CNS who informs the patient of the diagnosis should offer the information leaflet at this point.

1023 Borderline ovarian tumours Netv

5. VULVAL CANCER [59-62]

These guidelines are based upon and largely extracted from the following consensus documents and guidelines which are freely available to read and in which the evidence levels behind the guidance can be seen :

1. British Gynaecological Cancer Society (BGCS) Vulval Cancer Guidelines 2023 update: Recommendations for Practice[59]
2. European Society of Gynaecological Oncology Guidelines for the Management of patients with Vulval Cancer – Update 2023 [60]
3. The Royal College of Radiologists expert panel recommendations for radiotherapy treatment for vulval cancer 2024[61]
4. Ano-uro-genital mucosal melanoma UK national guidelines 2020[62](*Due for update 2023/24)*

5.1 Background to recommendations

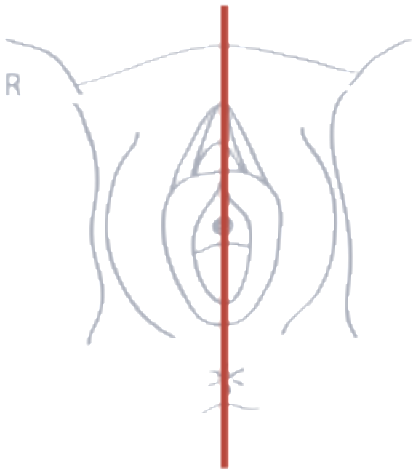
Vulval cancer is rare and accounts for approximately 3-5% of all gynaecological malignancies although the incidence is gradually rising. Each year approximately 1000 new cases of vulval cancer are diagnosed in the UK with around 380 deaths per year. Vulval cancer most often occurs in older women and rare in those under 25 although an increasing number of invasive tumours are being found in younger women, especially those who are immuno-compromised.

Vulval maturation disorders e.g. lichen sclerosis, and Vulval Intraepithelial Neoplasia (VIN) are known to predispose to vulval cancer. Lichen sclerosis mainly affects older women but can affect younger women. An increasing number of younger women are presenting with HPV-related VIN. Other rare conditions that pre-dispose to vulval cancer are Extra-Mammary Paget's Disease of the vulva (EMPD) and vulval melanoma in situ.

5.2 Diagnosis

A suspicion of vulval cancer should be raised by vulval ulceration, vulval lump or non-resolving vulval irritation or discomfort. Isolated vulval warts are uncommon in post-menopausal and elderly women and should be viewed with suspicion.

- In any patient suspected to have vulvar cancer, diagnosis should be established by a punch/incision biopsy which should include the area of epithelium where there is a transition of normal to malignant tissue. These can generally be obtained with local anaesthetic as an out-patient. Diagnostic biopsies should be of a sufficient size (greater than 1-mm depth) to allow measurement of depth of invasion and orientated to allow quality pathological interpretation.
- In patients with multiple vulvar lesions, all lesions should be biopsied separately (with clear documentation of mapping) and placed in separate histology pots to allow accurate localisation.
- The site and size of the lesion are important variables in treatment planning for vulvar cancer and these should be assessable at the centre. Careful examination of the lesion is mandatory and proper documentation of the size and location is important. A disposable measuring tape is a useful tool in the clinic. Suspected spread to adjacent structures (e.g. urethra, anus, bone) should be noted. Both groins should be examined.
- **As a minimum**, a detailed diagram of the vulva is required, indicating each biopsy site. Use of a schematic diagram, which can be annotated is encouraged (see example below) Ideally, consideration should be given to obtaining photographic documentation of all lesions.



The red line indicates the virtual midline and enables accurate localisation and surgical planning

- **Excision biopsy should be avoided**, where possible, since this may compromise surgical treatment options and surgical planning and can limit options for more conservative treatment with wide local excision and sentinel node biopsy. This is especially the case if the lesion is small, as the vulva can heal well and the original site is then hard to identify at the time of more definitive treatment. However, there may be exceptions to this, for instance in someone who is very elderly or frail it may be acceptable to excise a small, symptomatic lesion under local anaesthetic for palliation and planning of subsequent treatment. This should ideally be performed by the gynaecological oncologist who will perform subsequent treatment. **For this reason it is preferable to refer a woman with a small lesion thought to be malignant, directly to the centre without a biopsy rather than trying to excise the lesion locally.**
- All patients with vulvar cancer should be referred to a Gynaecological Oncology Centre (GOC) and treated by a multidisciplinary gynaecological oncology team.

- Review of diagnostic biopsy should be undertaken by a specialist

gynaecological pathologist and reported according to joint BAGP and BGCS guidelines.

- The histological report for diagnostic biopsies should contain the following information:
- Histological sub-type.
- P16 and P53 immunohistochemistry: For squamous cancers it is increasingly recognised that HPV-associated squamous carcinomas have better outcomes than HPV-independent cancers. Block positive p16 staining by immunohistochemistry is a surrogate marker of HPV aetiology and p16 staining is recommended on all vulval squamous cell carcinomas. Most HPV-independent tumours harbour P53 mutations and therefore immunohistochemistry for P53 is also indicated.
- Documentation of the HPV status of the tumour is strongly recommended (whether HPV-associated or HPV-independent)
- Depth of invasion. This is an independent prognostic factor which, in conjunction with tumour size, helps distinguish between FIGO stage IA and stage IB tumours.

Tumour grade is no longer provided as the HPV status has far more prognostic significance than the grade.

- Following excision, the following should also be reported on the vulval specimen:
- Final depth of invasion
- Margin status
- Presence of lympho-vascular space invasion
- Presence of peri-neural invasion

These features are additional prognostic indicators available following primary surgery:

- Lymph node involvement
- Number of involved lymph nodes
- Presence or absence of extra-capsular space invasion
- Size of any nodal metastases (≤2mm = micro-metastasis; ≥2cm = macro-metastasis; Isolated Tumour Cells (ITC))

Surgery for vulval cancer should be performed by a gynaecological oncologist. Therefore, all patients with vulval cancer should be referred to the Cancer Centre. This includes patients with basal cell carcinoma (BCC) and other histological sub-types.

5.3 Further investigations and staging

5.3.1 Squamous cell carcinoma

Squamous cell carcinoma most commonly spreads via inguinal lymph nodes and rarely presents at distant sites. Tumours that encroach on midline structures such as vagina, urethra and anus have a higher chance of pelvic node involvement.

Ultrasound scan combined with colour doppler in the hands of an expert examiner can show detailed changes in lymph node morphology and vascular architecture. Ultrasound (USS) combined with colour doppler has a good accuracy in assessing groin nodes, ,It is however, operator- and equipment-dependant. A meta-analysis of ultrasound assessment of groin nodes in patients with vulval cancer, showed pooled sensitivity of 85 %; specificity of 86 %; positive predictive value (PPV) of 65 % and NPV of 92 % [59].

- Prior to sentinel lymph node (SLN) biopsy, clinical examination and imaging of the groins are required to identify metastatic disease.
- **The groins can be assessed with ultrasound alone if sentinel biopsy is indicated based on other features**, but cross-sectional imaging (with

computerised tomography of chest, abdomen and pelvis [CT CAP], can provide additional information on the presence of pelvic lymphadenopathy and distant disease and should be always be **undertaken prior to full lymphadenectomy**.

- Those with suspicious groin nodes on clinical examination and/or imaging may be further investigated with USS-guided fine needle aspiration (FNA) or core biopsy, where node positivity would change management.
- Staging with full body, cross-sectional imaging (CT CAP) should be considered for all those with suspected or diagnosed with Stage III or greater disease, as the presence of distant metastatic disease will influence the extent of loco-regional treatment options. CT is also suggested for those with locally extensive disease who are not fit for radical treatment, to aid discussion and planning of treatment options.
- Due to its high soft tissue resolution, MRI should be considered for tumours with equivocal or clear involvement of midline structures, **if this will direct surgical management**.
- Positron emission tomography (PET-CT) is not recommended for the routine staging of vulval cancer. PET-CT has limited value in detecting lymph node metastases less than 5 mm and in necrotic nodes, and inflammatory nodes can be false positive.
- Examination under general anaesthesia (EUA) may be required in order to plan further management for patients with locally advanced disease, Other relevant team members such as plastic/colorectal surgeons or a clinical oncologist may be co-opted as required. This should be arranged and carried out by the centre clinician.

5.3.2 Vulval Melanoma

Mucosal melanoma of the vulva arises in non-hair bearing mucosa. It commonly presents with a more locally advanced lesion than cutaneous melanoma. The risk of metastatic disease (both lymphatic and haematogenous spread) is high.

- Histological assessment should assess depth of invasion (Breslow Index) and should also include routine testing for BRAF and C-Kit mutations on the initial diagnostic specimen as this may inform treatment options. Other genes known to be mutated in mucosal melanoma are NRAS, GNAQ and GNA11. These may become of clinical relevance or allow entry into clinical trials and should form part of routine testing.
- Recommended imaging at diagnosis includes CT chest, abdomen and pelvis and also CT or MRI head, since systemic disease and intra-cranial lesions are not uncommon. For full details the Ano-Uro-genital Mucosal Melanoma guidelines should be read[62]

5.3.3 Basal Cell Carcinoma

Distant disease spread is rare and no imaging is required, unless there is clinical suspicion of nodal disease.

5.3.4 Bartholin's Gland Carcinoma

Bartholin's gland carcinomas may present with more advanced disease since they arise deep to the surface of the skin and are less clinically obvious. Pre-operative imaging with CT chest, abdomen and pelvis is therefore recommended. There is also an increased risk of loco-regional spread at diagnosis. MRI pelvis may therefore help to delineate the degree of involvement of adjacent structures.

5.3.5 Adenoid cystic carcinoma

Adenoid cystic carcinoma of the vulva is a very rare tumour that arises from Bartholins and Skenes glands. There are no RCTs to guide management and treatment is based on case reports and series. Pure adenoid cystic carcinomas of the vulva appear unrelated to HPV infection. They are typically slow growing tumours. Spread to lymph nodes is less common than for the more common types of vulval cancer

There is a tendency for local recurrence and distant metastatic spread. The most common site of distant metastasis is to the lungs, however, metastases to bone, liver and brain have also been reported. CT scan of chest, abdomen and pelvis is therefore recommended

5.3.6 Extra-Mammary Pagets Disease of the Vulva (EMPD)

Invasive EMPD is rare and represents 1–2 % of all vulval cancer. Patients with non-invasive EMPD may have an increased risk of an underlying malignancy. Underlying urological, colorectal, uterine and breast cancers have all been reported. The risks are lower than with Mammary Paget's Disease however and more recent data suggests that routine screening for secondary malignancies can be safely omitted for those patients with primary cutaneous non-invasive EMPD as defined by immunohistochemistry.

- Therefore, when non-invasive EMPD is diagnosed, investigations to exclude a co-existing malignancy, e.g., of the breast, gynaecological, urological and colorectal tracts, are only required if there are symptoms concerning for other malignancies.

- Where invasive EMPD is diagnosed, CT scan of chest, abdomen and pelvis is recommended to identify metastasis.

Imaging guidelines for different vulval cancer sub-types is provided in the table below.

Imaging guidelines for vulval cancers

Pathway Point	Histology	Imaging modality
Diagnosis	**Squamous cell**	Not indicated (histological diagnosis)
Staging	**Squamous cell**	DOI ≤ 1mm AND ≤2cm size – not indicated DOI >1mm OR >2cm size: • If tumour meets other criteria for SLNB – USS groins (high negative predictive value) • If tumour does not meet criteria for SLNB - CT scan chest, abdomen pelvis • Suspected stage 3 disease or greater – CT scan chest, abdomen and pelvis • MRI scan may be considered if there is suspected or known involvement of midline structure (anus, urethra, vagina) *and* this would determine surgical management • MRI scan of pelvis and vulva is required for patients proceeding directly to radical radiotherapy • PET-CT scan indicated for patients proceeding directly to radical radiotherapy
Follow-up	**Squamous cell**	For patients that have had SLNB with negative SLN –USS groins every 3 months for 2 years For patients that have received radical (chemo)RT as definite treatment- MRI +/- CT or PET-CT at 10-12 weeks post completion of treatment Imaging not routinely indicated otherwise
Suspected recurrence	**Squamous cell**	Depends upon size and site of recurrence: • CT chest abdomen and pelvis to assess for distant metastasis and nodal recurrence • MRI scan may be useful to determine extent of local vulval recurrence

		• PET-CT and MRI pelvis indicated if exenterative surgery is being considered. Small "recurrences" ≤1mm DOI and ≤2cm in max size (stage 1A), may represent new tumour within field change and do not require imaging
Diagnosis	**Vulval melanoma**	Not indicated (histological diagnosis)
Staging	**Vulval melanoma**	CT chest abdomen and pelvis *PLUS* MRI or CT brain US and FNA or core biopsy if suspicious nodes on CT scan PET-CT indicated if planned surgery would involve more than wide local excision and groin node dissection
Follow-up	**Vulval melanoma** *organised by Melanoma Team.*	**Years 1-3** • 3-monthly clinical examination to include palpation of inguinal lymph nodes • Baseline CT thorax, abdomen and pelvis 2-3 months post-surgery • 6-monthly CT thorax, abdomen and pelvis (inc. groins) • Consider 6 monthly CT or MRI scan of brain (to be discussed with patient) **Years 4 and 5** • 6-monthly clinical examination to include palpation of inguinal lymph nodes • 12-monthly CT thorax, abdomen and pelvis (inc. groins) • Consider 12 monthly CT or MRI scan of brain (to be discussed with patient)
Suspected recurrence	**Vulval mucosal melanoma**	CT chest abdomen and pelvis to assess for distant metastasis and nodal recurrence MRI scan may be useful to determine extent of local vulval recurrence Consider PET-CT after discussion with Melanoma Team

Diagnosis/Staging/Follow-up	**Basal Cell Carcinoma**	Not indicated (unless enlarged or suspicious nodes clinically)
Diagnosis	**Bartholins Gland Carcinoma**	Not indicated (histological diagnosis)
Staging	**Bartholins Carcinoma**	CT chest abdomen and pelvis (to assess distant and nodal metastasis) MRI scan pelvis (to assess extent of local disease)
Follow-up	**Bartholins Carcinoma**	Not routinely indicated post-surgery Imaging may be indicated after non-surgical treatment to assess response and appropriate modality will be selected by treating oncologist
Suspected recurrence	**Bartholins Carcinoma**	CT chest abdomen and pelvis to assess for distant metastasis and nodal recurrence MRI scan may be useful to determine extent of local vulval recurrence PET-CT and MRI pelvis indicated if exenterative surgery is being considered.
Diagnosis	**EMPD**	Not indicated (Histological diagnosis)
Staging	**EMPD**	**Non-invasive primary EMPD vulva -** Not routinely indicated unless concerning symptoms **Invasive primary EMPD vulva -** CT scan of chest, abdomen and pelvis
Follow-up	**EMPD**	Not routinely indicated
Suspected recurrence	**EMPD**	**Invasive primary EMPD vulva** CT scan of chest, abdomen and pelvis Local vulval recurrence of **non-invasive EMPD does not require imaging**

5.4 Treatment of primary squamous cell carcinoma of the vulva

5.4.1 Surgical management of the primary vulval tumour

Most tumours at stage I, II and III are treated with primary surgery. In stage IV disease, palliative surgical procedures may be performed to manage pain, which is difficult to control by other means, or to deal with fistulation. Surgery for vulval cancer should be performed in the cancer centre by a Gynaecological Oncologist

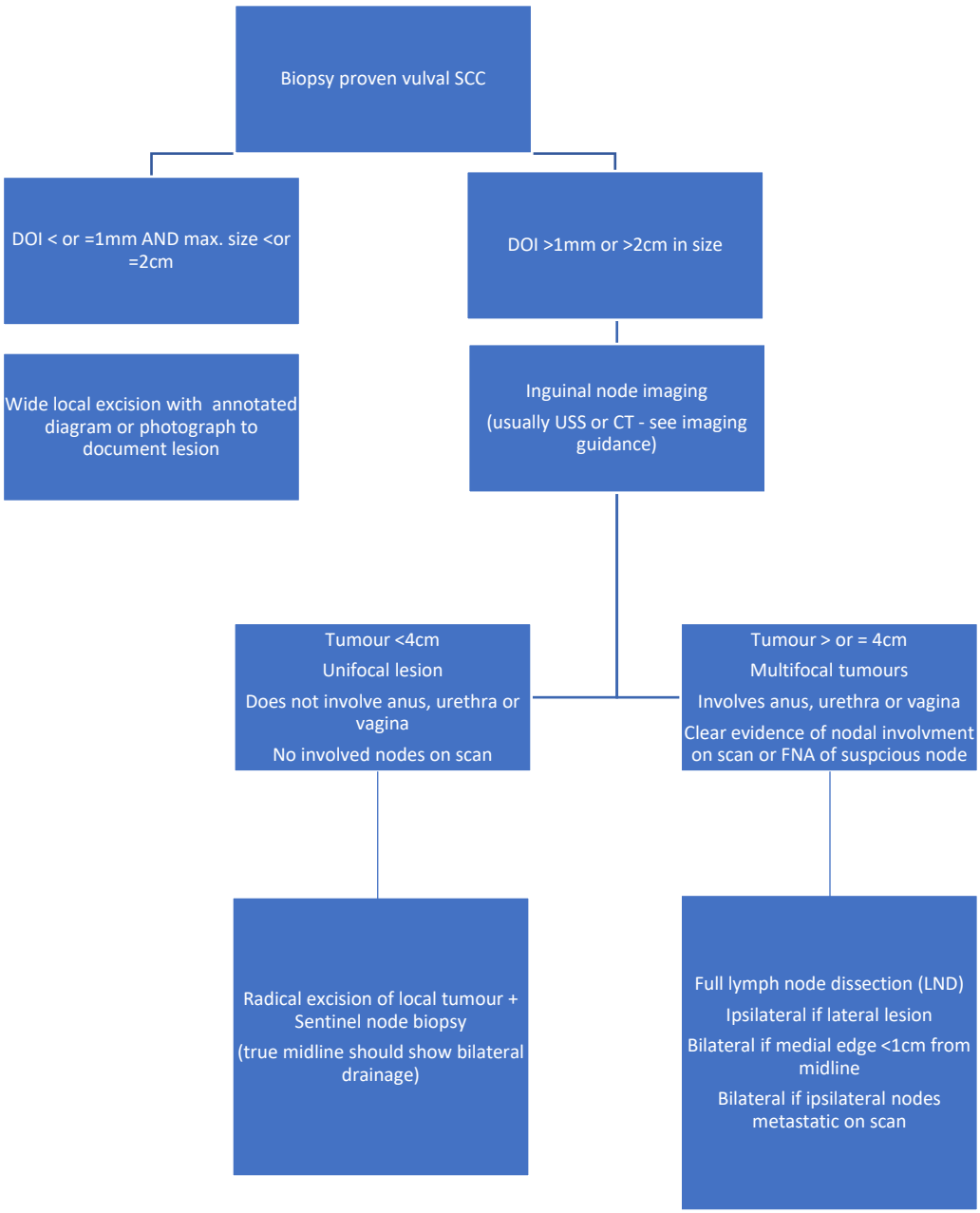
An outline of the surgical management is shown in the algorithm below which is reproduced from the British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: An update on recommendations for practice 2023.

- The aim of surgery for the primary tumour is removal of the cancer with clearance at all microscopic margins, including the deep margin (R0).

More recent studies show that margins should be clear of disease, but that large negative margins are no longer required in node-negative patients treated with surgery alone. Another recent series did not show an association with margin status unless margins were <2 mm. Therefore, the aim should be to achieve a microscopic clearance margin of 2mm or greater.

- It is acceptable, and may be desirable, to limit radicality to preserve structure and function whilst achieving an R0 resection (e.g. preservation of clitoris, urethra, anus).

The distal 1-2cm of urethra can be excised if needed to ensure clearance and does not usually cause urinary incontinence.



Algorithm for the surgical management of vulval squamous cell carcinoma

- Consider additional, more superficial resection of differentiated vulvar intraepithelial neoplasia (d-VIN) in addition to radical local excision of invasive tumours.
- When invasive disease extends to the pathological excision margins of the primary tumour, re-excision is the treatment of choice.

Vulval recurrence is more often a new primary tumour within an area of field change due to underlying lichen sclerosis or VIN, rather than a true local recurrence of a previously excised tumour.

- Where the tumour involves the anus, primary treatment with definitive chemo-radiation should be considered in an effort to preserve function. Alternatively, use of chemo-radiation in a neo-adjuvant setting may allow subsequent surgical excision without loss of faecal continence.
- For some women, surgical excision may require formation of colostomy either as a temporary measure to aid wound healing after reconstruction or following definitive surgery to remove the anus and lower rectum (ano-vulvectomy).
- Where primary radical surgery is expected to compromise sexual function, psychosexual counselling should be offered prior to any procedures.

Reconstructive surgery may be useful in some cases. The primary aim of reconstructive surgery is to facilitate complete, curative resection of the tumour with appropriate margins and preservation of function. The secondary aims are to enable wound healing by secondary intention and to reduce morbidity due to scarring.

The anatomy of the vulva is such that for small resections and anterior resections direct (primary) closure is often possible with a good result. A tension-free closure is the aim. Primary closure following surgery to the posterior vulva is more likely to result in a closure under tension with wound breakdown, scarring and poor functional outcome. Therefore,

simple reconstructive techniques may be required to facilitate a good tension-free closure. Following wider resections, repeated excisions or post-radiotherapy surgery reconstruction may also be indicated. Leaving wounds open to heal by secondary intention is also an option in some cases and can achieve good functional and cosmetic results.

There are numerous options for reconstruction ranging from simple local flaps (transposition flaps, rotational flaps, advancement flaps) , which are often within the skill set of the treating gynaecological oncologist, to more complex reconstructive techniques (split or full-thickness skin grafts, distant myo-cutaneous flaps or free flaps) which usually require joint surgery with a plastic surgeon. Plans for reconstruction should be made in advance of the definitive surgery to allow appropriate pre-operative counselling.

5.4.2 Surgical management of the lymph nodes

- Lateralised tumours need only have surgical management to the ipsilateral groin initially if there is no evidence of nodal involvement on pre-operative imaging. Lateralised lesions are defined as the leading medial tumour edge being at least 1 cm away from the midline.
- With midline lesions, surgical management of the groins should be bilateral.
- Sentinel node dissection is the treatment of choice for small (<4 cm), unifocal tumours without clinical or radiological evidence of lymph node metastasis at presentation.
- In the case of women having sentinel node surgery, a midline tumour whose leading edge comes 0.5-1cm of the midline but does not encroach directly on the midline, may be safely treated with unilateral sentinel node excision if representative injections and subsequent lymphatic mapping do not identify contra-lateral drainage.
- A true midline tumour (involves the virtual midline) must demonstrate bilateral drainage on pre-operative lymphoscintigram.

- **Where sentinel node biopsy is considered, the following criteria must be met. If these criteria are not met, lymphadenectomy is mandatory:**

- The tumour should be unifocal
- The tumour should measure < 4 cm
- The depth of invasion on biopsy should be >1mm (i.e. histological and clinical stage 1A tumours should not have nodal surgery at all)
- Pre-operative imaging should exclude suspicious groin nodes. In the event of a concerning inguino-femoral lymph node on imaging, an ultrasound scan-guided fine needle aspirate (FNA) of the node, should be undertaken. SLNB may be undertaken thereafter if FNA does not identify metastatic disease.
- The tumour should not encroach on the vagina, urethra or anus.
- It must be possible do representative peri-lesional injection of tracer at 3 – 4 sites.

- Use of radioactive tracer is mandatory in all cases. Use of dye is optional.
- Blue dye is the most commonly used dye, but Indo-cyanine green ICG is an acceptable alternative.
- If using more than one tracer(i.e. radioactive trace plus dye) it is recommended that the same operator injects all tracers used to improve correlation and detection of the SLN(s).
- Pre-operative lymphoscintigram is advised to enable the preoperative identification, location, and number of sentinel lymph nodes.
- When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.

Case selection and appropriate training are of paramount importance when undertaking SLN biopsy (SLNB) for vulvar cancer. There is a documented learning curve for SLNB in vulvar cancer. The European Society of Gynaecological Oncology (ESGO) guideline recommends a minimum throughput to maintain competency in this technique, but the exact number of cases required is a subject of debate.

- Pathological evaluation of sentinel lymph nodes should include serial sectioning at levels of at least every 200 µm. If the H&E sections are negative, immunohistochemistry should be performed.

For tumours >4 cm and/or multifocal disease, inguinofemoral lymphadenectomy via separate groin incisions is recommended.

- Women undergoing ipsilateral dissection and lymphadenectomy should have clinically negative nodes on that side pre-operatively. If the ipsilateral groin nodes contain metastasis, then the contralateral groin nodes need removal.
- When performing lymphadenectomy, superficial inguinal and deep femoral nodes should be removed. Superficial groin node dissection alone should not be performed as it is associated with a higher risk of groin recurrence.
- Preservation of the saphenous vein is recommended.
- Pelvic lymphadenectomy is not routinely indicated. However, the removal of bulky (>2 cm) pelvic nodes should be considered due to the limitations of radiotherapy in controlling bulky nodal disease.

5.4.3 Management of the positive SLN

- Where disease is identified in the SLN, additional treatment to the groin(s) should occur as there is a significant risk of disease (8-35%) in other nodes within the lymphatic basin.
- The GROINSS-VII trial showed that radiotherapy (50Gy) to the groin is a safe alternative for inguino-femoral lymphadenectomy in patients with sentinel node metastasis ≤2 mm or Isolated Tumour cells (ITCs), with minimal toxicity. The rate of isolated groin recurrence rate in women treated with radiotherapy after SLN surgery was 1.6% (95%CI:0–3.8) and the rate of lymphoedema was less in women treated with SLN biopsy and radiotherapy compared to those that had inguinal-femoral lymphadenectomy +/- radiotherapy (107% versus 22.9%). Therefore, **women with SLN micro-metastasis (≤2 mm or ITCs) should be offered radiotherapy rather than completion inguino-femoral lymphadenectomy.**
- **When metastases >2mm are found in the sentinel node, full inguino-femoral lymphadenectomy is mandated**. Women with metastases >2mm in a SLN have a higher risk of recurrence when treated with radiotherapy alone (22%) compared with those that had completion inguino-femoral lymphadenectomy +/- radiotherapy (6.9%). **Current standard of care is ipsilateral inguinofemoral lymphadenectomy on the affected side**.

5.4.4 Management of the unaffected groin in patients with bilateral lymphatic drainage and SLN biopsy with finding of unilateral positive lymph node

The incidence of a non-sentinel contralateral metastasis (2.9%) is comparable to the rate of groin recurrence after identification of a unilateral negative SLN.

- Where bilateral drainage is demonstrated, but metastatic disease is only identified in one groin, the incidence of contralateral metastasis is low and further treatment may be limited to the affected groin, although evidence for this is limited.
- In the prospective GROINSS-VII study, most non-sentinel contralateral recurrences, occurred in tumours of >3cm and therefore treatment to the contralateral groin is recommended for those with bilateral draining primary tumours >3cm where the ipsilateral SLN is positive.

5.4.5 Bulky groin node involvement

Limiting surgery to the debulking of involved groin nodes (where feasible) rather than full groin lymphadenectomy can reduce the morbidity of dual modality treatment without adversely affecting the control of disease.

In the case of bulky nodal disease, previous recommendation was to debulk prior to radiotherapy to gain better control in the groin. This recommendation has changed following developments in radiotherapy which mean that it is possible to boost the nodal dose with better effect.

There is no consensus as to whether to perform groin dissection after primary radiotherapy treatment where there has been a complete response. Surgery in an irradiated groin is associated with significant morbidity.

5.5 Adjuvant radiotherapy (or chemo-radiotherapy)

Most radiotherapy for vulval cancer is given in the adjuvant setting. The need for adjuvant radiotherapy is based upon the groin node status and the surgical margins. Positive margins and positive (involved) groin nodes are the strongest poor prognostic factors. The aim is to reduce the risk of disease recurrence balancing the benefits against the long term effects of radiotherapy. As noted above, recurrence in the vulva is more often a new primary tumour within an area of field change due to underlying lichen sclerosis or VIN, rather than a true local recurrence of a previously excised tumour.

Surgery to a tumour within an irradiated vulva is more challenging and associated with increased morbidity and wound complications even with the use of plastic reconstruction. Treatment decisions must therefore be evidence-based as far as possible taking all available prognostic information into account. The Royal College of Radiologists and the BGCS Guidelines are used as a reference[59,62].

The indications for adjuvant radiotherapy (or chemo-radiotherapy) are:

- Inguinofemoral radiotherapy is recommended instead of completion inguinofemoral lymphadenectomy for patients with an involved sentinel lymph node with micro-metastases (≤2 mm)
- Positive (microscopically involved) vulval margins and further surgery not feasible – radiotherapy may be given to the vulva alone if groin nodes are negative
- Close margins (≤3mm) and further surgery not feasible – radiotherapy may be given to the vulva alone if groin nodes are negative
- This is what ESGO says – "In case of close but clear pathological margins with extensive LVSI, peri-neural involvement, or LN involvement, post-op vulvar radiotherapy may be considered on an individualised basis to reduce the frequency of local recurrences"
- 1 involved lymph node - There is evidence for a survival advantage with adjuvant radiotherapy when there is 1 involved lymph node, but evidence for concomitant chemotherapy is not proven
- 1 lymph node with micro-metastases in the setting of full LN dissection is a relative indication for adjuvant radiotherapy to the nodal basin alone
- 2 or more involved lymph nodes is a definite indication for chemo-radiation
- Extracapsular lymph node spread is a definite indication for chemo-radiation

Adjuvant radiotherapy should be commenced no later than 2 months after surgery the aim being to complete radiotherapy <105 days after the date of surgery (based on survival data).

5.6 Definitive / radical radiotherapy (or chemo-radiotherapy for medically fit patients)

Radical radiotherapy (or chemo-radiotherapy) is recommended as treatment for patients with potentially curable tumours that are either unresectable or where resection would compromise function. This may include some stage 2 tumours if radical resection would lead to urinary or faecal incontinence and may be used in an attempt to avoid permanent colostomy, where the tumour involves the anus or where surgery would require ano-vulvectomy.

Radical treatment may also be indicated where there are large or unresectable nodes at diagnosis or in patients who are not fit for surgery or anaesthesia.

5.7 Palliative radiotherapy

Palliative radiotherapy is recommended for patients that are not fit enough for radical treatment or those patients with metastatic disease.

The palliative care team should be involved early on with these patients.

5.8 Recurrent squamous cell cancer

Both treatment and prognosis depend upon the site and extent of recurrence. Management can be challenging. Treatment plans should be made within the context of a multi-disciplinary team taking into account a number of factors most notably:

- Site(s) of disease
- Previous treatment(s) used
- Performance status
- Aim of treatment i.e. curative/radical versus palliative

The following are the recommendations for management of recurrent disease from the

most recent BGCS guidelines:

- Surgical re-excision of local and/or groin node relapse should be considered in patients with relapsed disease amenable to surgery, in analogy with the primary presentation of the disease.
- Imaging by CT (or PET-CT when appropriate) of the thorax/abdomen/pelvis is recommended prior to any treatment to tailor adequate approaches.
- SLNB can be considered for new disease/recurrent disease in the vulva, if the new focus of invasion meets criteria for primary SLNB **and there has been no previous surgery to the relevant groin(s)**. Data regarding the safety and efficacy of this approach is very limited.
- In patients not amenable to surgery, palliative chemotherapy, or radiotherapy, or combination of both should be considered, depending on the previous treatment modalities of the patient, the patient's preferences and the patient's fitness status.
- Systemic treatment may be considered in patients with distant metastases, but published data are insufficient to recommend a preferred protocol.
- Patients not suitable for active treatment should have a focus on Best Supportive Care with involvement of the Palliative Care Team.

Treatment for non-squamous carcinomas

5.8.1 Malignant melanoma

Malignant melanoma is the second most common malignant vulval tumour.

- Histologically confirmed vulvar melanoma should be discussed and management agreed at the specialist site-specific gynaecological cancer and melanoma MDTs.
- Surgical management should consist of a local excision to achieve margins free of microscopic disease by >1 mm (R0) in the least radical fashion (referred to as a "narrow-margin excision"). There is no evidence that more radical surgery is beneficial
- If margins are microscopically involved (R1), further salvage surgery is normally recommended. If this is not possible, or is declined, options involve:

- Watch and wait, treating recurrences as identified and appropriate at the time;
- Adjuvant radiotherapy with the aim of reducing local recurrence;
- Systemic therapy (chemotherapy and/or immunotherapy may used in the treatment of melanoma).

- Inguino-femoral lymphadenectomy/lymph node dissection (IFLND) has not been shown to improve survival.

The following surgical guidelines summarise and are taken from the UK Ano-Uro-Genital Mucosal Melanoma Guidelines:

- Surgery for vulvo-vaginal melanoma should be performed in centres regularly performing complex vulvo-vaginal surgery, and are regularly managing complex melanoma within a MDT.
- Resectability should be assessed by investigations outlined in the imaging investigations section.
- A patient's baseline morbidities must be assessed and if the surgery is predicted to impact significantly on quality of life or sphincter function will be compromised this must be carefully discussed with the patient; other management options may be considered e.g. Radiotherapy, systemic therapy, close observation depending on the clinical scenario, or palliative care.
- The aim of surgical management of vulval and vaginal melanomas should be to achieve an R0 (microscopically clear > 1mm) margin in the least radical fashion. There is no evidence that radical surgery has an impact on overall survival.
- The considerations set out in the recommendation above also apply to melanomas near or on the clitoris and distant urethra/urethral meatus.
- Melanomas at these sites present particularly challenging scenarios and patients with these tumours need careful counselling and in the case of the latter, input from urological colleagues.
- Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease.

The Eighth Edition of the AJCC TNM staging system for mucosal melanoma is shown below:

Classification System for Melanoma (Eighth Edition)			
T	TX	Primary tumor cannot be assessed (after curettage...)	
	T0	No evidence of primary tumor	
	Tis	Melanoma in situ	
	T1	= 1 mm	**a (< 0.8 without ulceration)**
			b (< 0.8 mm with ulceration or 0.8-1 mm with or without ulceration)
	T2	> 1 mm-2 mm	**a (without ulceration)**
			b (with ulceration)
	T3	> 2 mm-4 mm	**a (without ulceration)**
			b (with ulceration)
	T4	> 4 mm	**a (without ulceration)**
			b (with ulceration)
N	NX:	Nearby lymph nodes cannot be assessed (prior resection for another reason, body habitus...)	
	N0	No involvement of nearby lymph nodes as determined clinically/radiologically	
	N1	N1a: micrometastasis **in a lymph node** (clinically occult)	
		N1b: clinically detected lymph node	
		N1c: in transit, satellite, or microsatellite metastasis without lymph node involvement	
	N2	N2a: micrometastasis **in 2 or 3 lymph nodes** (clinically occult)	
		N2b: metastasis **in 2 or 3 lymph nodes**	
		N2c: metastasis in a lymph node (occult or clinically detected) and in transit, satellite, or microsatellite metastasis	
	N3	N3a: **4 or more** micrometastases in lymph nodes	
		N3b: **4 or more** metastases in lymph nodes, at least one of them clinically evident or presence of **matted lymph nodes**	
		N3c: 2 or more micrometastases or clinically detectable lymph node metastases or presence of matted lymph nodes and **in transit, satellite, or microsatellite metastasis**	
M	M0	No evidence of lymph node metastasis	
	M1	**M1a:** distant metastasis in **skin, soft tissue** (including muscle), **and/or nonregional lymph nodes**	
		- M1a(0): Normal LDH	
		- M1a(1): Elevated LDH	
		M1b: pulmonary metastasis with/without M1a	
		- M1b(0): Normal LDH	
		- M1b(1): Elevated LDH	
		M1c: distant metastasis in **organs other than the CNS** with/without M1a and M1b	
		- M1c(0): Normal LDH	
		- M1c(1): Elevated LDH	
		M1d: metastasis of the CNS with/without M1a, M1b, or M1c	
		- M1d(0): Normal LDH	
		- M1d(1): Elevated LDH	

AJCC TNM Staging System for Melanoma (Eighth Edition)			
Tis	N0	M0	Stage 0
T1a-T1b	N0	M0	Stage IA
T2a	N0	M0	Stage IB
T2b-T3a	N0	M0	Stage IIA
T3b-T4a	N0	**M0**	Stage IIB
T4b	N0	M0	Stage IIC
T0	N1b/1c	M0	Stage IIIB
T0	N2b/2c, N3b/3c	M0	Stage IIIC
T1a/b-T2a	N1a, N2a	M0	Stage IIIA
T1a/b-T2a	N1b/1c, N2b	M0	Stage IIIB
T2b/T3a	N1a-N2b	M0	Stage IIIB
T1a/T3a	N2c/N3a,b,c	M0	Stage IIIC
T3b/T4a	N1-N3	M0	Stage IIIC
T4b	N1a-N2c	M0	Stage IIIC
T4b	N3a/b/c	M0	Stage IIID
Any T, Tis	Any N	M1	Stage IV

5.8.2 Bartholin's gland carcinoma

This is a rare form of vulval cancer that tends to be deeply seated and associated with metastatic disease. It is managed in the same way as squamous carcinoma of the vulva. SLNB is not appropriate and full inguino-femoral lymphadenectomy is indicated. Dissection is often needed deep into the ischio-rectal fossa and the proximity to the anal canal may necessitate partial resection and temporary colostomy.

5.8.3 Basal cell carcinoma and Verrucous carcinoma

These squamous variants are rarely associated with lymph node metastasis and can be managed by excision with the aim of achieving microscopically clear margins (R0 resection). Groin node dissection is not indicated. In basal cell carcinoma, radiotherapy treatment should be considered if surgical resection is thought to compromise sphincter function.

5.8.4 Extra-mammary Paget's disease

Non-invasive EMPD

In the absence of any evidence of invasion the following are treatment options:

- Excision of the vulval EMPD
- Topical Imiquimod cream 5%

Recurrence of non-invasive EMPD is common after either treatment modality.
Where surgery has been used, further surgery may not reduce the risk of recurrence and imiquimod 5% may be considered or if the patient has been treated with this already, watchful waiting may be appropriate if invasion has been excluded.

Invasive EMPD

Invasive EMPD is treated similarly to squamous cell cancer of the vulva.
Where depth of invasion is >1mm, lymphadenectomy is recommended, ipsilateral or bilateral, depending on position. There are no data regarding the safety or effectiveness

of sentinel lymph node biopsy in invasive EMPD and sentinel node biopsy is therefore not recommended.

Women with EMPD vulva should ideally be managed in a specialist multi-disciplinary vulval clinic.

5.9 Follow-up

The vulva is an area that may be difficult for women to self-monitor and the aims of follow-up are to identify recurrence in a timely fashion as well as detect and manage adverse effects of treatment. As with other gynaecological cancers, there is little robust evidence to guide appropriate follow-up intervals.

Women who have had treatment for vulval cancer are not suitable for either telephone or patient-initiated follow up and must be seen for face-to-face consultation to include clinical examination of the groins and vulva. Some women can be safely discharged at 5 years but consideration to longer-term follow-up may be given to those women who have ongoing vulval dermatosis or HPV-related high-grade VIN or those who have had recurrence within the 1st 5 years of follow-up.

5.9.1 Follow-up of Vulval squamous cell carcinoma (VSCC)[59]

There is no proven regimen for follow up of VSCC. However, recurrence rates/new foci are common, especially on a background of Lichen Sclerosis.

Follow-up should include clinical examination of the vulva and groins and assessment of physical and psychological consequences of treatment.

Follow-up interval should be tailored to the individual taking account of any active vulval skin disease and individual risk factors for recurrence.

All patients should be told to report new lesions and be seen urgently since interval cancers are not uncommon and should be treated promptly.

Patients treated with surgery alone for uncomplicated early-stage disease

- 3-6 monthly for years 1 and 2
- 6-12 monthly in years 3-5
- Women that have had sentinel node biopsy with negative (uninvolved) nodes should have 3 monthly ultrasound scan of the groins for the first 2 years of follow-up
- Routine imaging is not indicated outside of the guidance above.
- Women with no recurrence at 5 years and with no active vulval disease may be discharged.
- Long-term follow-up may be indicated for woman that remain at significant risk of recurrence due to active dermatosis.

Patients treated with surgery + adjuvant radiotherapy (involved nodes; positive or close margins and poor prognostic factors)

Follow-up for women that have received dual modality treatment is often shared between the surgical and clinical oncology teams although where appropriate, one or other team may take responsibility for all of the follow-up after discussion.

- Follow-up intervals may be the same as those for women treated with surgery alone with review visits alternating between the surgical team and clinical oncology team as appropriate.
- Women with no recurrence at 5 years and with no active vulval disease may be discharged.

(Chemo)radiotherapy alone

Surgery in this group of women who have been treated radically, will usually be the only option for women with local recurrence. Therefore patient treated for stage 1B or 2 disease who have been treated with (chemo)radiotherapy alone, should have follow-up with the gynaecological oncologist using the same follow-up schedule above.

Women who have had more advanced disease treated should have bespoke follow-up determined by the clinical and surgical oncology team depending upon any residual disease, sequalae of treatment and options for further treatment.

5.9.2 Malignant melanoma

Refer to UK ano-genital melanoma guideline for the follow-up of vulvar melanoma. This will usually be shared follow-up between the gynaecological oncology team and the melanoma oncologist. The use of imaging in follow-up is determined by the melanoma guidance and is usually undertaken by the melanoma team. The gynaecological oncologist should assess for signs of local disease recurrence at each surgical review..

5.9.3 Basal cell carcinoma

An initial follow up 3 months following surgery may be appropriate to check healing and local recurrence. Further follow up is not required, if completely excised.

5.9.4 Extra-Mammary Pagets Disease

Patients with EMPD should have long-term follow-up. There is no evidence-based schedule for follow-up. Follow-up intervals should be individualised taking into account current disease status and symptoms.

5.10 Patient Information

Following confirmation of the diagnosis and recommended treatment plan at the MDT the Unit Lead and CNS should relay the information to the patient together with the information booklet ‘vulval cancer’.

Vulval cancer (2013).pdf

1024 Examination under anaesthesia.dc

The information on the mode of treatment can also be given at this stage.

If the patient is treated at the cancer centre a check should be made to ascertain the patient has received the relevant patient information and if found to be missing, given at this stage. If the mode of the treatment is changed at upon review of the patient then the relevant information given.

Appendix

Revised 2021 FIGO staging of vulvar cancer.

Stage	Characteristics
I	Tumor confined to the vulva IA—Tumor size ≤ 2 cm and stromal invasion ≤ 1 mm * IB—Tumor size > 2 cm or stromal invasion > 1 mm *
II	Tumor of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
III	Tumor of any size with extension to the upper part of adjacent perineal structures or with any number of nonfixed, nonulcerated lymph nodes IIIA—Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤ 5 mm IIIB—Regional ** lymph node metastases > 5 mm IIIC—Regional ** lymph node metastases with extracapsular spread
IV	Tumor of any size fixed to the bone or fixed, ulcerated lymph node metastases, or distant metastases IVA—Disease fixed to the pelvic bone or fixed or ulcerated regional ** lymph node metastases IVB—Distant metastases

* Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion. ** Regional refers to the inguinal and femoral lymph nodes.

6. GYNAECOLOGICAL SARCOMAS [12]

6.1 Background and specific considerations

Gynaecological sarcomas comprise a number of diverse and rare tumours including specific visceral sarcomas affecting the uterus and ovary and miscellaneous sarcomas of soft tissue that happen to arise within the field of surgical expertise of gynaecological oncologists in the perineum and pelvis. They include the following:

- uterine leiomyosarcoma,
- endometrial stromal sarcoma, (section 3.12.1)
- ovarian sarcomas,
- Perineal, vulval and vaginal sarcomas.

These sarcomas, like other sarcomas, would be ideally managed by teams with sufficient case load to gain specific experience but in practice this may be very difficult to achieve. IOG for Sarcoma specifies that patients with gynaecological sarcoma should have treatment planning supported by joint input from a sarcoma MDT and a gynaecological MDT.

*Carcino-sarcomas are epithelial type tumours and **not sarcomas** and therefore do not come under the remit of the sarcoma guidelines.*

6.2 Patient presentation and referral pathway

Patients with gynaecological sarcomas are likely to present with symptoms and signs indistinguishable from other benign and malignant pelvic tumours i.e. pelvic pain, disturbance of micturition, vaginal bleeding etc. They tend to present to their GP or through their Emergency Medicine department and are referred on to local gynaecological services (Cancer Unit).

The Gynaecological Cancer Lead Clinician in the Cancer Unit will refer to one of the network Gynaecological MDTs if a malignant tumour is suspected.

It is recognised that a specific pre-operative diagnosis of sarcoma will not always be apparent although radiological appearances may sometimes suggest sarcoma.

Where sarcoma is suspected, a pre-operative biopsy may be performed in some cases but may be omitted and can be difficult to obtain in many patients. Therefore, the practical solution is that:

- Initial staging and work-up should be carried out by the receiving Gynaecological MDT.
- Notification to the Sarcoma MDT should be made **as soon as a sarcoma diagnosis is suspected.**
- If a sarcoma diagnosis is made or strongly suspected pre-operatively then the Sarcoma MDT should be involved in pre-operative treatment planning
- Where the surgical procedure for a suspected sarcoma is a standard gynaecologic operation such as total abdominal hysterectomy or oophorectomy this should be performed by a Gynaecological oncologist from the referring Gynaecological MDT.
- Where the anatomic location or other factors mean that complex pelvic surgery is required, the patient should be referred to the Pelvic MDT at the Christie Hospital; pre-operatively if possible or, if a surgical procedure has already been performed then post-operatively.

6.3 Staging investigations

Where a pre-operative diagnosis of sarcoma is suspected or confirmed it is recommended that pre-operative staging investigations should include CT scan of chest, abdomen and pelvis.

6.4 Surgical treatment

6.4.1 Uterine sarcoma

Where a pre-operative diagnosis of uterine sarcoma / leiomyosarcoma is suspected or confirmed it is recommended that the surgical procedure should include the following:

- Total abdominal hysterectomy. (Bilateral salpingectomy should be considered as potential risk reducing procedure for type 2 ovarian cancer)
- Oophorectomy is not necessary for surgical control if disease is clinically confined to uterus but may be considered if the patient is post-menopausal or (for palliative

control) if there is gross tumour involvement of ovaries.

- Morcellation of fibroids should be avoided in postmenopausal women
- Lymphadenectomy is not necessary for surgical control if the lymph nodes are not clinically enlarged but nodal excision biopsy is recommended where there is lymphadenopathy.
- Omentectomy is not required for surgical control.
- There is no data on the benefit of adjuvant chemotherapy or radiotherapy

In cases with suspected leiomyosarcoma restricted to the uterus, total hysterectomy could be carried out in local units by a consultant of the gynaecological oncology MDT.

Patients with advanced or recurrent LMS are usually challenged with chemotherapy unless complete surgical resection is possible

Management of patients with primary or recurrent Leiomyosarcoma requires a multidisciplinary team approach preferably with the participation of the regional sarcoma team. Referral to the sarcoma MDT can be made by the local diagnosing unit or the regional SMDT. Completion of the Sarcoma referral form should be emailed to sarcoma.mdt@mft.nhs.uk

6.4.2 Ovarian sarcoma

Where a pre-operative diagnosis of ovarian sarcoma is suspected or confirmed it is recommended that the surgical procedure should include the following:

- Unilateral oophorectomy
- Contra-lateral ovarian biopsy
- Omental biopsy
- Hysterectomy is not required for surgical control

6.4.3 Vulval, vaginal and perineal sarcoma

Where a pre-operative diagnosis of vulval, vaginal or perineal sarcoma is suspected or confirmed it is strongly recommended that definitive resection is discussed with the Pelvic Surgical Team at Christie Hospital and with the Sarcoma

Team reconstructive surgeons prior to surgery. Sarcoma cases should be discussed at both the specialist gynaecological cancer MDT as well as the sarcoma MDT at the Christie Hospital.

6.5 Post-resection management

6.5.1 Pathology review

- Expert pathological review by a recognised sarcoma pathologist (Dr Patricke Shenjere [Christies] Dr Kat Boros and and Dr Asma Haider [MFT]) is required to comply with IOG.
- For uterine leiomyosarcoma, ER/PR status should be performed.
- For cases of endometrial stromal sarcoma, CD10 immunohistochemistry should be performed.
- Grade should be reported on the basis of mitotic index and morphology (NB Trojani system is **not** used)

6.5.2 Post-resection staging investigations

If a CT scan was not performed pre-operatively, this should be done post-operatively to complete staging.

6.5.3 Communication with Sarcoma MDT

The relevant Sarcoma MDT should be informed of the patient's details including: site, morphology, surgeon, hospital, date of surgery stage and Gynaecological MDT plans regarding adjuvant therapy.

6.5.4 Adjuvant therapy

Network guidelines for the selection of patients with gynaecological sarcoma for adjuvant therapy should be followed (see "3.18, Uterine Sarcoma"). In summary, patients with:

- Completely resected FIGO stage I-IVA uterine leiomyosarcoma (LMS) – no adjuvant therapy.
- Incompletely resected stage III / IV uterine LMS FIGO – consider pelvic

radiotherapy (although strictly speaking this is not adjuvant therapy).

6.6 Follow-up

Following definitive treatment follow-up will comply with the standard sarcoma follow-up care plan. Follow-up can be shared between surgical team and treating clinical oncology team or with sarcoma clinical oncology team.

In summary:

Year 1:	clinic visits 3 monthly
Year 2:	clinic visits 3 monthly
Years 3-5:	clinic visits 6 monthly
Years 6-10:	annual visits

At each visit a pelvic examination and chest X-ray should be performed. No routine blood tests are required.

6.7 Relapsed or advanced disease

Women with relapsed or advanced disease should be referred to Dr Alex Lee (Christie hospital) for re-staging and to co-ordinate their multimodal therapy.

- Patients will have re-staging CT scan of chest abdomen and pelvis
- Systemic therapy including hormone therapy (for ESS) will be managed by Dr Alex Lee.

7 Clinical Nurse Specialist

Within the MDT, the CNS has a specific role for information, communication and psychological support. The clinical nurse specialist (CNS) or key worker is a point of contact for patients throughout their pathway that can ensure they have access to information and support services throughout. The CNS will ensure ongoing holistic needs assessments (HNAs) are carried out. This, in turn, improves patient satisfaction and empowerment with overall better outcomes. Patients with cancer should not notice their transition between organisations in the provider network. This transition should be seamless as to allow the patient to feel involved and integral when their care is transferred between specialist and local/primary care settings.

7.1 Key Worker

The key worker should be recorded in a patient's notes and be made clear to the patient along with the contact details of their key worker. The key worker role is to co-ordinate the patient's care (with the patients consent and agreement) and provide continuity of care and accessible support. The journey for the gynaecological cancer patient is complex and the key worker role may be transferred to other teams and CNS' along the clinical pathway.

The key worker should:

- Co-ordinate patient's care e.g ensure that the patient knows who and where to access information and advice
- Attend and actively participate in the MDT and other relevant meetings to allow for patient advocacy
- Offer business cards to patients so they have written and identifiable contact details
- Complete holistic needs assessments (HNAs) at diagnosis and within 31 days of treatment completion, making onward referrals where appropriate
- Provide specific information including self-help groups and support services
- Provide sensitive, non-judgemental support and information to patients and their families/friends affected by a diagnosis
- Ensure effective and time-appropriate referrals are made to suit the individuals needs/wishes
- Allow for open communication in the form of email, telephone and/or answer messages where possible
- Be present in clinic when a diagnosis is given, where a treatment plan is discussed and provide support for unexpected diagnosis

- Maintain a point of contact throughout the disease pathway, where appropriate
- Support survivorship models on improved education and support for patients, carers and healthcare professionals to promote supported self-management and personalised care planning.

7.2 Information

All patients with a diagnosis of gynaecological cancer should be offered clear and comprehensive information, both verbal and written, on all aspects and at all stages of the patient pathway. This information should include (but not limited to): referral, investigations, -diagnosis, disease, treatment options, side-effects, survivorship information, psychological support, complementary therapies and support groups/information workshops.

7.3 Communication

In order to facilitate their role in communicating with patients, carers and the extended MDT; the CNS is required to have undertaken an advanced communication skills training session and remain up to date with this training. The CNS plays a pivotal role in communicating effectively, ensuring timely and appropriate referrals are made and continuity of care is facilitated. Each MDT should have a core member trained to provide level 2 psychological support. Good, effective communication allows for a high standard of care for patients and ensures continuity of care between different stages of care and settings. On initial meeting with the patient, an impact assessment is carried out to highlight the patient wishes and what is most important to them, which in turn will feed into the MDT discussion and treatment plan.

7.4 Support

Support from the CNS has been identified as an integral part of ensuring patient participation in decision making and treatment planning. The CNS provides an important role in assessing and referring patients for problems in the areas of psychological distress, sexuality, body image, fertility, menopause, lymphoedema, incontinence, stoma care, complex symptom management, rehabilitation, spirituality, social care and finance. The CNS is responsible for carrying out and actioning on

outcomes from the Holistic Needs Assessment (HNA) alongside support from the Cancer Care Co-Ordinator/Care Support Worker.

7.5 Personalised Care and Support Planning

Personalised Care and Support Planning (PCSP) helps people living with cancer to take an active and empowered role in the way their care is planned and delivered, with interventions and care tailored around the things that matter most to them. The benefit of PCSP is to facilitate conversations with patients, identifying needs, developing a personalised care and support plan, signposting to local support areas and sharing the right information at the right time. PCSP is achieved by PCSP care plans based on HNAs, end of treatment summaries and health and wellbeing information and support. PCSP allows us to keep a record of conversations, decisions and agreed outcomes, understand a patients care and support needs (including their life and family dynamics) and know what is required to make their plan achievable and effective.

7.6 Holistic Needs Assessment

All gynaecological cancer patients' physical, emotional, social, psychological and spiritual needs should be appropriately assessed, identified and reviewed. This should be done in a timely and appropriate way, and resources can be targeted to those who will benefit from them. A HNA assessment can be carried out by either a Cancer Care Co-Ordinator/Care Support Worker (with CNS supervision) or the CNS themselves. A HNA is a simple questionnaire provided to highlight areas in which patients feel as though they could benefit from support in. This questionnaire allows the patient to discuss issues most important to them at that time, in order to inform and develop a care and support plan. The HNA can be completed in person, electronically or over the telephone – depending on the individuals needs and preferences. A patients' holistic needs are likely to change at different and key points in their cancer journey, for example after diagnosis concerns would likely be different to those concerns at the end of their treatment. Following each assessment, a care plan should be developed and shared between the patient, healthcare professionals and the GP including any actions for the GP to improve management and care. The

recommendation is that HNA's should be performed within 31 days of diagnosis and at the end of first-line treatment but also whenever a person requests one.

7.7 End of Treatment Summary

An end of treatment summary is a document produced by the hospital, either the consultant, CNS or Cancer Care Co-Ordinator/Care Support Worker (with CNS supervision) at the end of the initial treatment of cancer. It is a document designed to be shared with the patient and their GP. An end of treatment summary should include:

- An overview of any treatment the patient has received
- Details of any potential side effects of treatment
- The signs and symptoms of cancer recurrence
- Contact details to address any concerns

Once the end of treatment summary is complete, it can be shared either manually on paper or electronically on the hospital clinical systems which allows the GP to update their records and use the document when they conduct a Cancer Care Review.

7.8 Advanced Nurse Practitioners/ Nurse Clinicians

The MDT may include Advanced Nurse Practitioners (ANPs) and Nurse Clinicians (NCs) who are experienced trained Gynaecology Oncology Nurses who have had additional training in advanced practice. They may see patients pre, peri and post treatment/diagnosis, often in place of a doctor. They undertake aspects of the medical role but combine it with a holistic framework aiming to enhance the patient's journey.

8 SUPPORTIVE AND PALLIATIVE CARE

It is recognised that women and families should have supportive care from diagnosis onwards. This should include:

- Access to information about their disease, aspects of management, available services and how to access them. This may for example include local and national patient support networks.
- Advice on available practical and financial help
- Emotional and spiritual support, with specialist help for those with difficulties in adjustment and coping.
- An active rehabilitative approach to maximise functional recovery and adaptation to consequences of cancer and its treatment.
- A meticulous approach to the relief of pain and other symptoms at any stage. This should lead to early referral to specialist services if management of problems should prove difficult.

Pain associated with advanced pelvic tumour can be complex and difficult to control. A thorough assessment is an essential part of management: this will identify different sites and types of pain, e.g. soft tissue, visceral or neuropathic. Each individual pain must be dealt with appropriately.

If it is proving difficult to improve pain relief, or there are problems with side effects of drugs, it is important to seek advice as early as possible (see above in relation to other services). Uncontrolled cancer pain should be viewed as an oncological emergency and warrants admission to hospital or hospice. Neurolytic procedures are helpful for selected patients with sacral, perineal and some visceral pain. Cordotomy may be considered for a few patients with intractable, unilateral pelvic and limb pain. For others with central and bilateral pain, control using an indwelling spinal catheter can be achieved.

Palliative care describes a multidisciplinary approach to the needs of the individual with progressing or advanced cancer and her family, with the aim of maintaining best quality of life and support through the terminal stage and into bereavement. Palliative care is an integral part of the care provided by all primary and hospital teams. Specialist palliative care is provided by those with training and who work exclusively within this area across community, hospital and hospice settings.

8.1 Roles and Responsibilities

8.1.1 Gynaecological Cancer Specialist Team

Responsible for regular assessment of the individual and her situation as part of follow up: her main concerns, how she is coping, her expectations and wishes. Effective and time efficient consultations benefit from training in communication skills. All senior oncology staff should have the opportunity to undertake Advanced Communication Skills Training to fulfil the requirements of the Cancer Standards. Good communication between professionals across all services is essential and the specialist team have an important role in ensuring that others are kept up to date about clinical developments and management decisions.

8.1.2 General Practitioner

Central to the care of the patient and family and his/her involvement usually precedes the cancer diagnosis and may extend through bereavement and beyond. Often he/she will maintain an overview of the situation and ensure involvement of support services within the community.

8.2 Specialist Services

If the individual patient needs exceed the expertise available within the MDT there is a range of specialist services to which the patient can be referred. Referrals may be made through hospital or community teams, but early identification of potential or developing problems, and prompt referral, is essential. Specialist services in relation to gynaecological cancer may include:

- Psychological support, including psycho-sexual counselling
- Genetic counselling
- Lymphoedema management
- Pain Specialists
- Palliative Care
- Complementary therapies
- Cancer Information Services
- Specialist menopause advice
- Late effects of treatment

8.2.1 Specialist Psychological Support

This may be indicated for people with difficulties in psychological adjustment, leading to disabling anxiety and depression and much less commonly, psychiatric illness co-existing with cancer. Such problems may also extend to the carers and include complicated grief leading to abnormal bereavement. Each SMDT should have at least one core member of the team with direct clinical contact, who has completed the training necessary to enable them to practice at level 2 for the psychological support of cancer patients and carers, and should receive a minimum of 1 hours clinical supervision by a level 3 or level 4 practitioner per month (Gynaecology Measures 2014, 14-2E-201).

The provision for psycho-oncology services is extremely limited. Referrals if possible should be made to services local to the patient. If patients have been treated at Christies they can be referred to the Psycho-Oncology Team, which is led by Dr Tania Hawthorn, Consultant in Psycho-Oncology, Christie Hospital.

8.2.2 Fertility

Many of the treatments for gynaecological cancer can have an impact on a patient's fertility. This needs to be considered when discussing treatment options with patients so that they have a full understanding of this to enable them to be involved in the decision making process, discuss options for minimizing impact on fertility (where this is possible) and receiving appropriate support. NICE guidance around fertility preservation in cancer treatment (2004) states:

"Women preparing for medical treatment that is likely to make them infertile should be offered oocyte or embryo cryo-storage as appropriate, if they are well enough to undergo ovarian stimulation and egg collection, provided that this will not worsen their condition and that sufficient time is available...."

And also:

"People preparing for medical treatment that is likely to make them infertile should be offered counselling from someone who is independent of the treatment unit, to help them cope with the stress and the potential physical and psychological implications

for themselves, their partners and any potential children resulting from cryo-storage of gametes and/or embryos...."

(For more on the guidance: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10936)

Following the publication of NICE guidance on fertility a working group in Gr Manchester piloted and established a fertility pathway for female patients. This is now an established service provided by the Reproductive Medicine Dept. at St Mary's led by Dr Cheryl Fitzgerald. The service is currently subject for further updates. All pre-menopausal female cancer patients who want to discuss fertility options can be referred by fax (Fax to 0161 224 0957 or phone to discuss 0161 276 6494). Ideally patients should be referred as early as possible in their diagnostic pathway. Once referred, the Reproductive Medicine Department will contact the patient by telephone with an appointment date and time. This appointment will be at St Mary's Hospital Manchester and staff will aim to see each patient within seven to ten days of referral.

8.2.3 Sexual Dysfunction Assessment & Management

Women who undergo treatment for any gynaecological cancer may experience physical and/or psychological sexual issues afterwards, which may affect their own sexuality, body image and fertility or their intimate relationships with their partners. Women require information prior to treatment about possible sexual dysfunction afterwards. Assessment of sexual function/dysfunction should be routine follow-up post-surgery, radiotherapy and/or chemotherapy. Following radiotherapy, to the vagina, patients are advised and educated in the use of vaginal dilators in order to prevent/minimise vaginal stenosis as per International Guidelines on Vaginal Dilation after Pelvic Radiotherapy (Grade C). They are also given basic information when appropriate about returning to sexual activity & HRT.

If women have sexual dysfunction/sexuality problems beyond the scope of the team providing follow-up they should be referred to the appropriate specialist. The Sexual Rehabilitation Clinic at St. Mary's Hospital offers a service to any woman post gynaecological cancer treatment, with either physical or psychosexual problems by

an appropriately trained Advanced Nurse Practitioner, psychosexual therapist and gynaecologist. Service provided at St. Mary's Hospital (Lead Karen Donnelly, St Marys 0161276-8714). Patients who have been treated at Christie can also be referred to the Christie Psycho-Oncology Team (Lead for Psycho-Sexual Service – Dr Josie Butcher, who also has clinical sessions at St Luke's Hospice, Winsford). For patients who have had radiotherapy they can be referred back to the Clinical Oncology Nurse Led Clinic (Lead Karen Johnson 0161 446 8101). There will also be psycho-sexual services local to where patients live including generic services such as RELATE.

8.2.4 Genetic Counselling

Provided as a specialist out-patient service at St. Mary's Hospital and the Christie Hospital (lead: Professor Gareth Evans).

8.2.5 Lymphoedema Management

In gynaecological cancer, swelling of one or both legs in the absence of hypo-albuminaemia or vein thrombosis is usually due to lymphatic obstruction. This may be a consequence of treatment itself or active pelvic disease. The team has a responsibility to refer such patients to a specialist lymphoedema service for assessment and management. Proactive treatment can significantly reduce lymphoedema and control swelling even in the presence of progressive disease. It is important to recognise the need for early referral of patients at high risk of lymphoedema development, as well as those showing early signs of the problem.

Acute infective episodes may present a florid cellulitis but frequently may be a case of mild erythema and general malaise. These should always be actively treated initially with Amoxicillin 500mg 8-hourly and if there is any evidence of Staph aureus (folliculitis, pus, crusting) then Flucloxacillin 500mg 6-hourly should be prescribed in addition or alternative. Patients allergic to Penicillin should be prescribed erythromycin 500mg 6-hourly or clarithromycin 500mg 12 hourly severe episodes may require in-patient treatment. Full guidelines for treating cellulitis in lymphedema can be found in the 'Consensus Document on the Management of Cellulitis in

Lymphoedema produced by the British lymphology society and The Lymphoedema Support Network (http://www.lymphoedema.org/Menu3/Cellulitis%20Consensus.pdf)

Current provision of lymphoedema support in Greater Manchester and Cheshire is patchy. Lymphoedema services are currently available at

- Christie Hospital including service at satellite sites at Oldham and Salford - contact: 0161 446 3795
- St. Ann's Hospice, Heald Green Little Hulton -contact), contact 0161 437 8136/: 0161 498 3684
- East Cheshire Hospice, Macclesfield contact01625 610 364
- Dr Kershaw's Hospice, Oldham contact) 0161 624 2727
- Springhill Hospice, Rochdale, contact 01706 649920
- Neil Cliffe Cancer Care Centre, , Wythenshawe contact 0161 291 2912
- Willow Wood Hospice, Tameside contact 0161 366 2135
- Long Term Condition Unit, Boston House, Wigan contact-01942 525566/01942 482244
- St Luke's Hospice, Winsford 01606 555683/555682

Beechwood Cancer Care Stockport & Bolton Hospice - provide Key Worker level only and only accept referrals with mild to moderate lymphoedema, affecting one limb only. Referrals can be made centrally via the Christie Service.

8.2.6 Fistulae

Fistulae may arise as a consequence of advanced pelvic disease but are also late problems following pelvic radiotherapy to locally advanced tumour where there is invasion of adjacent bladder and bowel.

In the absence of clinical evidence of active disease, a CT scan should be performed to assess with a view to surgical management.

Those patients with fistulae associated with progressive malignancy should have surgical assessment to consider palliative bowel or urinary diversions.

Uncontrolled loss of small bowel contents leads to skin excoriation. Palliative care measures may include attempts to solidify/bulk the stool using Loperamide and Fybogel.

8.2.7 Complementary Therapies

These may be available to in-patients at some hospitals (contact your local unit for information). Some information about complementary therapies available to out-patients may be accessed through the Cancer Information Services. They are also part of the range of services provided for patients at hospices; both in-patient and day care setting. They may provide a useful introduction to palliative care services.

8.2.8 Pain Specialist Teams

These are hospital based and provide out-patient clinic services. Often pain associated with active, progressing cancer is managed by palliative care specialists as there are often multiple co-existent problems; however pain specialists provide valuable advice and help for those with difficult and intractable pain. Referral to a chronic pain service may be appropriate for those patients who are cured of their cancer but live with difficult pain as a result of treatment or the disease. Often this management requires a multidisciplinary approach in which the focus has moved from the cancer itself to rehabilitation.

8.2.9 Specialist Palliative Care Teams

These are multidisciplinary and have specialist palliative care nurses and doctors as core members. The palliative care nurse specialists are often referred to “Macmillan nurses” whether working in hospital or community, and often provide support and advice from diagnosis onwards. (It should be noted that other staff, including cancer nurse specialists, physiotherapists and so on may carry the Macmillan title if their posts were pump primed by the cancer charity). In general, specialist palliative care professionals aim to work alongside the oncology or primary care team and would not take over care of the patient except when in an in-patient hospice setting. They network closely with colleagues across hospital, community and hospice settings.

They should be seen as a resource, particularly in difficult and distressing situations and those where considerable on-going support to patient and family is required.

Hospices are substantially funded by independently raised monies plus a small contribution from Primary Care Trusts. They provide a range of services which include in-patient care for symptom control, brief (1-2 weeks) respite for families and terminal care. They are unable to make commitments for indefinite intermediate/continuing care, where nursing home may be more appropriate. Hospice services include counselling, family support, management of breathlessness and lymphoedema. Day care at hospices provides access to a range of multi-professional services including medical assessment, as well as support for those who are socially isolated as a result of their malignant disease.

Palliative care advice to professionals is available through a helpline at St. Ann's Hospice (0880 970 7970).

8.2.10 Treatment induced menopause

Treatment-induced menopause can have a significant impact on quality of life for pre-menopausal women. It is important to discuss this early in the treatment and for decisions to be made by the treating team about appropriateness of HRT. Women can then be supported and informed about their choices in managing their menopause, its symptoms and any pomaybe needs update in this section from Claire Mitchell?? tential long-term consequences. As the long-term prescribing of HRT will probably be undertaken by GP's it is important that at the end of treatment and end of oncology follow-up.

9 Teenage and Young Adults (TYA)

Patients under 25yrs with a suspected cancer should also be discussed at the TYA MDT in addition to a Gynae MDT. Patients aged 19-24 years inclusive should be offered choice of referral to a Principal Treatment Centre (Young People) for treatment. The TYA MDT offers holistic expertise in not only treating the cancer, but also in ensuring the young person's psychosocial and emotional needs are addressed. (Teenage and Young Adults Measures, 2014)

10 Acute Oncology

10.1 Complications of systemic anti cancer therapy or radiotherapy

24 Hour Hotline is provided by the Christie for any patients who are on or have had recent chemotherapy or radiotherapy. Contact 0161 446 3658

10.2 Metastatic Spinal Cord Compression (MSCC)

MSCC can be a complication of metastatic gynaecological malignancy and prompt diagnosis is essential to improving the outcome and quality of life for patients. Clinicians who have a patient they are worried about should contact the MSCC Co-ordinating service urgently, which is based at The Christie on 0161 446 3658.

APPENDIX I FIGO Staging for Gynaecological Cancers

A. Carcinoma of the Cervix (UPDATED 2019)

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy with deepest invasion ≤ 5mm
IA1	Measured stromal invasion of ≤3.0mm in depth
IA2	Measured stromal invasion of >3.0mm and not >5.0mm
IB	Invasive carcinoma confined to the uterine cervix, with measured deepest invasion ≥5 mm
IB1	Tumour measures <2 cm in greatest dimension.
IB2	Tumour measures >2 cm and <4 cm in greatest dimension
IB3	Tumour measures >4 cm in great dimension
Stage II	Cervical carcinoma invades beyond the uterus but not to the pelvic side wall or to the lower third of the vagina.
IIA	Limited to the upper two-thirds of the vagina without parametrial invasion
IIA1	Clinically visible lesion ≤4.0cm in greatest dimension
IIA2	Clinically visible lesion >4.0cm in greatest dimension
IIB	With obvious parametrial invasion but not up to the pelvic wall
Stage III	The tumour extends to the pelvic side wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney, and/or involves pelvic and/or para-aortic lymph nodes
IIIA	Tumour involves lower third of the vagina with no extension to the pelvic side wall.
IIIB	Extension to the pelvic side wall and/or hydronephrosis or non-functioning kidney.
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. Bullous oedema alone does not permit a case to be ascribed to stage IV.
IVA	Spread of the tumour to adjacent organs.

IVB	Spread to distant organs.

B. Carcinoma of the vagina

Stage 0	**Intra-epithelial neoplasia grade 3 (VAIN, carcinoma *in situ*)**
Stage I	**Carcinoma limited to vaginal wall**
Stage II	**Carcinoma involves sub-vaginal tissue but has not extended to pelvic wall**
Stage III	**Carcinoma extends to pelvic side-wall**
Stage IV	**Carcinoma extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder or rectum. Bullous oedema alone does not permit a case to be ascribed to stage IV.**
IVA	Carcinoma involves bladder and/or rectal mucosa and/or direct extension beyond the true pelvis.
IVB	Spread to distant organs.

C. Carcinoma and carcinosarcoma of the endometrium (2009)

Stage I	**Tumour confined to the corpus uteri**
IA	No or less than 50% myometrial invasion
IB	Invasion ≥ 50% of myometrial thickness
Stage II	Tumour invades cervical stroma but does not extend beyond the uterus*
Stage III	**Local and or regional spread of the tumour**
IIIA	Tumour invades the serosa of the corpus uteri and/or adnexae**
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic nodes
Stage IV	**Tumour invades bladder and/or bowel mucosa and/or distant**

	metastases	
		Tumour invasion of bladder and/or bowel mucosa
		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

∗Endocervical glandular involvement only should be considered as stage I and no longer as stage II.

∗∗Positive cytology has to be reported separately without changing the stage

D. Carcinoma of the ovary (2014)

Stage I	**Tumour limited to the ovaries**
IA	Tumour limited to one ovary; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings
IB	Tumour limited to both ovaries; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings
IC	Tumour limited to one or both ovaries with any of the following:
IC1-3	IC1: Surgical spill IC2: Capsule rupture before surgery or tumour on ovarian surface IC3: Malignant cells in the ascites or peritoneal washings
Stage II	**Tumour involves one or both ovaries with pelvic extension**
IIA	**Extension and/or implants on uterus and/or tube(s); no malignant cells in** ascites or peritoneal washings
IIB	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings.
Stage III	**Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis** Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis IIIA1: Positive retroperitoneal lymph nodes only IIIA1(i) Metastasis ≤ 10mm IIIA1(ii) Metastasis >10mm IIIA2: Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIA	
IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis. Included extension to capsule of liver/spleen
Stage IV	**Distant metastasis (excludes peritoneal metastasis)***
	IVA: Pleural effusion with positive cytology IVB: Hepatic and/or splenic parenchymal mstasis to extra-abdominal c

E. Carcinoma of the vulva (updated 2021)

Stage I	**Tumour confined to the vulva**
IA	Lesions ≤2cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0mm, no nodal metastasis
IB	Lesions >2cm in size or with stromal invasion >1.0 mm, confined to the vulva or perineum, with negative nodes
Stage II	**Tumour of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes**
Stage III	**Tumour of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node**
IIIA	Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
IIIB	Regional lymph node metastases >5 mm
IIIC	Regional lymph node metastases with extra-capsular spread
Stage IV	**Tumour of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases**
IVA	Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases
IVB	Distant metastases

Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.
Regional refers to inguinal and femoral lymph nodes.

F. Uterine leiomyosarcomas and endometrial stromal sarcomas (ESS)

Stage I	Tumour limited to uterus
IA	≤5cm
IB	>5cm
Stage II	Tumour extends beyond uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
Stage III	Tumour invades abdominal tissues (not just protruding into the abdomen
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV	
IVA	Tumour invades bladder and/or rectum
IVB	Distant metastases

Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumours

G. Uterine adenosarcomas

Stage I	Tumour limited to uterus
IA	Tumour limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than 50% myometrial invasion
Stage II	Tumour extends beyond uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
Stage III	Tumour invades abdominal tissues (not just protruding into the abdomen
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV	
IVA	Tumour invades bladder and/or rectum
IVB	Distant metastases

APPENDIX II

RISK OF MALIGNANCY INDEX FOR OVARIAN MASSES

The Risk of Malignancy Index scoring system is based on ultrasound findings, menopausal status and serum CA-125 levels. It has been validated in a series of prospective cohort studies. More recent publications have demonstrated its value in routine clinical practice as a tool for triaging patients for cancer centre surgery and also indicated that it behaves comparably to more complex diagnostic models.

RMI scoring system

Ultrasound features	multilocular cyst	0= no abnormalities
	Solid areas	1= one abnormality
	Bilateral lesions	3= two or more abnormalities
	Ascites	
	Intra-abdominal ascites	
Menopausal status	pre-menopausal	=1
	Post-menopausal	=3
CA-125	U/ml	=absolute value

RMI score= ultrasound score x menopausal status x CA125

A cut-off score of >250 has been commonly employed, with reported sensitivities of 70-75% and specificities of c90%. Positive predictive values of 85-90% have been reported.

APPENDIX III

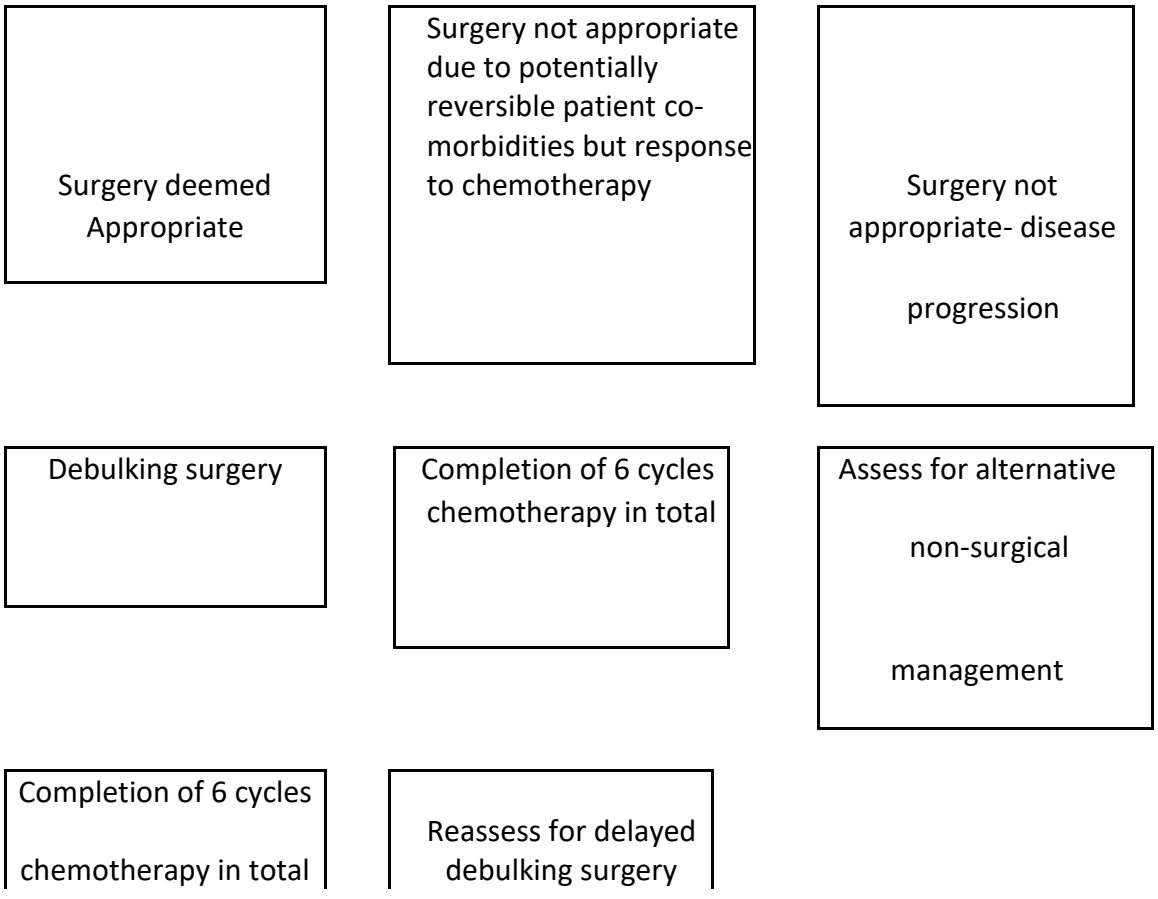
CARE PATHWAY FOR THE USE OF NEO-ADJUVANT CHEMOTHERAPY IN OVARIAN CANCER

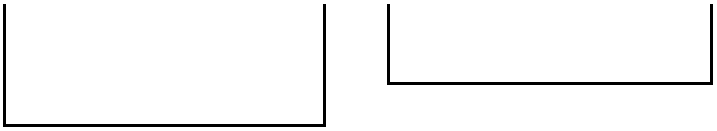
Patient performance status or co-morbid factors preclude upfront surgery OR tightly defined disease characteristics indicate effective debulking unlikely (see section 4.5.3)

Histological confirmation of diagnosis, baseline CT assessment of disease extent, FBC, biochemical profile, GFR3 cycles of neo-adjuvant carboplatin-based chemotherapy

Reassessment of patient performance status and radiological assessment of disease extent 1-2 weeks after 3rd cycle chemotherapy

Review by gynaecological oncologist 3 weeks after 3rd cycle chemotherapy- to be arranged at commencement of neo-adjuvant treatment. To assess feasibility for surgery





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