All Wales Guideline for the Management of Uterine Cancer

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Foreword

Uterine cancer affects around 500 women in Wales each year. The incidence has risen by around 50% in the last 20 years, driven by changes in lifestyle and a rising incidence of risk factors such as obesity. Most uterine cancers are endometrial adenocarcinomas, but patients can also develop other types of cancer such as sarcoma. Most patients are treated surgically; patients may also require risk-based adjuvant treatment depending on surgical findings and multidisciplinary team working is essential. Patients need timely expert help and support to navigate through their cancer diagnosis, treatment and after-effects.

In preparing this guideline, specialists from around Wales have come together to form a consensus document which can be used by those who plan and deliver gynaecological cancer services. The aim of the guideline is to help improve and coordinate care and bring about uniformity fo treatment for women with uterine cancer in Wales.

Scope of this document

This document covers the screening, prevention, diagnosis and treatment of uterine cancer. It also considers support of patients and consequences of cancer treatment.

The document focuses on the main uterine cancers: endometrial carcinoma, carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma.

Endometrial hyperplasia should be managed according to guidelines published by the Royal College of Obstetricians and Gynaecologists and the British Society for Gynaecological Endoscopy (RCOG/BSGE, 2016).

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1 Background

1.1 Incidence, mortality and age

1.1.1 Incidence

Cancer of the uterus is the fourth most common cancer in females in the UK (CRUK, 2017). The majority of cancers arise in the endometrium. In 2014 there were 549 cases of uterine cancer in Wales, giving a European age-standardised rate of 33.8 per 100,000 women and a lifetime risk of around 1 in 40 women. Uterine cancer accounts for 5% of all new cancer cases in females. The incidence has increased by over 50% in the last 20 years, reflecting changing lifestyles. There is no significant variation in incidence in different ethnic groups in the UK.

1.1.2 Mortality

In Wales there were 122 deaths from endometrial cancer in 2014, and it is the 9th most common cause of cancer death in women in the UK, accounting for 3% of female cancer deaths (CRUK, 2017). Over the last 20 years, the European age-standardised mortality rate has increased, reflecting a rise in incidence rates.

1.1.3 Age

The risk of uterine cancer increases with age, particularly from the age of 40, occurring most commonly in postmenopausal women (CRUK, 2017). The peak incidence is in the 65-69 year old age group. The peak death rate is in the over 85 year old age range, reflecting a worse prognosis in older women.

1.2 Aetiology

The main risk factor for endometrial carcinoma aside from increasing age, is an excess of endogenous oestrogens associated with obesity. The relative risk (RR) of developing endometrial cancer in obese women is 2.21 ($p<0.001$; Esposito *et al.,* 2014). Hypertension and hyperlipidaemia are also associated factors. Diabetes mellitus, in particular type II, is associated with an increased risk (odds ratio [OR] 2.1; 95% CI 1.40 - 3.41) (Rosato *et al.,* 2011).

Nulliparity, infertility and polycystic ovarian syndrome, late menopause and early menarche are also risk factors for endometrial cancer (Colombo *et al.,* 2016).

Unopposed oestrogen therapy increases the risk of endometrial cancer (Ali *et al.,* 2014).
Women with oestrogen secreting tumours such as granulosa cell tumours of the ovary are at increased risk of endometrial carcinoma.

Women taking tamoxifen, either as treatment or prevention for breast cancer are at increased risk of endometrial cancer (Swerdlow *et al.,* 2005).

Women with Lynch Syndrome (LS; hereditary non-polyposis colorectal cancer, HNPCC) have an autosomal dominant inherited germline mutation in a DNA mismatch repair gene. Women with mutations in MLH1, MSH2, MSH6 or PMS2 have an up to 40-60% lifetime risk of developing

endometrial or colorectal cancers and a 9-12% lifetime risk of developing ovarian cancer (Lancaster *et al.,* 2015).

Leiomyosarcomas can occur by malignant change in a uterine fibroid, though the overall incidence of malignant change in a fibroid is extremely low.

2. Pathology

Endometrial carcinoma and carcinosarcoma accounts for over 90% of all uterine cancer. In 2009 in the UK, 76.9% of all cases of uterine cancer were endometrioid adenocarcinoma, with a further 7.4% being clear cell or papillary serous cancer, while 6.2% were mixed epithelial and mesenchymal (NCIN, 2013).

2.1 Types of tumour

The following types of malignant epithelial tumours occur in the body of the uterus (WHO, 2003; Ganesan *et al.,* 2014):

2.1.1 Epithelial tumours

- Adenocarcinoma
    - Endometrioid (variants: with squamous differentiation; villoglandular variant; secretory variant; ciliated cell variant)
    - Mucinous adenocarcinoma
    - Serous adenocarcinoma
    - Clear cell adenocarcinoma
    - Mixed adenocarcinoma
- Squamous cell carcinoma
- Transitional cell carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma

2.1.2 Mixed epithelial and mesenchymal tumours

- Carcinosarcoma
- Adenosarcoma

2.1.3 Mesenchymal tumours

- Endometrial stromal and related tumours
    - Endometrial stromal sarcoma (low grade)
    - Undifferentiated endometrial sarcoma
- Smooth muscle tumours
    - Leiomyosarcoma (epithelioid and myxoid variants)

Other tumours can occur, such as gestational trophoblastic tumours and lymphoid tumours: these are out of the scope of this document.

Carcinosarcoma (previously called malignant mixed Müllerian tumour, MMMT) is included in the treatment of uterine carcinoma, because carcinosarcoma is now regarded as being a high grade variant of carcinoma, where the sarcomatous element has arisen by metaplastic transformation of carcinoma. Carcinosarcoma is rare, accounting for fewer than 5% of all uterine cancers (Arend *et al.,* 2011).

Endometrial carcinomas have traditionally been divided into type I and type II cancers. Type I comprises all grades of endometrioid tumours arising in women with features such as obesity, hyperlipidaemia, infertility and late onset menopause, whereas type II cancers arise in women who have none of these features or else the signs are not clearly defined (Bokham, 1983). More recently, this classical dualistic model has been updated based on new molecular evidence with regard to The Cancer Genome Atlas Research Network (TGCA) and four distinct genomic subtypes are recognized: POLE ultramutated; hypermutated, microsatellite instability (MSI); copy number-low microsatellite stable (MSS) and copy number-high, serous like tumours (Wilczyński *et al*., 2016). This may become more relevant in the proposed new staging for endometrial cancer which will take account of genomic subtypes.

2.2 Grade

The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) grading system for endometrioid adenocarcinoma comprises three grades (1, 2 and 3). Serous and clear cell cancers and carcinosarcoma are graded as high grade.

2.3 Dataset

Pathology reports should be compiled in accordance with The Royal College of Pathologists core dataset for reporting of endometrial cancer, which is described as follows (Ganesan *et al.,* 2014):

2.3.1 Clinical core data items:

- type of specimen
- other clinical details

2.3.2 Pathological core data: macroscopic:

- specimen type
- attached anatomical structures
- accompanying specimens
- maximum dimension of tumour

2.3.3 Pathological core data: microscopic:

- tumour type
- tumour grade
- myometrial invasion
- tumour free distance to serosa
- lymphovascular invasion
- cervical stromal invasion
- vaginal involvement
- uterine serosal involvement

- parametrial involvement
- adnexal involvement
- lymph node involvement
- omental involvement
- provisional FIGO stage

2.3.4 Summary of non-core data items

2.3.4.1 Pathological data: macroscopic

- specimen weight and measurements.

2.3.4.1 Pathological data: microscopic

- percentages of different components of mixed carcinomas
- morphological components of carcinosarcomas
- cervical surface and gland (crypt) involvement
- distance of tumour from cervical (or vaginal) margin
- percentage of myometrium involved by tumour
- background endometrium
- peritoneal involvement
- peritoneal cytology
- distant metastases
- extracapsular spread of lymph node metastases
- ancillary investigations
- block key
- provisional TNM stage

3 Staging

Staging of endometrial carcinoma was defined by the FIGO in 2009 (Pecorelli *et al.,* 2009). Carcinosarcomas of the uterus should be staged using the same system (FIGO, 2009).
Table 1 shows the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging of endometrial carcinoma and carcinosarcoma. Tables 2 and 3 show the FIGO staging for endometrial stromal sarcoma and adenosarcoma, and leiomyosarcomas/ endometrial stromal sarcomas respectively.

Table 1 FIGO staging for endometrial carcinoma and carcinosarcoma	
FIGO Stage	Description
I	Tumour confined to the corpus uterus
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of myometrium
II	Tumour invades cervical stroma, but does not extend beyond the uterus. Endocervical glandular involvement should be considered as stage I and no longer as stage II.
III	Local and/or regional spread of the tumour
IIIA	Tumour involves serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and /or parametrial involvement
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic nodes with or without pelvic lymph nodes
IV	Tumour invades bladder and/or bowel mucosa and /or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastasis including intra-abdominal metastases and /or inguinal nodes
Positive cytology as to be reported separately without changing the stage. Adapted from Pecorelli *et al.*, 2009 and FIGO 2009. Note that endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.	

Table 2 FIGO staging for endometrial stromal sarcomas and adenosarcomas (FIGO 2009)	
FIGO Stage	Description
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 half myometrial invasion
II	Tumour extends to the pelvis
IIA	Adnexal involvement
IIB	Tumour extends to extrauterine pelvic tissue
III	Tumour invades to abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	>one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumour invades bladder and/or rectum
IVB	Distant metastasis

Table 3 FIGO staging for uterine leiomyosarcomas and endometrial stromal sarcomas (FIGO 2009)	
FIGO Stage	Description
I	Tumour limited to uterus
IA	<5 cm
IB	>5 cm
II	Tumour extends to the pelvis
IIA	Adnexal involvement
IIB	Tumour extends to extrauterine pelvic tissue
III	Tumour invades to abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	>One site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumour invades bladder and/or rectum
IVB	Distant metastasis

4. Screening and prevention

4.1 Screening

4.1.1 Screening in the general population

There is no evidence that screening for endometrial cancer in asymptomatic women in the general population improves outcomes from endometrial cancer and there is no national screening programme for the general population. Abnormal endometrial cells may be detected, however, in asymptomatic women during cervical screening. Women who have normal endometrial cells 'out of phase' or postmenopausally will be advised to see their GP, and their GP is informed.

4.1.2 Tamoxifen

There is no evidence for routine screening in women taking tamoxifen, but women taking tamoxifen should be advised of the symptoms of endometrial cancer and the need to report these, if they occur.

4.1.3 Lynch syndrome

Lynch syndrome, (formerly known as hereditary non-polyposis colorectal cancer; HNPCC) is associated with a significant increase in the risk of colorectal, endometrial and ovarian cancers. There is no definite evidence for the role of screening for endometrial cancer for women with Lynch syndrome, although this option is available to women. Hysterectomy is known to be protective for endometrial cancer. Patients suspected of having Lynch syndrome should be referred to the All Wales Medical Genetics Service. Options that should be discussed with affected women include:

- From age 35: annual hysteroscopy, biopsy and ultrasound until hysterectomy.
- Once family is complete (e.g. around 35-40 years): hysterectomy with or without bilateral salpingo-oophorectomy.

Usually hormone replacement therapy is prescribed in premenopausal women who become menopausal after surgery for Lynch syndrome (Vasen *et al.,* 2013).

4.2 Prevention

All women should be encouraged to adopt lifestyle changes that reduce the risk of cancer, for example by maintaining a healthy weight and engaging in regular physical activity. These also reduce the risk of other risk factors such as diabetes and hypertension.

Women with an intact uterus should not be prescribed unopposed oestrogen.

5 Indications for referral

Women who are suspected of having uterine cancer should be referred to their local gynaecological unit.

5.1 NICE referral guidance (NICE, 2015a)

NICE guidance recommends referring women using a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause.)

A suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer should be considered in women aged under 55 with post-menopausal bleeding.
Direct access ultrasound scan to assess for endometrial cancer should be considered in women aged 55 and over with:

- Unexplained symptoms of vaginal discharge who:
    - Are presenting with these symptoms for the first time or
    - Have thrombocytosis or
    - Report haematuria or
- Visible haematuria and:
    - Low haemoglobin levels or
    - Thrombocytosis or
    - High blood glucose levels

5.2 Postmenopausal women

Ninety percent of patients with endometrial cancer present with postmenopausal bleeding (PMB). Examination in primary care where possible should include abdominal, vaginal and speculum examination (but referral should not be delayed to complete this and a referral should be sent at point of suspicion). Any patient with postmenopausal bleeding or suspicion of uterine cancer should be referred to a rapid access gynaecological clinic and they should be seen within 2 weeks of referral from the GP or any other source.

5.3 Pre- and perimenopausal women

Although uterine cancer is most likely to occur in postmenopausal women, it can also occur in pre- and perimenopausal women. Unexplained vaginal bleeding (e.g. intermenstrual bleeding, menorrhagia or postcoital bleeding) should prompt a gynaecological examination to be performed. If an abnormality is found on examination suggesting vulval, vaginal or cervical cancer, the patient should be referred by the referring clinician to a gynaecologist to be seen within two weeks. If there is no abnormality on examination in perimenopausal women, patients should have further assessment (transvaginal ultrasound scan, referral to gynaecologist), particularly if they have features conferring a risk of malignancy:

- Additional symptoms such as pain, dyspareunia, heavy bleeding
- Risk factors for endometrial cancer (e.g. family history, raised BMI, tamoxifen)
- Women $\geq$ 45 years

5.4 Women who have abnormal endometrial cells detected on cervical smear

These women will be directly referred to a colposcopy unit, who will arrange further investigation. It is standard for women to be seen within 2 weeks of receipt of referral.

5.5 Other symptoms and presentations

Uterine cancer occasionally presents in the absence of vaginal bleeding. Suspicious symptoms include unexplained vaginal discharge and haematuria. Symptoms which may indicate locally advanced or metastatic disease include weight loss, pelvic pain, bone pain, jaundice, pulmonary symptoms.

Other presentations of endometrial cancer include: as an incidental finding after hysterectomy; after screening or surveillance tests in high risk women; as an incidental finding during investigations for other symptoms.

6 Diagnostic and treatment pathways

Timely diagnosis and treatment is of paramount importance in endometrial cancer. The development of predefined pathways for patients presenting with typical symptoms is strongly encouraged. Patients on the Urgent Suspected Cancer (USC) pathway should remain on the pathway until treatment or until a diagnosis of endometrial cancer or pre-cancer has been confidently excluded. Patients with atypical hyperplasia should remain on the USC pathway until treated, because of the risk of co-existing endometrial cancer. Other cancers such as sarcomas, fallopian tube and ovarian cancers can present with abnormal bleeding, and these possibilities should also be considered during the diagnostic work-up.

7 The role of the multi-disciplinary team (MDT)

The role of the MDT is to agree the clinical facts through multidisciplinary specialist review, bringing together all clinical and diagnostic information and advise the clinical team delivering the care on evidence based treatment options and clinical trials. Whilst strong individual and consensus views

should be recorded, it is the individual consultant and his/her team that has direct clinical responsibility for the care of the patient (Jones and Allan, 2014).
All cases of endometrial cancer and atypical hyperplasia should be discussed and managed by members of the gynaecological MDT. Definitive treatment should be performed within 62 days for patients on the USC pathway and within 31 days of diagnosis for patients on the non-USC pathway. However, Wales has been moving towards a single cancer pathway in 2019 which will eliminate hidden waits in the 31 day pathway.

8 Clinical assessment

Clinical assessment of women suspected of having uterine cancer is mandatory. Recording of the patient's history and characteristics and a thorough examination should be carried out. Risk factors to document include age, past history of diabetes or hypertension, hereditary cancers (e.g. Lynch syndrome) and past or current tamoxifen use. Physical examination should include weight, body mass index (BMI), abdominal examination, gynaecological examination including inspection of the vulva, vagina, cervix, anus and urethra, bimanual examination of uterus and adnexal structures and speculum examination. Consideration should be given to rectal examination (if rectal bleeding or other pathology suspected) and cervical smear (if due).

9 Initial investigation

It is vital that all units have a clear referral pathway where all patients with red flag symptoms (NICE 2015a) are triaged and assessed in a timely fashion. These patients should be optimally managed in a one stop diagnostic clinic where they will have access to all diagnostic tools (i.e TVS, outpatient hysteroscopy and polyp resection, endometrial sampling). A same-day diagnostic model that can provide a diagnosis and/or exclude endometrial cancer has high patient preference rates (Timmermans et al, 2007).

9.1 Transvaginal ultrasound scan

Ultrasound, preferably transvaginal ultrasound scan (TVS) is the first investigation used to investigate unexplained, abnormal uterine bleeding. It allows the evaluation of the endometrium, including the thickness of the endometrium and the size of the tumour. Myometrial invasion, cervical involvement, and ovarian or tubal pathology frequently can be determined. As a minimum, the following should be documented (Leone *et al.,* 2010):

- Endometrial thickness
- Contour (regular or irregular)
- Whether the endometrium is viewed in its entirety
- Presence of adnexal masses or free fluid.

9.2 Endometrial biopsy

A cut-off of 3mm, 4 mm and 5 mm have a sensitivity of 98%, 95% and 90% respectively for detecting endometrial cancer (Timmermans *et al.,* 2010). In postmenopausal women with an endometrial thickness of 4-mm or more, an outpatient Pipelle® biopsy should be performed. A biopsy is also recommended if the endometrium cannot be visualized or is irregular, and in symptomatic women

taking tamoxifen regardless of endometrial thickness. Premenopausal women with menorrhagia or abnormal bleeding should be considered for endometrial sampling.

9.3 Hysteroscopy and biopsy

Hysteroscopy and biopsy, ideally as an outpatient procedure at the time of the initial visit (level 4), are performed if a Pipelle® is not feasible because of patient discomfort, cervical stenosis or if the Pipelle® specimen is inadequate. Additionally, hysteroscopy should be performed if the ultrasound has indicated structural abnormalities seen on ultrasound that require direct visualisation level 3).Ideally the clinician should have access to equipment to enable outpatient resection of the polyp without morcellation (Level 5). About 10% of patients represent with recurrent bleeding, and a hysteroscopy rather than pipelle should be considered to rule out malignancy (Level 5).

10 Pathology review

The pathological specimen should be reviewed by a pathologist who is a member of a gynaecological multidisciplinary team. This will allow characterisation of the histological type and grade of the specimen, which are required to form a treatment plan.

11 Staging investigations and pre-treatment work-up

Treatment will be determined by the histological type, grade and stage of the tumour, the patient's comorbidity and the patient's wishes.

11.1 Staging investigations – imaging

General principles

1. All imaging request forms for a patient on a cancer pathway target (e.g. 31 days for USC) must be appropriately marked with this information and with the priority box ticked Urgent.
2. All imaging requests for cancer investigation should adhere to the Cancer Network referral protocols and any other specific requirements set out under each cancer site-specific set of standards.
3. All urgent requests must be delivered and/or otherwise communicated to the appropriate Radiology Dept within 1 working day of signature by the referrer in strict accordance with the agreed referral route as indicated by the Radiology Department in their written referral guidelines.
4. In order to avoid unnecessary travel, imaging should always be arranged as close to the patient's home as is possible without detriment to quality and safety. This is a core commitment of Welsh Government as outlined in the NHS Wales Delivery plan: "Together against Cancer". Arrangements should be in place at the patient's local hospital to accept appropriate referrals for imaging from approved clinicians across the network.

Standard: Imaging departments should provide clear, written information to MDTs on the range of investigations provided and their availability. Where availability is limited or intermittent,

particularly for complex investigations, there should be written alternative referral pathways agreed with the Cancer Network.

Standard: All Departments of Clinical Radiology should have written policies on the referral and imaging investigations of patients with cancer or suspected cancer by cancer site. These should reflect the latest advice from the Royal College of Radiologists which includes recommendations on imaging protocols (Rockall *et al.,* 2014).

- All patients with proven or probable endometrial cancer currently have MR staging as standard, unless there are contraindications. This must include the upper abdomen to assess for para-aortic lymph nodes.
- CXR is sufficient for routine assessment of thoracic spread as this is uncommon without adverse risk factors on other imaging/clinical assessment.
- CT scan of thorax, abdomen and /or pelvis may also be considered as an additional option for example when MRI scanning is contraindicated or when there are adverse risk factors such as serous papillary and clear cell carcinoma or high grade uterine sarcomas.
- For newly presenting patients with endometrial cancer, PET scanning is commissioned in Wales for staging of patients being considered for exenterative surgery (WHSSC, 2014).

11.2 Other investigations

- Raised serum CA125 correlates with higher stage disease (Yildiz *et al.,* 2012), but there is no evidence that it is clinically useful in endometrial cancer.

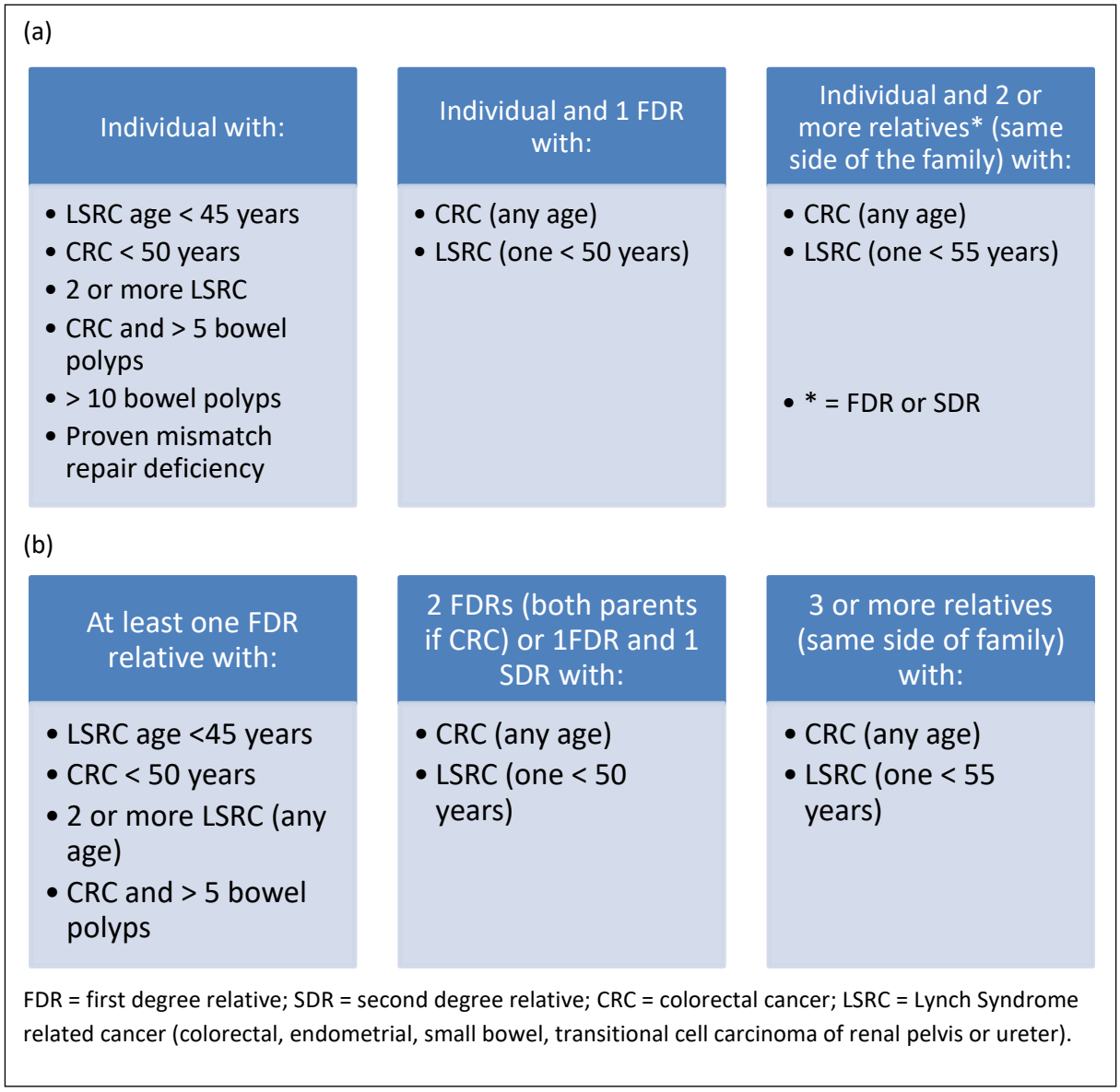
11.3 Pretreatment work-up

- General assessment and medical assessment of comorbidities.
- FBC.
- Renal, liver, bone profile.
- Group and save (as per local protocols).

11.3.1 Family history

Check family history if not already done so, and offer genetics referral to women who meet the All Wales Genetics Service Guidelines. Endometrial cancer is one of the Lynch Syndrome Related Cancers (LSRCs; endometrial, small bowel, transitional cell carcinoma of the renal pelvis or ureter). Referral to the All Wales Medical Genetics Service is indicated in patients with endometrial cancer if one or more of the following criteria are met (AWMGS, 2016) as shown in Figure 1.

Figure 1 Genetics referral criteria (a) for patients with a personal history of Lynch Syndrome related cancer (LSRC) and (b) for patients with a family history of LSRC.



FDR = first degree relative; SDR = second degree relative; CRC = colorectal cancer; LSRC = Lynch Syndrome related cancer (colorectal, endometrial, small bowel, transitional cell carcinoma of renal pelvis or ureter).

12 Referral to the cancer centre

Patients with stage IA, grade 1 or 2 endometrial carcinoma can be treated surgically in their local cancer unit. Patients with stage 1b (grade 1 or 2) should be referred centrally for a decision about site of surgery, however consideration should be given to performing surgery in the cancer centre. Patients with a higher stage, high grade (grade 3) or type 2 disease should be referred to the cancer centre for treatment.

It is important that referrals to the cancer centre are done as soon as possible. Cancer units and cancer centres should discuss and agree local protocols for referral to ensure that patients'

treatments are not delayed. This may include referring patients before all staging investigations are complete, if it is clear that a referral to the cancer centre is indicated.

13 Initial management of apparent stage I and II endometrial carcinoma and carcinosarcoma

13.1 Surgery

Surgery should be undertaken by gynaecologists who are core members of a gynaecological MDT. Women with provisional stage IA grade 1 or 2 cancers at pre-operative assessment can have surgery in a cancer unit. All other women should have surgery in the cancer centre by gynae-oncology specialist surgeons.

Unless contraindicated, all women having surgery for endometrial cancer and atypical hyperplasia should have the following as a minimum, with additional procedures as discussed subsequently:

- Careful inspection and/or palpation of the abdomen and pelvis (diaphragm, liver, omentum, pelvic and para-aortic lymph nodes, pelvic and bowel peritoneal surfaces).
- Total hysterectomy.
- Bilateral salpingo-oophorectomy.

13.1.1 Route of surgery

Historically the standard treatment for endometrial cancer has been via the abdominal route. Increasingly, total laparascopic hysterectomy (TLH), laparoscopically assisted vaginal hysterectomy (LAVH) and robotic surgery are being used. NICE guidance recommends that current evidence on the safety and efficacy of laparoscopic hysterectomy (TLH and LAVH) for endometrial cancer is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit (NICE, 2010). *(Level 1)*

13.1.2 Role of pelvic lymphadenectomy

The role of pelvic lymphadenectomy in stage I disease is not fully determined. There is no evidence that pelvic lymphadenectomy improves overall survival in early stage endometrial cancer (Kitchener *et al.* 2009), but it can be useful as a staging procedure and it allows tailoring of adjuvant therapy (Colombo *et al.,* 2016).

Pelvic lymphadenectomy is not indicated in patients with low risk disease (stage IA, grade 1 or 2) who have no enlarged lymph nodes on imaging. *(Level 2)*

A tailored approach can be used for lymphadenectomy according to the risk of lymph node metastases (Todo *et al.,* 2014). Consideration should be given to performing pelvic lymphadenectomy in patients who are at greater risk of lymph node metastases, such as those with stage IB, grade 3 tumours, non-endometrioid tumours (serous, clear cell, undifferentiated and carcinosarcoma) and stage II disease. Patients with enlarged, suspicious nodes on imaging should also be considered for pelvic lymphadenectomy or pelvic lymph node sampling with removal of the enlarged nodes only. *(Level 5)*

The role of sentinel lymph node biopsy in endometrial cancer is evolving and there is evidence of good diagnostic performance. However currently there is not sufficient evidence to support its inclusion in routine clinical practice, though some centres could consider it an area of service development.

13.1.3 Role of para-aortic lymph node removal

The role of para-aortic lymphadenectomy is not defined. It is recommended that para-aortic lymph node removal is considered in patients who have enlarged or suspicious lymph nodes on imaging or at surgery. *(Level 5).* Para-aortic lymph node dissection of normal-sized or non-suspicious nodes should only be undertaken as part of a clinical trial.

13.1.4 Role of omentectomy

There is no evidence that omentectomy improves outcomes in women with endometrial cancer but it can be used as a staging procedure. Its role is limited to those women thought to be at particular risk of omental disease, such as those with type II tumours or those with a suspicion of omental spread detected at surgery. *(Level 5).*

13.1.5 Radical hysterectomy in stage II disease

A SEER analysis of 1577 patients showed no benefit to radical hysterectomy in patients with stage II cancer (Wright *et al.,* 2009). Radical hysterectomy is not indicated routinely in stage II disease and its use is restricted to situations where the surgically clear resection margins would obviate the need for adjuvant radiotherapy.

13.2 Radical radiotherapy

If patients are unsuitable for surgery (e.g. because of comorbidity or personal preference), radical radiotherapy is a treatment option.

13.3 Fertility sparing options

There is current interest in the use of progestogens alone in grade 1 stage I endometrial carcinoma as a fertility sparing option. There are no randomised trials to support this approach but there are reported case series showing response rates of around 75% (Park *et al.* 2013a). Patients should be monitored closely with repeat biopsies, and normalising the patient's BMI. Surgery should be offered to non-responders and following completion of family.

13.4 Palliative treatment

Rarely patients with stage I or II disease will not be well enough to receive any form of radical treatment. In these situations, palliative treatment and care should be initiated.

14 Initial management of apparent stage III and IV endometrial carcinoma and carcinosarcoma

In patients with stage III and IV cancer, treatment decisions will be based on the tumour extent, the patient's general condition and the patient's wishes.

14.1 Radical treatment options

For patients who are treated with radical intent, multimodality treatment is generally offered, starting with surgery. Where possible, cytoreduction is performed if it is anticipated that zero macroscopic disease can be achieved. If complete macroscopic clearance is not considered to be achievable then neoadjuvant chemotherapy is an option with surgery delayed, as with ovarian cancer, until after 3 or 4 cycles of chemotherapy. Rarely, patients with locally advanced endometrial cancer may be treated with pelvic exenteration.

For patients who have inoperable disease, whose disease can be encompassed by a radical radiotherapy field, and who are well enough, radical radiotherapy or chemoradiotherapy are options.

14.2 Palliative treatments

Patients with distant metastatic disease or who are unfit for radical treatment, require palliative treatments which are primarily aimed at maximizing quality of life.

Symptomatic benefits may be achieved with treatments such as radiotherapy, chemotherapy or hormonal treatments. Sometimes, palliative surgery is indicated to alleviate specific symptoms. Occasionally long term disease control can be achieved with hormonal treatments for metastatic low grade cancers. Options for palliative treatment are discussed in more detail later.

15 Risk groups in endometrial carcinoma and carcinosarcoma

15.1 Risk factors

In surgically-treated patients, decisions around adjuvant treatment are made using a risk-based approach. Many patients require no adjuvant therapy. For stratification of risk factors, there are several different classification systems. It is recommended that the risk groups from the ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer are used to guide treatment (Colombo *et al.,* 2016).

15.2 Staging

It is important to note that following surgery and histological examination, the pathological stage of the tumour can be determined. This may result in up-staging or down-staging of disease compared with the apparent pre-surgical stage. An example is if regional nodal metastases are detected in a patient whose imaging showed no abnormally enlarged lymph nodes, the stage becomes stage III.

Table 4 shows the risk groups (adapted from Colombo *et al.,* 2016).

Table 4 Risk groups in endometrial cancer adapted from Colombo *et al.,* 2016	
Risk Group	Criteria
Low risk	• Stage IA, grade 1-2, no LVSI
Intermediate risk	• Stage IB, grade 1-2, no LVSI
High intermediate risk	• Stage IA, grade 3, +/- LVSI • Stage IA/B, grade 1-2, LVSI unequivocally positive
High risk	• Stage IB, grade 3, +/- LVSI • Stage II • Stage III (no residual disease) • Non endometrioid (serous, clear cell, undifferentiated, carcinosarcoma)
Advanced	• Stage III residual disease • Stage IVA
Metastatic	• Stage IVB

LVSI = lymphovascular space invasion

16 Adjuvant treatment options in patients with low, intermediate and high risk carcinomas and carcinosarcomas

16.1 Choice of adjuvant treatment

The aim of adjuvant treatment is to reduce the risk of recurrence of endometrial cancer, either by reducing the risk of local recurrence or improving overall survival.

Adjuvant post-surgical treatment involves the modalities of radiotherapy (external beam and/or brachytherapy) or chemotherapy.

Adjuvant hormonal treatment confers no benefit and should not be used as adjuvant treatment in endometrial carcinoma (Gien *et al.,* 2008).

There is a lack of evidence from randomised trials to guide treatment in all situations (Colombo *et al.,* 2016). Principles of treatment are to offer radiotherapy based on risk factors for recurrence, extent of surgery and the comorbidity and wishes of the patient.

16.1.1 Low risk – no adjuvant treatment

Patients with stage IA, grade 1 or 2 tumours with no LVSI have a very good prognosis and no adjuvant treatment is indicated (Sorbe *et al.,* 2009). *(Level 2)*

16.1.2 Intermediate risk - adjuvant treatment

The PORTEC 1 and PORTEC 2 studies showed that vaginal vault brachytherapy is as effective as external beam radiotherapy in reducing the risk of vaginal vault recurrence in intermediate risk

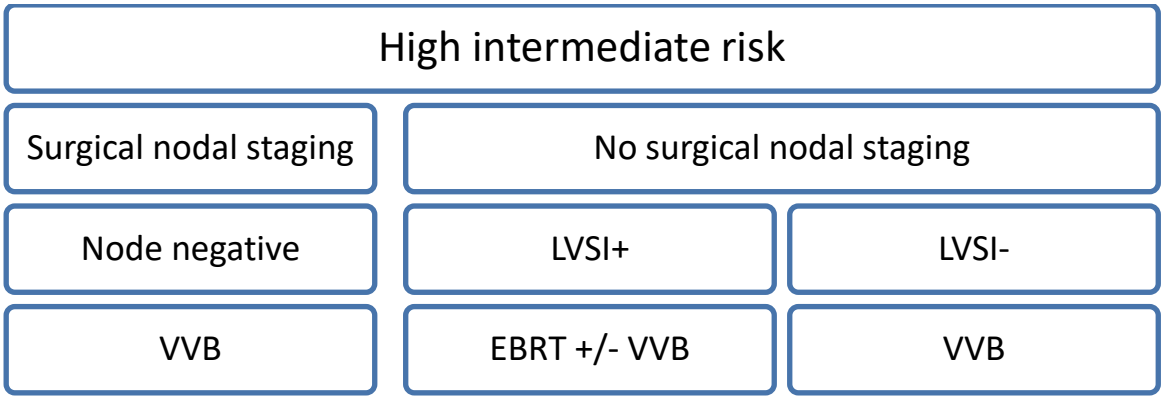
patients and with fewer side effects (Creutzberg *et al.,* 2000; Nout *et al.,* 2010). Patients with stage IB, grade 1 or 2 tumours should be offered vaginal vault brachytherapy. *(Level 2)*

16.1.3 High intermediate risk – adjuvant treatment

Both the PORTEC 1 and GOG 99 studies identified a group of patients who gain the greatest benefit for external beam radiotherapy, based on number of risk factors (Creutzberg *et al.,* 2000; Keys *et al.,* 2004). For patients with high intermediate risk tumours, treatment will depend on whether nodal staging (i.e. lymph node dissection) has taken place. It is important to note that lymph node sampling alone does not equate to full nodal staging. The GOG study showed that even in patients who have a lymphadenectomy, external beam radiotherapy reduces the risk of recurrence, but the recurrences were predominantly at the vaginal vault, a site where vaginal vault brachytherapy is known to reduce the risk of recurrence (Creutzberg *et al.,* 2000; Keys *et al.,* 2004). Therefore, for patients who have had pelvic lymphadenectomy, vaginal vault brachytherapy is considered adequate adjuvant treatment for the radiotherapy component of treatment. *(Level 5)*

Lymphovascular space invasion is an independent risk factor for endometrial cancer (Briët *et al.,* 2005). Patients with high intermediate risk cancer and lymphovascular space invasion who have not had surgical staging should be offered external beam radiotherapy. *(Level 2)*
The role of chemotherapy as adjuvant treatment for endometrial cancer is not fully defined. The recent PORTEC 3 trial showed no significant benefit to chemotherapy in high risk patients with stage I and II disease, though patients with stage III disease had a statistically significant 11% improvement in failure free survival at five years (de Boer *et al.,* 2016). Figure 2 shows recommended adjuvant treatment options in high intermediate risk endometrial cancer.

Figure 2**.** Adjuvant treatment options in high intermediate risk endometrial carcinoma



LVSI = lymphovascular space invasion; VVB = vaginal vault brachytherapy; EBRT = external beam radiotherapy

16.1.3.1 High risk – adjuvant treatment

For patients with high risk disease, there is a risk of both local and distant relapse.

16.1.3.2 High risk stage I - endometrioid

For patients with high risk stage I disease, treatment depends on whether surgical nodal staging has taken place.

Surgical nodal staging - node negative

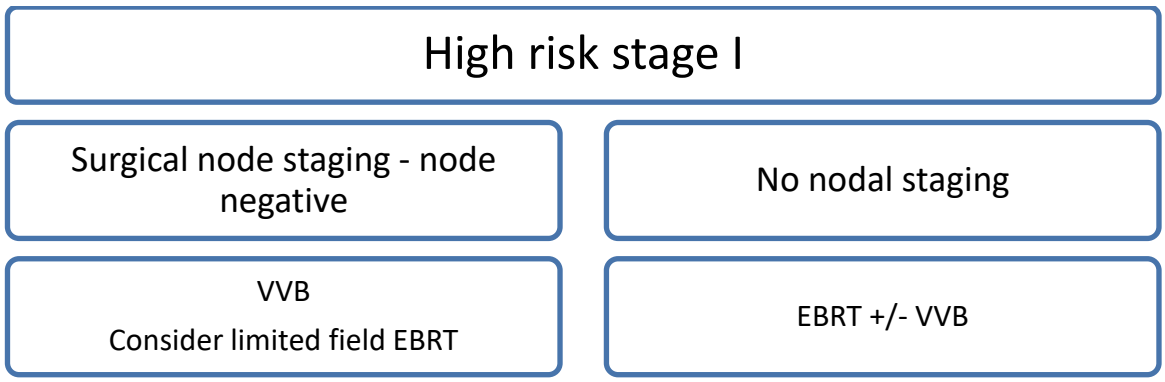
Patients with high risk stage I disease who have had pelvic lymphadenectomy should be offered vaginal vault brachytherapy. *(Level 2).* Consideration should be given to offering limited field external beam radiotherapy e.g. if the patient is thought to be at risk of recurrence in the parametrium. *(Level 5)*

No surgical nodal staging

Patients with high risk stage I disease who have not had nodal staging should be offered external beam pelvic radiotherapy with or without vaginal vault brachytherapy. *(Level 2)*

The role of chemotherapy in high risk stage I endometrioid cancer is unclear. Two pooled clinical trials showed that adjuvant chemotherapy improves progression free survival with a trend towards overall survival (Hogberg *et al.* 2010). The PORTEC 3 study also did not show a significant survival advantage of chemotherapy for patients with stage I-II disease (deBoer *et al.,* 2017). *(Level 1)* The question of chemotherapy is still being investigated and the results are awaited of the ENGOT-EN2-DGCG-EORTC-55102 trial looking at postoperative chemotherapy or no further treatment in patients with node-negative stage I-II intermediate or high risk endometrial cancer.

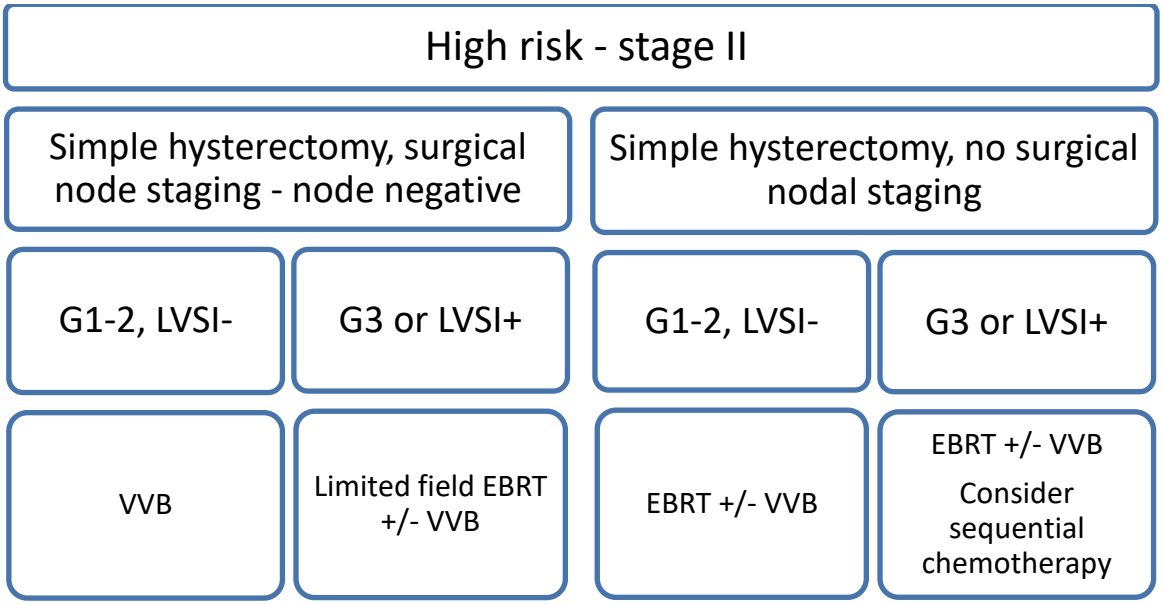
Figure 3 Recommended adjuvant treatment options in high risk stage I disease



16.1.3.3 Stage II - endometrioid

A SEER study of 1198 women with stage II endometrial cancer showed increased survival in women who received adjuvant radiotherapy (Wright *et al.,* 2009). There is a lack of evidence from randomised trials to guide individualised treatment for patients with stage II cancer, based on whether surgical nodal staging has taken place and the presence of risk factors such as grade 3 cancer or lymphovascular space invasion. Similarly, there is no proven survival benefit to adjuvant chemotherapy. Patients with no surgical nodal staging who are thought to be at risk of having occult stage III disease could be considered for chemotherapy. A suggested scheme is based on the recommendations of Colombo *et al.,* (2016) and shown in Figure 4. *(Levels 2-5)*

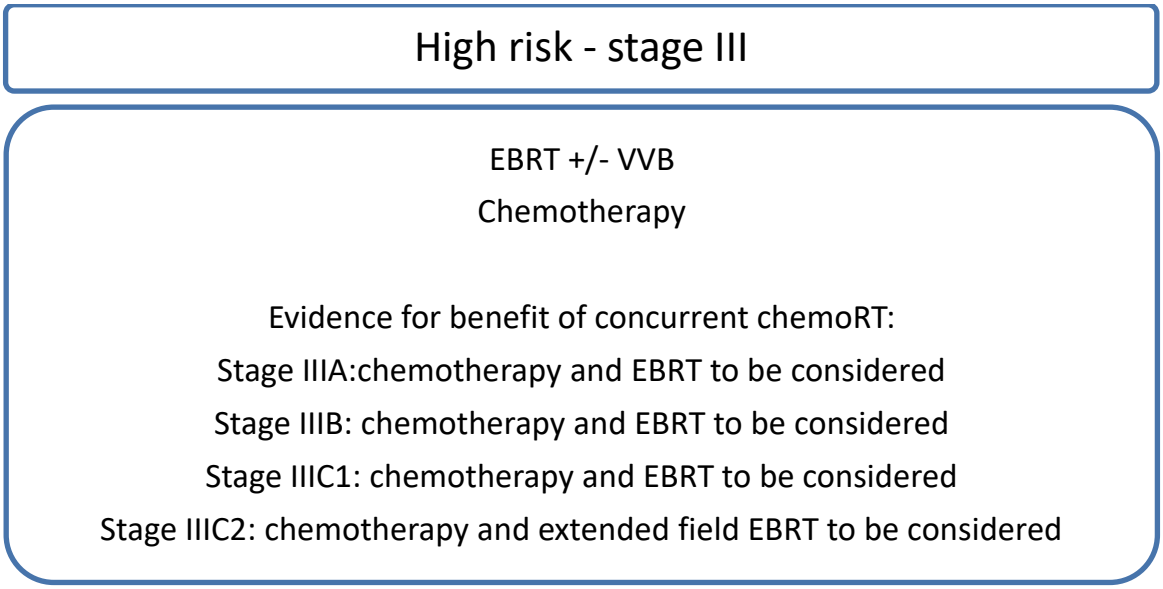
Figure 4 Recommended adjuvant treatment options in stage II endometrial cancer.



16.1.3.4 Stage III

The use of external beam radiotherapy has been associated with improved survival in patients with node-positive endometrial cancer (Klopp *et al.,* 2009; Secord *et al.,* 2013). A meta-analysis of adjuvant chemotherapy showed a survival advantage to adjuvant chemotherapy in patients with advanced stage cancer (Park *et al.,* 2013b). In patients with stage III disease, external beam radiotherapy (+/- vaginal vault brachytherapy) is recommended together with chemotherapy. *(Levels 2, 3)*

Figure 5 Adjuvant treatment options in stage III disease



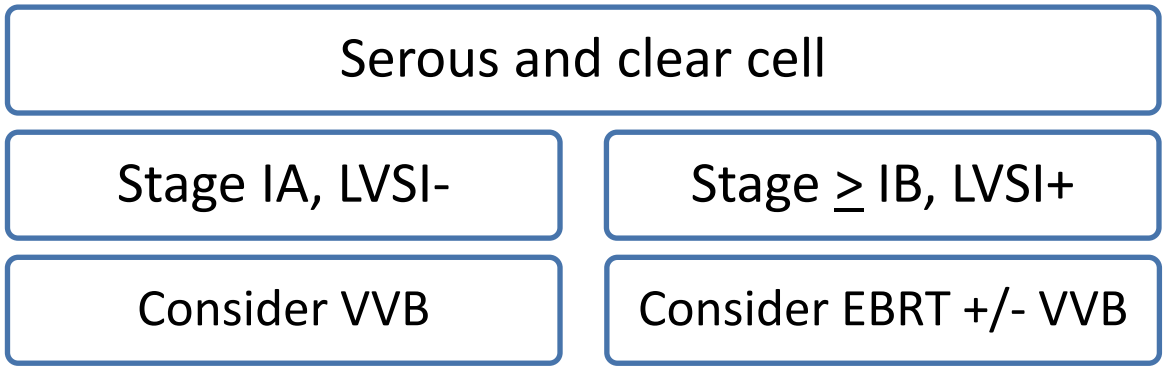
16.1.3.5 Non-endometrioid cancers

Patients with serous, clear cell, carcinosarcoma and undifferentiated tumours are at increased risk of recurrence due to the high risk of spread at the time of diagnosis (Colombo *et al.,* 2016). Although in recent years, adjuvant chemotherapy has been considered in these patients because of the greater

risk of relapse, it should be noted that PORTEC 3 study did not show any statistical benefit in overall survival for serous cancer (de Boer *et al.,* 2018). As mentioned previously, the results of the ENGOT-EN2-DGCG-EORTC-55102 trial looking at chemotherapy or no adjuvant treatment are awaited.

16.1.3.6 Serous and clear cell

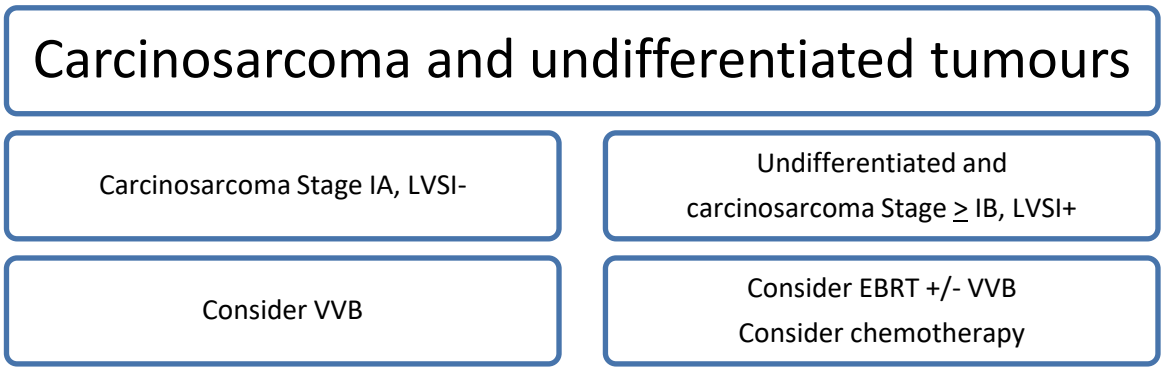
Figure 6 Adjuvant treatment options in serous and clear cell carcinoma



16.1.3.7 Carcinosarcoma and undifferentiated tumours

Carcinosarcoma and undifferentiated tumours are rare uterine cancers with poorer outcomes than other tumour types. Because of the poorer outcomes, adjuvant treatment should be considered but there is no firm evidence to guide decisions. Carcinosarcomas were excluded from the PORTEC 3 study. One cohort study showed that patients receiving chemotherapy had improved progression free survival but there is no demonstrated benefit in overall survival (Cantrell *et al.,* 2012). Patients with carcinosarcoma stage IA have a better prognosis than those with other stages, therefore brachytherapy alone can be considered for patients with no LVSI. For patients with carcinosarcoma stage ≥IB and undifferentiated tumours, chemotherapy and EBRT +/- VVB should be considered.

Figure 7 Adjuvant treatment options in carcinosarcoma and undifferentiated tumours



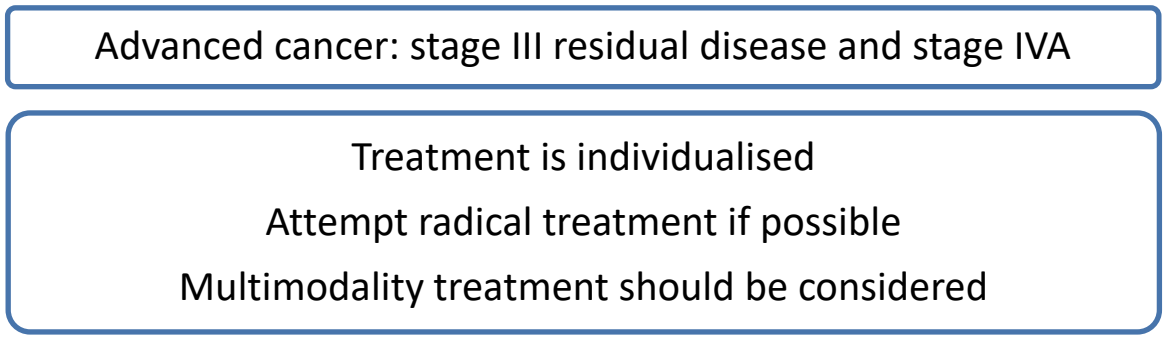
17 Post surgical treatment for advanced cancer (stage III residual disease and stage IVA)

For patients with stage III cancer with known residual disease, and those with stage IVA cancer who have had surgery, treatment is individualised. As a general principle, radical treatment should be attempted where possible and multimodality treatment should be considered, but treatment

decisions are made balancing the risk of morbidity of further treatment, and taking into account the patient's general condition and wishes.

Postoperative cross-sectional imaging should be obtained to supplement surgical findings with regard to the site and size of residual disease. If disease remains after surgery and if radical treatment is attempted, this should be started as soon as reasonably possible after surgery.

Figure 8 Post-surgical treatment options in advanced cancer (stage III residual disease and stage IVA cancer



18 Treatment of stage IVB endometrial carcinoma and Carcinosarcoma

Chemotherapy and hormonal treatments are indicated as palliative treatments in patients with metastatic disease as discussed subsequently in the section on recurrence. Surgery may be indicated in selected cases for palliation. Palliative radiotherapy may be helpful for localised symptom control (e.g. vaginal bleeding)

19 Treatment of recurrent endometrial carcinoma and carcinosarcoma

Treatments for recurrent endometrial cancer are individualised and depend on the site of the recurrence, the patient's performance status and comorbidity, what treatments have previously been used, and the patient's wishes. A decision should be made on whether a radical treatment option exists. Patients suitable for radical treatment are typically patients with low volume isolated recurrences or small numbers of metastases.

PET scanning in recurrent disease

PET scanning is commissioned in Wales for the following situations in endometrial cancer:

1. Staging or re-staging for patients with carcinoma of the endometrium being considered for exenterative surgery.
2. Suspected recurrence of endometrial cancer where other imaging is equivocal and where there is a potential radical treatment option.

19.1 Local relapse at the vaginal vault

Patients who relapse with an isolated central recurrence at the vaginal vault should be considered for radical treatment. For those who have not received radiotherapy, or have received only vaginal vault brachytherapy, radical radiotherapy should be considered.

19.1.1 Pelvic exenteration

For patients with an isolated relapse at the vaginal vault who have previously received radical radiotherapy to the pelvis, or those in whom radiotherapy is contraindicated, pelvic exenteration should be considered. One study reported a five-year survival of 40% (Khoury-Collado *et al.,* 2012). Pelvic exenteration is a major surgical procedure with a significant risk of short- and long-term morbidity affecting the bowel, urinary system and sexual function. Pelvic exenteration should be considered in women for whom a complete resection is considered feasible, who are physically able to tolerate the procedure and who are prepared to accept the significant functional changes. PET-CT scanning is recommended prior to the procedure, and pre-operative counselling is required.

19.2 Other isolated or oligo-metastases

Occasionally, patients with small volume metastases can be considered for radical treatment. Examples include isolated lymph node recurrences and pulmonary metastases. Treatment options that should be considered include radiotherapy, stereotactic radiotherapy, and surgery.

19.3 Palliative treatments

19.3.1 Systemic anti-cancer therapy

19.3.1.1 Chemotherapy

Chemotherapy may provide palliation in advanced symptomatic disease. Single agent carboplatin is well tolerated and has a response rate of around 30%, which is comparable with more toxic combinations such as cisplatin and doxorubicin. Carboplatin and paclitaxel has been reported to have response rates of 63 to 87% (Akram, *et al.,* 2005; Michener *et al.,* 2005).

In fit patients, carboplatin and paclitaxel should be offered as first line treatment (Columbo *et al.,* 2016). Single agent carboplatin is an alternative for patients who do not wish to lose their hair or who are not well enough for doublet therapy.

There are no randomised trials of chemotherapy in second line treatment of endometrial cancer and there is no standard chemotherapy regimen that can be recommended. For women who relapse more than six months after platinum-based chemotherapy, further platinum-based combination treatment could be considered (Ueda *et al.,* 2011). For women who relapse less than six months after chemotherapy, the role of further chemotherapy is of unclear benefit (Ueda *et al.,* 2011), although single agents could be considered, including paclitaxel, doxorubicin and etoposide. Clinical trials should be considered if available.

19.3.1.2 Hormonal therapy

For patients with advanced, metastatic or recurrent endometrial cancer not amenable to surgery, hormonal treatments may provide useful palliation. In a large clinical trial of medroxyprogesterone acetate, the response rate was 37% for grade 1 tumours, 23% for grade 2 and 9% for grade 3

(Thigpen *et al.* 1999). Responses are therefore most likely to occur in patients with grade 1 or 2 tumours. A typical dose of medroxyprogesterone acetate is 200 mg daily, and megestrol acetate is 160 mg daily. Determining the hormone receptor status of the tumour can be of benefit as patients with hormone receptor positive disease also have a higher chance of responding to hormonal treatment (Decruze and Green, 2007).

20 Treatment of uterine sarcomas

The main treatment for uterine sarcomas is surgery with total hysterectomy and bilateral salpingo-oophorectomy.

There is no evidence supporting the use of adjuvant radiotherapy in leiomyosarcoma or endometrial stromal sarcoma stage I/II (Reed *et al.,* 2008).

Patients with advanced or metastatic disease may respond to palliative treatments. Patients with metastatic endometrial stromal sarcoma may respond to progestogens or anti-oestrogens. Chemotherapy typically has response rates for 15-30% for regimens based on doxorubicin or ifosfamide. Gemcitabine and docetaxel have a response rate of 53% in unresectable leiomyosarcoma (Hensley *et al.,* 2002).

Patients with soft tissue sarcoma should have their care plan confirmed by a sarcoma multidisciplinary team (NICE, 2015b).

21 Follow up

There is a lack of evidence to suggest what follow up patients should receive following treatment for endometrial cancer. Aims of follow up include: to detect potentially curable recurrences, to detect and treat consequences of cancer treatment, and to provide psychological support. Follow up may be doctor- or nurse-led. Patients with low risk cancers (stage IA, grade 1) can be considered for a symptom-led follow up meaning that patients are seen in secondary care only if they develop symptoms. There is no proven benefit to routine radiological imaging in follow up: a recent questionnaire study showed that only 9% of respondents in the UK requested any sort of routine tests during follow up (Leeson *et al.,* 2014). Patients should be followed up as close to their home as possible.

A suggested scheme is as follows:

- Three-monthly for the first year.
- Six-monthly for the second year.
- Annually until five years.
- Discharge at five years if all well.

Follow-up vaginal vault smears are not routinely recommended in women who have had their cervix removed and these women are ceased from the cervical screening programme. If cervical intraepithelial neoplasia or cervical glandular intraepithelial neoplasia has been detected before hysterectomy or in the hysterectomy specimen, women should have follow up vault smears as according to Cervical Screening Wales guidance (CSW, 2011).

22 Complications of treatment

Treatment for endometrial cancer can result in significant morbidity.

22.1 Lymphoedema

All women who develop lower-limb lymphoedema should have access to the four cornerstones of lymphoedema care:

- Skin care to maintain a good tissue condition and reduce the risk of infection.
- External compression in the form of elastic compression garments that help reduce new lymph formation and encourage lymph drainage by improving the efficiency of muscle pump.
- A programme of exercise and movement to promote lymph drainage without over exertion.
- Simple lymphatic drainage: a method of lymph drainage that can be carried out by the patient or carer and involves a series of simple hand movements.

The aims of this regimen are to rehabilitate the cancer patient, to reduce any disability as far as possible, to help the patient to achieve an independent lifestyle and to give the patient the skills to manage their own condition (British Lymphology Society, 2009). Referral to the local lymphoedema service is recommended if a patient has lymphoedema.

22.2 Complications following pelvic radiotherapy

Late radiation changes as a result of pelvic radiotherapy can be associated with bowel, bladder and psychosexual problems, in addition to lymphoedema. Follow up strategies should be designed to detect such changes. The use of screening tools such as the ALERT-B questionnaire for gastrointestinal symptoms can aid detection of chronic symptoms related to pelvic radiotherapy (Taylor *et al.,* 2016).

Patients who develop troublesome gastrointestinal symptoms should be investigated using an algorithm-based approach (Andreyev *et al.,* 2013).

Patients with troublesome urinary symptoms should be considered for pelvic floor exercises or Urological referral.

Patients with psychosexual problems should have access to appropriate counselling.

22.3 Menopausal symptoms

It is rarely necessary to consider hormone replacement therapy in women treated for endometrial cancer because the majority of women are either post- or perimenopausal. In addition, hormone replacement therapy is generally avoided in patients who have been treated for endometrial cancer, because of the theoretical risk that dormant cancer cells could be stimulated to grow.

However, a small proportion of women diagnosed at a young age, and may experience troublesome post-menopausal symptoms. A randomised placebo-controlled study of oestrogen therapy in stage I or II endometrial cancer showed no difference in the rate of recurrence between the two groups after a median follow-up time of 35.7 months (Barakat *et al.,* 2006). This trial was considered

incomplete due to poor compliance in the group assigned oestrogen replacement therapy and poor accrual which resulted in early study termination. Nevertheless, there remains no definite evidence that hormone replacement therapy is harmful and it therefore can be considered in young women with low risk disease. *(Level 5)*

Hormone replacement therapy can also be considered in young women with Lynch syndrome who have a prophylactic hysterectomy and bilateral salpingo-oophorectomy.

23 The role of the Clinical Nurse Specialist (CNS)

All women with a diagnosis of endometrial cancer should be offered the support of, and have access to, a CNS, in order to facilitate the women's needs throughout the cancer journey, including those of her partner or carer.

Within an MDT, the CNS is in an ideal position, frequently as the key worker, to be able to address the often complex and sensitive issues identified and experienced by the patient (NICE, 2004). Access to self help, support groups and charitable organisations may also be of significant benefit, allowing women to share experiences and seek support from other women diagnosed and treated for the same condition.

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Appendix 1: Methodology

These guidelines were written in accordance with the Cancer NSAG Guidance for Clinical Guideline Development including:
Literature review by Library and Knowledge Management Service, Public Health Wales
Email to members of the Wales Cancer Networks asking for expressions of interest in contributing to guideline development
Initial meeting
Circulating of draft document to those who had expressed an interest
Modification in response to comments
Circulating to wider network for consultation

Appendix 2: Levels of evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

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