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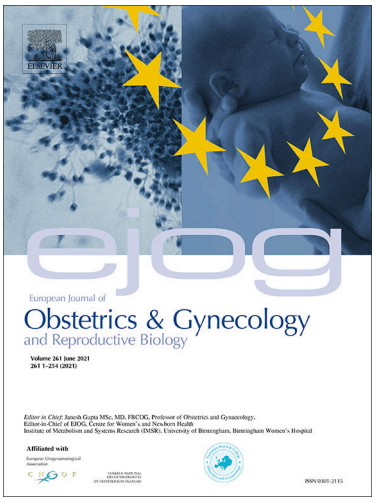

Expert Opinion

British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice

Jo Morrison, Janos Balega, Lynn Buckley, Andrew Clamp, Emma Crosbie, Yvette Drew, Lisa Durrant, Jenny Forrest, Christina Fotopoulou, Ketan Gajjar, Raji Ganesan, Janesh Gupta, John Hughes, Tracie Miles, Esther Moss, Meenu Priyadarshini Nanthakumar, Neil Ryan, Axel Walther, Alex Taylor

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British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice

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1 Introduction

1.1 Methodology

The remit of this guideline is to collate and propose evidence-based guidelines for the diagnosis and management of uterine cancer. This document covers all uterine cancers of any histological type.

1.1.1 Hierarchy of evidence

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document. Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines (available on the RCOG website at https://www.rcog.org.uk/globalassets/documents/guidelines/clinical-governance-advice/clinical-governance-advice-1c.pdf. See appendix Table 1 and Table 2 for further details.

Evidence was searched in the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE up to October 2020, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field. Recent ESGO-ESTRO-ESP guidelines on endometrial cancer were also reviewed in the preparation of this guideline.[1]

1.1.2 Guideline development process

1. These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
2. The guideline development process is detailed below:
    a) Co-chairs, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;
    b) Lead then identified a team called the guideline team (GT) to develop the 1st draft;
    c) 1st draft was submitted to the GC;
    d) GC recommended changes and approved 2nd draft;
    e) 2nd draft was then submitted to council members and officers;
    f) Council and officers approved 2nd draft and recommended changes;
    g) 3rd draft was sent to national and international peer review, including relevant charities;
    h) GC made changes based on peer review comments

i) 4th draft was sent back to council for approval

j) Final draft was approved by council and officers.

1.2 Management of conflict of interest

GT and GC members are required to declare interests and to step back from decisions where there may be any real or perceived conflict of interest. Please see section 17 for details of declared conflicts of interest.

2 Background

2.1 Epidemiology

Most uterine cancer arises from the endometrium (lining of the womb). Uterine (womb) cancer is the sixth most common cancer worldwide for females, and the 14th most common cancer overall, with over 380,000 new cases diagnosed in 2018.[2] Uterine cancer is now the fourth most common cancer in females in the UK. Incidence in the UK has increased by around 55% since the 1990s with ~9,400 women diagnosed per year in 2015-2017 and led to 2,409 deaths in 2018.[3] 72% of women with adult uterine cancer diagnosed in 2013-2017 in the UK are predicted to survive ten or more years. This increase in incidence is largely due to increasing obesity.[4] The incidence of endometrial cancer (EC) increases with age and was highest in females aged 75 to 79 in the UK (2015-2017). Endometrial cancer deaths in England are more common in females living in the most deprived areas due to a combination of factors.[3, 5, 6]

2.2 Molecular Classification

Recommendation:

All patients with endometrial cancer (EC) should be offered testing for Lynch syndrome (see Table 4). (Grade C)

EC is a heterogenous disease, however, similarities in histopathological and clinical parameters drove Bokhman's thesis of two pathogenic types;[7] cancers that arose in obese women, with

hyperoestrogenism and hyperlipidaemia, were different to those who lacked these characteristics, defined as type I and type II cancers respectively. As technology has advanced, so too has our understanding of the mutational landscape seen in endometrial cancer, as outlined in Figure 1. The National Cancer Institute cancer genomic programme 'The Cancer Genome Atlas' (TCGA) [8] identified four distinct molecular subgroups seen in EC: DNA polymerase epsilon catalytic subunit (*POLE)* mutants; mismatch repair deficient (MMRd); copy number low; and copy number high. These subgroups translated into four distinct prognostic groups, with decreased survival observed in the copy number low and high cohorts and improved survival seen in *POLE* and MMRd tumours. In addition, traditional histological subtypes (see section 5) mapped onto the somatic profiles with copy number low tumours being almost exclusively endometrioid and copy number high being almost exclusively serous (Table 3).

MMR deficient EC may occur spontaneously or as a result of Lynch syndrome, an autosomal dominant cancer predisposition condition.[9] Up to one in 280 people have Lynch syndrome, although the vast majority are unaware.[10, 11] Around 3% of all endometrial cancers are due to Lynch syndrome.[12] Therefore, a diagnosis of endometrial cancer presents an opportunity to identify women with Lynch syndrome.[13]. Cascade testing of relatives identifies on average three further carriers of Lynch syndrome.[14] Healthy carriers can be offered symptom education, family planning, bowel cancer screening and risk-reducing surgery.[9] Lynch syndrome testing can be initiated by gynaecologists, which is both acceptable to patients and clinicians.[14] The universal testing of endometrial cancer is cost effective [15] and is now endorsed by the National Institute Health and Care Excellence (Table 4**)**.[16] In addition to identifying women with Lynch syndrome, the screening of endometrial cancer for MMRd can identify tumours amenable to checkpoint inhibition. Checkpoint inhibitors have been shown to be highly effective in MMRd cancers, including endometrial cancer.[17] However, their use in endometrial cancer remains limited largely to clinical trials at this stage.

The molecular study of EC has identified other key driver mutations, in addition to the four molecular groupings of the TCGA. *PTEN* is a tumour suppressor gene with a locus of chromosome 1023q.[18, 19] *PTEN* mutations are found in atypical endometrial hyperplasia, indicating it may be an early event in carcinogenesis.[19] Somatic loss of heterozygosity is often seen in *PTEN* expression within EC.[20]

In such a state there is a loss of one allele secondary to non-disjunction in mitosis. If the remaining wild type allele is dysfunctional, or mutates into a dysfunctional state, *PTEN* expression is lost. Indeed, *PTEN* loss has been found in up to 83% of type I ECs and therefore has prognostic significance.[21]

The gene for tumour protein p53, is located on the short arm of chromosome 17.[22] Cancers in which *p53* function has been lost tend to be less chemosensitive and are associated with poor prognosis.[23] In EC abnormal *p53* expression (*p53*abn) is associated with poor outcome, especially when seen in type I tumours.[24] Furthermore, in type II ECs, *p53* expression and International Federation of Gynaecology and Obstetrics (FIGO) grade were the only two independent prognostic indicators, with increased levels leading to decreased 5-year survival.[25] In EC *CTNNB1* mutations (*CTNNB1*mut) were observed in *POLE*, MSI and copy number low subgroups, but are a rare event in copy number high cancers.[8] *CTNNB1*mut are seen in atypical endometrial hyperplasia (AEH) indicating this may be an early event in carcinogenesis.[26] It is known to signify poorer recurrence free survival in low grade/early-stage disease, although it is conversely associated with decreased rates of deep myometrial invasion and lymphovascular space invasion.[27] There is also an association between *CTNNB1*mut and obesity,[28] which is pertinent given the link between obesity and EC.[29] Furthermore, there are targeted treatments that show promise in *CTNNB1*mut EC.[30]

BRCA 1 and *2* mutations and their association with EC remains controversial.[31-33] Although data from the TCGA suggests that up to 30% of EC is associated with *BRCA1* mutation (*BRCA1*mut) the majority of these are likely to be passenger mutations.[8] Work exploring the functional loss of homologous recombination through *BRCA* profiling found a signature in 41% of non-endometrioid EC and was closely associated with a *p53*mut profile.[34]

In summary, the use of molecular profiling in EC enables a better-informed prognosis, targeted treatments and the potential to identify those with a genetic cancer predisposition. As the technologies necessary to sequence EC become cheaper and more accessible, clinicians will have to acclimatise to incorporating genetic information into their clinical care.

2.2.1 Clinical implications of the molecular classification of endometrial cancer

Defining the molecular profile of an EC is important for guiding clinical management. Survival is improved in those EC that demonstrate ultra-mutated (*POLE*mut) and hyper-mutated (*MMR*d) phenotypes.[8] This information can feed into our established risk stratification based on the stage and grade of the disease (Table 5). Therefore, a stage II high grade EC with a known *POLE*mut would be lower risk than an identically staged and graded EC with a known p53 mutation. A robust schema of how this could be achieved in clinical practice has been published.[35] The ongoing PORTEC-4a study will hopefully provide definitive data on the need for and the type of adjuvant therapy in stage I and II EC based on their molecular profile (https://clinicaltrials.gov/ct2/show/NCT03469674). Indeed, recently published international guidance has endorsed considering limiting adjuvant therapy in stage II *POLE*mut EC.[1] However, this recommendation is based on prospective cohort study data and therefore should be viewed with a degree of caution until confirmed by trial data.

Tumours with MMRd demonstrate an excellent response to checkpoint inhibition therapy.[36, 37] This finding is true in cases recurrent and/or metastatic disease.[37] In response to these data, in May 2017 the Federal Drugs Agency approved pembrolizumab for all microsatellite high cancers.[38] This was the first time a cancer treatment had been approved on the basis of a molecular characteristic and not limited a specific cancer site or histology. There are no randomised control trials looking at the application of check point inhibitors in EC, however, excellent responses have been reported.[39] Therefore, in EC with known MMRd that is resistant to conventional therapy, check point inhibition could be considered. Current trials are ongoing which seek to explore the use of checkpoint inhibitors in the advanced and/or recurrence setting (https://clinicaltrials.gov/ct2/show/NCT04634877, https://clinicaltrials.gov/ct2/show/NCT03884101, https://clinicaltrials.gov/ct2/show/NCT03603184, https://clinicaltrials.gov/ct2/show/NCT03981796).

EC with *BRCA1/2*mut maybe amendable to treatment with Poly (ADP-ribose) polymerase inhibitors (PARPi). This class of treatment has been shown to be efficacious in ovarian cancer with *BRCA1/2*mut and/or homologous recommendation deficiency.[40] There is limited evidence that EC with *PTEN*mut may respond to PARPi.[41] The ongoing COPELIA study

(https://clinicaltrials.gov/ct2/show/NCT03570437) is exploring the use of Olaparib in EC. A phase one trial is also looking at the utility of PARPi in the recurrence setting and is open to women with recurrent EC (https://www.clinicaltrials.gov/ct2/show/NCT03586661). The DUO-E (https://clinicaltrials.gov/ct2/show/NCT04269200) and DOMEC (https://clinicaltrials.gov/ct2/show/NCT03951415) studies will explore combining check point inhibition treatment alongside PARPi therapy.

Recent NICE guidance recommended the introduction of Lynch syndrome screening for all those diagnosed with endometrial cancer (see Table 4).[16] The initial step is four-panel immunohistochemistry (IHC) testing for MMR deficiency (MLH1, MSH2, MSH6 and PMS2). If the IHC is abnormal, with loss of MLH1, or both MLH1 and PMS2, expression MLH1 promoter hypermethylation testing on tumour DNA should be used to differentiate sporadic and Lynch syndrome-associated cancers.

If MSH2, MSH6 or isolated PMS2 IHC is abnormal, with loss of protein expression, germline testing for Lynch syndrome should be offered. If MLH1, or MLH1 and PMS2, IHC is abnormal, with loss of protein expression, *and* promoter hypermethylation is not detected, germline testing for Lynch syndrome should be offered. Those with MLH1 promoter hypermethylation are more likely to have sporadic changes rather than Lynch syndrome. However, those with a strong family history should be offered referral to clinical genetics for further advice and management.

Patients will need information about the possible implications of these tests, for both themselves and their relatives. Information and counselling for Lynch testing can be delivered by an appropriately trained healthcare professional. This may involve clinical nurse specialists with appropriate training, similarly to BRCA testing in ovarian cancer. Those with a positive germline tests for Lynch syndrome should be referred to clinical genetics for further counselling.

2.3 Screening and prevention

2.4 Screening

2.4.1 Screening in the general population

Recommendation:

Evidence does not suggest that screening asymptomatic women in the general population with transvaginal ultrasound scanning (TVS) or endometrial sampling improves outcomes from endometrial cancer (EC). (Grade D)

There is currently no screening programme in the UK for women at average or high risk of endometrial cancer (EC). The goal of screening is to identify atypical hyperplasia and endometrial cancer at the earliest possible stage to maximise the chance of cure, enable fertility-sparing management, minimise treatment-related morbidity and/or reduce deaths from the disease.[42] Endometrial thickness (ET) measured by transvaginal ultrasound (TVS) is an effective means of triaging symptomatic postmenopausal women for further investigations.[43] However, a systematic review of 32 studies involving 11,100 participants concluded that ET has no value as a screening tool due to its extremely poor diagnostic accuracy in asymptomatic postmenopausal women.[44] Endometrial sampling is indicated for symptomatic women with a thickened endometrium on TVS but its use in asymptomatic women is limited by poor patient acceptability and a high rate of failure, non-diagnostic samples and need for repeat investigations.[45] No high-quality studies have evaluated the effectiveness of TVS or endometrial sampling to improve outcomes from EC in the context of general population screening.

2.4.2 Screening in high-risk groups

Women with Lynch syndrome

Recommendations:

Women with Lynch syndrome could be offered annual screening with a transvaginal ultrasound scan (TVS), hysteroscopy and/or endometrial sampling from the age of 35 years after counselling about the risks, benefits and limitations of screening. (Grade C)

Women with Lynch syndrome and abnormal vaginal bleeding should be counselled to seek urgent medical attention for suspected endometrial cancer. (Grade C)

Lynch syndrome is an inherited cancer predisposition syndrome affecting the DNA MMR system (as in section 2.2 and reviewed in [46]). Carriers are at increased risk of early-onset colorectal, endometrial, ovarian and several other cancers. Lifetime risks for EC are 40-60% depending on the MMR gene and type of pathogenic variant involved.[47, 48] These risks justify screening women with Lynch syndrome for EC, although there is currently no high-quality evidence that screening improves outcomes from the disease.[9] Screening is not an alternative to risk-reducing hysterectomy, but could be considered for premenopausal women with Lynch syndrome who have yet to complete their families. TVS, hysteroscopy and/or endometrial sampling are most commonly employed. It is debatable whether a TVS is of benefit in premenopausal women except to direct further investigations. There is no formalised programme in place and provision for endometrial screening for women with Lynch syndrome, which varies between institutions.[49] Women should be educated about 'red flag' symptoms for EC, the occurrence of which should prompt urgent investigations to exclude sinister endometrial pathology.[50, 51]

Women taking tamoxifen

Recommendations:

Evidence does not support screening with TVS and/or endometrial sampling (Grade C)

Abnormal vaginal bleeding, and other red flag symptoms as per NICE guidelines (NG12), [52] should prompt urgent investigation by TVS, hysteroscopy and endometrial sampling (Grade D)

Tamoxifen is a selective oestrogen receptor modulator (SERM) used for treatment and prevention of breast cancer.[53] Its inhibitory action in the breast is stimulatory in the endometrium and responsible for a four-fold increased risk of EC in postmenopausal long-term users.[54]. Screening for endometrial pathology by TVS is complicated by tamoxifen-induced benign sub-epithelial stromal hypertrophy, which causes a grossly abnormal endometrial signal.[55] TVS has a low positive predictive value and a high false positive rate, even at an ET cut-off of 10 mm, leading to unnecessary invasive diagnostic procedures and associated harms.[56] Abnormal bleeding in long-term, current or ex-users of tamoxifen should be taken seriously, however, and warrants urgent investigation for suspected EC. [50, 51]

2.4.3 Prevention in the general population

Recommendation:

Women who attain and maintain a healthy or overweight BMI through bariatric surgery, dietary intervention and/or regular physical activity reduce their risk of endometrial cancer. (Grade A)

Obesity is strongly linked to endometrial carcinogenesis through unopposed oestrogen excess, insulin resistance and chronic inflammation.[56] The relationship is strongest for type I, endometrioid tumours, although type II tumours have also been linked to obesity. There is a dose-response relationship that equates to a 60% greater EC risk for every 5 kg/m^2 increase in BMI above healthy weight and a 10-15% lifetime risk for BMI ≥40 kg/m^2.[57] In Europe, excess body weight has been estimated to account for 60% of all new EC cases per year.[58] Women with BMI ≥40 kg/m^2 who achieve and sustain weight-loss through bariatric surgery, particularly gastric bypass or sleeve gastrectomy, or through dietary intervention, have a reduced EC risk compared to women who do not.[59-61] The World Cancer Research Fund/American Institute for Cancer Research showed that physical activity also reduces EC risk, particularly in women with obesity, compared to those with sedentary lifestyles.[62, 63]

Progestin-containing hormonal contraceptives reduce EC risk in women of the general population. Ever-use of the combined oral contraceptive pill is associated with a 35% reduction in EC risk that persists for at least 30 years [64], but cannot be recommended as a primary prevention strategy in women with obesity due to the oestrogen-related increased risk of stroke and venous thromboembolic disease in

women with a BMI ≥35 kg/m^2.[65] Ever-use of the levonorgestrel-releasing intrauterine (LNG-IUS) system confers a 78% reduction in EC risk compared to never-use.[66]

2.4.4 Prevention in high-risk groups

Recommendation:

Risk reducing hysterectomy should be recommended an effective means of preventing endometrial cancer in Lynch syndrome in those who have finished their families. (Grade C)

Prophylactic hysterectomy and bilateral salpingo-oophorectomy, when fertility is no longer required, is an effective strategy for preventing endometrial and ovarian cancer in Lynch syndrome [67]. Current evidence suggests recommending risk reducing surgery from the age of 35 years in *MLH1* and *MSH2* pathogenic variant carriers, from 40 years in *MSH6* pathogenic variant carriers and after the age of 50 years in *PMS2* pathogenic variant carriers, because the premenopausal risk of gynaecological cancer in the latter group is extremely low.[68] Women undergoing risk-reducing hysterectomy may consider concurrent risk-reducing bilateral salpingo-oophorectomy, due to their 10-17% additional lifetime risk of ovarian cancer.[47] Oestrogen-only hormone replacement therapy (HRT) after a surgically induced menopause is recommended until at least the natural age of menopause, due to its protective effect on colorectal cancer risk [69], which is extremely pertinent for women with Lynch syndrome, as well as its beneficial impact on quality of life, urogenital, bone, and cardiovascular health.[70]

Aspirin reduces cancer risk in Lynch syndrome and its use is associated with good safety data in young adults, although the optimal dose for cancer chemoprevention is still uncertain.[71] Alternative risk-reducing strategies that warrant further study include the LNG-IUS and other progestin preparations, which are expected to reduce EC risk in Lynch syndrome by invoking endometrial decidualization, atrophy and apoptosis, but there is currently a lack of high-quality evidence to support the.[72]

3 Presentation and diagnosis

The reader is directed to RCOG guidelines on the management of endometrial hyperplasia and National Institute for Health and Clinical Care Excellence (NICE) guidance (NG12) on referrals for suspected cancer.[52] Updates on referral pathways during the COVID-19 pandemic can be found in the Joint RCOG, BSGE and BGCS guidance for management of abnormal uterine bleeding in COVID-19 pandemic.[73]

3.1 Presenting Symptoms

Recommendation:

Pre- and post-menopausal women should be referred for investigation of symptoms suspicious for endometrial cancer in line with NICE guidance. [52, 74] (Grade C)

The most common symptom of women with EC is postmenopausal bleeding (PMB), which is defined as vaginal bleeding that occurs at least a year after the last menstrual period and in those who are not taking hormone replacement therapy (HRT).

The probability of EC in women with PMB is 5-10%.[75] A recent systematic review of 129 studies showed a 9% pooled risk of EC in women with PMB.[76] This risk increases with age, with an estimated cancer risk of 50% in women over the age of 70 years presenting with PMB.

The risk of EC in premenopausal women is lower with 6.5% of uterine cancers diagnosed in those under 50 years of age in the UK between 2015-17.[3] However, EC should be suspected in premenopausal women with persistent intermenstrual or heavy menstrual bleeding, especially if there is a background of irregular, dysfunctional menstruation that suggests anovulation. Symptoms that suggest advanced disease at presentation include abdominal pain, distention, bloating, change in bowel or bladder habits or new cough.

In the UK, recommendations for diagnosis and referral are based on guidance from the National Institute for Health and Care Excellence (NICE).[52, 74]

3.2 Diagnostic methods

3.2.1 History and examination

Women presenting with PMB, unscheduled bleeding on HRT, persistent intermenstrual or irregular bleeding, haematuria or post-menopausal women with abnormal vaginal discharge should undergo an abdominal, speculum and pelvic examination at their clinical assessment. (Grade D)

Premenopausal women with persistent intermenstrual or persistent irregular bleeding, and women with infrequent heavy bleeding who are obese or have polycystic ovary syndrome, or taking tamoxifen, and in those for whom treatment for heavy menstrual bleeding (HMB) has been unsuccessful require histological assessment, as per NICE guidelines, via an urgent gynaecology assessment, rather than via a rapid access gynaecology clinic within two weeks. (Grade D)

When a patient presents with any of the above presenting symptoms, the primary healthcare professional should undertake a full abdominal and pelvic examination, including speculum examination of the cervix.[52] This includes a detailed gynaecological history (early menarche/late menopause, known endometrial hyperplasia, parity, cervical screening history), drug history (including use of HRT, oral contraceptive pill, tamoxifen) and any relevant medical, family and surgical history (obesity, treatment for breast cancer, diabetes mellitus, hypertension, and Lynch syndrome). Clinical examination in primary care is recommended, since visualisation of an abnormal cervical lesion would affect the referral pathway.

Cervical screening is ineffective in the diagnosis of endometrial cancer, although opportunistic cervical screening, in those eligible who are overdue at the time of pelvic examination, should be considered. Endometrial cells found on a cervical smear of a postmenopausal woman is associated with a 3-5% risk of endometrial cancer and requires further evaluation.[77]

3.2.2 Indications for referral

Women not on HRT who have PMB should be referred to a rapid access gynaecology clinic to be seen within two weeks.[52] Women on HRT with unscheduled bleeding should have their HRT discontinued for six weeks; those with persistent bleeding should be referred to a rapid access gynaecology clinic, as above, without re-starting HRT since this may interfere with TVS assessment. Women on tamoxifen with postmenopausal bleeding or persistent intermenstrual bleeding with a negative pelvic examination also require referral.[52]

NICE guidance [52] also recommends that women over 55 years of age require TVS and assessment if they have:

- 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.

Premenopausal women with irregular and/or heavy menstrual bleeding should be managed as per NICE guidance.[74]

3.2.3 Investigations

Recommendations:

Transvaginal ultrasound (TVS) with double thickness measurement of endometrium should be employed as initial investigation for women presenting with PMB. (Grade B)

The best diagnostic strategy in patients with suspected endometrial cancer remains controversial, which include TVS, contrast sonography, hysteroscopy and endometrial biopsy. The sequence of

investigations for evaluating women with PMB will depend upon available resources and expertise, clinical judgement and patient preferences.

TVS followed by endometrial biopsy, if needed, is the most cost-effective strategy for the UK population in which the prevalence of endometrial carcinoma is lower than 15%.[78] Adnexal pathology identified at ultrasound should be documented in the ultrasound report and investigated, as appropriate.

Accuracy of TVS and cut off for endometrial thickness

Recommendations:

Double-layer endometrial thickness measurements on TVS with a cut off of ≥4 mm should be investigated. (Grade B)

An endometrial thickness of <4 mm and in the absence of any irregularity of the endometrial profile (presence of fluid, disparity of any endometrial thickness measurements within the endometrial echo) does not require further investigations unless there is recurrent PMB. (Grade B)

TVS is a more accurate diagnostic method (compared to transabdominal scan) for measuring the ET. Double-layer endometrial thickness should be measured as the maximum anterior to posterior thickness.[79] There are no advantages offered by the use of 3-dimensional ultrasonography.[80]

The first step in the diagnostic pathway of PMB should be the measurement of endometrial thickness followed by endometrial sampling. Sensitivities of 98%, 95% and 90% are seen with cut-off levels of 3 mm, 4 mm and 5 mm of ET respectively to exclude endometrial cancer.[81, 82] Using a 4 mm ET cut-off value, transvaginal ultrasonography has a high negative predictive value (greater than 99%). Therefore, TVS can reliably exclude women with PMB who do not require endometrial biopsies (ET of < 4 mm), which avoids the need for unnecessary endometrial sampling.[83] There may be an argument for increasing the threshold for endometrial biopsy to an ET of ≥ 5 mm, as data suggest that the average

endometrial thickness in postmenopausal women may have increased over time.[84] A more recent systematic review of 44 studies, including 17,339 women found that the sensitivity was similar for ET cut offs of ≥3, ≥4 and ≥5 mm (ET ≥5 mm sensitivity = 96.2%, 95% CI 92.3 to 89.1%) , whereas the specificity for EC was better using a cut off of ≥5 mm (specificity = 51.5%, 95% CI 42.3 to 62.7%).[43] From these data, adopting a cut off of ≥5 mm would reduce the number of women requiring invasive biopsy by 17%. However, it is important to be aware that the diagnostic test accuracy of TVS is lower in black women, possibly due to increased presence of fibroids and greater proportion of non-endometrioid histological types of cancers, compared to white women. A simulated retrospective cohort study, from the Surveillance, Epidemiology and End Results (SEER) data, demonstrated a sensitivity of 47.5% (95% CI 46.0 to 49%) using a cut off of ≥4 mm in black women, compared to a sensitivity of 87.9% (95% CI 87.6 to 88.3%) in white women.[85] Poorer diagnostic test performance of TVS in black women was consistent when using a ≥3 mm or ≥5 mm cut off.

In asymptomatic postmenopausal women on HRT, measurement of the endometrial thickness alone is not diagnostically useful, but an upper endometrial thickness limit of 8 mm can be used. In symptomatic postmenopausal women with unscheduled vaginal bleeding whilst taking HRT or tamoxifen, an endometrial biopsy should be taken, if the endometrial thickness is greater than 5 mm.[86] Asymptomatic postmenopausal women with an endometrial thickness 4 mm or more, discovered incidentally on TVS, do not warrant routine endometrial sampling. A study of 81 women referred to a PMB clinic with asymptomatic endometrial thickening found that a cut off of ≥10 mm had a sensitivity of 100% for detecting endometrial cancer or atypical hyperplasia (sensitivity =100% (95% CI 40 to 100%); specificity = 60% (95% CI 48 to 71%; Area under the curve (AUC) = 0.8 (95% CI 0.66 to 0.93%). [87] Using a threshold of 11 mm yielded a similar diagnostic test accuracy as a cut off of ≥4 mm in women with symptomatic PMB in the overall cohort of 1995 women. Decisions regarding further evaluation must be made individually, based on existing risk factors.[88]

The definitive diagnosis of endometrial cancer is by histological sampling. If the findings from TVS are suggestive of cancer, or if ultrasound is not available, an urgent referral should be made to a diagnostic unit for further evaluation.[52] Recurrent PMB must prompt further evaluation by hysteroscopy and biopsy, even if the endometrial thickness on TVS is less than 4 mm.

Saline Infusion Sonography (SIS) is useful in the diagnosis of endometrial polyps and there may be a role for SIS as a triage for hysteroscopy in women with PMB.[89] However, there are no large studies evaluating the efficacy of SIS in diagnosing malignancy in women with PMB. Therefore, TVS followed by endometrial biopsy remains the method of choice.

Endometrial biopsy

Recommendation:

In patients with PMB, not on HRT, a TVS endometrial thickness measurement of ≥ 4 mm, an outpatient endometrial biopsy should be carried out. (Grade B)

Outpatient endometrial biopsy is a fast, easy and cost-effective method of diagnosing endometrial cancer. Both the Pipelle® and Vabra® aspirator devices used for endometrial sampling are diagnostically accurate for the detection of endometrial carcinoma.[90] A systematic review of 13 diagnostic evaluations showed that a Pipelle® biopsy has a high diagnostic accuracy when an adequate specimen is obtained (positive likelihood ratio (LR) 66, post-test probability of endometrial cancer of 81.7% for a positive test and 0.9% for a negative test (likelihood ration (LR) 0.14). Endometrial biopsy is also accurate in excluding endometrial cancer, even if an insufficient sample is obtained, provided the sampling device was inserted more than 4 cm through the cervical canal.[91] However, further evaluation (hysteroscopy) is warranted in cases of persistent abnormal vaginal bleeding, despite a negative endometrial biopsy.

In pre- and peri-menopausal women, NICE guidance advises endometrial biopsy only in the context of hysteroscopy.[74] However, this should not delay obtaining an endometrial sample for tissue diagnosis. If access to hysteroscopy is limited or likely to be delayed, a blind endometrial biopsy should be undertaken to exclude endometrial cancer or hyperplasia.[73]

Hysteroscopy

Recommendations:

If there is on-going concern, due to persistent symptoms, despite a negative Pipelle®, hysteroscopy should be considered. (Grade D)

Hysteroscopy is recommended, if outpatient endometrial biopsy by other means is not feasible, for women who have ultrasound irregularities, or for those at high risk of endometrial cancer. (Grade B)

Hysteroscopy should, where possible, be offered as an outpatient procedure. (Grade C)

Outpatient hysteroscopy, as a first investigation, could be considered for all those with an endometrial thickness >4 mm, depending on local pathways. (Grade D)

Pre-menopausal women with heavy menstrual bleeding should be offered hysteroscopy and directed biopsy, as per NICE guidance, although via a gynaecology clinic; rapid access clinic 2-week wait targets do not apply. [74] **(Grade D)**

Recurrent PMB should be investigated by hysteroscopy and endometrial biopsy. (Grade D)

Hysterectomy may be considered in cases of unexplained recurrent PMB. (Grade D)

Hysteroscopy should be recommended for patients at high risk for endometrial cancer and patients in whom outpatient biopsy has failed or was non-diagnostic. Patient acceptability and diagnostic accuracy with outpatient hysteroscopy are comparable to hysteroscopy under anaesthesia. Hysteroscopy under regional or general anaesthesia should be performed for those who cannot tolerate outpatient examination and biopsy, those who do not consent to outpatient biopsy, and for patients with cervical stenosis, which cannot be managed in the outpatient setting.

Hysteroscopy allows for direct visualisation of the uterine cavity and is therefore beneficial in detecting structural irregularities, such as endometrial polyps and submucosal fibroids. The accuracy of hysteroscopy in diagnosing endometrial cancer and hyperplasia in women with abnormal uterine bleeding was determined by a systematic review of data on 26,346 women.[90] A positive hysteroscopy result (LR 60.9) increased the probability of cancer to 71.8% from a pre-test probability of 3.9%, whereas a negative hysteroscopy result (LR 0.15) reduced the probability of cancer to 0.6%.

An RCT has shown a prevalence rate of 6% premalignancy in endometrial polyps diagnosed by hysteroscopy in women with PMB who had previously had a normal endometrial biopsy.[89] However, more high-quality studies and cost-benefit analysis are required before hysteroscopy can be recommended as a routine for all women with PMB.

The risk of positive peritoneal cytology seems to be slightly increased following a hysteroscopic diagnosis of endometrial cancer. However, available evidence suggests that prognosis and effect on survival associated with hysteroscopy is no different from other diagnostic methods.[92]

In cases of recurrent PMB, where the patient has been investigated and no cause identified, hysterectomy may be indicated and should be discussed with the patient; small primary lesions, especially of fallopian tube origin, may be undiagnosed by imaging techniques.[93]

3.3 Pathways for management of endometrial cancer

Recommendations:

All women with confirmed or suspected endometrial cancer should be discussed at a specialist gynaecological cancer multidisciplinary team meeting (SMDT). (Grade D)

Women with presumed FIGO Stage IA endometrioid cancer, G1 or G2, may undergo surgery by a gynaecologist at a Gynaecological Cancer Diagnostic Unit who is a core member of an SMDT. (Grade D)

Women with high grade endometrial cancer (serous, clear cell, carcinosarcoma, endometrioid G3) or suspected FIGO 1B (≥50% myometrial invasion on MRI) or above should undergo surgery at a Cancer Centre by a subspeciality-trained surgeon who is a core member of an SMDT.

Women requiring radiotherapy or systemic therapy should be treated by a medical/clinical oncologist who is a core member of an SMDT. (Grade D)

At all times women should have an identified key worker and responsible clinician. (Grade D)

Treatment summaries, including symptoms of recurrence, should be provided to all women on completion of each episode of treatment and on discharge to primary care. (Grade D)

Robust failsafe mechanisms should exist for all steps along the pathway. (Grade D)

Appropriate data collection infrastructure and staffing support should be in place to allow proper assessment of the safety and effectiveness of all parts of the service. (Grade D)

Women with endometrial cancer in the NHS should have access to a holistic needs assessment with a cancer clinical nurse specialist (CNS) or key worker. (Grade D)

The NHS Cancer Plan set target Cancer Wait Times for investigation and treat of patients with suspected cancer [94]. These were built upon by subsequent documents including The Cancer Reform Strategy [95] and The NHS Long Term Plan.[96] The devolved nations have separate, albeit largely aligned, documents.(e.g. [97] and NI-gov-doh-cancer-recovery-plan.pdf) Women suspected of having endometrial cancer should be seen within two weeks of referral and should have begun treatment within 62 days of referral. The target of 31 days from the date of the decision to treat until starting treatment, defined as treatment was discussed and agreed with the patient, applies to all cancer diagnoses

whether or not referred as a suspected cancer (14-day pathway). Women should be given a diagnosis within 28 days of referral.

3.3.1 Where women are treated

The SMDT is now central to planning cancer care in the UK and the 2013/14 NHS Standard Contract for Complex Gynaecology states that “it is essential that all patients with a suspected gynaecological tumour are discussed at an expert multi-disciplinary team”.[98] The MDT provides the opportunity for peer review of pathology, radiology and clinical decision making, providing quality assurance and support to treating clinicians. These service specifications, based on the Improving Outcomes document, recommend treatment of grade 1/2 endometrial cancers FIGO IB or above, or any grade 3 endometrial cancer, in a cancer centre; grade 1/2 endometrial cancer thought to be stage FIGO IA can be treated in diagnostic centres (cancer unit).[98, 99] For current FIGO staging see Table 6.

Cancer clinical nurse specialists (CNS) help to care for people with cancer by assisting with decision-making, supporting self-care, symptom management and providing emotional support.[100-102]

3.3.2 After treatment

Supportive care and follow up are described below (see sections 13 and 14). End of treatment summaries should be provided after each episode of treatment and after discharge from secondary care. Summaries should state the diagnosis, stage, grade and treatment received. Women should be given information about what to look out for and whom to contact, if they experience problems that suggest recurrence or side effects/ complications of treatment that negatively affect their quality of life.

Rapid access to palliative care will be of high importance to avoid unnecessary suffering and distress. Local services must ensure that mechanisms are in place such that these women can access palliative care without delay.

3.3.3 Failsafe

Failsafe mechanisms are required to ensure that women needing investigation and treatment negotiate the healthcare system reliably, which should also ensure that women are assessed and treated appropriately.

A clear failsafe mechanism for reinvestigation of recurrent postmenopausal bleeding is required, in both primary and secondary care, to ensure that women understand that they should re-present to their primary care team, despite being discharged with reassuring investigations, if they experience continued bleeding.

4 Imaging and pre-operative work-up

4.1 Pre-operative investigations

Recommendations:

Pre-operative surgical assessment, including assessment of clinical frailty, is recommended to assess the appropriateness and route of surgery. (Grade D)

Involvement of specialists in perioperative care of the older person (POPS) can improve outcomes following surgery and their involvement in the SMDT is recommended. (Grade C)

CA125 estimation occasionally may direct investigations toward detecting unexpected metastatic disease but without other indications is not recommended as part of routine practice. (Grade D)

Clinical assessment is needed to determine the feasibility and route of surgery. Assessment of the uterine size and extent of tumour will help the surgeon assess the safely of total vaginal, laparoscopic

or open surgery and the appropriateness of surgery. Clinical frailty score is predictive of outcomes following surgery for endometrial cancer.[103, 104] Clinical frailty assessment and multi-disciplinary assessments and care, including specialists with experience in perioperative medicine for older people undergoing surgery (POPS), is recommended although data specific to gynaecological cancer surgery is limited.[105, 106] A national audit of patients undergoing emergency laparotomy demonstrated improved survival in those who had involvement of POPS teams.[107]

CA125 is often raised non-specifically in the presence of bulky metastatic disease. Its place has not been tested in any randomised trial, although there are rare case reports where it has changed practice. However, the yield is so small, especially if the history, chest X-Ray, pelvic ultrasound and clinical examination suggest the risk is so low that it cannot be recommended as part of routine practice.

4.2 Imaging

Recommendations:

Imaging of the pelvis should be performed preoperatively to aid decisions regarding route and extent of surgery and whether surgery is appropriate. (Grade D)

The yield from CT scanning of the pelvis in low-grade disease is very low, is very unlikely to alter the ultimate outcome, and so is not indicated routinely. (Grade D)

Chest radiology, either CT or plain X-ray depending on the grade of tumour, is part of staging and should be performed in all women with endometrial cancer. (Grade D)

Women with high-risk histology types, or deep myometrial invasion of locally advanced disease, should have a CT of the chest/abdomen/pelvis preoperatively. (Grade D)

CT Chest/abdomen/pelvis is recommended for staging of high-grade endometrial cancer. (Grade D)

MRI pelvis (+/- abdomen) may be helpful to assess extent of loco-regional disease and estimate depth of myometrial invasion, if results would direct location of surgery and management of lymph nodes. (Grade D)

MRI of the abdomen and pelvis is recommended in patients for whom conservative management with progesterone IUS is planned, in order to assess appropriateness of conservative management and as a baseline for tumour response assessment (Grade D).

PET-CT with F^{-19} Deoxyglucose is not currently used in the initial staging of endometrial cancer outside of clinical trials. (Grade D)

Patients with unexpected high-risk findings in definitive histology (post-operatively) will require CT chest, abdomen and pelvis to plan appropriate adjuvant radiotherapy or chemotherapy, if not performed pre-operatively. (Grade D)

See appendix for FIGO staging (
Table 6) and stratification of EC by risk categories (Table 5). A review of 702 women with primary EC, showed that pre-operative CT findings altered treatment plans in only six patients.[108] The risk of metastatic disease for women with a short history, reassuring ultrasound, normal chest X-ray and grade 1 or 2 carcinomas is low.[109] In contrast, clear cell, serous papillary and solid poorly differentiated cancers have a significant risk of metastatic disease. In these cases, a staging CT scan of abdomen, chest (and pelvis, if pelvic MRI not performed) may inform discussions about pelvic lymphadenectomy and occasionally avoid a hysterectomy when there is no prospect of cure. In other cases, an imaging finding may direct the surgery to explore a lymph node, other suspected secondary deposits, or with the option of lymph node mapping to plan postoperative radiotherapy or triage to chemotherapy.

MRI of the abdomen and pelvis may be considered as an alternative to CT of the abdomen and pelvis as an initial staging examination in high-risk histology types, if the extra information from MRI will alter the surgical approach or patient management. A systematic review of 18 studies (693 women) with

endometrial cancer found that MRI is the most accurate imaging tool to determine the lymph node status of patients.[110] However, even with optimal MR imaging, the sensitivity and specificity of MRI is insufficient to rule out lymph node metastasis, compared to ultra-staging of the lymph node (ultra-section and immunohistochemistry) as a reference standard, and so whether it should be used to modify the surgical approach is moot. To achieve the highest sensitivity and specificity requires optimal scanning conditions and needs significant time in the scanner to obtain multi-parametric MRI; not all patients can tolerate such extensive MRI examination, which limits any benefit of MRI in the general population outside of clinical trials. MRI pelvis can provide information on depth of myometrial infiltration, which may be useful to triage patients between surgery at cancer units or centres, depending on local circumstances.

Imaging of the chest should be performed pre-operatively to aid decisions on site of surgery and whether surgery is appropriate. Imaging of the chest can be with a chest X-ray alone in low-grade histology types as this may spare women with unexpected chest metastasis from unnecessary surgery. Chest x-ray is relatively insensitive for nodules less than 5 mm in size and so is less useful in patients with high-risk histology types, and CT of the chest should be performed as part of the staging imaging of the abdomen and pelvis.

There are no reliable data to support the routine use of preoperative PET-CT staging in endometrial cancer.[111, 112] In particular there is no evidence that FDG-PET-CT alters treatment outcome for patients. FDG-PET-CT offers little benefit over standard imaging for staging, because endometrial cancer very rarely metastasises beyond the peritoneum and lungs at initial presentation, and FDG-PET-CT is not sufficiently sensitive in nodal disease to rule out the presence of micro-metastasis.

5 Pathology of endometrial cancer

The diagnosis and management of endometrial carcinoma and carcinosarcoma is based on robust pathological input. Correct typing and grading of endometrial carcinomas determine the type of surgery and subsequent adjuvant therapy.[113] After hysterectomy, documentation of features of endometrial carcinoma, such as the type and grade of carcinoma, depth of myometrial invasion, the presence of

serosal or adnexal or cervical involvement, lymphovascular space invasion and lymph node metastases are core items of information needed for patient management. These items are included in structured pathology reports in the form of datasets that allow easy extraction of the necessary information. In all instances, pathologists reporting cancer resection specimens should include the minimum data items as reporting proformas as indicated in the Royal College of Pathology dataset for reporting of endometrial cancers.[114] Accurate typing of endometrial cancers facilitates enrolment of patients into trials, for epidemiological analysis and association with genetic syndromes.

Most endometrial carcinomas are diagnosed on biopsies that are obtained by either an outpatient sampling procedure, outpatient polypectomy using devices such as Myosure®, or endometrial curettage under general anaesthesia. In some cases, endometrial curettage may be required to obtain sufficient tissue for tumour diagnosis. When handling endometrial biopsy specimens, all the submitted tissue should be processed. Where the biopsy confirms malignancy, the report should clearly specify the subtype of tumour present and the FIGO grade. It is recognised that there may be disparity in tumour grade between the endometrial biopsy and the subsequent hysterectomy specimen. Unequivocal distinction between atypical hyperplasia and grade 1 endometrioid adenocarcinoma can be difficult on small biopsies. In a significant proportion of cases diagnosed as atypical hyperplasia on endometrial biopsy, the resected uterus contains endometrioid adenocarcinoma.[115] Patients with a diagnosis of atypical endometrial hyperplasia may benefit from discussion at the gynaecological oncology SMDT and their management should be based on the results of clinical, pathological and imaging findings.

When dealing with hysterectomy specimens, guidelines recommend one section per cm considering the largest tumour dimension with an alternative to submit at least four blocks of tumour.[116]

Endometrial carcinoma should be classified according to the 2020 WHO Classification (Table 8).[117] Bokhman, first described two main pathogenetic types based on epidemiological studies.[118] Type I carcinomas are generally low-grade, oestrogen-related, often clinically indolent and histologically mostly of endometrioid type. Type II carcinomas are high grade, aggressive carcinomas, unrelated to oestrogen and histologically usually serous and clear cell type. It is increasingly understood that this dualistic model has significant overlapping features at the clinical, pathological, and molecular

levels.[119] The Cancer Genome Atlas Research Network (TCGA) performed an integrating genomic, transcriptomic and proteomic characterization of endometrial carcinoma [8]. Exome sequence analysis revealed four groups of tumours. Group 1 carcinomas (7% of endometrial carcinomas), have somatic inactivating hotspot mutations in the POLE exonuclease domain and a very high mutational burden (ultramutated); there is a disproportionate (and high) frequency of FIGO grade 3 endometrioid carcinomas, some of which resemble serous carcinomas. Irrespective of grade, group 1 tumours have an improved prognosis, although this is not confirmed in all recent literature.[120] Use of this classification is, as yet, not possible outside the research environment. However, when there are difficulties in typing of high grade endometrial cancers,[121] there can be partial analysis along molecular grounds that may contribute to correlation with clinical outcome. When cancers that are difficult to type are encountered it may be beneficial to obtain specialist opinion.

A number of ancillary tests can be done by pathologists reporting endometrial carcinomas. These include p53 status and hormone receptor immunohistochemistry.[122] In October 2020, NICE published guidance on testing strategies for Lynch syndrome in people with endometrial cancer and recommended that all diagnoses of endometrial cancer should be offered testing for Lynch syndrome.[16] Lynch syndrome is an autosomal dominant syndrome which occurs due to a germline mutation in one of the mismatch repair (MMR) genes, with subsequent loss of associated protein expression. Mutation of MLH1 or MSH2 genes is most common, but other important MMR genes include MSH6 and PMS2. Lynch syndrome is one of the most common cancer susceptibility syndromes. Individuals with Lynch syndrome have a 50%-70% lifetime risk of colorectal cancer, 40%-60% risk of endometrial cancer, 10% risk of ovarian cancer and increased risks of several other malignancies.[123]

6 Primary treatment of endometrial carcinoma with surgery

Enhanced recovery after surgery (ERAS) programmes improve outcomes following gynaecological oncology surgery and should be standard of care. (Grade A)

Standard surgery is a total hysterectomy and BSO without vaginal cuff or parametrectomy (Grade D).

Hysterectomy/salpingectomy with ovarian conservation can be considered in pre-menopausal patients with grade 1 endometrioid EC, <50% myometrial invasion and no extra-uterine disease on imaging (MRI/CT) with low-risk disease. (Grade D)

Enhanced recovery after surgery (ERAS) programmes were introduced in the 1980s. ERAS programme elements, include: pre-operative calorie drinks; drinking clear fluids until the time of surgery; careful intraoperative fluid management; use of non-opioid analgesia, including rectus sheath catheters; and early mobilisation and feeding. An RCT in colorectal surgery demonstrate significant improvements in adverse events, time to mobilisation and length of stay after surgery [124], also demonstrated in a RCT in gynaecological oncology [125]. A recent systematic review in gynaecological oncology has confirmed these benefits and studies demonstrate these programmes are of value in obese patients [126]. Adoption of ERAS programmes and monitoring of performance and outcomes measures should be standard of care for patients having surgery for EC.

EC survival correlates with FIGO stage at diagnosis, reinforcing the need for accurate staging, since this will determine the patient's need for adjuvant chemotherapy and/or radiotherapy. Staging is currently surgical with histological verification [127].

Standard surgery is a total hysterectomy and BSO without vaginal cuff or parametrectomy. Oophorectomy is advised in order to exclude ovarian metastases. Hysterectomy/salpingectomy with ovarian conservation can be considered in pre-menopausal patients with grade 1 endometrioid EC, <50% myometrial invasion and no extra-uterine disease on imaging (MRI/CT). Long-term oncological safety data for ovarian conservation is based on retrospective studies. A meta-analysis of studies investigating stage I/II EC in patients under 50 years or who were premenopausal showed no adverse impact on recurrence free survival (risk ratio (RR) 1.11, 95% CI 0.59 to 2.10).[128] Salpingectomy at the time of hysterectomy does not appear to result in an earlier age of menopause.[129]

6.1 Route of surgery

Minimal access surgery has not been shown to have adverse oncological outcome on EC, as compared to open surgery, is associated with a significantly lower risk of post-operative morbidity and is therefore the preferred route in suitable patients. (Grade A)

An updated Cochrane systematic review analysed nine RCTs comparing open versus laparoscopic surgery, either total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hysterectomy (LAVH), for early-stage EC.[130] Of the nine studies, six included survival data. No significant difference was identified in overall survival (n = 3993) (HR 1.04, 95% 0.86 to 1.25; moderate-certainty evidence) and no significant increase in recurrence risk (n = 3710) (HR 1.14, 95% CI 0.90 to 1.43; moderate-certainty evidence) between the two surgical approaches. The laparoscopic approach was associated with lower peri/post-operative morbidity and length of hospital stay, in particular three RCTs reported significantly lower blood loss (n = 313) (mean difference (MD) –106.82 mL, 95% CI –141.59 to –72.06; low-certainty evidence). There is less evidence available for the use of laparoscopic surgery in high-risk and advantaged stage disease. A retrospective multi-centre study comparing minimally invasive surgery (MIS) (35% laparoscopy, 65% robotic) and open surgery (n = 389) reported no significant difference in progression-free survival (PFS), overall survival (OS) and pattern of recurrence.[131]

Robotic-assisted surgery appears to be non-inferior to laparoscopy and laparotomy for the treatment of endometrial cancer, although long-term oncological outcome data are lacking. (Grade B)

An RCT compared the surgical outcomes of laparoscopic and robotic-assisted (RA) hysterectomy BSO and pelvic lymphadenectomy for EC (n = 99).[132] The results showed no difference in peri/post - operative complications or length of hospital stay, however, operating time was significantly slower in the RA group. A difference was seen in the conversion to laparotomy rate between the two groups, although this did not reach significance, no cases for RA versus five cases for the laparoscopic group, which is supported by other observational studies, with a meta-analysis reporting a significant

difference.[133] Robotic-assisted (RA) laparoscopy has also been shown to be non-inferior to laparotomy for hysterectomy, BSO, pelvic and infra-renal para-aortic lymph node dissection in EC in an RCT (n=96) [134]. No difference was reported in peri-operative morbidity, however, blood loss and hospital stay were lower than the open route, although operative time was longer. These studies were included in a Cochrane review of RA surgery in gynaecology, combining gynaecological surgery for benign and malignant indications.[135] In total 12 RCTs (n=1016) were included demonstrating little or no difference in overall complication rates for hysterectomy compared to conventional laparoscopic surgery, when combining benign and malignant indications, (RR 0.92, 95% CI 0.54 to 1.59; low-certainty evidence), but slightly shorter hospital length of stay with RA surgery (MD -0.30 days, 95% CI -0.53 to -0.07; very low-certainty evidence). RA surgery may have a particular role in the surgical management of patients with high BMI, however, there are a lack of prospective studies confirming this.

The data on financial cost of RA surgery are conflicting, dependent on the method of analysis and have changed over time. Although the capital costs of RA surgery are high, the benefits from reduced hospital stay and post-operative morbidity can have a favourable balance in certain healthcare settings. UK real-world data has shown that patients having RA, as compared to laparoscopy, had more co-morbidities ($p<0.001$) precluding a direct comparison of costs in non-randomised populations.[5] The Cochrane review reported that overall costs of RA surgery may be less than open surgery (MD -1568.00 US dollars, 95% CI -3100.75 to -35.25; low certainty evidence) although the only study included comparing costs of conventional laparoscopy versus RA for hysterectomy included women having surgery for benign indications, which demonstrated higher costs for RA surgery (1564.0 US dollars, 95% CI 1079.57 to 2048.43).[135]

6.2 Management of lymph nodes

Lymphadenectomy of non-bulky nodes is a diagnostic procedure and has not been shown to reduce the risk of recurrence or improve survival. (Grade A)

Lymphadenectomy for non-bulky nodes is not recommended, especially for low-risk EC. (Grade A)

Sentinel lymph node biopsy (SLNB) has a high diagnostic test accuracy and should replace lymphadenectomy of non-bulky nodes for staging. (Grade B)

Surgical staging, including sentinel lymph node biopsy and omental biopsy, may be appropriate for women with disease greater than low risk. (Grade C)

Recruitment of patients with high grade disease and non-endometrioid endometrial cancers into trials investigating the role of sentinel node surgery in clinical management pathways is strongly recommended. (Grade C)

A Cochrane review, including data from two randomised controlled trials (RCT) [136, 137] found little or no differences in overall (OS) (pooled HR 1.07, 95% CI 0.81 to 1.43; moderate-certainty evidence) and recurrence-free survival (RFS) (HR 1.23, 95% CI 0.96 to 1.58; moderate-certainty evidence) between women who underwent routine lymphadenectomy and those who had removal of bulky nodes only.[138] Women had presumed early-stage disease, based on pre and/or intra-operative assessment, and included all grades of disease. LND was associated with a higher risk of surgery-related systemic morbidity (RR 3.72, 95% CI 1.04 to 13.27; high-certainty evidence) and the subsequent development of lymphoedema/lymphocysts (RR 8.39, 95% CI 4.06 to 17.33; high-certainty evidence). A recent study reported that the risk of lower leg lymphoedema increases by 6% for every additional lymph node dissected, resulting in objective rates of 67% in the obese EC population at 24 months following surgery,[139] and significantly reducing patients' long-term quality of life.[140]

Low risk EC (stage 1A grade 1/2, tumour size <2 cm) is associated with a low probability of lymph node metastases (1.4%).[141]

The prognostic value of systematic pelvic *and* para-aortic lymphadenectomy has not been investigated in prospective randomised trials. Retrospective studies, with high risk of bias, show a survival benefit with systematic pelvic and para-aortic lymphadenectomy in EC patients with high-risk features.[142-146]

The Endometrial Cancer Lymphadenectomy Trial (ECLAT) (ClinicalTrials.gov Identifier: NCT03438474) opened in Germany in 2018 aiming to randomize 640 patients to obtain a systematic pelvic and para-aortic lymphadenectomy up to the renal veins or no lymphadenectomy. The ECLAT-trial will now be supported by investigators from the Republic of Korea. Selective Targeting of Adjuvant Therapy for Endometrial Cancer (STATEC; ClinicalTrials.gov Identifier: NCT02566811) was started in 2015 and terminated due to poor recruitment in 2019.

6.2.1 Sentinel lymph node sampling

The use of sentinel lymph node biopsy (SLNB) is increasing in EC and has been shown to have a high negative predictive value, however, to date there are no trials comparing long-term survival outcomes. Sensitivity of 100% (95% CI 92 to 100) and negative predicted value (NPV) of 100% (95% CI 98 to 100) with a bilateral mapping rate of 95% have been reported in the prospective SHREC-trials using indocyanine green (ICG) and RA surgery.[147] The FIRES study was a multicentre prospective study of 385 patients undergoing RA surgery for clinical stage I EC.[148] Three hundred and forty women underwent ICG SLNB, followed by PLND and PALND in 196 cases. Successful mapping was achieved in 86% of cases. Of the 41 patients with positive nodes, 36 had a sentinel node identified, which was positive in 35 of the 36 cases (NPV of 99.6%, 95% CI 97.9 to 100). A small number of isolated positive para-aortic nodes were identified in both these studies (1.5% in [148] and 0.78% in [147]). The SENTIFAIL study was a retrospective case series of 376 patients undergoing laparoscopic SLNB using ICG, which identified lymphovascular space involvement, non-endometrioid histology, and enlarged lymph nodes at surgery as independent predictors of SLNB failure.[149] A Cochrane review of the diagnostic test accuracy of SLNB, limited to 33 studies with evidence of ultrastaging, reported a pooled sensitivity of SLNB of 91.8% (95% CI 86.5% to 95.1%; total 2237 women, of whom 409 had SLN involvement; moderate-certainty evidence).[150] Overall, the mean SLN detection rate was 86.9% (95% CI 82.9% to 90.8%; moderate-certainty evidence) and ranged from 77.8% (95% CI 70.0% to 85.6%) for blue dye alone (559 women; 11 studies; low-certainty evidence) to 100% for ICG and technetium-99m (32 women; 1 study; very low-certainty evidence).

The BGCS has published a consensus document on SLNB setting out recommendations and readers are referred to this document for further information.[151] The advantages of SLNB include reduced risk of lymphoedema and increased pick up of positive nodes, which would guide planning of adjuvant radiotherapy.[152] Despite the wide spread adoption of this technique, there is a lack of long-term patient outcome data, including post-operative morbidity, adjuvant radiotherapy/chemotherapy rates and risk of recurrence and surgeons were recommended to audit their outcomes and recruit to registered clinical trials. The prognostic significance of the additional pathological information that can be obtained from ultrastaging of SLNB (micro-metastases and isolated tumour cells) is as yet not known, as the percentage of positive nodes from SLNB is higher than systematic lymphadenectomy alone.[153] Although data demonstrate good diagnostic test accuracy of SLNB techniques in clinical management pathways, a therapeutic benefit of SLNB has yet to be established in a clinical trial.[154]

6.2.2 Pelvic and para-aortic node dissection

The incidence of positive pelvic and para-aortic lymph nodes is dependent on the histological subtype and stage of disease.[155] This therefore emphasises the need for accurate prediction of myometrial invasion and grade of histology pre-operatively. Of women with grade 3 and clinical stage I disease with outer myometrial invasion, 28% were subsequently found to have lymph node involvement.

The majority (77%) of positive para-aortic nodes occur above the level of the IMA and therefore the upper limit of a para-aortic lymphadenectomy is recommended to be up to the renal vessels.[156] There are no RCTs comparing pelvic and para-aortic lymphadenectomy with either pelvic lymphadenectomy alone or no lymphadenectomy. The removal of clinically abnormal lymph nodes alone is known to be an inaccurate means of staging endometrial cancer. Benedetti-Panici et al. demonstrated a four-fold increase in the rate of detection of lymph node metastases when systematic lymphadenectomy was performed in comparison to the removal of enlarged nodes only.[136]

The impact of combined pelvic and para-aortic lymph node dissection (PPALND) compared to only pelvic lymph node dissection (PLND) on survival outcomes of intermediate and/or high-risk patients is not known. A recent systematic review and meta-analysis included 13 retrospective studies with a total

of 7,349 patients.[157] The results identified a significantly lower risk of death for PPALND/PLND (HR 0.54, 95% CI 0.35 to 0.83; I^2 = 62.1%) and decreased risk for recurrence (HR 0.51, 95% CI 0.28 to 0.93). The 5-year OS rate (RR 1.13, 95% CI 1.04 to 0.24; I^2 = 57.3%) and 5-year DFS rate (RR 1.23, 95% CI 1.14 to 1.31; I^2 = 85.5) were also significantly higher than PLND alone. These results are from non-randomised studies and at critical risk of bias, so need to be interpreted with caution and investigated further in prospective, randomised trials.

6.3 Surgical management of overt stage II disease

In patients with overt stage II endometrial cancer, total hysterectomy with bilateral salpingo-oophorectomy is adequate. Radical hysterectomy should only be considered to obtain tumour-free margins. (Grade B)

There is lack of prospective randomised studies comparing surgical staging with simple hysterectomy versus radical hysterectomy in overt stage II endometrial cancer. Recent retrospective studies found that radical hysterectomy does not significantly improve survival in stage II endometrial cancer.[158-161] In a meta-analysis of patients with stage II endometrial cancer (n=2,866), radical hysterectomy did not show a significant survival benefit for either OS (pooled HR 0.92, 95% CI 0.72 to 1.16; P = 0.484) or PFS (pooled HR 0.75; 95% CI 0.39 to 1.42; P = 0.378).[162] The result remained consistent after it was balanced with possible impact from adjuvant radiotherapy (pooled HR 0.85, 95% CI 0.62 to 1.16; P = 0.300).

7 Primary treatment - non-surgical management

7.1 Patients unfit for surgical management

Women who are unfit for standard surgical management may be treated by vaginal hysterectomy, definitive pelvic radiotherapy or progestin/aromatase inhibitors. The choice of treatment depends on patient characteristics and local preferences. (Grade D)

Vaginal hysterectomy may be considered for women who cannot undergo abdominal or laparoscopic hysterectomy. (Grade C)

Combined external beam radiation therapy (EBRT) and intra-cavitary brachytherapy may be considered for women with high grade tumours, deep myometrial invasion and/or stage II disease. Intra-cavitary brachytherapy alone may be considered for women with low grade, stage I tumours without deep myometrial invasion. (Grade B)

Progestin therapy may be considered in women with low grade tumours to postpone standard surgical management for 3-6 months for temporary or reversible medical reasons. (Grade B)

Progestin (and/or aromatase inhibitors in postmenopausal women) may be considered in women in whom surgery/radiotherapy is not an option. (Grade B)

Vaginal hysterectomy may be considered for women who are unfit for standard surgical management. For women with low grade, early stage disease, this is likely to be curative.[163] Primary pelvic radiotherapy is an option for women who are unfit for surgery, although recurrence rates of up to 18% have been described in retrospective case series.[164] Combined EBRT and vaginal brachytherapy is recommended for women with high grade tumours and/or deep myometrial invasion and/or stage II disease, in whom the risk of occult pelvic sidewall disease is appreciable.[165-169] Progestin therapy may be considered for postponing surgical management for temporary reasons of poor medical fitness or for surgery pre-habilitation, for example in the COVID-19 pandemic or during the acute recovery phase following myocardial infarction, stroke or fractured neck of femur. Intrauterine progestin may be preferred due to the low toxicity profile and small retrospective case series indicate moderate success rates.[170]

7.2 Fertility-preserving management

Women wishing to preserve their fertility should be managed in specialist centres. Assessment should include specialist pathology review, imaging by MRI scan and fertility clinic referral to confirm eligibility. (Grade A)

Women with atypical hyperplasia or Stage 1A grade 1 endometrial cancer without myometrial invasion may be suitable for fertility-sparing management. Women should be carefully

counselled regarding success rates, the need for close surveillance before/after treatment, recurrence rates and the need for hysterectomy if treatment fails/once childbearing is complete. (Grade A)

Treatment is by medroxyprogesterone acetate (400-600 mg/day) or megestrol acetate (160-320mg/day) and/or levonorgestrel-releasing intrauterine system (LNG-IUS) for 6-12 months. Hysteroscopic resection prior to progestin therapy may be considered. Additional prescription of gonadotrophin-releasing hormones may be considered. (Grade B)

Strict surveillance during treatment includes endometrial biopsy and repeat imaging at 3 monthly intervals to exclude progressive disease. (Grade B)

Women should be supported to maximise their chances of pregnancy after successful fertility-sparing treatment because recurrence is common and their window of opportunity may be short. (Grade A)

After 6-months of proven disease regression, maintenance progestin therapy should be considered in responders wishing to delay pregnancy. Endometrial surveillance by biopsy and/or scan at 3-6 monthly, then 6-12 monthly intervals is appropriate during follow up. Progestin therapy may be considered for intrauterine recurrence. Hysterectomy and bilateral salpingectomy is indicated if conservative management fails and once childbearing is complete. Ovarian preservation may be considered in young women who do not have Lynch syndrome. (Grade B)

The demand for fertility-sparing approaches for the management of atypical hyperplasia and endometrial cancer is increasing alongside the rising incidence of the disease in young women.[171] Fertility-sparing management is safe in women with low grade disease confined to the endometrium providing the initial diagnosis is accurate and treatment is accompanied by careful monitoring.[172] Predictors of success include low volume disease on MRI scan and minimal or no myometrial invasion.[173] Expert pathology review of the index biopsy is essential to confirm the diagnosis. Women whose tumours are mismatch repair (MMR) deficient by immunohistochemistry without *MLH1* hypermethylation should undergo definitive germline testing for Lynch syndrome.[16] Genetic counselling should also be considered for young women with a strong familial history who test negative for Lynch syndrome. Baseline MRI scanning is important to benchmark treatment success and should assess endometrial thickness, the presence or absence of myometrial invasion and identify synchronous adnexal pathology. Conservative management is unlikely to be successful in the presence

of definite myometrial invasion, but adenomyosis or fibroids may complicate this assessment. It is important to seek expert opinion regarding fertility expectations particularly for women with primary infertility of >1 year duration, significant obesity or advancing age.

There are no randomised controlled trials comparing the effectiveness of different conservative management strategies. Most experience is with oral progestin and success rates of up to 76-86% have been reported.[174] The LNG-IUS is a reasonable alternative to oral progestin and has the advantage of delivering high concentrations of progestin directly to the tumour, fewer systemic side effects and ensures perfect compliance.[175] Alternative regimens include combined oral and intrauterine progestin, progestin plus gonadotrophin-releasing hormone, progestin plus metformin and hysteroscopic resection followed by progestin, although their relative effectiveness and side effect profiles are poorly studied.[176-180] Pooled outcomes from case series suggest a conservative treatment overall success rate of 76%, a relapse rate of 26% and live birth rate of 26%.[174]

Management during treatment is focused on detecting progressive disease so that early recourse to hysterectomy is ensured. This involves repeat biopsies and imaging at 3, 6 and 12 months. It is important to use the progestin treatment window to maximise fertility success by supporting women to achieve a healthy body mass index (BMI) through low calorie diet.[181] Expedited bariatric surgery (gastric bypass, sleeve or band) may be appropriate in selected cases, particularly those with BMI>40kg/m^2. [182, 183] Complete pathological response at 6-12 months may need confirmation after stopping progestin, which complicates histological assessment. In follow up, most recommend 3-6 monthly biopsies in the first year and annual biopsies thereafter. Maintenance progestin by LNG-IUS or low dose oral preparations reduces recurrence risk but prevents pregnancy, requiring careful coordination with planned fertility interventions.[184]

7.3 Surgery for more advanced disease at presentation

Recommendations:

In FIGO stage III/IV EC, debulking surgery, including bulky nodes, should be considered if complete macroscopic resection is feasible, and, if the patient is deemed fit for radical surgery

with acceptable morbidity and quality of life, as limited evidence shows that this may improve survival. However, more limited surgery with hysterectomy for palliation of symptoms, or other palliative treatment options are alternatives and should be discussed with the patient (Grade D)

Routine systematic pelvic and para-aortic lymph node dissection of non-suspicious nodes is not recommended (Grade D)

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

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

Surgical cytoreduction is associated with survival advantage in advanced EC, however, high quality data are lacking. Smaller retrospective case series have found survival benefit with complete cytoreduction in advanced EC.[185-187] Barlin *et al.* performed a meta-analysis of 14 retrospective case series, including 10 studies related to primary disease and 4 studies of recurrent EC.[188] Macroscopic surgical resection was possible in 18-75% of cases. Achievement of a macroscopic cytoreduction was associated with an improvement in median OS, such that each 10% increase in cytoreduction to no gross evidence of disease was associated with a 9.3 month increase in OS. Similarly, Eto *et al.* demonstrated a 15 month increase in OS when macroscopic resection of intra-abdominal metastases was achieved in patients with stage IVB EC (median OS 48 months with macroscopic resection versus 23 months with 'optimal' resection versus 14 months with 'suboptimal' resection).[189] In another retrospective study, using data from SEER database for advanced EC with extra-peritoneal metastasis, surgery was associated with improved survival in women with extra-peritoneal metastasis.[190]

A retrospective observational study of 41 patients with Stage IIIC EC found a significantly longer disease specific survival time in those patients with macroscopic resection of bulky nodal disease compared with those left with gross residual disease (37.5 months versus 8 months; P = 0.006).[142] The presence of gross residual nodal disease was an independent prognostic factor of survival on

multivariate analysis. This result was replicated by Havrilesky et al. who demonstrated that failure to debulk gross lymph node metastases was associated with a 6.8-fold worsening of disease specific survival at five years.[146]

There is absence of high-quality evidence to support diagnostic or therapeutic value of full pelvic and para-aortic lymphadenectomy in advanced endometrial cancer, although retrospective studies show a survival benefit with systematic pelvic and para-aortic lymphadenectomy in EC patients with high-risk features.[142-146, 191] In a retrospective analysis using data from SEER database, compared to women with a pelvic-only lymph node dissection, women with pelvic and aortic dissections had lower all-cause (HR = 0.74, 95% CI = 0.63 to 0.88) and EC-specific (HR = 0.79, 95% CI = 0.66 to 0.95) mortality [192].

The use of neoadjuvant chemotherapy (NACT) in the context of treating advanced EC has not been formally assessed in randomised controlled trials and is addressed separately (see section 9). In some cohorts, NACT and interval debulking surgery (IDS) has resulted in decreased operative time and hospital stay without worsening OS.[193-195]

There is limited evidence regarding the role of palliative surgery in EC. Hysterectomy may be used in this setting for the control of distressing symptoms, such as bleeding, pain and malodorous discharge. A retrospective analysis of 13 patients with gynaecological tumours undergoing palliative exenteration suggested an improvement in quality of life following the procedure; however, the numbers included are too small to draw any generalised conclusions.[196] Decisions regarding the role of surgery in this setting should be made on an individual basis, taking into consideration patient wishes and symptoms. A national register of patients undergoing neoadjuvant chemotherapy for endometrial cancer is an aspiration.

8 Primary treatment – adjuvant treatment

This section provides evidence-based information on adjuvant radiotherapy (external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT)) and systemic therapy after hysterectomy for endometrial cancer, including early (stage I or II) uterine adenocarcinoma and completely resected stage III disease. The ESMO-ESGO-ESTRO 2014 consensus meeting defined risk groups based on histology and stage.[113] These have been modified in the 2020 ESGO-ESTRO-ESP endometrial cancer guidelines to include molecular classification, when available, as summarised in section 2.2 and Table 5.[1] Ideally, adjuvant treatment should commence within 6-8 weeks of surgery.

8.1.1 Low-risk endometrial cancer

Recommendation:

No adjuvant treatment is recommended for those with low-risk EC. (Grade A)

If molecular classification is available, consider omitting adjuvant treatment in those with stage I-II and *POLE*mut. (Grade C)

Multiple clinical studies have demonstrated no benefit for adjuvant treatment for women with low-risk EC, based on conventional histological classification.[197-201] EC stage I and II with a *POLE* mutation (*POLE*mut) have excellent prognosis from case series.[202, 203] At present *POLE*mut analysis is not widely available in the UK. However, this should be encouraged, as data suggest that these patients may do well without adjuvant treatment, even with what was previously thought to be higher risk disease based on histological classification alone. In a retrospective analysis of the PORTEC-3 study, high risk patients with *POLE*mut did well in both arms, although this study compared the addition of chemotherapy to EBRT and so all patients received EBRT.[204] It is hoped that this will be answered by the on-going PORTEC-4a study.[205]

8.1.2 Intermediate-risk endometrial cancer

Recommendations:

Vaginal vault brachytherapy (VBT) can be recommended to reduce the risk of vaginal recurrence (Grade A)

Omission of adjuvant brachytherapy can be considered especially for patients aged less than 60 years (Grade A)

Where molecular classification is available, those with *POLE*mut EC may be considered as low risk and those with *p53*abn EC with myometrial invasion considered high risk (see relevant sections for recommendations). (Grade C)

For those with *p53*abn EC restricted to a polyp or without myometrial invasion, there are no RCT data to guide treatment and any adjuvant therapy should be individualised. (Grade D)

Data from several studies have not demonstrated a significant benefit to adjuvant EBRT compared to VBT for intermediate-risk EC.[206-214] The PORTEC-1 trial included 714 patients with Stage IC Grade 1-2 or Stage IB Grade 2-3 EC (as per 1999 FIGO staging criteria, now considered Stage IB Grade 1-2 or Stage IB Grade 2-3 as per 2018 FIGO staging [127]).[215-217] After surgery, patients were randomly allocated to external-beam pelvic radiotherapy (EBRT) or no additional treatment (NAT). The 15 year follow up results reported the 15-year actuarial locoregional recurrence (LRR) rates to be 6% for EBRT versus 15.5% for NAT ($P < 0.0001$) with the majority of recurrences being in the vagina in the NAT arm, but no OS advantage. Risk factors included high grade, deep myometrial invasion and age over 60 years and with two risk factors present the risk of locoregional recurrence was 23% compared to 5% with EBRT. This defined the high-intermediate risk group investigated in the subsequent PORTEC-2 trial.

Of the 714 women who were evaluated, 39 had isolated vaginal relapse; 35 (87%) were treated with curative intent, usually with EBRT and VBT), and surgery in some. A complete remission was obtained in 31 (89%), and the three-year survival after vaginal relapse was 73%. At five years, the survival after vaginal relapse was 65%, making an observation programme an alternative option to a policy of routine

radiotherapy, especially in younger women who have a lower risk of relapse. Similar results have been reported in a Danish population-based study which reported 14% locoregional relapse without adjuvant therapy.[218]

PORTEC-2 was a randomised trial for women with what was previously classified as high-intermediate risk (HIR) EC, comparing pelvic EBRT with VBT.[214] Four hundred and twenty-seven women with EC were randomised to VBT or EBRT. Ten-year vaginal relapse was equivalent (3.4% versus 2.4%), although 10-year pelvic recurrence was more frequent in the VBT group (6.3% versus 0.9%; P=0.004). However, 10-year isolated recurrence was not significantly different (2.5% versus 0.5%) and there was no difference in OS (69.5% versus 67.6% at 10 years; P = 0.72).

Long term follow-up of women in the PORTEC 2 trial shows that late toxicity from EBRT, compared with VBT alone, was significant.[214] Women who received EBRT had higher rates of urinary incontinence, diarrhoea, and faecal leakage that limited their daily activities. The clinical significance is illustrated by use of incontinence products by women more than 10 years after radiotherapy, compared with no additional treatment (day and night use, 42.9% versus 15.2%, respectively). Random allocation to radiotherapy was associated with lower SF-36 quality of life scores on the scales "physical functioning" (P = 0.004), "role-physical" (P = 0.003) and "bodily pain" (P = 0.009). The radiotherapy technique was conventional four-field box technique. Following vaginal brachytherapy, global functioning was normal although there was some impact on sexual functioning.

A Cochrane review included seven RCTs involving 3,628 women following surgery for stage I EC, comparing EBRT versus no EBRT (or VBT), and one trial (645 women) comparing VBT with no additional treatment.[201] EBRT did not improve OS rates nor survival duration (time-to-event data: five trials, 2,965 women; HR 0.99, 95% CI 0.82 to 1.20; and dichotomous data: seven trials, 3628 women; RR 0.98, 95% CI 0.83 to 1.15). Adjuvant radiotherapy delayed the onset of recurrence in the pelvis and altered the pattern of recurrence to that of predominantly distant metastases.

Retrospective molecular classification and analyses of the PORTEC 1-2 cohorts have demonstrated that those with tumour L1CAM and *p53*abn overexpression or substantial LVSI are at higher risk for

pelvic and distant recurrence.[203, 219, 220] Women with these characteristics would now be considered as high-intermediate risk (HIR – see section 8.1.3 below).

The on-going PORTEC 4a trial uses molecular markers to determine adjuvant treatment.[205, 221-223] FIGO Stage I intermediate risk EC patients are divided in to favourable (no adjuvant treatment), intermediate (VBT) and unfavourable (EBRT) by molecular classification as compared with the standard arm of VBT based on histological classification.

Women with *p53*abn tumours and non-endometrioid tumours including serous carcinoma and carcinosarcoma confined to a polyp or with no myometrial invasion were not included in previous RCTs. The tumours were previously classified as high risk but cohort studies have shown these tumours have a good prognosis and therefore the use of adjuvant chemotherapy and EBRT may have limited benefit. In a similar approach to high grade endometrioid adenocarcinoma, vaginal brachytherapy can be considered.[206] Surveillance with no additional treatment would be an alternative option particularly if the disease was confined to a polyp and there was no residual disease at hysterectomy.

8.1.3 High-intermediate-risk endometrial cancer

Recommendations:

When surgical staging of lymph nodes has been performed:

- **Consider adjuvant vaginal brachytherapy alone, if no LVSI. (Grade A)**
- **EBRT is recommended for substantial LVSI and for Stage II tumours with high grade or deep myometrial invasion. (Grade A)**

When surgical staging of lymph nodes has not been performed:

- **Adjuvant EBRT is recommended. (Grade A)**
- **Adjuvant chemotherapy can be considered, when substantial LVSI is present. (Grade B)**
- **Adjuvant brachytherapy alone can be considered for stage II low grade endometrioid cancers without deep invasion. (Grade B)**

If molecular classification is known, those with *POLE*mut and *p53*abn consider management as per low and high-risk disease sections. (Grade C)

The recent ESGO-ESTRO-ESP guidelines [1] have defined this group as including (see Table 5):

- Stage I EC, if there is substantial LVSI, regardless of grade or depth of invasion;
- Stage IB G3 endometrioid regardless of LVSI status;
- Stage II endometrioid EC.

This new definition of the HIR EC group includes tumours previously classed as high-risk Stage I/II disease and has a substantial risk of recurrence, even when there has been surgical staging of the lymph nodes. GOG-99 compared EBRT versus no additional treatment in patients with stage I and II EC with intermediate and high-intermediate risk factors (including a high intermediate risk (HIR) subgroup of patients defined as those with (1) G2-3 tumour, presence of LVSI, deep myometrial invasion; (2) age ≥50 years with any two risk factors; or (3) ≥70 years with any risk factor). All patients had undergone pelvic and para-aortic lymphadenectomy and were by definition node negative.[200] Those with HIR had a substantial reduction in pelvic and vaginal recurrence at 2 years (26% versus 6%).

A recent RCT (GOG-249) comparing VBT and chemotherapy (VBT/C) to EBRT for HIR EC demonstrated similar OS for EBRT VBT/C (HR 1.04, 90% CI 0.71 to 1.52), with similar late toxicities, but more acute toxicity in the VBT/C group.[224] Pelvic or para-aortic nodal recurrences were more common with VBT/C (9% v 4%). The conclusion was that EBRT is the standard of care for this group of patients.

GOG249 was the first randomised adjuvant trial in which an intensity-modulated radiotherapy technique (IMRT) was used for the majority of patients, which accounts for the reduced toxicity compared to previous trials when conventional radiotherapy was used.

If EBRT is omitted for node-negative patients, close follow up to detect early recurrences is recommended. For those without substantial LVSI or G1 stage II disease, VBT alone can be considered, if surgical staging of lymph nodes has been undertaken. The role of chemotherapy is discussed in the following section 8.2 and may be considered for tumours with extensive LVSI particularly if nodal status is unknown.

8.1.4 High-risk endometrial cancer

Recommendations:

EBRT with concurrent and adjuvant chemotherapy or alternatively sequential chemotherapy and radiotherapy is recommended. (Grade A)

Chemotherapy alone or with VBT may be an alternative option, if systematic lymphadenectomy has been performed. (Grade B)

This risk group has also changed and now includes the following:

- Stage III-IVA MMRd/NSMP and/or endometrioid cancers with no residual disease
- stage I-IVA *p53*abn endometrial carcinoma with myometrial invasion and no residual disease
- Stage I-IVA serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion and no residual disease.

There is a high risk of both loco-regional and distant recurrence for this group of patients. External beam radiotherapy reduces the risk of recurrence and has been traditionally the standard of care for stage III disease. In the PORTEC-3 trial, the addition of concurrent and adjuvant chemotherapy to EBRT was compared to EBRT only. In the updated results after longer follow up, there was a statistically significant 5% overall survival benefit at 5 years and a 7% failure-free survival benefit in the combined therapy group, with the greatest overall survival benefit seen in stage III and serous cancers. Other RCTs, and a meta-analysis of the studies, have looked at the addition of chemotherapy to pelvic EBRT and/or VBT.[224-227] The role of adjuvant chemotherapy is discussed in more detail below in section 8.2.

The above sections are summarised in Table 10 and provide guidance for adjuvant treatment in endometrial cancer (modified from ESGO-ESTRO-ESP guidelines [1]).

8.2 Adjuvant chemotherapy

Recommendations:

Postoperative carboplatin-paclitaxel chemotherapy is associated with a FIGO stage and histological/ molecular subtype dependent improvement in progression-free survival and overall survival irrespective of radiotherapy treatment. (Grade A)

The use of a four-group molecular classifier provides robust prognostic information and predicts benefit from adjuvant chemotherapy. Centres should work towards adopting this into routine practice. (Grade C)

If molecular subtyping has not been performed:

- **adjuvant chemotherapy is a recommended treatment option for:**
  - **women with stage III/IVA endometrial adenocarcinoma of all histological subtypes (Grade A)**
  - **women with myoinvasive stage I or II serous endometrial carcinoma (Grade B)**
  - **women with myoinvasive stage I or II clear cell or undifferentiated endometrial carcinoma or carcinosarcoma. (Grade C)**
- **Adjuvant chemotherapy can be discussed as a potential treatment option with:**
  - **women with stage IB or II grade 3 endometrioid endometrial carcinoma where lymphadenectomy has not been performed or there is substantial lymphovascular space invasion. (Grade B)**

If molecular subtyping has been performed:

- **Women with *POLE*mut endometrial cancer do not require adjuvant chemotherapy. (Grade C)**

- **Adjuvant chemotherapy is recommended for:**
    - **women with stage I (myoinvasive)–IVA *p53*abn endometrial cancer;(Grade C)**
    - **women with stage III/IVA endometrial cancer with no specific molecular profile (NSMP). (Grade C)**
- **Adjuvant chemotherapy can be discussed as a potential treatment option with;**
    - **women with stage III/IVA MMRd endometrioid endometrial cancer. (Grade C)**
    - **women with myoinvasive stage I-II non-endometrioid high grade histological subtypes that are NSMP or MMRd. (Grade C)**
- **Entry into molecularly stratified adjuvant trials should be actively considered. (Grade D)**

Concurrent cisplatin-radiotherapy followed by carboplatin-paclitaxel or sequential carboplatin-paclitaxel and radiotherapy are appropriate treatment regimens, if combined modality adjuvant treatment is necessary. (Grade A)

Prior to 2019, there were nine randomised trials [226-232] that examined the role of adjuvant chemotherapy for high-risk, high grade endometrial carcinomas; however, all had serious limitations, used drugs that are either no longer viewed as first choice, or with suboptimal doses and dose intensity. Five randomised trials compared no additional treatment with additional chemotherapy after hysterectomy and radiotherapy and four compared platinum-based combination chemotherapy directly with radiotherapy. Indiscriminate pooling of survival data from 2,197 women, as part of a Cochrane meta-analysis, showed a small overall survival advantage from adjuvant chemotherapy (RR 0.88, 95% CI 0.79 to 0.99).[233] Sensitivity analysis focused on trials of modern platinum-based chemotherapy regimens and found the relative risk of death to be 0.85 (95% CI 0.76 to 0.96); number needed to treat for an additional beneficial outcome (NNT) was 25 and an absolute risk reduction of 4% (1% to 8%). Chemotherapy reduced the risk of developing the first recurrence outside the pelvis (RR 0.79, 95% CI 0.68 to 0.92; 5% absolute risk reduction; NNT 20). Despite the above statistics, the precise survival advantage from adjuvant chemotherapy in these studies is difficult to quantify because of significant heterogeneity.

In the last two years, survival outcomes from three important large randomised controlled trials evaluating the integration of carboplatin-paclitaxel, now considered the standard-of-care first-line

cytotoxic regimen for endometrial cancer, into adjuvant treatment have been published and added significantly to the evidence base.[224, 225, 234, 235]

The GOG249 trial randomised 601 women with stage I age-modified, high-intermediate risk category or stage II endometrioid cancer or stage I-II serous or clear cell carcinoma with negative peritoneal cytology to either pelvic radiotherapy (RT) or vaginal brachytherapy (VBT) followed by 3 cycles of carboplatin-paclitaxel chemotherapy (CT).[224] Most women (89%) entering GOG249 had undergone pelvic lymphadenectomy as part of their initial surgery. At a median follow-up of 53 months, 5-year recurrence-free survival (RFS) was 76% in both treatment arms (HR 0.92 for VBT-CT compared to RT, 95% CI 0.65 to 1.30) and subgroup analysis did not demonstrate any heterogeneity of treatment effect by age, race, performance status or histological subtype. There was little or no difference in 60-month OS (HR 1.04, 90% CI 0.71 to 1.52). In patients who had not undergone lymphadenectomy the HR for RFS was 0.69 in favour of VBT-CT compared to HR 0.96 in patients who underwent lymphadenectomy. However, VBT-CT was not associated with a significant RFS improvement in either group. The incidence of pelvic and para-aortic lymph node recurrence was lower in the group that received RT (4% vs 9%; HR 0.47, 95% CI 0.24 to 0.94). Treatment-related toxicity, in particular neurotoxicity and fatigue were higher in the VBT-CT treatment group.

GOG258 randomised 813 patients with stage III-IVA endometrial carcinoma of any histological subtype or patients with stage I-II serous/clear cell carcinoma with positive peritoneal cytology to six cycles of CT or concurrent cisplatin- RT followed by four cycles of CT (CTRT); 736 patients met full eligibility criteria and were included in the final efficacy analysis.[234] Only 2% of patients entering GOG258 had stage I-II disease, 18% had serous carcinoma and 3% clear cell. In patients allocated to CTRT, 75% completed all treatment while 85% of CT patients completed all six cycles. After a median FU of 47 months, 5-year RFS was 59% with CTRT and 60% with CT alone (HR 0.90, 95% CI 0.71-1.15) and no heterogeneity of effect was seen on exploratory subgroup analyses. Overall survival data are immature. However, the patterns of disease recurrence were significantly different between treatment arms. The incidence of vaginal recurrence (2% vs 7%; HR 0.36) and pelvic/ para-aortic nodal recurrence (11% vs 20% HR 0.43) were lower in the CTRT arm, however the incidence of distant recurrence was higher with CTRT as opposed to CT (27% vs 21%; HR 1.36).

The PORTEC3 trial randomised 660 women who had undergone hysterectomy and BSO for stage I Grade 3 endometrioid endometrial cancer with deep myoinvasion and/or substantial LVSI, stage II-III endometrioid cancer or myoinvasive stage I-III serous or clear cell endometrial cancer to either adjuvant pelvic radiotherapy (RT) or concurrent cisplatin-RT followed by 4 cycles of CT. [225, 235] Baseline patient characteristics were broadly distributed across FIGO stage (stage I 30%; stage II 26%; stage III 45%) and histological subtype (G1-2 endometrioid 39%; G3 endometrioid 32%; serous 16%; clear cell 9%). Just over half of the patients (57%) had undergone lymphadenectomy during their initial staging surgery. Almost all patients (99%) completed RT in both arms while 71% of patients in the CTRT completed the planned four cycles of combination chemotherapy. Analyses of the co-primary endpoints, OS and failure-free survival (FFS) were published in 2018 [225] and updated in a post-hoc analysis with an additional 12 months follow-up in 2019 [235]). At the time of this second analysis median FU was 72.6 months and 150 OS events had occurred. In the intent-to-treat population, both 5-year FFS (76.5% versus 69.1% HR 0.70, 95% CI 0.52 to 0.94) and 5-year OS (81.4% versus 76.1%; HR 0.70, 95% CI 0.51 to 0.97) were significantly improved with CTRT compared to RT alone. Exploratory subgroup analysis indicated that the benefit of CTRT was greatest for patients with FIGO stage III disease, with a 5-year OS of 78.5% versus 68.5% (HR 0.63, 95% CI 0.41 to 0.99) and 5-year FFS of 70.9% versus 58.4% (HR 0.61, 95% CI 0.42 to 0.89), compared to those with stage I-II disease, who had a 5-year OS of 83.8% versus 82.0% (HR 0.83, 95% CI 0.51 to 1.35) and 5-year FFS of 81.3% versus 77.3% (HR 0.86, 95% CI 0.55 to 1.34). CTRT was associated with improved survival outcomes in patients with serous cancers (n = 102; 5-year OS 71.4% versus 52.8% (HR 0.48, 95% CI 0.24 to 0.94); 5-year FFS 59.7% versus 47.9% (HR 0.42,95% CI 0.22 to 0.80). While this differential impact of adjuvant chemotherapy in serous endometrial carcinoma was not seen in prior studies,[226] the use of modern IHC stains and central histopathological review in PORTEC3 increases the validity of this finding.[236] The difference in FFS between treatment arms was due to a higher incidence of distant metastases as first site of recurrence in the RT arm (21.4% vs 29.4%; HR 0.74), the incidence of pelvic recurrences was similar between arms.

The incorporation of lymphadenectomy as part of primary surgical staging was used as a stratification factor at PORTEC3 trial randomisation, although lymphadenectomy did not correlate with FFS or OS

on univariate analysis. Women who did not undergo lymphadenectomy during their initial surgery may or may not have had a greater improvement in FFS with CTRT versus RT compared to those who did (no lymphadenectomy HR 0.58, 95% CI 0.37 to 0.91; lymphadenectomy performed HR 0.77, 95% CI 0.54 to 1.14).

CTRT was associated with a higher incidence of ≥ grade 3 adverse events by CTCAEv3.0 during treatment compared to RT alone (61% vs 13%). Adverse events were predominantly uncomplicated haematological events, gastrointestinal or pain-related.[237] This increased toxicity translated to a clinically significant lower Quality of Life (QoL) measured using EORTC QLQc30 and CX24 tools at six months from trial randomisation in the CTRT arm. However, by 12 months, reported QoL were similar in both arms, apart from persisting symptoms from peripheral sensory neuropathy, reported in 25% of patients who received CTRT compared to 6% who received RT alone. A sub-study evaluating patient preferences for adjuvant chemotherapy conducted in 83 patients participating in PORTEC3, using time trade-off questionnaires, reported that more than 50% of women surveyed at trial entry judged a minimum 5% increase in long-term survival justified receiving adjuvant chemotherapy. Of note, when the questionnaire was repeated nine months after trial entry, a smaller magnitude of survival benefit for CT was judged sufficient by those women who received CTRT on trial indicating that the negative impacts of chemotherapy toxicity did not impact on this decision.[238]

Taken together, these trials support the use of adjuvant carboplatin-paclitaxel chemotherapy as part of standard care for women with stage III-IVA endometrial cancer of all histological subtypes and also those with myoinvasive stage I and II serous cancers. Although GOG258 did not demonstrate a survival advantage with combined modality treatment over six cycles of CT, the increased incidence of vaginal and pelvic recurrences in the chemotherapy alone arm supports the use of combined modality treatment either as concurrent cisplatin-radiotherapy followed by carboplatin-paclitaxel or sequential carboplatin-paclitaxel and radiotherapy. However, chemotherapy alone or with vaginal brachytherapy could be an option, if systematic lymphadenectomy has been performed.

In women with stage I-II grade 3 endometrioid endometrial cancer who have undergone surgical lymph node staging or who do not have substantial LVSI, the benefits of adjuvant chemotherapy are uncertain

and pending the outcome of the ENGOT-EN2 trial,[239] adjuvant chemotherapy is not recommended outside of a clinical trial.

The small numbers of women with clear cell endometrial carcinoma and the exclusion of carcinosarcoma from PORTEC 3 and GOG258/249 mean it is not possible to determine the absolute benefit for adjuvant chemotherapy in these settings. However, the increased risk of metastatic disease and consequent poor prognosis of these rare histological subtypes supports the use of adjuvant chemotherapy in myoinvasive disease. This recommendation is also supported by retrospective cohort studies,[240, 241] which report better survival outcomes associated with the use of adjuvant chemotherapy.

Molecular predictors of prognosis and adjuvant treatment efficacy

The Cancer Genome Atlas identified a four-subgroup molecular classification for endometrial cancer with significant prognostic value (detailed in section 2.2).[242] This molecular classifier can be replicated robustly using a surrogate panel of routine immunohistochemical markers (TP53 and MMR proteins) and evaluation of *POLE*mut status in FFPE tissue and maintains its prognostic value indicating that it may have a role in routine clinical practice.[203] This molecular classifier has now been evaluated in 423 patients from the PORTEC3 trial who provided consent for research access to FFPE tissue.[204] This molecular analysis cohort was representative of the whole PORTEC3 trial population and allocation using hierarchical testing to one of the 4 molecular subgroups (*POLE*mut (12.4%); MMRd (33.4%); *p53*abn (22.7%); No Specific Molecular Profile (NSMP) (31.5%)) was possible in 97% of cases. Correlation of molecular subgroup with survival outcomes confirmed the strong prognostic value of the molecular classifier and analysis of differences in adjuvant treatment effects (CTRT versus RT) by molecular subgroup demonstrated the potential importance of this four-subgroup molecular classifier as a predictive biomarker of adjuvant chemotherapy efficacy.

Patients with a *POLE*mut tumour had an excellent prognosis irrespective of disease stage or treatment allocation (5-year RFS 100% with CTRT and 97% with RT). Patients with *p53*abn endometrial cancer had the poorest prognosis but gained significant benefit from CTRT compared to RT (5-year RFS 57%

versus 36%; HR 0.52, 95% CI 0.30-0.91). MMRd endometrial cancer was associated with an intermediate prognosis and did not gain benefit from combined modality adjuvant treatment (5-year RFS 68% versus 76%; HR 1.29, 95% CI0.68-2.45). In the subgroup with NSMP, an intermediate prognosis was also noted and CTRT may or may not be associated with an improvement in RFS (5-year RFS 80% versus 68%; HR 0.68, 95% 0.36 to 1.30). This analysis shows the validity of implementing the molecular classification of endometrial cancer in to clinical prognostication and decision-making and it is being utilised in the forthcoming international RAINBO adjuvant trial programme to allocate patients to appropriate trial arms.

8.3 Adjuvant hormonal therapy

Recommendation:

There is no role for adjuvant hormonal therapy outside clinical trials. (Grade A)

A Cochrane review found little or no difference in the risk of death at five years between adjuvant progestogen therapy and no further treatment in a meta-analysis of four studies (RR = 1.00, 95% CI 0.85 to 1.18).[243]

8.4 Adjuvant radiotherapy

Recommendation:

IMRT technique should be used to reduce the risk of acute and long-term toxicity. (Grade B)

8.4.1 External beam radiotherapy (EBRT) technique

For external beam radiotherapy, Intensity-modulated radiotherapy (IMRT/VMAT) techniques are recommended because the more conformal dose distribution increases normal tissue sparing compared to a four-field conventional or 3D-conformal plan, resulting in reduced toxicity.[244] The clinical target volume (CTV) includes the pelvic lymph nodes (external iliac, internal iliac, obturator,

distal common iliac), parametria and upper vagina. The upper common iliac lymph nodes are included when there is cervical stromal involvement and/or pelvic lymph node involvement. Extended field radiotherapy up to the level of the renal vessels is used in the case of involved para-aortic nodes or involvement of high common iliac nodes. The combination of extended field radiotherapy with chemotherapy using modern intensity-modulated radiation therapy/volumetric modulated arc therapy (IMRT/VMAT) techniques has been shown to be feasible in the PORTEC-3 and GOG-258 trials.[237] The prescription dose is typically 45 to 50.4 Gy in 25 to 28 fractions over five weeks.

The CTV should be individualised when there is a positive resection margin, pelvic peritoneal disease or vaginal involvement. An integrated or sequential EBRT boost should be delivered to any residual lymph node disease, sites of extracapsular nodal spread and positive lateral resection margins with a total dose of 55-65 Gy $EQD2_{10}$.

8.4.2 Vaginal brachytherapy

The clinical target volume is usually the upper third (minimum 3 cm) of the vagina to a depth of 5 mm (both superiorly and halfway along the active length). The HDR brachytherapy dose is typically 21 in three fractions or 24 Gy in four fractions, normalised to 0.5 cm from the applicator surface, or 8 Gy in two fractions when given following EBRT. A higher dose is required for treatment of residual disease or positive margins.

The treatment planning options are to use a standard library plan for each applicator size and treatment length or to use image-guided adaptive brachytherapy (IGABT). Image-guided adaptive brachytherapy is strongly recommended when there is residual vaginal disease following surgery using similar principles to treatment for recurrent disease.

9 Primary treatment - chemotherapy

Recommendations:

Neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) may be an alternative approach in the treatment of selected patients with advanced EC who are considered poor candidates for primary debulking surgery (PDS). Generally, NACT should be reserved for patients where it would be expected that PDS would not achieve complete macroscopic resection. Prospective studies investigating this approach are strongly recommended. (Grade D)

Carboplatin-paclitaxel is the recommended standard first-line chemotherapy regimen for the treatment of advanced/recurrent endometrial cancer regardless of histologic subtype (Grade A)

Progestogens are a suitable alternative for the treatment of low-grade hormone-receptor positive advanced/recurrent endometrioid endometrial cancer (Grade B)

Patients with advanced/recurrent endometrial cancer should be considered for entry into first-line clinical trials evaluating targeted therapies. (Grade D)

9.1 Neoadjuvant chemotherapy

In those women with stage III-IV EC where there is evidence of substantial extra-uterine spread or significant lymph node metastases at time of primary diagnosis, there is considerable controversy about the optimal management and while primary surgery is offered by many centres, there are now several retrospective cohort studies describing the safe use of NACT in advanced endometrial cancer.[195, 245-247] In the largest series reported by de Lange et al, 102 patients who were deemed not suitable for PDS due to disease extent or poor performance status were included.[245] All patients commenced NACT, 89% received carboplatin-paclitaxel. The response rate to NACT was 76% and 78% underwent IDS with 47% (48/102) having complete cytoreduction. Median OS was 27 months. Outcomes did not differ by histological subtype of endometrial cancer. Other retrospective studies comparing cohorts of women with advanced endometrial cancer who were managed with PDS and adjuvant treatment versus NACT and IDS reported shorter duration of surgery and lower perioperative morbidity in women receiving NACT.

NACT may therefore be considered in selected cases with evidence of disease breaching through the serosa and where there is significant pelvic and para-aortic nodal or peritoneal spread after careful discussion at the MDT.

9.2 Palliative systemic therapy

Historically, doxorubicin-cisplatin doublet chemotherapy had been considered as the standard treatment option for advanced/recurrent endometrial cancer on the basis of Gynecologic Oncology Group (GOG) studies. Subsequently the phase III GOG0177 trial demonstrated that the addition of paclitaxel to doxorubicin-cisplatin (TAP) given with G-CSF support was superior to doublet chemotherapy with a higher response rate and 3-month prolongation in OS.[248] However, this triplet regimen is associated with substantial toxicity, which limited its adoption in routine UK clinical practice. In response to these concerns regarding toxicity and promising phase II efficacy of carboplatin-paclitaxel (CT), the GOG conducted the GOG0209 trial, a randomised phase III non-inferiority comparison between TAP and CT in women with stage III/ IV or recurrent chemotherapy-naïve endometrial cancer.[249] 1381 women were enrolled and after a median follow up of 124 months, the trial met its primary non-inferiority endpoint for OS (CT 37 months versus 41 months TAP; HR 1.002, 90% CI 0.90 to 1.12). In those patients with measurable disease at trial entry, the RECIST response rate was 52% in both treatment arms. Subgroup analyses by treatment effect showed no significant differences by FIGO stage, age, prior RT or presence/ absence of measurable disease. Heterogeneity of effect was seen by histologic subtype. Patients with Grade 1 endometrioid endometrial cancer had superior outcome with CT, although no differences were seen between treatment arms for other histological subtypes including grade 3 endometrioid and serous carcinomas. CT was better tolerated with less grade 2 sensory neuropathy, grade 3 thrombocytopenia, vomiting, diarrhoea and metabolic abnormalities reported. Quality of life outcomes also favoured CT. This trial definitively establishes carboplatin-paclitaxel as the standard-of-care first-line chemotherapy for advanced/recurrent endometrial cancer of all histologic subtypes. Phase II trial data also support the use of CT as first-line therapy for advanced/ recurrent uterine carcinosarcoma.[250]

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. Clinical trial data regarding endocrine therapy is heterogeneous and there is a lack of large randomised studies. 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%.[251] The likelihood of response was higher in women with oestrogen or progesterone receptor-positive disease although many studies did not report hormone receptor status or define a standardised methodology or cut-off for defining positive disease. While the OS reported in most was less than one year, some women will get long-lasting disease control with endocrine therapy. Progestogens, such as Medroxyprogesterone acetate (200 mg once daily) are considered the most appropriate first-line endocrine therapy [252] although alternatives, such as tamoxifen or aromatase inhibitors [253] can be considered, particularly in patients at high risk of vascular complications with progestogen therapy.

While conventional cytotoxic chemotherapy and endocrine therapy have clinically meaningful efficacy for many women with advanced or recurrent endometrial cancer, improving the effectiveness of first-line systemic therapy is a key priority. Many promising targeted therapies, informed by our rapidly advancing knowledge of the molecular biology of endometrial cancer, are undergoing evaluation in clinical trials. These include immunotherapeutic approaches, HER2-targeted drugs in serous endometrial cancer and combined CDK4/6 inhibitors and aromatase inhibition in hormone-receptor positive tumours. It is recommended that open clinical trials should be discussed actively with potentially eligible patients.

10 Primary Treatment - radiotherapy

Definitive radiotherapy can be considered for unresectable locally advanced disease and no evidence of distant metastases. This comprises EBRT to the pelvis followed by image-guided brachytherapy. Concurrent chemotherapy may be considered to enhance the radiation effect although the evidence base for concurrent chemotherapy is weaker than that for cervical cancer. Brachytherapy should boost sites of macroscopic disease in the uterus, parametrium or vagina using GEC-ESTRO principles. [254, 255]

11 Management of recurrent disease

Recommendations:

Patients with recurrent endometrial cancer should be managed by MDTs with expertise in the management of recurrent cancers (Grade D).

All patients should undergo baseline cross-sectional imaging (Grade B).

Where possible, a biopsy, for re-assessment of oestrogen and progesterone receptor status and molecular profile, should be considered. (Grade D)

All patients who are candidate for surgical resection or radiotherapy should undergo PET-CT scan to exclude multisite disease (Grade B).

Approximately 7% of patients with stage 1-2 EC recur within three years and half of these recurrences are located in the pelvis.[256-258] Survival is largely dependent on the site of recurrence: patients with isolated vaginal vault recurrence have a 73% 3-year overall survival versus 14% for those with distant recurrence.[257] Management of patients with endometrial cancer recurrence depends on the site of recurrence, previous treatment received and the fitness and wishes of the patient.

Patient groups according to previous treatment:

- Radiotherapy pre-treated patients
- Radiotherapy naïve patients

Sites of recurrence:

- Locoregional
  - Isolated vaginal vault
  - Pelvic
- Oligometastatic – mainly nodal

- Peritoneal carcinomatosis
- Distant – lung, liver
- Multisite

The management of patients with recurrent uterine cancer is challenging and should only be carried out by MDTs with expertise in management of recurrent gynaecological cancers. Surgery, radiotherapy including stereotactic radiation, chemotherapy, targeted therapy and hormonal therapy should be considered in each case, or if such expertise is not available, second opinion from expert cancer centres should be sought.

11.1 Work up prior to treatment for recurrent disease

The treatment of recurrent endometrial cancer is often challenging due to the sites of relapse, the age of the patient and long-term effects of prior therapy. In particular, the input from palliative care physicians should be sought as many patients either have symptoms from their cancer, or are likely to experience symptoms following salvage therapy or further disease progression in the future.[259] Biopsy from the recurrence should be considered for routine pathology assessment and confirmation of oestrogen and progesterone receptor status, as these may differ from the results from the primary cancer.[1] All patients should have their MMR deficiency status established.[16]

All patients should undergo a CT of the thorax, abdomen and pelvis as first line radiological investigation. If surgical resection or targeted radiotherapy is planned for unifocal or oligo-metastatic recurrence, an MRI-scan and PET-CT scan should be considered to exclude multisite recurrence and help to determine resectability. Based on recent meta-analyses of studies evaluating the utility of PET/CT in relapsed endometrial cancer, PET/CT has a sensitivity of 95%, and specificity of 92%. It is not clear if PET/CT is equally sensitive and specific in all subtypes.[260, 261]

11.2 Treatment of recurrent disease

These guidelines are intended for patients with all types of recurrent epithelial tumours including carcinosarcoma. Patients with recurrent uterine sarcoma should be managed according to sarcoma guidelines (see section 12.1.2).

11.2.1 Locoregional recurrence

Recommendations:

Patients with isolated vaginal recurrence who are radiotherapy naïve should be considered for radical radiotherapy. (Grade B)

Patients with isolated vaginal vault recurrence, who have received pelvic/vault radiotherapy previously, should only be considered for surgery, if resection is achievable with clear margins (Grade D)

Relapse that on CT scanning appears to be confined and amenable to radical therapy, particularly, if exenteration is considered, should be staged using a PET/CT scan prior to starting radical therapy. (Grade C)

For patients treated surgically for pelvic recurrence, those with positive margins/residual disease, post-operative radiotherapy or brachytherapy should be considered, if normal tissue tolerance allows. (Grade D)

Radiotherapy naïve patients

Patients with single site pelvic recurrence, particularly those with vaginal vault disease can be considered for treatment with curative intent.[262] Isolated vaginal recurrence in patients who have not received prior radiotherapy can effectively be treated with salvage radiotherapy. Long-term follow-up of stage 1 patients with mostly adenocarcinoma in the PORTEC trial showed that in the observation only arm, radiotherapy achieved an 89% complete response rate and a 65% 5-year survival. This compares

to a 5-year survival rate of 43% in previously irradiated patients, which was no different to those patients who experienced distant metastases.[257]

In retrospective series, radiotherapy seems to be better than surgery in this setting.[256] The size of tumour at recurrence may help select patients more suited to salvage radiotherapy, with the most commonly suggested cut-off being 2 cm.[263, 264] Surgery with or without radiotherapy is a viable alternative, only in highly selected patients, when complete resection is possible.[265]

There are no good data to support the use of radiotherapy as consolidation therapy for resection margins involved with microscopic disease (R1); however, this practice seems sensible, if normal tissue tolerance allows, given the poorer prognosis conferred by the R1 resection margin.[266]

Radiotherapy pre-treated patients

Recommendations:

Pelvic exenteration can be considered for patients with single-site, central pelvic recurrence and is performed with the aim to achieve margins clear of microscopic disease. (Grade D)

Following local therapy for recurrence, additional chemotherapy is of uncertain benefit, but can be considered. (Grade D)

Patients with vaginal recurrence, who have received previous radiotherapy have a poorer prognosis (43% 5-year survival).[257] In this clinical scenario, surgical resection is the first choice in fit patients, if complete resection of the recurrence is feasible. The type of surgery depends on the site and extent of the recurrence and includes vaginal vault resection, partial cystectomy, pelvic exenteration.[262, 267, 268] Pelvic exenteration is considered for a patient with single-site, central pelvic recurrence and is performed with the aim to achieve margins clear of microscopic disease. When pelvic exenteration is planned as a curative procedure on carefully selected patients, up to 72% 5-year overall survival has been reported in highly selected cohorts.[268] Surgical resection of vaginal or pelvic sidewall

recurrences are challenging procedures due to previous radiotherapy and patients' comorbidities, and therefore should be performed by specialist centres with experience in surgery for recurrent disease in a pre-irradiated field.

The need for postoperative chemotherapy or hormonal treatment should be decided upon histopathological features, such as the surgical margin status, nodal status, presence of LVSI. Patients who are unfit or not feasible for surgical resection should be considered for palliative stereotactic radiotherapy, chemotherapy or hormonal treatment.

11.2.2 Oligometastatic recurrence

Patients with up to five sites of metastatic disease, confirmed on PET-CT scan, could be considered for radical topical treatment, either targeted radiotherapy or surgical resection, with or without subsequent systemic treatment.[1] A disease-free interval of >6 months and good performance status are suggested requirements prior to consideration of radical treatment for metastatic disease. The most common metastatic sites are para-aortic or pelvic lymph nodes, liver and lung. Results from small studies on stereotactic ablative radiotherapy (SABR) in patients with recurrent gynaecological cancers are promising with good response rates. In a phase 2 clinical trial, 61% response rate was achieved for oligometastatic recurrence of gynaecological cancers.[269] Other studies on patients with recurrent gynaecological cancers (including cervical cancers with central pelvic, pelvic sidewall or para-aortic recurrence only) identified tumour volume (>24-30 cm^3) being an independent adverse prognostic factor.[270, 271]

For bulky retroperitoneal nodal recurrences, surgical resection may be an effective treatment strategy. Although the evidence is weak from small, single institutional studies, at high risk of selection and publication bias, all studies concur that complete resection of disease results in favourable survival.[272, 273] A study of 27 patients with recurrent endometrial cancer reported a 43-month median disease-specific survival on those receiving optimal resection, whilst another study of 67 cases showed an estimated 5-year progression-free survival of 42 and 17% in optimally and suboptimally cytoreduced patients, respectively.[274, 275]

11.2.3 Multi-site recurrence

Patients with multisite peritoneal and/or extra-abdominal recurrences should be considered for palliative systemic treatment and should ideally be referred to the palliative care team for help with symptom control, alongside active treatment. The role of secondary cytoreductive surgery is not clear in this setting, as most case series have combined patients with unifocal, oligometastatic disease and peritoneal carcinomatosis.

First-line systemic anticancer therapy

Recommendation:

Chemotherapy-naïve patients who relapse with systemic disease or those who relapse more than 6 months after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel. (Grade A)

Fit patients with disseminated recurrent disease should be offered systemic therapy. The standard of care is combination chemotherapy with carboplatin AUC 5-6 and paclitaxel 175 mg/m^2, which showed equivalent efficacy but less toxicity to the more intensive three-arm combination of cisplatin, doxorubicin and paclitaxel.[276] Pegylated liposomal doxorubicin (e.g. Caelyx® 30 mg/m^2) can be combined with carboplatin in fit patients, and has also been used followed by carboplatin/paclitaxel with acceptable toxicity.[277]

Other agents also have activity in this setting (doxorubicin, cisplatin, paclitaxel, cyclophosphamide,[278] although generally single agent chemotherapy is less effective than doublet chemotherapy.[248, 279, 280]

PD-1/PD-L1 inhibitors have shown very good activity in second-line therapy (see second-line systemic therapy below); there is no reason to believe that they would not be active, and potentially superior to

chemotherapy, in first line treatment. At present, they are not licensed for first line treatment, but may be available depending on local funding arrangements. Ongoing randomised trials are evaluating the efficacy of combining chemotherapy with a checkpoint inhibitor for advanced and recurrent endometrial cancer.

Second-line and other systemic treatment options

Recommendations:

For patients who relapse more than 6 months after carboplatin and paclitaxel, further platinum-based chemotherapy can be considered. [Grade C]

For patients who relapse less than 6 months after carboplatin and paclitaxel, there is no treatment that could be considered standard of care. (Grade D)

Patients requiring second-line systemic therapy should be offered PD-1/PD-L1 inhibitors if the cancer is mismatch repair deficient, or carries a *POLE* mutation, or has a high tumour mutational burden. (Grade B)

A greater than 6 months treatment-free interval after carboplatin and paclitaxel suggests further possible benefit from a re-challenge with the same drugs. Other platinum doublets, e.g. with pegylated liposomal doxorubicin 30 mg/m^2 or gemcitabine 1000 mg/m^2 may also provide useful clinical benefit [281], but potential toxicities have to be taken into account in an individualised approach (see also hormonal therapy below).

For progression within six months of prior chemotherapy, or relapse within six months of adjuvant carboplatin and paclitaxel, response rates with second line chemotherapy are disappointing, but pegylated liposomal doxorubicin at a dose of 40-50 mg/m^2 has been used with good palliation in some patients even if the response rate (9.5%) and overall survival (8.4 months) are modest.[282] Topotecan at a dose of 0.5 to 1.5 mg/m^2/day given for five days every three weeks produces a response rate of

9% and a maximal response duration of 6.9 months, at a cost of 60% grade 4 neutropoenia.[283] The use of weekly paclitaxel at 60-80 mg/m^2 is only supported by anecdotal evidence; based on the useful activity in ovarian cancer and its good tolerability, it is an option for selected patients. It has been used as the standard arm in two clinical trials in second line uterine cancer treatment; neither has reported yet.[284, 285]

Trials with targeted therapies have shown promising results in patients with advanced or recurrent endometrial cancer. Patients with recurrent MMRd endometrial cancer had a 57% response rate to pembrolizumab 200 mg, an anti-programmed cell death protein 1 (PD-1) agent in a Phase II trial with a median progression-free survival of 26 months.[286] Similarly, in the GARNET trial, dostarlimab produced a 42% objective response rate in 71 patients.[287]

Single agent anti PD-1/PD-L1 therapies have had limited efficacy for tumours with proficient mismatch repair protein expression. The combination of pembrolizumab and lenvatinib was initially studied as third-line therapy in a phase II clinical trial with a response rate of 64% observed in patients with MSI–high tumours and 36% in 11 patients with microsatellite-stable cancers (n = 11).[288]. This combination has been confirmed to have significant activity in the phase III KEYNOTE 775 trial which randomised between the combination of pembrolizumab and lenvatinb versus investigator's choice of single agent chemotherapy. The results presented in abstract form reported the overall survival was 18.3 months in the combination arm versus 11.4 months with chemotherapy, while progression free survival was 7.2 versus 3.8 months.[289]

As the driving feature for response appears to be phenotypes with a high tumour mutational burden,[290] triggered by either MMRd, *POLE*mut, or other mechanisms, patients exhibiting any of these features in their tumour should be offered inhibitors of the PD-1/PD-L1 system where these are funded.[39]

Hormonal treatment

Recommendation:

Hormonal therapy can be the first choice in those with low grade, hormone receptor positive, disease. Selected cases with long disease-free interval, well-differentiated tumours, lung only metastases and high progesterone receptor expression in the tumour may be candidates for primary hormonal therapy. (Grade C)

Hormonal treatment (progestogens, selective oestrogen receptor modifiers, aromatase inhibitors) has a variable response rate (5 to 50%) in the management of recurrent endometrial cancers, although a Cochrane review did not identify any survival benefit.[291, 292] Although the response rate is highest in grade 1 endometrioid carcinomas, poorly differentiated cancers can also respond (38% versus 22%).[293] Expression of oestrogen receptor is correlated with response to hormonal treatment, though progesterone receptor expression did not have such correlation [294]. Trials with tamoxifen 20-40 mg daily showed similar survival (8.8 months) but lower response rates (10.3%).[295] Likewise, aromatase inhibitors have disappointing response rates (7-9%), the overall survival for letrozole and anastrozole are of a similar magnitude as for other hormonal agents, with 8.8 months and 7 months, respectively, and a clinical benefit rate of 44%.[253, 296, 297]

Standard treatment is progesterone (medroxyprogesterone acetate 200 mg or megestrol acetate 160 mg daily). An alternating regime of megestrol acetate (MA) 80 mg twice daily for three weeks, followed by tamoxifen 20 mg twice daily for three weeks to upregulate progesterone receptors, may improve outcomes compared to MA alone with response rates of 27% and a median overall survival of 14 months at the cost of slightly more grade 3/4 side effects.[291, 293] In view of the venous thromboembolic (VTE) complications associated with progesterone or tamoxifen, VTE preventive measures should be considered. Although phase II studies on aromatase inhibitors in recurrent endometrial cancer showed rather modest partial response rates (7-9%), the recent PARAGON trial demonstrated clinical benefit in 44% of patients with ER/PR positive recurrent endometrial cancers.[253, 296, 297]

12 Management of uterine sarcoma

Recommendations:

Standard treatment for all localised uterine sarcomas is total hysterectomy and bilateral salpingectomy. Lymphadenectomy for staging purposes is not indicated. (Grade C)

Patients with low grade endometrial stromal sarcoma should not have post-operative hormone replacement therapy. Use of adjuvant anti-oestrogen therapy is not routinely indicated. (Grade D)

Adjuvant pelvic radiotherapy has not been shown to improve local control or survival, and is not routinely indicated in FIGO stage I and II uterine sarcoma. However, it could be considered for selected high-risk cases. (Grade B)

Advanced/ metastatic uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma are treated systemically with the same drugs as soft tissue sarcomas at other sites. Gemcitabine and docetaxel may be particularly useful for LMS. (Grade B)

Advanced/ metastatic endometrial stromal sarcoma can be treated with anti-oestrogen therapy, with an aromatase inhibitor or progestogen. (Grade D)

Patients with sarcoma should be treated with involvement of sarcoma multidisciplinary teams. (Grade D)

The majority (~ 75%) of sarcomas arise from the soft tissue and these soft tissue sarcomas (STS) represent around 80 histological entities, with even more molecular subtypes, characterised by a low incidence in all populations. Uterine STS is rare, accounting for only 2% of all gynaecological cancers, hence there is a paucity of high-quality evidence to guide management of these patients. Evidence from trials and guidelines for other STS is often adopted.[298] Individual patient treatment recommendations

should be directed by MDTs, including involvement of sarcoma MDTs, and where possible patients should be considered for appropriate clinical trials. For FIGO staging of endometrial sarcomas, see Table 7.

Uterine sarcomas include leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS) and uterine adenosarcoma. The World Health Organisation (WHO) classifies endometrial stromal sarcomas into five distinct categories: endometrial stromal nodule (ESN); low-grade endometrial stromal sarcoma (LG-ESS); high-grade endometrial stromal sarcoma (HG-ESS); undifferentiated endometrial sarcoma (UES); and uterine tumour resembling ovarian sex cord tumour (UTROSCT) (see Table 11).[299, 300] Uterine carcinosarcomas (previously known as malignant Mullerian Mixed Tumours) are considered as epithelial cancers and their management are not considered here.

12.1 Leiomyosarcoma (LMS)

Recommendations:

The cornerstone of management of early uterine leiomyosarcoma (uLMS) is total hysterectomy +/- bilateral salpingectomy. (Grade D)

Oophorectomy in young women is not mandatory. (Grade D)

Routine pelvic lymphadenectomy is not recommended. (Grade D)

Morcellation of fibroids should be avoided in peri- and postmenopausal women. (Grade D)

Limited data do not support the use of adjuvant chemotherapy or radiotherapy in uLMS. (Grade D)

Patients with advanced or recurrent LMS are usually offered chemotherapy unless complete surgical resection is possible. (Grade D)

Management of patients with primary or recurrent leiomyosarcoma requires an MDT approach preferably with discussion with the regional sarcoma team. (Grade D)

Uterine leiomyosarcomas (uLMS) account for 1% of all uterine malignancies and 35-40% of all uterine sarcomas, and therefore are the most common type of gynaecological sarcomas.[301-303] uLMS is commonly diagnosed postoperatively as a result of hysterectomy or myomectomy for presumed benign uterine pathologies.[304] However, although rapidly growing pelvic masses can be a sign of uterine sarcoma, Parker et al., in their series of patients undergoing hysterectomy for a rapidly growing uterus found only one uLMS out of 371 women.[305]

Leiomyosarcoma has a poor prognosis with recurrence rate of up to 70% and overall 5-year survival for all stages of 39%.[306] Survival is greatly dependent on the stage of disease, with a reported five-year survival of 95%, 45%, 48%, 18% for stage I, II, III and IV, respectively.[307] Mitotic index, age are also important prognostic factors.[308]

12.1.1 Early stage leiomyosarcoma

Surgery

Leiomyosarcoma is usually a postoperative diagnosis after hysterectomy or myomectomy.[304, 309] If the diagnosis is known or suspected prior to surgery, extrafascial total abdominal hysterectomy is the cornerstone of the management. Ovarian metastases are uncommon (2%) in early stage (I-II), therefore oophorectomy in young women is not mandatory.[310, 311] Independent predictors of disease specific survival in patients with uLMS included age, race, stage, grade, and primary surgery. Oophorectomy was not found to have an independent impact on survival in a large series of 1396 patients from the SEER database.[311]

Systematic pelvic lymphadenectomy for staging purposes is not routinely recommended, as the incidence of lymph node involvement is low (6.6%) [311] and lymph node dissection has not been

shown to be associated with any survival benefit.[306] Debulking of enlarged lymph nodes should be considered for reduction of disease burden, if acceptable surgical morbidity.

Women who had a supracervical hysterectomy due to presumed benign fibroids, should be offered reoperation for cervical excision and removal of any potential visible disease in the pelvis and consideration of BSO in perimenopausal and menopausal women.

Morcellation

Recent studies reported rates of incidental malignancy in morcellated uterine fibroids higher than previously expected. Wright et al in their study of 36,470 patients who underwent morcellation found uterine cancer in 0.27% of the cases.[312] Depending on the modelling methodology used, the estimated prevalence of uterine sarcoma was 1 in 305 to 1 in 360 women, and for leiomyosarcoma, the estimated prevalence was 1 in 570 to 1 in 750 women.[313] A meta-analysis demonstrated that uterine fibroid morcellation increased the overall (62% vs. 39%) and intra-abdominal (39% vs. 9%) recurrence rates as well as death rate (48% vs. 29%).[314] In one cohort study, morcellation was associated with a three-fold increase of recurrence (HR 3.18, 95% CI 1.5 to 6.8) and shorter survival (10.8 months versus 39.6 months; P = 0.002).[315] In women aged 50 years and over, the FDA does not support the use of laparoscopic power morcellators for myomectomy.[316] Due to the low incidence of sarcomas in presumed benign fibroids in low-risk women, and the benefits of minimal invasive surgery, several techniques have been described to reduce the risk of sarcoma cells in the event of occult malignancy at use of a morcellator. These include mainly placing the fibroid in an waterproof laparoscopic retrieval bag and perform the morcellation after exteriorization through one of the trocars under direct vision.[313]

For women in whom the tumour was morcellated and the diagnosis of a leiomyosarcoma was made in retrospect, surgical exploration and staging could be recommended to ensure complete tumour resection, especially when initial surgery was not performed by a gynaecological oncologist. In a small study in patients with no evidence of extrauterine disease at time of surgery, who underwent morcellation and were subsequently diagnosed with uLMS, re-exploration was performed within a

median of 33 days; two of seven patients with presumed early-stage disease had disseminated intraperitoneal malignancy at the time of re-exploration.[317]

Adjuvant treatment for uterine leiomyosarcoma

Recommendations:

The routine use of post-operative radiotherapy is not recommended. It may be considered for selected high-risk cases, such as those with positive surgical excision margins. (Grade B)

Current data support do not support the use of adjuvant chemotherapy in early stage uLMS and the conclusion is that observation is the standard of care for this population. (Grade B)

For women with stage III or stage IV disease who have undergone complete surgical resection and are at high risk of disease recurrence /progression; adjuvant chemotherapy rather than postoperative surveillance could be considered but whether treatment improves PFS or OS survival has not been established. (Grade C)

Adjuvant radiotherapy (RT)

The use of adjuvant RT has no impact on survival outcomes for women with early-stage uLMS. This was demonstrated in an EORTC phase III RCT (EORTC 55874), which enrolled women with stage I and II uterine sarcomas and randomly assigned them to treatment with postoperative RT (51 Gy in 28 fractions over 5 weeks) or observation.[318] Among the 103 women with uLMS, pelvic RT did not result in a significant difference in either local or distant progression rates compared with observation. There was a non-significant trend towards a reduction in overall survival (OS) in the radiotherapy treated group (hazard ratio for survival 0.64, 95% CI 0.36 to 1.14). The routine use of post-operative radiotherapy is not recommended; however, it may be considered for selected high-risk cases such as those with positive surgical excision margins.

Adjuvant chemotherapy

There is a paucity of data around the use of adjuvant chemotherapy in early stage uLMS, the following studies have been reviewed:

Doxorubicin

The GOG conducted a phase III trial in 156 women with stage I or II uterine sarcoma (all histologies including uLMS) who were randomly assigned treatment with postoperative doxorubicin versus observation.[319] The adjuvant doxorubicin had no impact on PFS or OS.

Docetaxel and gemcitabine

Fixed-dose-rate gemcitabine (900 mg/m^2 over 90 minutes on days 1 and 8) plus docetaxel (75 mg/m^2 on day 8) administered with hematopoietic growth factor support has been evaluated in a small, single arm (n = 25) in women with completely resected, high-grade uLMS.[320] In women with stage I or II disease, 59% remained progression free at three years (median PFS 39 months). At a median follow-up of 49 months, the two-year PFS rate was 45% and median PFS was 13 months.

In a retrospective cohort study of 111 women with stage I uterine LMS, 33 women treated with adjuvant gemcitabine-docetaxel had a similar risk of recurrence (HR 1.01, 95% CI 0.57 to 1.80, P = 0.97) for recurrence and mortality (HR 1.28, 95% CI 0.69 to 2.36, P= 0.48) compared with the 77 women who did not receive adjuvant chemotherapy.[321] There was little or no difference in the three-year OS rates (59% *vs.*66%).

Docetaxel and gemcitabine followed by doxorubicin

SARC 005 was a prospective, phase II trial that enrolled 47 women with early stage uLMS.[322] All patients received four cycles of fixed-dose-rate gemcitabine plus docetaxel, followed by four cycles of doxorubicin. Treatment compliance was high with 89% percent of women receiving all eight planned cycles. The median time to recurrence was 27 months, and the three-year PFS rate was 57%. The SARC 005 regimen was subsequently tested in a prospective, phase III RCT conducted by the GOG (GOG 277) in collaboration with the EORTC and CRUK.[323] Women who had undergone surgical resection of high-grade FIGO stage I uterine uLMS were randomised to SARC 005 versus observation. The study closed after enrolment of only 38 patients due to slow accrual. Mean survival time for OS

was 34.3 months (95% CI, 25.3 to 43.3 months) in the chemotherapy arm and 46.4 months (95% CI, 43.6 to 49.1 months) in the observation arm and were not suggestive of an improvement with treatment.

12.1.2 Advanced stage or recurrent leiomyosarcoma

Recommendations:

Individualisation of surgical treatment can be considered for patients with limited extrauterine spread and no residual disease is achievable. (Grade C)

For women with metastatic, unresectable recurrent uLMS, who maintain a good performance status palliative chemotherapy should be offered. (Grade C)

In chemotherapy-naïve setting consider single agent doxorubicin as first-line and second line therapy. (Grade B)

Combination of doxorubicin with docetaxel or gemcitabine can be considered. (Grade C)

Beyond first/second line setting the choice among chemotherapy options is based on patient preference, organ function, and performance status. Consider trabectedin in selected patients. (Grade C)

Olaratumab or bevacizumab in combination with doxorubicin is not recommended in recurrent, metastatic uLMS. (Grade B)

Consider the use of aromatase inhibitors -anastrozole and letrozole in women with low volume, indolent uLMS that is ER/PR positive. (Grade D)

Consider appropriate clinical trials. (Grade D)

Surgery

For women with advanced disease, the role of surgery is controversial and whether a patient should be considered for surgery depends on the tumour dissemination of the disease, the resectability and associated morbidity profile. In cases of widespread disseminated disease, surgery has not been shown to be associated with any survival benefit, may delay systemic treatment with negative impact on the overall outcome and should therefore not be recommended.[324, 325] Individualisation of surgical treatment can be considered for patients with limited extrauterine spread and no residual disease at the end of surgery was the most important prognostic factor in these small patient cohorts.[326, 327]

Surgery may be reasonable for palliation in women experiencing significant pelvic symptoms (i.e, pain or vaginal bleeding) not otherwise manageable. For patients with localized recurrences surgical resection may be offered to appropriately selected patients, however, the data supporting this approach are limited.

Adjuvant chemotherapy

Women with stage III or stage IV disease who have undergone macroscopic surgical resection are at high risk of disease recurrence/progression. Adjuvant chemotherapy, rather than postoperative surveillance could be considered, but whether treatment improves PFS or OS survival has not been established. As discussed above, 25 women with stage I including up to stage IV uLMS received docetaxel and gemcitabine in this GOG trial.[320] However, this study lacked a control arm, and it remains unclear whether treatment results in an improvement in survival in the advanced setting. Chemo-radiation as primary non-surgical treatment for women with advanced uLMS remains investigational.

Palliative chemotherapy

In metastatic disease where surgical resection is not indicated, chemotherapy is palliative and can be offered to appropriate patients who are maintaining good performance status and overall organ function. Emphasis should be placed on offering good palliative care in parallel to systemic treatments.

Doxorubicin

Single-agent doxorubicin is an alternative first-line treatment to gemcitabine-docetaxel for metastatic LMS in patients with normal cardiac function. Doxorubicin is also an option for second-line treatment for patients who have already received gemcitabine-docetaxel as first-line treatment. In a randomised phase III trial for metastatic sarcoma (of any histology) fixed-dose-rate gemcitabine-docetaxel was compared to doxorubicin as first-line treatment. Of the 27 women with LMS (all sites) the two regimens were similar with no significant difference in ORR and PFS.[328] Their recommendation was that "Doxorubicin should remain the standard first-line treatment for most patients with advanced soft-tissue sarcoma".

Gemcitabine and docetaxel

In the GOG 87L trial 47 women were treated with fixed-dose rate gemcitabine plus docetaxel.[329] The overall response rate (ORR) was 36% with the major toxicity being myelosuppression with grade 3 or 4 neutropenia seen in 37% of patients. In GOG 131G, 51 patients received this regimen in the second-line setting (90% had doxorubicin in the first line). The ORR was 27% and median progression-free survival (PFS) was 5.6 months (range 0.7 to 27 months).[330]

Gemcitabine/docetaxel and bevacizumab

The GOG 0250 phase III trial investigated the additional of bevacizumab to gemcitabine-docetaxel and results demonstrated no significant improvement in PFS or OS and similar ORR for the triplet to that seen with the chemotherapy alone arm.[331]

Doxorubicin and olaratumab

The addition of olaratumab, a monoclonal antibody against platelet derived growth factor receptor alpha (PDGFα) to doxorubicin demonstrated an improvement in OS in phase II clinical trial over doxorubicin alone.[332] However, the phase III Announce RCT involving over 500 patients, including those with

uLMS, failed to show a benefit.[333] Olaratumab in combination with doxorubicin is not recommended in recurrent, metastatic uLMS.

Trabectedin

Trabectedin, given IV over 24 hrs every three weeks, can be considered for patients with recurrent STS after failure of treatment with anthracyclines. In a cohort of 48 uLMS patients, the ORR with Trabectedin was 59.6%, although this was at the expense of high toxicity, with 78% of patients having G3/4 neutropenia and 24% had G3/4 febrile neutropenia.[334] In a subsequent, randomized, first-line treatment phase II trial, adding the trabectedin to doxorubicin versus doxorubicin alone did not result in any significant difference in ORR or PFS and the combination resulted in significantly more toxicity.[335]

12.1.3 Endocrine therapies

The aromatase inhibitors, anastrozole and letrozole, have been associated with low (<10%) ORR in patients with uLMS.[336] This approach may be an option for selected women with low volume ER/PR positive disease.

12.2 Endometrial stromal sarcoma (ESS)

Recommendations:

Surgical resection of ESS with hysterectomy and bilateral salpingo-oophrectomy is recommended for women with early-stage disease and in more advanced disease where disease is resectable. (Grade C)

Ovarian conservation may be considered in pre-menopausal women with low-grade ESS and does not appear to negatively affect OS, but may increase the risk of recurrence. (Grade C)

Limited data do not support adjuvant chemotherapy or radiotherapy in surgically resected low grade-ESS (Grade D)

Consider hormonal therapies for women with advanced or metastatic LG-ESS. (Grade C)

Endometrial stromal sarcomas (ESS) are a subset of uterine mesenchymal neoplasms that make up approximately 1% of all uterine cancers. They are classified into five distinct categories: endometrial stromal nodule (ESN); low-grade endometrial stromal sarcoma (LG-ESS); high-grade endometrial stromal sarcoma (HG-ESS); undifferentiated endometrial sarcomas (UES); and uterine tumour resembling ovarian sex cord tumour (UTROSCT).

LG-ESS are relatively indolent tumours with good prognosis and a propensity for late recurrences. The majority are ER and PR positive and many are characterised by specific cytogenetic features such as the chromosomal translocation (7;17) with JAZF1-SUZ12, EPC1-PHF1 or JAZF1-PHF1 transcripts [337].

HG-ESS are distinguished by their aggressive behaviour, advanced stage at presentation and poor prognosis. Specific cytogenetic features are (translocation of chromosomes (10;17), with YWHAE-FAM22 transcript.

12.2.1 Early-stage endometrial stromal sarcoma

Surgical treatment

Surgical treatment with total hysterectomy +/- bilateral salpingo-oophorectomy (BSO) is the cornerstone of the treatment of ESS. There is no role for systematic LND for staging purposes, since this has not been associated with any survival benefit.[338, 339]

In view of the hormonal receptor positivity of the tumours, oophorectomy was previously recommended, even in pre-menopausal women. However, national cancer database analysis of OS of patients with LG-ESS who did (n = 490) and did not (n = 191) undergo BSO were 96.2% and 97.1%, respectively (P = 0.05).[340] After controlling for comorbidities BSO was not associated with improved OS survival (HR 1.28, 95% CI 0.51 to 3.19). An earlier systematic review of 17 non-randomised studies, including 786

participants, by the same group found that ovarian conservation was associated with increased recurrence in LG-ESS, but did not have an effect on OS.[341] This recommendation is in line with the 2014 Gynecologic Cancer InterGroup (GCIG) consensus review.[339]

There are limited preliminary data on fertility-sparing approach in young women with ESS after hysteroscopic resection; currently this approach should only be considered within the context of research studies.[342]

Adjuvant treatment for early-stage endometrial stromal sarcomas

LG-ESS

For women with stage I LG-ESS adjuvant treatment is not recommended. For those with stage II-IV disease adjuvant endocrine therapy, using medroxyprogesterone acetate or megestrol acetate could be considered, but evidence to support this approach is based on small retrospective studies only.[343] A systematic review of non-randomised studies did not support adjuvant chemotherapy or radiotherapy for completely resected LG-ESS.[344]

HG-ESS and UES

Both high-grade endometrial stromal sarcoma (HG-ESS) and undifferentiated endometrial sarcomas (UES) have a high risk of recurrence. However, there is no clear evidence that adjuvant systemic therapies or radiotherapy impacts positively on OS over surveillance only. Adjuvant treatment is not recommended in completely resected HG-ESS and UES.

12.2.2 Recurrent or metastatic endometrial stromal sarcoma

Surgical treatment

Surgical resection may be considered in cases where macroscopic resection can be achieved with acceptable morbidity.[344] Selected patients with recurrent LG-ESS and HG-ESS who present with a solitary metastasis could be considered for metastasectomy.

Systemic treatment

LG-ESS

For women who are treatment naïve, endocrine therapy is the primary treatment for recurrent and metastatic LG-ESS. Data to support this are limited to small, largely retrospective studies, but with many patients achieving durable responses in both first- and second-line settings.[345] The following agents have shown activity in recurrent, metastatic LG-ESS: medroxyprogesterone acetate; megestrol acetate; aromatase inhibitors; and Gonadotropin-releasing hormone analogues. The selective oestrogen receptor modulators, e.g. tamoxifen or toremifene, should not be administered to women with LG-ESS due to their partial agonist activity on endometrial stromal cells.[346] Following failure of endocrine therapies cytotoxic chemotherapies can be offered as per evidence for uLMS, although data are limited.

HG-ESS and UES

Palliative chemotherapy should be offered to appropriate patients who have good performance status and overall organ function. Emphasis should be placed on offering good palliative care in parallel to systemic treatments. Data to guide chemotherapy choices are limited and often evidence is from STS trials of multiple histology types. The recommendations for these patients are similar to those patients with metastatic or recurrent uLMS (see section 12.1.2). Participation in clinical trials should be encouraged.

12.3 Uterine adenosarcoma

Recommendations:

Surgical treatment with hysterectomy and BSO is recommended. (Grade D)

Routine lymphadenectomy is not recommended, as for other uterine sarcomas. (Grade C)

The role of adjuvant treatment for adenosarcoma is unclear and cannot be recommended. (Grade D).

Data for treatment of recurrent/advanced disease is very limited, are based on treatment for LG-ESS and uLMS, depending on presence of sarcomatous overgrowth, and patients should be considered for clinical trials, where available. (Grade D)

12.3.1 Management of early-stage uterine adenosarcomas

Uterine adenosarcomas are mixed tumours, composed of benign glandular and low grade sarcomatous stromal components. The majority of women present with early-stage disease (80% stage I) with good prognosis.[347] Uterine adenosarcoma with sarcomatous overgrowth, however, is a high-risk sarcoma with >25% high grade sarcomatous component and with poor prognosis (median overall survival of 55.4 months compared to 112.4 months for patients with no sarcomatous overgrowth).[347] Another case series found that 2-year PFS and OS rates were both 20% in those with sarcomatous overgrowth versus 100% for without sarcomatous overgrowth.[348]

Surgery

Due to its low prevalence, there are no high-quality, evidence-based treatment strategies available for uterine adenosarcoma, although for early-stage disease, total hysterectomy with BSO is usually performed.[348] Standard treatment for all localised uterine sarcomas is total hysterectomy and bilateral salpingectomy. Lymphadenectomy for staging purposes is not indicated.

Adjuvant treatments for early stage uterine adenosarcoma

The role of adjuvant radiation, chemotherapy, or endocrine therapy for the treatment of adenosarcoma is unclear and adjuvant therapies cannot be recommended.

Management of recurrent, metastatic uterine adenosarcoma

For patients with recurrent uterine adenosarcoma, secondary cytoreduction could be considered for patients who are fit enough for major surgery and have disease amenable to surgical resection.[348] Given the poor prognosis of this group of patients, regardless of treatment, this would need to be carefully considered. For inoperable localised recurrence salvage radiotherapy may be an option.

For patients with metastatic adenosarcoma without sarcomatous overgrowth, endocrine therapy with similar approach to LG-ESS can be considered, but data is very limited. For metastatic adenosarcomas with sarcomatous overgrowth, consider chemotherapy as per uLMS (see section 12.1.2) However, there is no consensus on which chemotherapy to use and patients where possible should be offered clinical trials.

13 Follow up after treatment

13.1 Follow-up for endometrial cancer

Recommendations:

Individualised follow-up strategies, including patient-led follow-up and telephone follow-up, should be considered once treatment is complete, following a holistic needs assessment. These should stratify patients by anticipated risks of recurrence, side effects of treatment and take into account patient or local factors. (Grade D)

Alternative modes of follow-up, such as telephone follow-up, do not appear to be inferior to hospital follow-up, in terms of quality of life for stage I endometrial cancer. (Grade B)

Follow-up should focus on detecting potentially treatable recurrences, such as isolated vaginal vault tumour, in women who could tolerate salvage radiotherapy or exenterative surgery. (Grade D)

Women should receive information on symptoms that should prompt urgent review. (Grade D)

The organisation of clinics should include continuity of care, address survivorship issues and prescribe in advance the frequency and purpose of follow-up. (Grade D)

Routine follow-up to detect recurrence can be discontinued in women not considered fit for any further treatment after discussion with the patient and appropriate links with community palliative support established where needed. (Grade D)

Evidence does not support the use of routine imaging or biochemical testing in follow-up for endometrial cancer. (Grade D)

Follow-up describes the continued care of women after EC treatment. Traditionally patients have been followed up in face-to-face hospital clinics for 5 years following their diagnosis of endometrial cancer). In 2008-2009, there were over 80,000 gynaecology oncology follow-up hospital appointments in England [349]. The primary aim is to detect and treat recurrences early, although there is no evidence that attending clinic-based follow up improves survival.[350-355] Moreover, there is evidence that traditional follow-up may not meet the physical and psychological needs of cancer survivors.[356] Women often find examinations uncomfortable and have heightened levels of anxiety prior to routine appointments.[357]

The National Cancer Survivorship Initiative (NCSI) with the charity Macmillan Cancer Support are driving improvements in cancer survivorship towards more self-management based on individual

needs.[358] The British Gynaecology Cancer Society (BGCS) have published guidelines on patient-led follow-up (PLFU) in all gynaecological malignancies [359] in line with the National Cancer Survivorship Initiative (NCSI) through NHS improvement that have implemented stratified pathways in breast, colorectal and prostate cancer.[360] These guidelines stratify patients according to their risk for recurrence and advise appropriate follow-up pathways.

PLFU requires the patient to call the gynaecological oncology team directly with worrying symptoms, such as vaginal bleeding, weight loss, persistent abdominal pain or worsening bladder or bowel habit. These symptoms should be detailed in an End of Treatment (EOT) summary which should be discussed with the patient as they move to PLFU. A copy of the EOT summary should also be sent to the GP. Use of PLFU is increasing across the UK, particularly in patients with low-risk EC.[361, 362] Telephone follow-up has also been shown to be non-inferior to clinic-based follow-up regarding psychological and social outcomes in low-risk EC and could be used as part of follow-up pathways.[360] Table 12 shows some important criteria patients must meet prior to offering PLFU.

13.2 Technique

Identifying vaginal vault disease requires visual inspection of the vagina. Tumour breaching the vagina may be visible and can be detected by a trained health care practitioner. There is no prodromal atypia and therefore vault cytology is inappropriate.[355] There is no evidence to suggest that general practitioners, hospital consultants, nurse colposcopists or trained nurse specialists have better outcomes. Continuity of care may be associated with greater satisfaction and nurse specialists. Pelvic side wall and central recurrent disease may be identified by bimanual vaginal examination, rectal examination or ultrasound.

13.3 Stratified follow up

The traditional practice of seeing all women at three to four monthly intervals for two years, followed by annual visits, is not evidence-based. Advocates of intensive clinical follow-up suggest that early

detection of disease is important, particularly as most women have not had adjuvant treatment and are salvageable, if disease is confined to the vault. However, only a small minority of patients will develop recurrent disease and the majority of those will present with vaginal bleeding between clinic appointments.[363] Studies show that routine follow-up may delay presentation with symptoms.[363, 364]

Suggested risk-stratified follow-up strategies are outlined in Table 12 and the reader is referred to the BGCS PIFU guidelines for further details.[359]

Patients with low-risk EC can be offered PIFU (if they fulfil the general eligibility criteria) at the end of their treatment. Patients with intermediate-risk EC commonly offered vaginal brachytherapy, without external beam radiotherapy, following their hysterectomy.[365] They are therefore more likely to suffer from treatment related side effects than patients with low-risk EC. If this is the case then patients should be seen and assessed in clinic for their treatment related side effects. However, these patients still have a low risk of recurrence and can therefore be offered patient initiated follow up at the end of their treatment, if they fulfil eligibility criteria.

For those with intermediate-risk (who decline vault brachytherapy), high-intermediate-risk, high-risk or advanced EC at presentation follow-up should be recommended. A systematic review designed to inform the Canadian healthcare system on optimum follow-up strategies for EC reviewed 16 non comparative observational studies.[355] Survival graphs show that most of the deaths from high grade disease occur within the first two years, although well differentiated tumours and adjuvant radiotherapy are associated with much longer remission intervals. This implies that follow-up appointments should be most frequent in the first 24 months for high grade tumours. Systems to calculate individualised recurrence rates, sites and timing based on all the risk factors of age, lymphovascular space invasion, node status, and adjuvant therapy are being developed. A study on the effect of follow-up on overall survival is ongoing.

Patients with high-intermediate risk EC have a 20% chance of recurrence [366] mostly within the first two years after treatment [364] and should be seen for clinic-based follow-up for two years. However,

patients could be offered PIFU after two years, as the chance of recurrence after this time is low at less than 7%.[364]

13.4 Eliciting symptoms at follow-up

Recommendations:

Women should have an opportunity to address their symptoms attributable to their cancer and its management after completion of treatment. (Grade D)

Women who have received brachytherapy should have a vaginal examination and dilation therapy advised, if they are clinically at risk of vaginal stenosis, or if they have an intention in the future of having penetrative sex. (Grade D)

The first follow up visit after hysterectomy with curative intent offers an opportunity to ask about symptoms attributable to cancer and the consequences of treatment. It would be reasonable to ask women who have not had radiotherapy about the following: sexual function; fatigue; body image; pain; urinary function; vaginal bleeding; leg swelling; menopause symptoms; work, finances; and anxieties about recurrence. These can be elicited using a semi-structured clinical enquiry or a formal written assessment tool, according to local practice.

Women who have also had external beam radiotherapy should have additional regular enquiries about: defecation frequency (to consider loperamide or alternative); bleeding from the rectum; stools that float (to assess fat malabsorption); weight loss (to assess malabsorption); diarrhoea (to assess the risk of radiation colitis and malabsorption); rectal urgency and incontinence (to consider physiotherapy); haematuria, bladder urgency and capacity (to consider anticholinergics); vaginal dryness and dyspareunia (to consider vaginal lubricant) (See section 14.2 for further information).

13.5 Follow-up for uterine sarcomas

The evidence-base to inform the optimal follow up strategy for patient with uterine sarcoma is lacking. As early detection of recurrence with the aim of complete surgical resection is the only effective way of managing recurrent sarcoma, most soft-tissue sarcoma guidelines recommend regular CT scans and physical examination.[367]

14 Supportive care

Recommendations:

All patients should have a named keyworker to co-ordinate treatment and their care pathway and be given the contact details in a format they can understand. (Grade D)

Written information should be provided about treatment choices and side effects including late effects. (Grade D)

Prevention, identification and management of complications, late effects and quality of life issues following a cancer of the uterus diagnosis and treatment are essential part of personalised care. (Grade C)

Access to a CNS or equivalent and psycho-sexual counsellors should be available as part of the multi-disciplinary team. (Grade C)

The limited available evidence for hormone replacement therapy following treatment for FIGO stage I-II EC does not suggest significant harm. (Grade B)

Patients who develop lymphoedema should be referred to specialist lymphoedema services for assessment and management. (Grade C)

Patients with signs of radiation-induced enteropathy should have access to care from a team of professionals who may include oncologists, gastroenterologists, bowel surgeons, therapeutic radiographers, dieticians and specialist nurses. (Grade D)

Patients with troublesome urinary symptoms after treatment should have access to specialist continence services for assessment, diagnosis and conservative treatment. (Grade D)

Patients should be counselled regarding the increased risk and symptoms of pelvic insufficiency fractures and neuropathies (chemotherapy-induced peripheral neuropathy and radiation-induced lumbosacral plexopathy). (Grade D)

This section provides information on supportive care needs of patients following diagnosis and treatment of uterine cancer, with the aim of promoting access to personalised care, including holistic needs assessment (HNA), a care plan and health and wellbeing information and support in line with the NHS Long Term Plan [96] and Macmillan's guidance on providing personalised care for people living with cancer.[368] It includes information on prevention, identification and management of complications, late effects and quality of life issues aiming to guide/signpost the reader to agencies/services that provide appropriate intervention and support for the patient and their family if needed.

Patients should have the opportunity to address symptoms attributed to their cancer and its management before, during and after treatment. Predictable side-effects are dependent on treatment modality. Both physiological and psychosocial factors can impact on quality of life. Addressing possible and actual problems as they arise may help to reduce the negative impact experienced by patients. It is good practice to talk about symptoms that could be attributed to cancer and the consequence of treatment and this should also be addressed at each follow-up appointment or through holistic needs assessment.[368]

Patients should receive appropriate information so they are aware and informed of the relevant risks of short- and long-term side-effect during the consenting process, this should be recorded on the consent

form. Good quality information is available from both Macmillan and Eve Appeal charities which the patient can source themselves or be given in clinic.

- https://www.macmillan.org.uk/cancer-information-and-support/womb-cancer
- https://eveappeal.org.uk/wp-content/uploads/2018/07/The-Eve-Appeal-Womb-Cancer-Guide-Web.pdf
- https://be.macmillan.org.uk/be/p-25188-pelvic-radiotherapy-in-women-managing-side-effects-during-treatment.aspx
- https://be.macmillan.org.uk/be/p-25340-managing-the-late-effects-of-pelvic-radiotherapy-in-women.aspx

14.1 Clinical nurse specialist (CNS) support and holistic needs

Patients should have access to expertise and support, for the vast majority of patients this will be the CNS. The CNS is pivotal in ensuring that the patient has access to personalised care as in *The NHS Long Term* Plan.[96] The reader is referred to this document for further information but this includes:

- Personalised Care and Support Planning
- End of Treatment Summaries
- Primary Care Cancer Care Review
- Health and Wellbeing Information and Support

CNSs are well placed to ensure appropriate assessment takes place to ensure high-quality person-centred experience. Working alongside patients and utilising available tools to identify holistic needs will support focused conversations to promote individualised care.[369]

14.1.1 Psychosocial

The impact of cancer and treatment can affect quality of life, the psychosocial needs of patients should be addressed throughout. HNA should be performed at pivotal points in the cancer pathway. Patients

should have the opportunity to explore ways of improving their quality of life through appropriate support and signposting to living with and beyond cancer services, and psychological services where available.

14.1.2 Sexuality/sexual morbidity

Factual information on possible changes due to surgery, radiotherapy or chemotherapy should be given to the patient prior to treatment. This will acknowledge that the subject of sexuality is open should she need to seek further information, if difficulties occur.[370]

It should be remembered that treatments do not always result in higher risk of sexual dysfunction, especially minimally invasive approaches.[371, 372] However, the risk increases with addition of radiotherapy, up to 81% patients reporting sexual dysfunction [373] and the use of vaginal dilation therapy (using vaginal dilators or vibrators) following radiotherapy should be recommended to reduce the risk of stenosis.[374]

Assessment tools/patient reported outcome measures (PROMS) can help to identify sexual difficulties, promote discussions and management of sexual issues.[375] If sexual difficulties are present these should be addressed and where possible specific suggestions given, e.g. use of lubrication during intercourse or a course of vaginal oestrogen.[376] Where available, patients with ongoing difficulties should be referred to psychosexual services.

14.1.3 Hormone replacement therapy (HRT) following treatment for endometrial cancer

Most women with early-stage EC will be cured of their cancer and life-expectancy for many is good, making longer-term quality of life (QoL) issues important. Menopausal symptoms can significantly affect QoL for many women. A Cochrane review of HRT for women previously treated for endometrial cancer found one study with 1236 participants who had FIGO stage I-II EC.[377] It was difficult to draw firm conclusions, due to the very low-certainty of the evidence, however, rate of tumour recurrence was not significantly different during the 36-month follow-up (2.3% in the oestrogen arm versus 1.9% receiving

placebo (RR 1.17, 95% CI 0.54 to 2.50). This would align with results of several studies and a systematic review of ovarian preservation in pre-menopausal women with early-stage EC [378-384]. The risk of developing breast cancer was low (one woman in the HRT arm (0.16%) versus three in the placebo arm (0.49%) (RR 0.80, 95% CI 0.32 to 2.01; very low-certainty evidence). The study did not report on symptom relief, OS or PFS for HRT versus placebo. However, 94.3% in the HRT group had no evidence of disease versus 95.6% and 95.8% of women were alive at the end of follow-up in the HRT group versus 96.9% in the placebo group.[377] They concluded that, although the RCT-level evidence was limited, “The available evidence (both the single RCT and non-randomised evidence) does not suggest significant harm”. Management of menopausal symptoms after a gynaecological malignancy are reviewed in.[385]

14.1.4 Lymphoedema

Risk of developing lymphoedema depends on surgical intervention and increases in patients who have radiotherapy and/or lymphadenectomy. Studies vary incidence from 0 to 50% there are other factors that increase this risk, such as raised BMI, congestive cardiac failure and other co-morbidities.[386-390] Prophylactic information on reducing the risk of lymphoedema should be available to patients (http://www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/lymphoedema) and those who develop lymphoedema should be referred to specialist lymphoedema services for assessment and management of this condition.[391]

14.2 Management of late effects of treatment

Late effects are often permanent and progressive and can manifest many years after treatment completion. Patients (and their GPs) should be made aware that they can be seen in a clinic to investigate late effects, as well as potential recurrences.[392]

Late side effects are dependent on treatment modality and potentially pre-existing morbidities.[393] The PORTEC trial series showed that combined modalities and external beam radiotherapy (EBRT) lead to a greater burden of late effects than more localised treatments.[216, 237, 394-396] Almost three-quarters (72%) of all endometrial cancer patients survive ten or more years after diagnosis in the

UK, extending far beyond conventional follow-up periods.[397] Management and information for patients and GPs must therefore encompass those patients beyond formal follow-up programmes, legacy patients treated many years prior, and those on PIFU.

Consequences of endometrial cancer and its treatment and can include, but are not limited to, effects on gastrointestinal and genitourinary systems, bone pain/insufficiency fractures and nerve damage, sexual morbidity and lymphoedema.

- https://be.macmillan.org.uk/Downloads/CancerInformation/ResourcesForHSCP/InformationResources/MAC14942GYNAEGUIDEWEB.pdf;
- https://www.prda.org.uk/

14.2.1 Gastrointestinal (GI) late effects

Patients with signs of radiation-induced enteropathy should have access to care from a team of professionals who may include oncologists, gastroenterologists, bowel surgeons, therapeutic radiographers, dieticians and specialist nurses. GI effects from radiotherapy can include faecal urgency, diarrhoea, leakage, rectal bleeding, malabsorption syndromes, ileus/obstruction and small bacterial overgrowth. Data are not adequate to define how many patients experience permanent GI changes post gynaecological cancer treatments.[398]

In a Cochrane review there were no high-quality data to support the use of prophylactic interventions to reduce GI toxicity from pelvic radiotherapy.[399] Interventions suggested include dietary, improved delivery of radiotherapy with IMRT and pharmacotherapies. In terms of management, identification is the first challenge and patients should be asked if there are any new problems relating to bowel function. For patients on PIFU, using validated tool to assess symptoms, such as EORTC PRT23 [400] or ALERT B [401] is recommended good practice.[402]

GI symptoms following pelvic cancer treatment are complex and multifactorial and may be due to causes unrelated to the cancer or its treatment. They should be managed in a sequential manner using a validated algorithm.[398, 403] Initial management may involve simple lifestyle advice and medicines,

such as loperamide for diarrhoea and dietary changes for constipation. A Cochrane review of non-surgical options, including sucralfate for rectal bleeding look promising, but the quality of evidence remains very low.[404] More complex and persistent problems warrant referral to specialist services. A small study showed Sacral Nerve Stimulation (SNS) can improve faecal incontinence following pelvic radiotherapy without increased complication rates.[405]

- https://www.macmillan.org.uk/_images/practical-management-gi-symptoms-pelvic-radiation-disease_tcm9-300557.pdf;
- https://www.macmillan.org.uk/cancer-information-and-support/treatment/types-of-treatment/radiotherapy/pelvic-radiotherapy/managing-bowel-problems-after-pelvic-radiotherapy.

14.2.2 Urinary tract late effects

Women following diagnosis and treatment of EC have higher levels of urinary system disorders than the general population between 1 and 5 years (HR 1.64, 95% CI 1.50 to 1.78) and >5 to 10 years (HR 1.40, 95% CI 1.26 to 1.56).[406] Stricture, contraction, obstruction, inflammation, impaired pelvic floor function and detrusor over-activity are potential consequences of treatment. High grade toxicities appear to be rare in EC patients and increased age and raised BMI may be predictive of urinary late effects.[407]

Urinary incontinence is common, affecting up to 40% of the UK female population and becoming more prevalent with age and post-menopause.[408] It is therefore important to establish a baseline for urinary function prior to any treatment although there is no recommendation or guidance defining the best validated tool to use.[409] At follow up ask if there are any new problems relating to bladder function. Improved delivery of radiotherapy treatments to spare structures of the urinary system can reduce late effects,[409] however, there are no common guidelines for the delineation of the lower urinary tract in radiotherapy [410] and evidence for pharmacological interventions are lacking.

Treatment for increased urinary frequency, urgency and stress incontinence include coping strategies, absorbent containment products, pelvic floor muscle re-education and bladder retraining.[411]

Conservative pharmacotherapies and treatments such as anti-muscarinics and bladder instillations are preferable, as surgical interventions have high failure rates due to tissue ischaemia.[412, 413] Complex problems such as fistulae, haematuria and radiation induced interstitial cystitis require intervention from urology specialists, including National Radiation Cystitis Clinic at Guy's & St Thomas's Hospital. Hyperbaric oxygen therapy may have some benefits for late radiation cystitis.[414]

- https://www.macmillan.org.uk/cancer-information-and-support/treatment/types-of-treatment/radiotherapy/pelvic-radiotherapy/managing-bladder-problems-after-pelvic-radiotherapy.

14.2.3 Management of pelvic insufficiency fractures (PIF)

Pelvic radiotherapy significantly increases the risk of pelvic insufficiency fractures (PIF) in older women.[415] PIF occur under normal stresses on bones weakened by external beam radiotherapy. Recent meta-analyses of patients with gynaecology cancers treated with pelvic radiotherapy reported PIF rates of between 7.8% to 15.3%, developing 7 to 39 months post-treatment and the majority occurring within 2 years.[416-418] Pain is the main reported symptom, although up to 40% may be asymptomatic.[418] Patients should be made aware that pelvic pain, pain on weight bearing and immobility are signs of PIF.[418] MRI images are useful to diagnose PIF and exclude bone metastases.[419]

Pre-treatment screening for PIF risk factors, including bone density measurements, fracture risk assessment tool, age >65, low BMI (<20 kg/m^2), history of fragility fracture, oral corticosteroid use and smoking history are probably warranted in post-menopausal gynaecological cancer patients.[417, 420] Evidence for interventions to prevent PIF (including calcium and vitamin D supplementation, bisphosphonate therapies, or denosumab) are sparse and warrant further investigation.[421] Strategies to prevent fractures in these patients, such as the use of IMRT, may benefit this largely postmenopausal population at significant risk of PIF, but data are not conclusive.[417, 418] Conservative management for PIF includes rest, pain management and physiotherapy-led exercise for stable fractures.

- https://www.macmillan.org.uk/_images/endocrine-late-effects_tcm9-340519.pdf;

- https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/bone-health/pelvic-insufficiency-fractures.

14.2.4 Management of neuropathy and lumbosacral plexopathy

Chemotherapy-related neuropathy grade 2+ persists in 6% of patients 3 to 5 years after treatment for high-risk endometrial cancer.[396] Radiation-induced lumbosacral plexopathy (RILP) is an under-reported late effect of pelvic radiotherapy, it is a rare event, but potentially increasing with improved survival rates.[422, 423] Defining and avoiding the lumbosacral plexus during radiotherapy planning and delivery may reduce doses and late consequences.[424, 425] Patients with RILP present with bilateral lower limb pain, numbness, weakness, paresis or paralysis.[425] MRI may be useful to rule out recurrence and aid the diagnosis of RILP.[426] Management is limited to supportive care, as neurological damage is irreversible and there are currently no effective therapies.

15 Research priorities

Future areas of research:

Prevention and screening

- Individual risk scores for endometrial cancer, combining genetic and environmental factors.
- Risk factors specific to TCGA subtype.
- Can increased inherited cancer risk be identified in healthy women?
- Intentional weight loss, including bariatric surgery, as a means of endometrial cancer prevention
- Is endometrial cancer screening in high-risk women effective/beneficial?
- Chemoprophylaxis against endometrial cancer in high-risk women.

Diagnosis

- Development of new screening technologies that are less invasive/enable home testing.
- Better methods for risk-stratification of post-menopausal bleeding.
- The introduction of automated processes in diagnosis.
- The application of artificial intelligence in the diagnosis of endometrial cancer.
- Can the immune microenvironment facilitate endometrial cancer diagnosis, direct adjuvant treatments and inform prognosis?
- The identification of serum diagnostic biomarkers.

Treatment

- Prognostic role of micro-metastases and isolated tumour cells in sentinel lymph node biopsy (SLNB).
- Survival and quality of life outcomes of SLNB versus lymphadenectomy and/or no lymph node sampling.
- Indications for adjuvant chemotherapy and radiotherapy based on molecular profiling.
- The efficacy of targeted treatments, such as checkpoint inhibitors or PARP inhibitors in endometrial cancer.

- The impact of robotic surgical techniques on overall and disease-free survival.
- The role of cytoreductive surgery in advanced endometrial cancer.
- In those who wish to maintain their fertility, what parameters would predict effective hormonal therapy?
- Fertility-sparing treatments and longer-term pregnancy and cancer outcomes.
- In those who are unfit for surgery, what is the role for radiotherapy and/or hormonal treatments?
- Agreed protocols for monitoring those undergoing non-surgical treatment for endometrial cancer.
- The impact of intra-uterine manipulators on survival outcomes
- Intentional weight loss, including bariatric surgery, as a means of endometrial cancer treatment
- Role of proton therapy in endometrial cancer.
- Use of genomics in endometrial cancer to target treatment.
- Timing of systemic and surgical treatments in more advanced disease (neoadjuvant, adjuvant or a combination).

Survivorship

- Risks and benefits of hormone replacement therapy after treatment for endometrial cancer.
- Treatments to improve sexual function after treatment for endometrial cancer.
- How can co-existing co-morbidities be optimised to reduce all-cause mortality in endometrial cancer?
- Interventions to reduce the psychological morbidity of endometrial cancer survivorship.

16 Glossary

AUC – area under the curve

BGCS – British Gynaecological Cancer Society

BSO – bilateral salpingo-oophorectomy

CI – confidence interval

CNS – clinical nurse specialist

CRUK – Cancer Research UK

CT – computerized tomography (or carboplatin-paclitaxel chemotherapy or chemotherapy depending on context)

DFS – disease-free survival

EBRT – external beam radiotherapy

EC – endometrial cancer

EORTC - European Organisation for Research and Treatment of Cancer

EOT – end of treatment

ER – oestrogen receptor

ESN - endometrial stromal nodule

ESS – endometrial stromal sarcoma

ET – endometrial thickness

FDG - F-19 Deoxyglucose

FFS – failure-free survival

FIGO – International Federation of Gynaecological Oncology

GI – gastrointestinal

GOG – Gynecologic Oncology Group

HG – high grade

HR – hazard ratio

HRT – hormone replacement therapy

LAVH – laparoscopic assisted vaginal hysterectomy

LG – low grade

LNG-IUS – levonorgestrel intrauterine system

LR – likelihood ratio

IDS – interval debulking surgery

IMRT – intensity-modulated radiation therapy

MA – megestrol acetate

MDT – multidisciplinary team (or SMDT – specialist multidisciplinary team)

MMRd – Mismatch repair deficiency

MPA – medroxyprogesterone acetate

MRI – Magnetic resonance imaging

MSI – microsatellite instability

NACT - Neoadjuvant chemotherapy

NICE - National Institute Health and Care Excellence

NNT – number needed to treat

ORR – objective response rate

OS – overall survival

PARPi – Poly (ADP-ribose) polymerase inhibitor

PD-1 - programmed death 1 pathway

PD-L1 - Programmed death ligand 1

PDS – primary debulking surgery

PET-CT - Positron emission tomography-computed tomography

PFS – progression-free survival

PIF - pelvic insufficiency fractures

PLFU – patient-led follow-up

PLND – pelvic lymph node dissection/lymphadenectomy

POLE - polymerase epsilon catalytic subunit

PPALND – pelvic and para-aortic lymph node dissection/lymphadenectomy

PR – progesterone receptor

PROMS - patient reported outcome measures

RA – Robotic assisted surgery

RCT – randomised control trial

RFS – recurrence-free survival

RH – robotic hysterectomy

RILP - Radiation-induced lumbosacral plexopathy

RR – risk ratio

RT – radiotherapy

SABR – stereotactic ablative radiotherapy

SEER - Surveillance, Epidemiology, and End Results

SLNS/SLNB – sentinel lymph node sampling/ sentinel lymph node biopsy

SNS - Sacral Nerve Stimulation

STS – soft tissue sarcoma

TAH – total abdominal hysterectomy

TAP – paclitaxel, doxorubicin and cisplatin combination chemotherapy

TLH – total laparoscopic hysterectomy

TVU/TVS – trans-vaginal ultrasound scan

UES - undifferentiated endometrial sarcomas

USS – ultrasound scan

UTROSCT - uterine tumour resembling ovarian sex cord tumour

VBT – vaginal brachytherapy

VMAT - Volumetric Modulated Arc Therapy

17 Declared Conflicts of Interest

JM – Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Review Group Coordinating Editor - institutional funding by infrastructure and programme grant from National Institute for Health Research. Institutional funding from Public Health England SW Immunisation and Screening Team seed funding for quality improvement project. Unpaid advisory roles: Cochrane Council Co-Ed representative; NHS Cervical Screening Research Advisory Committee; NIHR Evidence Synthesis Research Advisory Committee; Deputy Editor in Chief to *The Obstetrician and Gynaecologist* Journal.

JB- No conflict of interest declared.

LB – GSK advisory board member.

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JG - Clinical Advisor to Femcare-Nikomed UK; legal expert opinion in criminal and medical negligence cases; Editor in chief to European Journal of Obstetrics and Gynecology.

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MPN- No conflict of interest declared.

NR - Honoraria from GlaxoSmithKline for an educational lecture for oncology trainees; Committee Member, Blair Bell Academic Committee, Royal College of Obstetrics and Gynaecology.

AW – Travel grant from AstraZeneca; trial monitoring group advisory board member for Keynote B21 Trial for Merck Sharp Dome.

AT – Travel grant from Merck

18 Appendices

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias 1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias 1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal 2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3 Non-analytical studies, e.g. case reports, case series
4 Expert opinion

Table 1 - Classification of evidence levels

Strength	
A	At least one meta-analysis, systematic reviews or RCTs rated as 1++ and directly applicable to the patient population or A systematic review of RCTs or a body of studies rated as 1+ directly applicable to the patient population and demonstrating consistency of results.
B	Evidence from Level 2++ studies directly applicable to the patient population or extrapolated from level 1 studies
C	Evidence from Level studies 2+ directly applicable to the patient population or extrapolated evidence from studies rated as 2++.
D	Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+

Table 2 – Grade of recommendations

TCGA Group	Somatic copy number alterations	Mutation rate (Mb)	Bokhamn type	Histology	Grade	Prognosis	Driver genes
POLE	-	200 x 10^6	I	Endometrioid	High	Good	Mixed
Microsatellite instability	+	20 x 10^6	I	Endometrioid	High and Low	Intermediate	*MLH1, MSH2, MSH6, PMS2*
Copy number low	++	2 x 10^6	I	Endometrioid	Low	Intermediate to poor	*PTEN/PI3k, KRAS, ARID1a, CTNNB1*
Copy number high	+++	2 x 10^6	I & II	Non-Endometrioid	High	Poor	*p53*

Table 3 A summary of the molecular subgroups of EC identified by The Cancer Genome Atlas Research

Step 1	Do an immunohistochemistry (IHC) 4-panel test for MLH1, MSH2, MSH6 and PMS2	If the MSH2, MSH6 or isolated PMS2 immunohistochemistry results are abnormal, confirm Lynch syndrome by genetic testing of germline DNA.
Step 2	If the IHC results for MLH1, or MLHI and PMS2 , are abnormal, use *MLH1* promoter hypermethylation testing to differentiate sporadic and Lynch syndrome-associated endometrial cancer	
Step 3	If the *MLH1* promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.	

Table 4 NICE guidance for steps in the immunohistochemistry testing strategy for Lynch Syndrome in endometrial cancer (adapted from [16])

Risk group	2014 ESMO-ESGO-ESTRO Consensus	2020 ESGO-ESTRO-ESP Guidelines	
		Molecular classification unknown	Molecular classification known
Low	· Stage IA endometrioid +low grade* +LVSI negative	· Stage IA endometrioid + low-grade* + LVSI negative or focal	· Stage I-II *POLE*mut endometrial carcinoma, no residual disease · Stage IA MMRd/NSMP endometrioid
Intermediate	· Stage IB endometrioid + low grade* + LVSI negative	· Stage IB endometrioid + low-grade* + LVSI negative or focal · Stage IA endometrioid + high-grade* + LVSI negative or focal · Stage IA non-endometrioid** without myometrial invasion	· Stage IB MMRd/NSMP endometrioid carcinoma + low-grade* + LVSI negative or focal · Stage IA MMRd/NSMP endometrioid carcinoma + high-grade* + LVSI negative or focal · Stage IA p53abn and/or non-endometrioid** without myometrial invasion
High-intermediate	· Stage IA endometroid + high grade*, regardless of LVSI status · Stage I endometrioid + low grade* + LVSI unequivocally positive, regardless of depth of invasion	· Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion · Stage IB endometrioid high-grade*, regardless of LVSI status · Stage II	· Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion · Stage IB MMRd/NSMP endometrioid carcinoma high-grade*, regardless of LVSI status · Stage II MMRd/NSMP endometrioid carcinoma
High	· Stage IB endometrioid + high grade* regardless of LVSI status · Stage II · Stage III endometrioid with no residual disease · Stage I-III non-endometrioid** with no residual disease	· Stage III-IVA with no residual disease · Stage I-IVA non-endometrioid** with myometrial invasion, and with no residual disease	· Stage III-IVA MMRd/NSMP endometrioid carcinoma with no residual disease · Stage I-IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease · Stage I-IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced	· Stage III with residual disease · Stage IVA	· Stage III-IVA with residual disease	· Stage III-IVA with residual disease of any molecular type
Metastatic	· Stage IVB	· Stage IVB	· Stage IVB of any molecular type

*** As per binary FIGO classification (Grade 1/2 = low; Grade 3 = high); ** includes serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed**

Table 5 – Prognostic risk groups in endometrial cancer – adapted from [1]

Stage	Stage grouping	FIGO Stage	Stage description*
I	T1 N0 M0	I	Tumour confined to corpus uteri (cervical gland involvement allowed but excludes cervical stromal invasion) (T1).
IA	T1a N0 M0	IA	No or less than 50% myometrial invasion (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	T1b N0 M0	IB	Invasion equal to or more than 50% of the myometrium (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	T2 N0 M0	II	Tumour invades cervical stroma, but it has not spread beyond the uterus (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
III	T3 N0 M0	III	Local and/or regional spread of tumour(T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	T3a N0 M0	IIIA	Tumour invades the serosa of the corpus uteri and/or adnexae (T3a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIB	T3b N0 M0	IIIB	Vaginal and/or parametrial involvement (T3b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIC1	T1-T3 N1, N1mi or N1a M0	IIIC1	Tumour confined to uterus (including serosa)/cervix/adnexae (T1 to T3). Metastases to pelvic lymph nodes (N1, N1mi, or N1a), but not to para-aortic nodes or distant sites (M0).
IIIC2	T1-T3 N2, N2mi or N2a M0	IIIC2	Tumour confined to uterus (including serosa)/cervix/adnexae (T1 to T3). Metastases to para-aortic lymph nodes (with or without pelvic node involvement) (N2, N2mi, or N2a), but not distant sites (M0).
IVA	T4 Any N M0		Tumour invasion of bladder and/or bowel mucosa (T4). It may or may not have spread to lymph nodes (Any N), but has not spread to distant sites (M0).
IVB	Any T Any N M1	IVB	Distant metastases, including to inguinal lymph nodes, intra-abdominal metastases, or to organs away from the uterus, such as the lungs, liver, or bones (M1). The cancer can be any size (Any T) and it might or might not have spread to other lymph nodes (Any N).

*The following additional categories are not listed above:

- TX: Main tumour cannot be assessed due to lack of information;
- T0: No evidence of a primary tumour;
- NX: Regional lymph nodes cannot be assessed due to lack of information.

Positive cytology should be reported separately without changing the stage as above.

Table 6 - FIGO Endometrial Carcinoma Staging 2018 (incorporating TMN classification) [127]

Stage		Definition
Leiomyosarcomas and endometrial stromal sarcomas		
I		Tumour limited to uterus
	IA	Less than 5 cm
	IB	More than 5 cm
II		Tumour extends beyond uterus, within pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumour invades abdominal tissues (not just protruding into abdomen)
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV		
	IVA	Tumour invades bladder and/or rectum
	IVB	Distant metastasis
Adenosarcomas		
I		Tumour limited to uterus
	IA	Tumour limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to 50% myometrial invasion
	IC	More than 50% myometrial invasion
II		Tumour extends beyond uterus, within pelvis
	IIA	Adnexal involvement
	IIB	Tumour extends to extrauterine pelvic tissue
III		Tumour invades abdominal tissues (not just protruding into abdomen)
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV		
	IVA	Tumour invades bladder and/or rectum
	IVB	Distant metastasis
Carcinosarcomas Stage as per carcinoma of endometrium (see **Table 6**)		

Table 7 – FIGO Uterine Sarcoma Staging 2018 [427]

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 8 - Histologic Types of endometrial carcinoma, according to WHO 2020 [117]

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

Table 9 - Grade of endometrial carcinoma, according to WHO 2020 [117]

Low risk	No adjuvant treatment
Intermediate risk	Vaginal brachytherapy Surveillance is an option • <60 yrs • polyp only
High-intermediate risk	External beam radiotherapy +/- VBT • particularly for no nodal staging, extensive LVSI or Stage II Vaginal brachytherapy is an option if node negative Consider chemotherapy only if no nodal staging and extensive LVSI
High risk	EBRT +/- VBT Chemotherapy with carboplatin and paclitaxel

Table 10 – Summary of adjuvant treatment in early-stage disease adapted from [1]

Mesenchymal tumours	
Leiomyosarcoma (LMS)	
Endometrial stromal tumours (ESS)	Low-grade endometrial stromal sarcoma (LG-ESS)
	High-grade endometrial stromal sarcoma (HG-ESS)
	Undifferentiated Endometrial sarcoma (UES)
	Uterine tumour resembling ovarian sex cord tumours (UTROSCT)
Miscellaneous	rhabdomyosarcoma
	Perivascular epithelioid cell tumour
Mixed Tumours	
Adenosarcoma	
Carcinosarcoma	Regarded an epithelial tumour and should be treated as such

Table 11 The WHO classification of uterine sarcomas adapted from [300]

General eligibility criteria for Patient-initiated Follow-up (PIFU)
Completed primary treatment for a gynaecological malignancy and are clinically well
Patients should be willing and able to access healthcare if on PIFU
Patients should be without significant treatment related side-effects that need ongoing management
Patients should not have recurrent disease
Patients should not be on active or maintenance treatment
Patients should not be on a clinical trial where follow-up schemes are defined and limited to hospital-based follow up
Patients should not have a rare tumour with uncertain risk of recurrence and need for ongoing management
Patients must be able to communicate their concerns without a significant language barrier or psychological comorbidity and have competence to agree to PIFU

Table 12 General principles for patient-initiated follow-up (PIFU) in endometrial cancer. Adapted from [359]

Endometrial Cancer	Clinic-based FU	Telephone FU +/- blood test	PIFU
Low risk (<10% risk of recurrence ROR)	If patient declines PIFU (for maximum of 2 years from end of treatment)	If patient declines PIFU (for maximum of 2 years from end of treatment)	Offer from end of treatment (after Holistic needs assessment at 3 months)
Intermediate risk	Can be offered if declines PIFU for 2 years from end of treatment	Can be offered if declines PIFU for 2 years from end of treatment	offer from end of treatment or after 2 years for all
High-intermediate risk	For 5 years (either telephone FU or clinic FU)	For 5 years (either telephone FU or clinic FU)	offer from 2 years from end of treatment in place of telephone FU or clinic FU.
High-risk	For 5 years (either telephone FU or clinic FU)	For 5 years (either telephone FU or clinic FU)	offer from 2 years from end of treatment in place of telephone FU or clinic FU.

Table 13 Risk stratification for patient-initiated follow-up (PIFU) in endometrial cancer. Adapted from [359]

19 References

1. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39.
2. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L A, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. . CA Cancer J Clin. 2021;68(6):394-424.
3. Cancer Research UK. Uterine Cancer Statistics. [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-One.
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and endometrial cancer. . 2018.
5. Moss EL, Morgan G, Martin AP, Sarhanis P, Ind T. Surgical trends, outcomes and disparities in minimal invasive surgery for patients with endometrial cancer in England: a retrospective cohort study. BMJ Open. 2020;10(9):e036222.
6. Njoku K, Barr CE, Hotchkies L, Quille N, Wan YL, Crosbie EJ. Impact of socio-economic deprivation on endometrial cancer survival in the North West of England: a prospective database analysis. BJOG. 2020.
7. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.
8. Cancer Genome Atlas Research N, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
9. Crosbie EJ, Ryan NAJ, Arends MJ, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21(10):2390-400.
10. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? Cancer Prev Res (Phila). 2011;4(1):1-5.
11. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-12.
12. Ryan NAJ, Glaire MA, Blake D, Cabrera-Dandy M, Evans DG, Crosbie EJ. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 2019;21(10):2167-80.
13. Ryan NAJ, McMahon R, Tobi S, et al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. PLoS Med. 2020;17(9):e1003263.
14. Ryan NA, Donnelly L, Stocking K, Evans DG, Crosbie EJ. Feasibility of Gynaecologist Led Lynch Syndrome Testing in Women with Endometrial Cancer. J Clin Med. 2020;9(6).
15. Snowsill TM, Ryan NAJ, Crosbie EJ. Cost-Effectiveness of the Manchester Approach to Identifying Lynch Syndrome in Women with Endometrial Cancer. J Clin Med. 2020;9(6).
16. National Institute for Health and Care Excellence. NICE Diagnostics Guidance [DG42]. Testing strategies for Lynch syndrome in people with endometrial cancer; 28 October 2020; https://www.nice.org.uk/guidance/dg42/resources/testing-strategies-for-lynch-syndrome-in-people-with-endometrial-cancer-pdf-10538078291892020.
17. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372(26):2509-20.
18. Tashiro H, Blazes MS, Wu R, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res. 1997;57(18):3935-40.
19. Levine RL, Cargile CB, Blazes MS, van Rees B, Kurman RJ, Ellenson LH. PTEN mutations and microsatellite instability in complex atypical hyperplasia, a precursor lesion to uterine endometrioid carcinoma. Cancer Res. 1998;58(15):3254-8.
20. Velasco A, Pallares J, Santacana M, et al. Loss of heterozygosity in endometrial carcinoma. Int J Gynecol Pathol. 2008;27(3):305-17.
21. Mutter GL, Lin MC, Fitzgerald JT, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.
22. Lane DP. Cancer. p53, guardian of the genome. Nature. 1992;358(6381):15-6.

23. Goldstein I, Marcel V, Olivier M, Oren M, Rotter V, Hainaut P. Understanding wild-type and mutant p53 activities in human cancer: new landmarks on the way to targeted therapies. Cancer Gene Ther. 2011;18(1):2-11.
24. Ito K, Watanabe K, Nasim S, et al. Prognostic significance of p53 overexpression in endometrial cancer. Cancer Res. 1994;54(17):4667-70.
25. Geisler JP, Geisler HE, Wiemann MC, Zhou Z, Miller GA, Crabtree W. p53 Expression as a Prognostic Indicator of 5-Year Survival in Endometrial Cancer. Gynecologic oncology. 1999;74(3):468 - 71.
26. Moreno-Bueno G, Hardisson D, Sarrio D, et al. Abnormalities of E- and P-cadherin and catenin (beta-, gamma-catenin, and p120ctn) expression in endometrial cancer and endometrial atypical hyperplasia. J Pathol. 2003;199(4):471-8.
27. Kurnit KC, Kim GN, Fellman BM, et al. CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. Modern Pathology. 2017;30(7):1032 - 41.
28. Liu Y, Patel L, Mills GB, et al. Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma. J Natl Cancer Inst. 2014;106(9).
29. Crosbie E, Morrison J. The emerging epidemic of endometrial cancer: Time to take action. Cochrane Database Syst Rev. 2014(12):ED000095.
30. Gao C, Wang Y, Broaddus R, Sun L, Xue F, Zhang W. Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. Oncotarget. 2018;9(4):5492-508.
31. Kitson SJ, Bafligil C, Ryan NAJ, et al. BRCA1 and BRCA2 pathogenic variant carriers and endometrial cancer risk: A cohort study. Eur J Cancer. 2020;136:169-75.
32. Lee YC, Milne RL, Lheureux S, et al. Risk of uterine cancer for BRCA1 and BRCA2 mutation carriers. Eur J Cancer. 2017;84:114-20.
33. Thompson D, Easton DF, Breast Cancer Linkage C. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358-65.
34. de Jonge MM, Auguste A, van Wijk LM, et al. Frequent Homologous Recombination Deficiency in High-grade Endometrial Carcinomas. Clin Cancer Res. 2019;25(3):1087-97.
35. Vermij L, Smit V, Nout R, Bosse T. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020;76(1):52-63.
36. De Felice F, Marchetti C, Tombolini V, Panici PB. Immune check-point in endometrial cancer. Int J Clin Oncol. 2019;24(8):910-6.
37. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11(1):3801.
38. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res. 2019;25(13):3753-8.
39. Musacchio L, Boccia SM, Caruso G, et al. Immune Checkpoint Inhibitors: A Promising Choice for Endometrial Cancer Patients? J Clin Med. 2020;9(6).
40. Wiggans AJ, Cass GK, Bryant A, Lawrie TA, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2015(5):CD007929.
41. Dedes KJ, Wetterskog D, Mendes-Pereira AM, et al. PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. Sci Transl Med. 2010;2(53):53ra75.
42. Gentry-Maharaj A, Karpinskyj C. Current and future approaches to screening for endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2020;65:79-97.
43. Long B, Clarke MA, Morillo ADM, Wentzensen N, Bakkum-Gamez JN. Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: Systematic review and meta-analysis. Gynecol Oncol. 2020;157(3):624-33.
44. Breijer MC, Peeters JA, Opmeer BC, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2012;40(6):621-9.
45. van Hanegem N, Prins MM, Bongers MY, et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2016;197:147-55.
46. Ryan NAJ, McMahon RFT, Ramchander NC, Seif MW, Evans DG, Crosbie EJ. Lynch syndrome for the gynaecologist The Obstetrician & Gynaecologist 2021;23:9-20.
47. Dominguez-Valentin M, Sampson JR, Seppala TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25.

48. Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. JAMA oncology. 2017;3(12):1702-6.
49. Ryan N, Nobes M, Sedgewick D, Teoh SN, Evans DG, Crosbie EJ. A mismatch in care: results of a United Kingdom-wide patient and clinician survey of gynaecological services for women with Lynch syndrome. BJOG. 2020.
50. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Correction to: Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther. 2018;35(4):590.
51. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther. 2018;35(4):577-89.
52. National Institute for Health and Care Excellence. NICE guidelines (NG12) Suspected cancer: recognition and referral. June 2015, update Sep 2020; Available at: https://www.nice.org.uk/guidance/ng12, . 2020.
53. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. 2014;32(21):2255-69.
54. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-88.
55. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol. 2000;18(20):3464-70.
56. Mackintosh ML, Crosbie EJ. Obesity-driven endometrial cancer: is weight loss the answer? BJOG. 2013;120(7):791-4.
57. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010;19(12):3119-30.
58. Renehan AG, Soerjomataram I, Tyson M, et al. Incident cancer burden attributable to excess body mass index in 30 European countries. Int J Cancer. 2010;126(3):692-702.
59. Anveden A, Taube M, Peltonen M, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. Gynecol Oncol. 2017;145(2):224-9.
60. Luo J, Chlebowski RT, Hendryx M, et al. Intentional Weight Loss and Endometrial Cancer Risk. J Clin Oncol. 2017;35(11):1189-93.
61. Ward KK, Roncancio AM, Shah NR, et al. Bariatric surgery decreases the risk of uterine malignancy. Gynecol Oncol. 2014;133(1):63-6.
62. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol. 2015;30(5):397-412.
63. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). Food, nutrition, physical activity, and the prevention of cancer: a global perspective Washington DC: AICR; 2007.
64. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216(6):580 e1- e9.
65. Faculty of Sexual and Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UK-MEC 2016). London, UK; 2016.
66. Jareid M, Thalabard JC, Aarflot M, Bovelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. Gynecol Oncol. 2018;149(1):127-32.
67. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261-9.
68. Dominguez-Valentin M, Crosbie EJ, Engel C, et al. Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. Genet Med. 2020.
69. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med. 2004;350(10):991-1004.

70. Kingsberg SA, Larkin LC, Liu JH. Clinical Effects of Early or Surgical Menopause. Obstet Gynecol. 2020;135(4):853-68.
71. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet. 2020;395(10240):1855-63.
72. Lu KH, Loose DS, Yates MS, et al. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res (Phila). 2013;6(8):774-81.
73. Guidance for the Management of Abnormal Uterine Bleeding in the Evolving Coronavirus (COVID-19) Pandemic. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/2020-05-21-joint-rcog-bsge-bgcs-guidance-for-management-of-abnormal-uterine-bleeding-aub-in-the-evolving-coronavirus-covid-19-pandemic-updated-final-180520.pdf. 2020.
74. National Institute for Health and Care Excellence. NICE guidelines (NG88) Heavy menstrual bleeding: assessment and management; 14 March 2018; https://www.nice.org.uk/guidance/ng88. 2018.
75. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. Br J Obstet Gynaecol. 1995;102(2):133-6.
76. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018;178(9):1210-22.
77. Burton ER, Sorosky JI. Recognition and Therapeutic Options for Malignancy of the Cervix and Uterus. Obstet Gynecol Clin North Am. 2017;44(2):195-206.
78. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. Cost-effectiveness of the use of transvaginal sonography in the evaluation of postmenopausal bleeding. Maturitas. 2003;45(4):275-82.
79. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol. 2003;188(2):401-8.
80. Rossi A, Forzano L, Romanello I, Fachechi G, Marchesoni D. Assessment of endometrial volume and vascularization using transvaginal 3D power Doppler angiography in women with postmenopausal bleeding. Int J Gynaecol Obstet. 2012;119(1):14-7.
81. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. Acta Obstet Gynecol Scand. 2002;81(9):799-816.
82. Timmermans A, Opmeer BC, Khan KS, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(1):160-7.
83. Wong AS, Lao TT, Cheung CW, et al. Reappraisal of endometrial thickness for the detection of endometrial cancer in postmenopausal bleeding: a retrospective cohort study. BJOG. 2016;123(3):439-46.
84. Jones ER, O'Flynn H, Njoku K, Crosbie EJ. Detecting endometrial cancer. The Obstetrician & Gynaecologist. 2021;23(2):103-12.
85. Doll KM, Romano SS, Marsh EE, Robinson WR. Estimated Performance of Transvaginal Ultrasonography for Evaluation of Postmenopausal Bleeding in a Simulated Cohort of Black and White Women in the US. JAMA oncology. 2021;7(8):1158-65.
86. Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998;280(17):1510-7.
87. Ghoubara AA-O, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer. (1364-6893 (Electronic)).
88. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Clinical usefulness of endometrial screening by ultrasound in asymptomatic postmenopausal women. Maturitas. 2004;48(4):421-4.
89. van Hanegem N, Breijer MC, Slockers SA, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. BJOG. 2017;124(2):231-40.
90. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG. 2002;109(3):313-21.

91. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA. 2002;288(13):1610-21.
92. Sainz de la Cuesta R, Espinosa JA, Crespo E, Granizo JJ, Rivas F. Does fluid hysteroscopy increase the stage or worsen the prognosis in patients with endometrial cancer? A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2004;115(2):211-5.
93. Royal College of Obstetricians & Gynaecologists- The distal fallopian tube as the origin of non-uterine pelvic high grade serous carcinomas. Scientific impact paper N0:44, Nov 2014 :2-8. . 2014.
94. NHS Cancer Plan. In: Department of Health, editor. London, UK2000.
95. Cancer Reform Strategy. In: Department of Health, editor. London, UK2007.
96. The NHS Long Term Plan. In: Department of Health and Social Care, editor. 2019.
97. Welsh Government/Llywodraeth Cymru. The quality statement for cancer. Cardiff, UK: Welsh Government/Llywodraeth Cymru; 2021.
98. NHS standard contract for complex gynaecology - specialist gynaecological cancers.

Schedule 2- The Services A. Service Specifications. In: NHS England, editor. 2013.
99. Guidance on Commissioning Cancer Services. Improving Outcomes in Gynaecological Cancers. The Manual. NHS Executive Catalogue No 16149, July 1999.
100. Cook O, McIntyre M Fau - Recoche K, Recoche K. Exploration of the role of specialist nurses in the care of women with gynaecological cancer: a systematic review. (1365-2702 (Electronic)).
101. Macmillan Cancer Support. Cancer Clinical Nurse Specialists. 2015.
102. Buckley L, Robertson S, Wilson T, Sharpless J, Bolton S. The Role of the Specialist Nurse in Gynaecological Cancer. (1534-6269 (Electronic)).
103. Adedayo P, Resnick K, Singh S. Preoperative frailty is a risk factor for non-home discharge in patients undergoing surgery for endometrial cancer. J Geriatr Oncol. 2018;9(5):513-5.
104. Driver JA, Viswanathan AN. Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older. Gynecol Oncol. 2017;145(3):526-30.
105. Martin FE, Kalsi T, Baker H, et al. Functional recovery in older women undergoing surgery for gynaecological malignancies: A systematic review and narrative synthesis. J Geriatr Oncol. 2020;11(7):1087-95.
106. Santhirapala R, Partridge J, MacEwen CJ. The older surgical patient - to operate or not? A state of the art review. Anaesthesia. 2020;75 Suppl 1:e46-e53.
107. Aitken RM, Partridge JSL, Oliver CM, et al. Older patients undergoing emergency laparotomy: observations from the National Emergency Laparotomy Audit (NELA) years 1-4. Age Ageing. 2020;49(4):656-63.
108. Connor JP, Andrews JI, Anderson B, Buller RE. Computed tomography in endometrial carcinoma. Obstet Gynecol. 2000;95(5):692-6.
109. Milam MR, Java J, Walker JL, et al. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol. 2012;119(2 Pt 1):286-92.
110. Selman TJ, Mann CH, Zamora J, Khan KS. A systematic review of tests for lymph node status in primary endometrial cancer. BMC Womens Health. 2008;8:8.
111. Rockall AG, Cross S, Flanagan S, Moore E, Avril N. The role of FDG-PET/CT in gynaecological cancers. Cancer Imaging. 2012;12:49-65.
112. Narayanan P, Sahdev A. The role of (18)F-FDG PET CT in common gynaecological malignancies. Br J Radiol. 2017;90(1079):20170283.
113. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30.
114. Ganesan R, Singh N, McCluggage WG. Dataset for histological reporting of endometrial cancer. London, UK: TheRoyalCollegeofPathologists; 2020.
115. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):812-9.
116. Malpica A, Euscher ED, Hecht JL, et al. Endometrial Carcinoma, Grossing and Processing Issues: Recommendations of the International Society of Gynecologic Pathologists. Int J Gynecol Pathol. 2019;38 Suppl 1:S9-S24.
117. WHO Classification of Tumours Editorial Board. Female genital tumours. Lyon, France2020. Available from: https://publications.iarc.fr/592.

118. Bokhman Ia V, Vishnevskii AS. [2 pathogenetic variants of corpus uteri cancer]. Akush Ginekol (Mosk). 1984(4):34-7.
119. Piulats JM, Guerra E, Gil-Martin M, et al. Molecular approaches for classifying endometrial carcinoma. Gynecol Oncol. 2017;145(1):200-7.
120. Stasenko M, Tunnage I, Ashley CW, et al. Clinical outcomes of patients with POLE mutated endometrioid endometrial cancer. Gynecol Oncol. 2020;156(1):194-202.
121. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol. 2013;37(6):874-81.
122. Cho KR, Cooper K, Croce S, et al. International Society of Gynecological Pathologists (ISGyP) Endometrial Cancer Project: Guidelines From the Special Techniques and Ancillary Studies Group. Int J Gynecol Pathol. 2019;38 Suppl 1:S114-S22.
123. Moller P, Seppala T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2017;66(3):464-72.
124. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007;245(6):867-72.
125. Sanchez-Iglesias JL, Carbonell-Socias M, Perez-Benavente MA, et al. PROFAST: A randomised trial implementing enhanced recovery after surgery for highcomplexity advanced ovarian cancer surgery. Eur J Cancer. 2020;136:149-58.
126. Bisch SP, Jago CA, Kalogera E, et al. Outcomes of enhanced recovery after surgery (ERAS) in gynecologic oncology - A systematic review and meta-analysis. Gynecol Oncol. 2021;161(1):46-55.
127. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. Int J Gynaecol Obstet. 2018;143 Suppl 2:37-50.
128. Jia P, Zhang Y. Ovarian preservation improves overall survival in young patients with early-stage endometrial cancer. Oncotarget. 2017;8(35):59940-9.
129. Hanley GE, Kwon JS, McAlpine JN, Huntsman DG, Finlayson SJ, Miller D. Examining indicators of early menopause following opportunistic salpingectomy: a cohort study from British Columbia, Canada. Am J Obstet Gynecol. 2020;223(2):221 e1- e11.
130. Galaal K, Donkers H, Bryant A, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 2018;10:CD006655.
131. Fader AN, Seamon LG, Escobar PF, et al. Minimally invasive surgery versus laparotomy in women with high grade endometrial cancer: a multi-site study performed at high volume cancer centers. Gynecol Oncol. 2012;126(2):180-5.
132. Maenpaa MM, Nieminen K, Tomas EI, Laurila M, Luukkaala TH, Maenpaa JU. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. Am J Obstet Gynecol. 2016;215(5):588 e1- e7.
133. Wang J, Li X, Wu H, Zhang Y, Wang F. A Meta-Analysis of Robotic Surgery in Endometrial Cancer: Comparison with Laparoscopy and Laparotomy. Dis Markers. 2020;2020:2503753.
134. Salehi S, Avall-Lundqvist E, Legerstam B, Carlson JW, Falconer H. Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial. Eur J Cancer. 2017;79:81-9.
135. Lawrie TA, Liu H, Lu D, et al. Robot-assisted surgery in gynaecology. Cochrane Database Syst Rev. 2019;4:CD011422.
136. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707-16.
137. ASTEC Study Group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125-36.
138. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2017;10:CD007585.
139. Pigott A, Obermair A, Janda M, et al. Incidence and risk factors for lower limb lymphedema associated with endometrial cancer: Results from a prospective, longitudinal cohort study. Gynecol Oncol. 2020;158(2):375-81.
140. Kim SI, Lim MC, Lee JS, et al. Impact of lower limb lymphedema on quality of life in gynecologic cancer survivors after pelvic lymph node dissection. Eur J Obstet Gynecol Reprod Biol. 2015;192:31-6.

141. Vargas R, Rauh-Hain JA, Clemmer J, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. Gynecol Oncol. 2014;133(2):216-20.
142. Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, Montz FJ. FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer. 2003;13(5):664-72.
143. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer. 2006;107(8):1823-30.
144. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol. 2005;23(16):3668-75.
145. Fotopoulou C, El-Balat A, du Bois A, et al. Systematic pelvic and paraaortic lymphadenectomy in early high-risk or advanced endometrial cancer. Arch Gynecol Obstet. 2015;292(6):1321-7.
146. Havrilesky LJ, Cragun JM, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. Gynecol Oncol. 2005;99(3):689-95.
147. Persson J, Salehi S, Bollino M, Lonnerfors C, Falconer H, Geppert B. Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. Eur J Cancer. 2019;116:77-85.
148. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384-92.
149. Sozzi G, Fanfani F, Berretta R, et al. Laparoscopic sentinel node mapping with intracervical indocyanine green injection for endometrial cancer: the SENTIFAIL study - a multicentric analysis of predictors of failed mapping. Int J Gynecol Cancer. 2020;30(11):1713-8.
150. Nagar H, Wietek N, Goodall RJ, Hughes W, Schmidt-Hansen M, Morrison J. Sentinel node biopsy for diagnosis of lymph node involvement in endometrial cancer. Cochrane Database of Systematic Reviews. 2021(6).
151. Fotopoulou C, Ind T, Baldwin P, et al. Sentinel lymph node consensus document of the British Gynaecological Cancer Society for endometrial, vulvar, and cervical cancers. Int J Gynecol Cancer. 2019;29(9):1348-50.
152. Leitao MM, Jr., Zhou QC, Gomez-Hidalgo NR, et al. Patient-reported outcomes after surgery for endometrial carcinoma: Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy. Gynecol Oncol. 2020;156(1):147-53.
153. Gomez-Hidalgo NR, Ramirez PT, Ngo B, et al. Oncologic impact of micrometastases or isolated tumor cells in sentinel lymph nodes of patients with endometrial cancer: a meta-analysis. Clin Transl Oncol. 2020;22(8):1272-9.
154. Obermair A, Abu-Rustum NR. Sentinel lymph node mapping in endometrial cancer - areas where further research is needed. Int J Gynecol Cancer. 2020;30(3):283-4.
155. Chi DS, Barakat RR, Palayekar MJ, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer. 2008;18(2):269-73.
156. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008;109(1):11-8.
157. Petousis S, Christidis P, Margioula-Siarkou C, et al. Combined pelvic and para-aortic is superior to only pelvic lymphadenectomy in intermediate and high-risk endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 2020;302(1):249-63.
158. Hasegawa T, Furugori M, Kubota K, et al. Does the extension of the type of hysterectomy contribute to the local control of endometrial cancer? Int J Clin Oncol. 2019;24(9):1129-36.
159. Nasioudis D, Sakamuri S, Ko EM, et al. Radical hysterectomy is not associated with a survival benefit for patients with stage II endometrial carcinoma. Gynecol Oncol. 2020;157(2):335-9.
160. Phelippeau J, Koskas M. Impact of Radical Hysterectomy on Survival in Patients with Stage 2 Type1 Endometrial Carcinoma: A Matched Cohort Study. Ann Surg Oncol. 2016;23(13):4361-7.
161. Takano M, Ochi H, Takei Y, et al. Surgery for endometrial cancers with suspected cervical involvement: is radical hysterectomy needed (a GOTIC study)? Br J Cancer. 2013;109(7):1760-5.
162. Liu T, Tu H, Li Y, Liu Z, Liu G, Gu H. Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis. Ann Surg Oncol. 2019;26(9):2933-42.
163. Peters WA, 3rd, Andersen WA, Thornton WN, Jr., Morley GW. The selective use of vaginal hysterectomy in the management of adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1983;146(3):285-9.

164. Podzielinski I, Randall ME, Breheny PJ, et al. Primary radiation therapy for medically inoperable patients with clinical stage I and II endometrial carcinoma. Gynecol Oncol. 2012;124(1):36-41.
165. Acharya S, Perkins SM, DeWees T, et al. Brachytherapy Is Associated With Improved Survival in Inoperable Stage I Endometrial Adenocarcinoma: A Population-Based Analysis. Int J Radiat Oncol Biol Phys. 2015;93(3):649-57.
166. Gannavarapu BS, Hrycushko B, Jia X, Albuquerque K. Upfront radiotherapy with brachytherapy for medically inoperable and unresectable patients with high-risk endometrial cancer. Brachytherapy. 2020;19(2):139-45.
167. Inciura A, Atkocius V, Juozaityte E, Vaitkiene D. Long-term results of high-dose-rate brachytherapy and external-beam radiotherapy in the primary treatment of endometrial cancer. J Radiat Res. 2010;51(6):675-81.
168. van der Steen-Banasik E, Christiaens M, Shash E, et al. Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma. Eur J Cancer. 2016;65:172-81.
169. Yaney A, Healy E, Wald P, et al. Toxicity and outcomes associated with high-dose rate brachytherapy for medically inoperable endometrial cancer. Brachytherapy. 2021;20(2):368-75.
170. Baker WD, Pierce SR, Mills AM, Gehrig PA, Duska LR. Nonoperative management of atypical endometrial hyperplasia and grade 1 endometrial cancer with the levonorgestrel intrauterine device in medically ill post-menopausal women. Gynecol Oncol. 2017;146(1):34-8.
171. Smrz SA, Calo C, Fisher JL, Salani R. An ecological evaluation of the increasing incidence of endometrial cancer and the obesity epidemic. Am J Obstet Gynecol. 2020.
172. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer. 2013;49(4):868-74.
173. Casadio P, La Rosa M, Alletto A, et al. Fertility Sparing Treatment of Endometrial Cancer with and without Initial Infiltration of Myometrium: A Single Center Experience. Cancers (Basel). 2020;12(12).
174. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266 e1-12.
175. Westin SN, Fellman B, Sun CC, et al. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. Am J Obstet Gynecol. 2021;224(2):191 e1- e15.
176. Masciullo V, Trivellizzi N, Zannoni G, et al. Prognostic impact of hysteroscopic resection of endometrial atypical hyperplasia-endometrioid intraepithelial neoplasia and early-stage cancer in combination with megestrol acetate. Am J Obstet Gynecol. 2020.
177. Novikova OV, Nosov VB, Panov VA, et al. Live births and maintenance with levonorgestrel IUD improve disease-free survival after fertility-sparing treatment of atypical hyperplasia and early endometrial cancer. Gynecol Oncol. 2021;161(1):152-9.
178. Wei J, Zhang W, Feng L, Gao W. Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: A meta-analysis and systematic review. Medicine (Baltimore). 2017;96(37):e8034.
179. Yang BY, Gulinazi Y, Du Y, et al. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. BJOG. 2020;127(7):848-57.
180. Zhang Q, Qi G, Kanis MJ, et al. Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. Oncotarget. 2017;8(34):57642-53.
181. Obermair A, Baxter E, Brennan DJ, et al. Fertility-sparing treatment in early endometrial cancer: current state and future strategies. Obstet Gynecol Sci. 2020;63(4):417-31.
182. Barr CE, Ryan NAJ, Derbyshire AE, et al. Weight Loss During Intrauterine Progestin Treatment for Obesity-associated Atypical Hyperplasia and Early-Stage Cancer of The Endometrium. Cancer Prev Res (Phila). 2021.
183. Liu MC, Gardner AB, Wolford JE, Tewari KS. Endometrial cancer in the morbidly obese: a review. Curr Opin Obstet Gynecol. 2020;32(1):42-50.
184. Cho A, Lee SW, Park JY, et al. Continued medical treatment for persistent early endometrial cancer in young women. Gynecol Oncol. 2021;160(2):413-7.

185. Rajkumar S, Nath R, Lane G, Mehra G, Begum S, Sayasneh A. Advanced stage (IIIC/IV) endometrial cancer: Role of cytoreduction and determinants of survival. Eur J Obstet Gynecol Reprod Biol. 2019;234:26-31.
186. Shih KK, Yun E, Gardner GJ, Barakat RR, Chi DS, Leitao MM, Jr. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol. 2011;122(3):608-11.
187. Solmaz U, Mat E, Dereli ML, et al. Stage-III and -IV endometrial cancer: A single oncology centre review of 104 cases. J Obstet Gynaecol. 2016;36(1):81-6.
188. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol. 2010;118(1):14-8.
189. Eto T, Saito T, Kasamatsu T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol. 2012;127(2):338-44.
190. Guo J, Cui X, Zhang X, Qian H, Duan H, Zhang Y. The Clinical Characteristics of Endometrial Cancer With Extraperitoneal Metastasis and the Value of Surgery in Treatment. Technol Cancer Res Treat. 2020;19:1533033820945784.
191. Yoon MS, Park W, Huh SJ, et al. Impact of paraaortic lymphadenectomy for endometrial cancer with positive pelvic lymph nodes: A Korean Radiation Oncology Group study (KROG 13-17). Eur J Surg Oncol. 2016;42(10):1497-505.
192. Cosgrove CM, Cohn DE, Rhoades J, Felix AS. The prognostic significance of aortic lymph node metastasis in endometrial cancer: Potential implications for selective aortic lymph node assessment. Gynecol Oncol. 2019;153(3):505-10.
193. Rabinovich A. Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma: a glimmer of hope in select patients. Arch Gynecol Obstet. 2016;293(1):47-53.
194. Vandenput I, Van Calster B, Capoen A, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer. 2009;101(2):244-9.
195. Wilkinson-Ryan I, Frolova AI, Liu J, et al. Neoadjuvant chemotherapy versus primary cytoreductive surgery for stage IV uterine serous carcinoma. Int J Gynecol Cancer. 2015;25(1):63-8.
196. Guimaraes GC, Baiocchi G, Ferreira FO, et al. Palliative pelvic exenteration for patients with gynecological malignancies. Arch Gynecol Obstet. 2011;283(5):1107-12.
197. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980;56(4):419-27.
198. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404-11.
199. ASTEC Study Group, Blake P, Swart AM, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet. 2009;373(9658):137-46.
200. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744-51.
201. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database of Systematic Reviews. 2012(4).
202. Church DN, Stelloo E, Nout RA, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. Journal of the National Cancer Institute. 2015;107(1):402 - dju.
203. Stelloo E, Nout RA, Osse EM, et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer—Combined Analysis of the PORTEC Cohorts. Clinical Cancer Research. 2016;22(16):4215.
204. León-Castillo A, de Boer SM, Powell ME, et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. Journal of Clinical Oncology. 2020;38(29):3388-97.
205. Wortman BG, Bosse T, Nout RA, et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 2018;151(1):69-75.
206. Barney BM, Petersen IA, Mariani A, Dowdy SC, Bakkum-Gamez JN, Haddock MG. The role of vaginal brachytherapy in the treatment of surgical stage I papillary serous or clear cell endometrial cancer. Int J Radiat Oncol Biol Phys. 2013;85(1):109-15.

207. Cham S, Huang Y, Tergas AI, et al. Utility of radiation therapy for early-stage uterine papillary serous carcinoma. Gynecol Oncol. 2017;145(2):269-76.
208. Donovan E, Reade CJ, Eiriksson LR, et al. Outcomes of Adjuvant Therapy for Stage IA Serous Endometrial Cancer. Cureus. 2018;10(9):e3387.
209. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816-23.
210. Qu XM, Velker VM, Leung E, et al. The role of adjuvant therapy in stage IA serous and clear cell uterine cancer: A multi-institutional pooled analysis. Gynecol Oncol. 2018;149(2):283-90.
211. Shinde A, Li R, Amini A, et al. Improved survival with adjuvant brachytherapy in stage IA endometrial cancer of unfavorable histology. Gynecol Oncol. 2018;151(1):82-90.
212. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study. Int J Radiat Oncol Biol Phys. 2012;82(3):1249-55.
213. Sunil RA, Bhavsar D, Shruthi MN, et al. Combined external beam radiotherapy and vaginal brachytherapy versus vaginal brachytherapy in stage I, intermediate- and high-risk cases of endometrium carcinoma. J Contemp Brachytherapy. 2018;10(2):105-14.
214. Wortman BG, Creutzberg CL, Putter H, et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 2018;119(9):1067-74.
215. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011;81(4):e631-8.
216. Nout RA, van de Poll-Franse LV, Lybeert ML, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol. 2011;29(13):1692-700.
217. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005;63(3):834-8.
218. Ortoft G, Hansen ES, Bertelsen K. Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: the Danish Endometrial Cancer Study. Int J Gynecol Cancer. 2013;23(8):1429-37.
219. Bosse T, Peters EE, Creutzberg CL, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015;51(13):1742-50.
220. Bosse T, Nout RA, Stelloo E, et al. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. Eur J Cancer. 2014;50(15):2602-10.
221. van den Heerik A, Horeweg N, Nout RA, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer. 2020;30(12):2002-7.
222. McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol. 2018;244(5):538-49.
223. Wortman BG, Nout RA, Bosse T, Creutzberg CL. Selecting Adjuvant Treatment for Endometrial Carcinoma Using Molecular Risk Factors. Curr Oncol Rep. 2019;21(9):83.
224. Randall ME, Filiaci V, McMeekin DS, et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early-Stage Endometrial Cancer. Journal of Clinical Oncology. 2019;37(21):1810-8.
225. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. The Lancet Oncology. 2018;19(3):295-309.
226. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – Results from two randomised studies. European Journal of Cancer. 2010;46(13):2422-31.
227. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study. Gynecologic Oncology. 2008;108(1):226-33.

228. Kuoppala T, Mäenpää J, Tomas E, et al. Surgically staged high-risk endometrial cancer: Randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecologic Oncology. 2008;110(2):190-5.
229. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. British Journal of Cancer. 2006;95(3):266-71.
230. Morrow CP, Bundy BN, Homesley HD, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: A Gynecologic Oncology Group study. Gynecologic Oncology. 1990;36(2):166-71.
231. Randall ME, Filiaci VL, Muss H, et al. Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2006;24(1):36-44.
232. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I–IV carcinosarcoma (CS) of the uterus. Gynecologic Oncology. 2007;107(2):177-85.
233. Johnson N, Bryant A, Miles T, Hogberg T, Cornes P. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database of Systematic Reviews. 2011(10).
234. Matei D, Filiaci V, Randall ME, et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. New England Journal of Medicine. 2019;380(24):2317-26.
235. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. The Lancet Oncology. 2019;20(9):1273-85.
236. de Boer SM, Wortman BG, Bosse T, et al. Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer. Annals of Oncology. 2018;29(2):424-30.
237. de Boer SM, Powell ME, Mileshkin L, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. The Lancet Oncology. 2016;17(8):1114-26.
238. Blinman P, Mileshkin L, Khaw P, et al. Patients' and clinicians' preferences for adjuvant chemotherapy in endometrial cancer: an ANZGOG substudy of the PORTEC-3 intergroup randomised trial. British Journal of Cancer. 2016;115(10):1179-85.
239. Mirza MR, Lundgren C, Kridelka F, Ferrero A, Amant F. A phase III trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate- or high-risk endometrial cancer. ENGOT-EN2-DGCG/EORTC 55102. Journal of Clinical Oncology. 2014;32(15_suppl):TPS5628-TPS.
240. Ko EM, Brensinger CM, Cory L, et al. Utilization and survival outcomes of sequential, concurrent and sandwich therapies for advanced stage endometrial cancers by histology. Gynecologic Oncology. 2020;159(2):394-401.
241. Xiang M, English DP, Kidd EA. Defining the survival benefit of adjuvant pelvic radiotherapy and chemotherapy versus chemotherapy alone in stages III-IVA endometrial carcinoma. Gynecologic Oncology. 2019;154(3):487-94.
242. Levine DA, Getz G, Gabriel SB, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
243. Martin-Hirsch PPL, Bryant A, Keep SL, Kitchener HC, Lilford R. Adjuvant progestagens for endometrial cancer. Cochrane Database of Systematic Reviews. 2011(6).
244. Klopp AH, Yeung AR, Deshmukh S, et al. Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018;36(24):2538-44.
245. de Lange NM, Ezendam NPM, Kwon JS, et al. Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer. Curr Oncol. 2019;26(2):e226-e32.
246. Khouri OR, Frey MK, Musa F, et al. Neoadjuvant chemotherapy in patients with advanced endometrial cancer. Cancer Chemotherapy and Pharmacology. 2019;84(2):281-5.
247. Bogani G, Ditto A, Leone Roberti Maggiore U, et al. Neoadjuvant chemotherapy followed by interval debulking surgery for unresectable stage IVB Serous endometrial cancer. 2019(2038-2529 (Electronic)).
248. Fleming GF, Brunetto VL, Cella D, et al. Phase III Trial of Doxorubicin Plus Cisplatin With or Without Paclitaxel Plus Filgrastim in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2004;22(11):2159-66.

249. Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). Journal of Clinical Oncology. 2020;38(33):3841-50.
250. Powell MA, Filiaci VL, Rose PG, et al. Phase II Evaluation of Paclitaxel and Carboplatin in the Treatment of Carcinosarcoma of the Uterus: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2010;28(16):2727-31.
251. Ethier J-L, Desautels DN, Amir E, MacKay H. Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. Gynecologic Oncology. 2017;147(1):158-66.
252. Thigpen JT, Brady MF, Alvarez RD, et al. Oral Medroxyprogesterone Acetate in the Treatment of Advanced or Recurrent Endometrial Carcinoma: A Dose-Response Study by the Gynecologic Oncology Group. Journal of Clinical Oncology. 1999;17(6):1736-.
253. Mileshkin L, Edmondson R, O'Connell RL, et al. Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial – ANZGOG 0903. Gynecologic Oncology. 2019;154(1):29-37.
254. Mahantshetty U, Poetter R, Beriwal S, et al. IBS-GEC ESTRO-ABS recommendations for CT based contouring in image guided adaptive brachytherapy for cervical cancer. Radiother Oncol. 2021;160:273-84.
255. Gill BS, Kim H, Houser C, et al. Image-based three-dimensional conformal brachytherapy for medically inoperable endometrial carcinoma. Brachytherapy. 2014;13(6):542-7.
256. Francis SR, Ager BJ, Do OA, et al. Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy. Gynecol Oncol. 2019;154(1):38-44.
257. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003;89(2):201-9.
258. Jeppesen MM, Jensen PT, Gilsa Hansen D, Iachina M, Mogensen O. The nature of early-stage endometrial cancer recurrence-A national cohort study. Eur J Cancer. 2016;69:51-60.
259. National Institute for Health and Care Excellence. Improving supportive and palliative care for adults with cancer 2004 [Available from: https://www.nice.org.uk/guidance/csg4.
260. Bollineni VR, Ytre-Hauge S, Bollineni-Balabay O, Salvesen HB, Haldorsen IS. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 2016;57(6):879-85.
261. Kadkhodayan S, Shahriari S, Treglia G, Yousefi Z, Sadeghi R. Accuracy of 18-F-FDG PET imaging in the follow up of endometrial cancer patients: systematic review and meta-analysis of the literature. Gynecol Oncol. 2013;128(2):397-404.
262. Campagnutta E, Giorda G, De Piero G, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer. 2004;100(1):89-96.
263. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. International Journal of Radiation Oncology*Biology*Physics. 2003;56:1366-72.
264. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecologic oncology. 2000;77:66-72.
265. Hardarson HA, Heidemann LN, dePont Christensen R, Mogensen O, Jochumsen KM. Vaginal vault recurrences of endometrial cancer in non-irradiated patients - Radiotherapy or surgery. Gynecol Oncol Rep. 2015;11:26-30.
266. Shepherd JH, Ngan HYS, Neven P, Fryatt I, Woodhouse CRJ, Hendry WF. Multivariate analysis of factors affecting survival in pelvic exenteration. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 1994;4:361-70.
267. Khoury-Collado F, Einstein MH, Bochner BH, et al. Pelvic exenteration with curative intent for recurrent uterine malignancies. Gynecol Oncol. 2012;124(1):42-7.
268. Schmidt AM, Imesch P, Fink D, Egger H. Pelvic Exenterations for Advanced and Recurrent Endometrial Cancer: Clinical Outcomes of 40 Patients. Int J Gynecol Cancer. 2016;26(4):716-21.
269. Kunos CA, Brindle J, Waggoner S, et al. Phase II Clinical Trial of Robotic Stereotactic Body Radiosurgery for Metastatic Gynecologic Malignancies. Front Oncol. 2012;2:181.
270. Ito M, Kodaira T, Koide Y, et al. Role of high-dose salvage radiotherapy for oligometastases of the localised abdominal/pelvic lymph nodes: a retrospective study. BMC Cancer. 2020;20(1):540.
271. Seo Y, Kim MS, Yoo HJ, et al. Salvage stereotactic body radiotherapy for locally recurrent uterine cervix cancer at the pelvic sidewall: Feasibility and complication. Asia Pac J Clin Oncol. 2016;12(2):e280-8.
272. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006;103(1):281-7.

273. Ren Y, Shan B, Shi D, Wang H. Salvage cytoreductive surgery for patients with recurrent endometrial cancer: a retrospective study. BMC Cancer. 2014;14:135.
274. Awtrey CS, Cadungog MG, Leitao MM, et al. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol. 2006;102(3):480-8.
275. Papadia A, Bellati F, Ditto A, et al. Surgical Treatment of Recurrent Endometrial Cancer: Time for a Paradigm Shift. Ann Surg Oncol. 2015;22(13):4204-10.
276. Miller D, Filiaci V, Fleming G, al e. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecologic Oncology. 2012;125:771.
277. Ang JE, Shah RN, Everard M, et al. A feasibility study of sequential doublet chemotherapy comprising carboplatin-doxorubicin and carboplatin-paclitaxel for advanced endometrial adenocarcinoma and carcinosarcoma. Annals of oncology. 2009;20:1787-93.
278. Humber CE, Tierney JF, Symonds RP, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Annals of Oncology. 2007;18(3):409–20.
279. Aapro MS. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Annals of Oncology. 2003;14:441-8.
280. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. Journal of clinical oncology. 2004;22:3902-8.
281. Meissner M, Walther A. What is the most commonly prescribed treatment for metastatic endometrial cancer in the second line setting in the UK, and how effective is this treatment? NCRI Annual Conference; 6-9 November 2016; Liverpool2016.
282. Muggia FM. Phase II Trial of the Pegylated Liposomal Doxorubicin in Previously Treated Metastatic Endometrial Cancer: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2002;20:2360-4.
283. Miller DS, Blessing JA, Lentz SS, E WS. A Phase II Trial of Topotecan in Patients with Advanced, Persistent, or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study. Gynecologic Oncology. 2002;87:247-51.
284. Millennium Pharmaceuticals Inc. A Study of Sapanisertib, Combination of Sapanisertib With MLN1117, Paclitaxel and Combination of Sapanisertib With Paclitaxel in Women With Endometrial Cancer [Available from: https://clinicaltrials.gov/ct2/show/NCT02725268.
285. Clamp A, Kristeleit RS, Jayson G. Does Cediranib With Paclitaxel, or Cediranib and Olaparib, Treat Advanced Endometrial Cancer Better Than Paclitaxel? (COPELIA) [Available from: https://clinicaltrials.gov/ct2/show/NCT03570437.
286. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020;38(1):1-10.
287. Oaknin A, Tinker AV, Gilbert L, et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA oncology. 2020;6(11):1766-72.
288. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 2020;38(26):2981-92.
289. Makker VC, N.; Casado Herráez, A.; et al. A multicenter, open-label, randomized phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women's Cancer Presented March 19, 2021; Virtual2021.
290. Kim JY, Kronbichler A, Eisenhut M, et al. Tumor Mutational Burden and Efficacy of Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Cancers (Basel). 2019;11(11).
291. van Weelden WJ, Massuger L, Enitec, Pijnenborg JMA, Romano A. Anti-estrogen Treatment in Endometrial Cancer: A Systematic Review. Front Oncol. 2019;9:359.
292. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev. 2010(12):CD007926.
293. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(1):10-4.

294. Singh M, Zaino RJ, Filiaci VJ, Leslie KK. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2007;106(2):325-33.
295. Thigpen JT, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19:364-7.
296. Ma BB, Oza A, Eisenhauer E, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers--a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynecol Cancer. 2004;14(4):650-8.
297. Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2000;78(2):212-6.
298. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. (1569-8041 (Electronic)).
299. Conklin CM, Longacre TA. Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol. 2014;21(6):383-93.
300. Soft Tissue and Bone Tumours. WHO Classification of Tumours 2020.
301. Francis M, Dennis NL, Hirschowitz L, et al. Incidence and survival of gynecologic sarcomas in England. Int J Gynecol Cancer. 2015;25(5):850-7.
302. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma. 2010;2010:506182.
303. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol. 2010;116(1):131-9.
304. Giuntoli RL, 2nd, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol. 2003;89(3):460-9.
305. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83(3):414-8.
306. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71(4 Suppl):1702-9.
307. Zivanovic O, Leitao MM, Iasonos A, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the international Federation of gynecology and obstetrics and american joint committee on cancer staging systems. J Clin Oncol. 2009;27(12):2066-72.
308. Iasonos A, Keung EZ, Zivanovic O, et al. External validation of a prognostic nomogram for overall survival in women with uterine leiomyosarcoma. Cancer. 2013;119(10):1816-22.
309. Leibsohn S, d'Ablaing G, Mishell DR, Jr., Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol. 1990;162(4):968-74; discussion 74-6.
310. Leitao MM, Sonoda Y, Brennan MF, Barakat RR, Chi DS. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. Gynecol Oncol. 2003;91(1):209-12.
311. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008;112(4):820-30.
312. Wright JD, Tergas AI, Burke WM, et al. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. JAMA. 2014;312(12):1253-5.
313. Zapardiel I, Boria F, Halaska MJ, De Santiago J. Laparoscopic Power Morcellation: Techniques to Avoid Tumoral Spread. J Minim Invasive Gynecol. 2020.
314. Bogani G, Cliby WA, Aletti GD. Impact of morcellation on survival outcomes of patients with unexpected uterine leiomyosarcoma: a systematic review and meta-analysis. Gynecol Oncol. 2015;137(1):167-72.
315. George S, Barysauskas C, Serrano C, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer. 2014;120(20):3154-8.
316. Food and Drug Administration. Product Labeling for Laparoscopic Power Morcellators. In: Food and Drug Administration, editor. Rockville, MD2020.
317. Oduyebo T, Rauh-Hain AJ, Meserve EE, et al. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014;132(2):360-5.
318. Reed NS, Mangioni C, Malmstrom H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008;44(6):808-18.

319. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. J Clin Oncol. 1985;3(9):1240-5.
320. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. Gynecol Oncol. 2009;112(3):563-7.
321. Littell RD, Tucker LY, Raine-Bennett T, et al. Adjuvant gemcitabine-docetaxel chemotherapy for stage I uterine leiomyosarcoma: Trends and survival outcomes. Gynecol Oncol. 2017;147(1):11-7.
322. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer. 2013;119(8):1555-61.
323. Hensley ML, Enserro D, Hatcher H, et al. Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study. J Clin Oncol. 2018:JCO1800454.
324. Leitao MM, Jr., Zivanovic O, Chi DS, et al. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. Gynecol Oncol. 2012;125(2):409-13.
325. Park JY, Kim DY, Suh DS, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989-2007. J Cancer Res Clin Oncol. 2008;134(12):1277-87.
326. Sagae S, Yamashita K, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology. 2004;67(1):33-9.
327. Dinh TA, Oliva EA, Fuller AF, Jr., Lee H, Goodman A. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990-1999) at the Massachusetts General Hospital. Gynecol Oncol. 2004;92(2):648-52.
328. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. The Lancet Oncology. 2017;18(10):1397-410.
329. Henry R, Hartley B, Simpson M, Doyle N. The development and evaluation of a holistic needs assessment and care planning learning package targeted at cancer nurses in the UK. Ecancermedicalscience. 2014;8:416.
330. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol. 2008;109(3):323-8.
331. Hensley ML, Miller A, O'Malley DM, et al. A randomized phase III trial of gemcitabine + docetaxel + bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma (uLMS): A Gynecologic Oncology Group study. Gynecologic Oncology. 2014;133:3.
332. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016;388(10043):488-97.
333. Tap WD, Wagner AJ, Schoffski P, et al. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. JAMA. 2020;323(13):1266-76.
334. Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol. 2015;16(4):457-64.
335. Martin-Broto J, Pousa AL, de Las Penas R, et al. Randomized Phase II Study of Trabectedin and Doxorubicin Compared With Doxorubicin Alone as First-Line Treatment in Patients With Advanced Soft Tissue Sarcomas: A Spanish Group for Research on Sarcoma Study. J Clin Oncol. 2016;34(19):2294-302.
336. O'Cearbhaill R, Zhou Q, Iasonos A, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. Gynecol Oncol. 2010;116(3):424-9.
337. Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol. 2011;35(9):1364-72.
338. Chan JK, Kawar NM, Shin JY, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer. 2008;99(8):1210-5.
339. Amant F, Floquet A, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for endometrial stromal sarcoma. Int J Gynecol Cancer. 2014;24(9 Suppl 3):S67-72.
340. Nasioudis D, Mastroyannis SA, Latif NA, et al. Effect of bilateral salpingo-oophorectomy on the overall survival of premenopausal patients with stage I low-grade endometrial stromal sarcoma; a National Cancer Database analysis. Gynecol Oncol. 2020;157(3):634-8.

341. Nasioudis D, Ko EM, Kolovos G, Vagios S, Kalliouris D, Giuntoli RL. Ovarian preservation for low-grade endometrial stromal sarcoma: a systematic review of the literature and meta-analysis. Int J Gynecol Cancer. 2019;29(1):126-32.
342. Laurelli G, Falcone F, Scaffa C, et al. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:61-6.
343. Chu MC, Mor G, Lim C, Zheng W, Parkash V, Schwartz PE. Low-grade endometrial stromal sarcoma: hormonal aspects. Gynecol Oncol. 2003;90(1):170-6.
344. Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systematic review. Obstet Gynecol. 2013;122(3):676-83.
345. Deshmukh U, Black J, Perez-Irizarry J, et al. Adjuvant Hormonal Therapy for Low-Grade Endometrial Stromal Sarcoma. Reprod Sci. 2019;26(5):600-8.
346. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. Gynecol Oncol. 2006;101(3):464-9.
347. Carroll A, Ramirez PT, Westin SN, et al. Uterine adenosarcoma: an analysis on management, outcomes, and risk factors for recurrence. Gynecol Oncol. 2014;135(3):455-61.
348. Tanner EJ, Toussaint T, Leitao MM, Jr., et al. Management of uterine adenosarcomas with and without sarcomatous overgrowth. Gynecol Oncol. 2013;129(1):140-4.
349. Department of Health. Hospital Episodes Statistics 2010 [Available from: http://www.hesonline.nhs.uk].
350. Gadducci A, Cosio S, Fanucchi A, Cristofani R, Genazzani AR. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res. 2000;20(3B):1977-84.
351. Agboola OO, Grunfeld E, Coyle D, Perry GA. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. CMAJ. 1997;157(7):879-86.
352. Allsop JR, Preston J, Crocker S. Is there any value in the long-term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol. 1997;104(1):122.
353. Owen P, Duncan ID. Is there any value in the long term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol. 1996;103(7):710-3.
354. Salvesen HB, Akslen LA, Iversen T, Iversen OE. Recurrence of endometrial carcinoma and the value of routine follow up. Br J Obstet Gynaecol. 1997;104(11):1302-7.
355. Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(3):520-9.
356. Sperling C, Sandager M, Jensen H, Knudsen JL. Current organisation of follow-up does not meet cancer patients' needs. Dan Med J. 2014;61(6):A4855.
357. Kew FM, Cruickshank DJ. Routine follow-up after treatment for a gynecological cancer: a survey of practice. Int J Gynecol Cancer. 2006;16(1):380-4.
358. Department of Health. Improving outcomes: a strategy for cancer. In: Department of Health, editor. London2011.
359. Newton C NA, Rolland P, Ind T, Larson-Disney P, Martin-Hirsch P, Beaver K, Bolton H, Peevor R, Fernandes A, Kew F, Sengupta P, Miles T, Buckley L, Manderville H, Gajjar K, Morrison J, Ledermann J, Frost J, Lawrence A, Sundar S, Fotopoulou C. British Gynaecology Cancer Society recommendations and guidance on patient-initiated follow up (PIFU). International Journal of Gynecologic Cancer. 2020;In press.
360. Watson EK, Rose PW, Neal RD, et al. Personalised cancer follow-up: risk stratification, needs assessment or both? Br J Cancer. 2012;106(1):1-5.
361. Coleman L, Newton C. Patient initiated follow up after gynaecological malignancy: National survey of current UK practice. Eur J Obstet Gynecol Reprod Biol. 2020;248:193-7.
362. Leeson S, Stuart N, Sylvestre Y, Hall L, Whitaker R. Gynaecological cancer follow-up: national survey of current practice in the UK. BMJ Open. 2013;3(7).
363. Nordin AJ, National Group of Gynaecology NL. Mode of detection of recurrent gynecological malignancy: Does routine follow-up delay diagnosis and treatment? Int J Gynecol Cancer. 2006;16(5):1746-8.
364. Vistad I, Bjorge L, Solheim O, et al. A national, prospective observational study of first recurrence after primary treatment for gynecological cancer in Norway. Acta Obstet Gynecol Scand. 2017;96(10):1162-9.
365. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27(1):16-41.

366. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;20(9):1273-85.
367. ESMO/European Sarcoma Network Working Group Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii102-12.
368. Macmillan Cancer Support. Providing personalised care for people living with cancer 2019.
369. Macmillan Cancer Support. Clinical Nurse Specialists an evidence review. 2012.
370. Holmes L, Miles T, White I. Female sexual health after a cancer diagnosis. Cancer Nursing Practice. 2015;14(7):16-22.
371. Aerts L, Enzlin P, Verhaeghe J, Poppe W, Vergote I, Amant F. Sexual functioning in women after surgical treatment for endometrial cancer: a prospective controlled study. J Sex Med. 2015;12(1):198-209.
372. Ferguson SE, Panzarella T, Lau S, et al. Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer. Gynecol Oncol. 2018;149(3):476-83.
373. Damast S, Alektiar KM, Goldfarb S, et al. Sexual functioning among endometrial cancer patients treated with adjuvant high-dose-rate intra-vaginal radiation therapy. Int J Radiat Oncol Biol Phys. 2012;84(2):e187-93.
374. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. Cochrane Database of Systematic Reviews. 2014(9).
375. White ID, Tennant A, Taylor C. Sexual Morbidity Assessment in Gyne-Oncology Follow-Up: Development of the Sexual Well-Being After Cervical or Endometrial Cancer (SWELL-CE) Patient-Reported Outcome Measure. J Sex Med. 2020;17(10):2005-15.
376. Flynn P, Kew F, Kisely SR. Interventions for psychosexual dysfunction in women treated for gynaecological malignancy. Cochrane Database of Systematic Reviews. 2009(2).
377. Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 2018;5:CD008830.
378. Gu H, Li J, Gu Y, Tu H, Zhou Y, Liu J. Survival Impact of Ovarian Preservation on Women With Early-Stage Endometrial Cancer: A Systematic Review and Meta-analysis. Int J Gynecol Cancer. 2017;27(1):77-84.
379. Hou T, Sun Y, Li J, et al. The Safety of Ovarian Preservation in Stage I Endometrial Endometrioid Adenocarcinoma Based on Propensity Score Matching. Comb Chem High Throughput Screen. 2017;20(7):647-55.
380. Lau HY, Chen MY, Ke YM, et al. Outcome of ovarian preservation during surgical treatment for endometrial cancer: A Taiwanese Gynecologic Oncology Group study. Taiwan J Obstet Gynecol. 2015;54(5):532-6.
381. Lau HY, Twu NF, Yen MS, et al. Impact of ovarian preservation in women with endometrial cancer. J Chin Med Assoc. 2014;77(7):379-84.
382. Lee TS, Lee JY, Kim JW, et al. Outcomes of ovarian preservation in a cohort of premenopausal women with early-stage endometrial cancer: a Korean Gynecologic Oncology Group study. Gynecol Oncol. 2013;131(2):289-93.
383. Lyu T, Guo L, Chen X, et al. Ovarian preservation for premenopausal women with early-stage endometrial cancer: a Chinese retrospective study. J Int Med Res. 2019;47(6):2492-8.
384. Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol. 2009;27(8):1214-9.
385. Brennan A, Brennan D, Rees M, Hickey M. Management of menopausal symptoms and ovarian function preservation in women with gynecological cancer. Int J Gynecol Cancer. 2021;31(3):352-9.
386. Hareyama H, Hada K, Goto K, et al. Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study. Int J Gynecol Cancer. 2015;25(4):751-7.
387. Hayes SC, Janda M, Ward LC, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol. 2017;146(3):623-9.
388. Lindqvist E, Wedin M, Fredrikson M, Kjolhede P. Lymphedema after treatment for endometrial cancer - A review of prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol. 2017;211:112-21.

389. Mitra D, Catalano PJ, Cimbak N, Damato AL, Muto MG, Viswanathan AN. The risk of lymphedema after postoperative radiation therapy in endometrial cancer. J Gynecol Oncol. 2016;27(1):e4.
390. Yost KJ, Cheville AL, Al-Hilli MM, et al. Lymphedema after surgery for endometrial cancer: prevalence, risk factors, and quality of life. Obstet Gynecol. 2014;124(2 Pt 1):307-15.
391. Macmillan Cancer Support. Part 1: Guidelines on Late Effects of Gynaecological Cancer: Pelvic Radiotherapy. London; 2014.
392. Newton C, Nordin A, Rolland P, et al. British Gynaecological Cancer Society recommendations and guidance on patient-initiated follow-up (PIFU). Int J Gynecol Cancer. 2020;30(5):695-700.
393. van Walree IC, Hamaker ME, de Rooij BH, et al. Do age and comorbidity impair recovery during two years after treatment for endometrial cancer? J Geriatr Oncol. 2020;11(7):1078-86.
394. de Boer SM, Nout RA, Jurgenliemk-Schulz IM, et al. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. Int J Radiat Oncol Biol Phys. 2015;93(4):797-809.
395. de Boer SM, Powell ME, Mileshkin L, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17(8):1114-26.
396. Post CCB, de Boer SM, Powell ME, et al. Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial. Int J Radiat Oncol Biol Phys. 2021;109(4):975-86.
397. Cancer Research UK. Womb Cancer Survival. 2020.
398. Muls A, Taylor A, Lalondrelle S, et al. A proposed tailored investigational algorithm for women treated for gynaecological cancer with long-term gastrointestinal consequences. Support Care Cancer. 2020;28(10):4881-9.
399. Lawrie TA, Green Jt Fau - Beresford M, Beresford M Fau - Wedlake L, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. (1469-493X (Electronic)).
400. Halkett GKB, Wigley CA, Aoun SM, et al. International validation of the EORTC QLQ-PRT20 module for assessment of quality of life symptoms relating to radiation proctitis: a phase IV study. Radiat Oncol. 2018;13(1):162.
401. Taylor S, Byrne A, Adams R, et al. The Three-item ALERT-B Questionnaire Provides a Validated Screening Tool to Detect Chronic Gastrointestinal Symptoms after Pelvic Radiotherapy in Cancer Survivors. Clin Oncol (R Coll Radiol). 2016;28(10):e139-47.
402. NHS England. Service Specification No. 170091S; Adult External Beam Radiotherapy Services. In: NHS England, editor. London2019.
403. Andreyev HJ, Muls AC, Norton C, et al. Guidance: The practical management of the gastrointestinal symptoms of pelvic radiation disease. Frontline Gastroenterol. 2015;6(1):53-72.
404. van de Wetering FT, Verleye L, Andreyev HJ, et al. Non-surgical interventions for late rectal problems (proctopathy) of radiotherapy in people who have received radiotherapy to the pelvis. Cochrane Database Syst Rev. 2016;4:CD003455.
405. Mege D, Meurette G, Trilling B, et al. Efficacy and safety of sacral nerve modulation for faecal incontinence after pelvic radiotherapy. Radiother Oncol. 2020;146:167-71.
406. Soisson S, Ganz PA, Gaffney D, et al. Long-term, adverse genitourinary outcomes among endometrial cancer survivors in a large, population-based cohort study. Gynecol Oncol. 2018;148(3):499-506.
407. Segal S, John G, Sammel M, et al. Urinary incontinence and other pelvic floor disorders after radiation therapy in endometrial cancer survivors. Maturitas. 2017;105:83-8.
408. Cooper J, Annappa M, Quigley A, Dracocardos D, Bondili A, Mallen C. Prevalence of female urinary incontinence and its impact on quality of life in a cluster population in the United Kingdom (UK): a community survey. Prim Health Care Res Dev. 2015;16(4):377-82.
409. Bosch R, McCloskey K, Bahl A, et al. Can radiation-induced lower urinary tract disease be ameliorated in patients treated for pelvic organ cancer: ICI-RS 2019? Neurourol Urodyn. 2020;39 Suppl 3:S148-S55.
410. Spampinato S, Tanderup K, Marinovskij E, et al. MRI-based contouring of functional sub-structures of the lower urinary tract in gynaecological radiotherapy. Radiother Oncol. 2020;145:117-24.
411. NationalI nstitute for Health and Care Excellence. Urinary incontinence and pelvic organ prolapse in women: management (NICE guidance [NG123]). In: NICE, editor. London 2019.

412. Pascoe C, Duncan C, Lamb BW, et al. Current management of radiation cystitis: a review and practical guide to clinical management. BJU Int. 2019;123(4):585-94.
413. Toia B, Seth J, Ecclestone H, et al. Outcomes of reconstructive urinary tract surgery after pelvic radiotherapy. Scand J Urol. 2019;53(2-3):156-60.
414. Villeirs L, Tailly T, Ost P, et al. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature. Int J Urol. 2020;27(2):98-107.
415. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. JAMA. 2005;294(20):2587-93.
416. Razavian N, Laucis A, Sun Y, et al. Radiation-Induced Insufficiency Fractures After Pelvic Irradiation for Gynecologic Malignancies: A Systematic Review. Int J Radiat Oncol Biol Phys. 2020;108(3):620-34.
417. Salcedo MP, Sood AK, Jhingran A, et al. Pelvic fractures and changes in bone mineral density after radiotherapy for cervical, endometrial, and vaginal cancer: A prospective study of 239 women. Cancer. 2020;126(11):2607-13.
418. Sapienza LG, Salcedo MP, Ning MS, et al. Pelvic Insufficiency Fractures After External Beam Radiation Therapy for Gynecologic Cancers: A Meta-analysis and Meta-regression of 3929 Patients. Int J Radiat Oncol Biol Phys. 2020;106(3):475-84.
419. Zhong X, Dong T, Tan Y, et al. Pelvic insufficiency fracture or bone metastasis after radiotherapy for cervical cancer? The added value of DWI for characterization. Eur Radiol. 2020;30(4):1885-95.
420. Eastlake L, Sheridan B, Yiannakis D. Insufficiency Fractures in Postmenopausal Gynaecological Patients Receiving Pelvic Radiotherapy: Can These be Prevented by Optimisation of Bone Health? Clin Oncol (R Coll Radiol). 2020;32(5):344-5.
421. van den Blink QU, Garcez K, Henson CC, Davidson SE, Higham CE. Pharmacological interventions for the prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults. Cochrane Database Syst Rev. 2018;4:CD010604.
422. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. Radiother Oncol. 2012;105(3):273-82.
423. Yi SK, Mak W, Yang CC, et al. Development of a standardized method for contouring the lumbosacral plexus: a preliminary dosimetric analysis of this organ at risk among 15 patients treated with intensity-modulated radiotherapy for lower gastrointestinal cancers and the incidence of radiation-induced lumbosacral plexopathy. Int J Radiat Oncol Biol Phys. 2012;84(2):376-82.
424. Pisani C, Deantonio L, Surico D, et al. Quality of life in patients treated by adjuvant radiotherapy for endometrial and cervical cancers: correlation with dose-volume parameters. Clin Transl Oncol. 2016;18(9):901-8.
425. Tunio M, Al Asiri M, Bayoumi Y, et al. Lumbosacral plexus delineation, dose distribution, and its correlation with radiation-induced lumbosacral plexopathy in cervical cancer patients. Onco Targets Ther. 2015;8:21-7.
426. Hwang E, Son H, Kim J, Moon S, Lee H. MR Imaging of Radiation-Induced Lumbosacral Plexopathy, as a Rare Complication of Concomitant Chemo-Radiation for Cervical Cancer. Investigative Magnetic Resonance Imaging. Investigative Magnetic Resonance Imaging. 2020;24(1):46-50.
427. Mbatani N, Olawaiye AB, Prat J. Uterine sarcomas. Int J Gynaecol Obstet. 2018;143 Suppl 2:51-8.