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Review article

BGCS uterine cancer guidelines: Recommendations for practice

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ABSTRACT

The British Gynaecological Cancer Society has issued the first Endometrial (Uterine) Cancer guidelines as recommendation for practice for the UK.

Contents

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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 for more details.

Evidence was searched in the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE up to August 2014, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field. Recent ASCO/ASTRO and ESMO-ESGO-ESTRO guidelines on endometrial cancer were also reviewed in the preparation of this guideline [1,2].

Guideline development process

- These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
- The guideline development process is detailed below
  - Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic
- Lead then identified a team called the guideline team (GT) to develop the 1st draft
- 1st draft was submitted to the GC
- GC approved draft and recommended changes
- Changes were accepted by the GT who produced the guidelines
- 2nd draft was then submitted to council members and officers
- Council and officers approved 2nd draft and recommended changes
- Changes were then accepted by GC and GT

- 3rd draft was sent to national and international peer review
- GC and GT then made changes based on peer review comments
- 4th draft was sent back to council for approval
- 4th draft was sent to BGCS members for feedback
- GC and GT then made changes based on members' feedback
- 5th draft was sent to public consultation including patient support groups
- GC and GT then made changes based on non-members' feedback
- Final draft was approved by council and officers.

1 Introduction

Uterine cancer is the sixth most common cancer worldwide for females, and the 14th most common cancer overall, with more than 319,000 new cases diagnosed in 2012 (5% of female cases and 2% of the total). Endometrial cancer incidence has increased by around 50% in the United Kingdom since the 1990s, to 8475 women in 2011 and causing 2025 deaths in 2012. 78% of women with adult uterine cancer diagnosed in 2010–2011 in England and Wales are predicted to survive ten or more years. (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/uterus/uk-uterine-cancer-statistics). This increase in incidence is likely due to increasing obesity, increased life expectancy and adjuvant tamoxifen for breast cancer and is confined to endometrioid endometrial cancer [3].

2 Screening and prevention of uterine cancer in the population and high risk groups

There is no evidence that screening asymptomatic women in the general population with transvaginal ultrasound scanning (TVS) or endometrial sampling reduces the mortality from endometrial cancer (EC). (Grade D)

In women with postmenopausal or abnormal vaginal bleeding TVS is widely used in the investigation of possible EC. A large meta-analysis found that an endometrial thickness (ET) of $\leq$4 mm reduced the probability of EC to <1% [4].

However, in women without abnormal vaginal bleeding, the same thresholds have unacceptably high false positive rates and poor sensitivity. Jacobs et al. [5] and Smith-Bindman [6] have published data suggesting better sensitivity of TVS at alternative ET cut-offs, however in the absence of mortality data or a consensus on recommended cut-offs, this cannot be extrapolated to justify the adoption of ultrasound screening of asymptomatic women.

Endometrial sampling, e.g. with a Pipelle©, is indicated in symptomatic women with a thickened endometrium on TVS, however its use in asymptomatic women may be limited by perceived limitations of acceptability. Endometrial biopsy can result in discomfort, bleeding, infection and rarely uterine perforation. In asymptomatic women, up to 25% of endometrial biopsies may yield insufficient tissue for diagnosis [7]. No studies have evaluated the efficacy of TVS or endometrial biopsy in reducing mortality from EC in the context of mass screening.

2.1 Selective screening of high risk groups

Women with Lynch Syndrome and their first degree relatives could be offered annual screening with TVS and endometrial biopsy from the age of 35 years after counselling about the risks, benefits and limitations of screening. (Grade C)

Premenopausal women with Lynch syndrome should be counselled to seek medical attention for persistent intermenstrual bleeding or irregular heavy periods. (Grade C)

Between two and 5% of cases of EC are inherited rather than sporadic. Lynch syndrome (previously called Hereditary Non Polyposis Colorectal Cancer (HNPCC)) is associated with a significantly increased risk of EC (both type I and II tumours) compared to the general population, with up to a 40–60% lifetime risk (cf. 3% in the general population) [8]. Lynch syndrome is caused by an autosomal dominant inherited mutation in DNA mismatch repair genes that promotes tumour development affecting the colon, endometrium and ovary. The risk differs depending upon the germline mutation. The mean age at diagnosis is 47 years, compared to 60 years for non-inherited EC, however in the limited comparison data available it appears that prognosis and survival are similar.

The high risk of EC in Lynch syndrome and an earlier age at onset, together with a detectable and treatable premalignant or early malignant stage, is justification for screening in these women [9]. There is no evidence that screening reduces mortality from EC. Screening does not take the place of risk reducing hysterectomy, and there are concerns that should screening reduce the uptake of hysterectomy the incidence of EC in this population may increase. It is debatable whether a TVS is of benefit in a premenopausal woman. Equally, if the ET in a postmenopausal woman is within normal limits it is unclear what additional benefit would be derived from an endometrial biopsy. There is no formalised programme in place and provision for these patients varies between institutions.

Routine screening with TVS, endometrial biopsy, or both has not been shown to be effective in patients on tamoxifen. (Grade C) Postmenopausal women taking tamoxifen should be routinely questioned at breast cancer follow-up visits about symptoms of vaginal bleeding/discharge and should be made aware of the risks. Symptoms in these women should be investigated with hysteroscopy as well as biopsy and ultrasound. (Grade D)

Tamoxifen is a selective oestrogen receptor modulator (SERM) widely used in the treatment of breast cancer and has recently been approved for breast cancer prophylaxis in the UK. It has been associated with an increased risk of endometrial polyps, hyperplasia and cancer. Results from the National Surgical Adjuvant Breast and Bowel Project P-1 trial reported a doubling of EC risk (RR 2.53 cf. placebo, 95% CI 1.35–4.97), amongst postmenopausal women (RR 4.01, 95% CI 1.70–10.90). Premenopausal women treated with tamoxifen did not have an increased risk of EC (RR 1.21, 95% CI 0.41–3.60) [10].

Adjuvant tamoxifen maybe used up to 10 years after breast cancer treatment and use should be reassessed if endometrial hyperplasia is identified [11]. Pre-treatment screening of postmenopausal women may be beneficial to identify high-risk groups with pre-existing occult abnormalities.

Ultrasound measurements of endometrial thickness are poorly correlated with endometrial pathology in asymptomatic women using tamoxifen due to tamoxifen induced sub-epithelial stromal hypertrophy. Ultrasound has a high false positive rate, even at an endometrial thickness cut-off of 10 mm [12], and a low positive predictive value in this group.

2.2 Prevention in the general population

Maintaining a healthy body mass index (BMI) reduces the risk of EC. Obese women who lose weight through bariatric surgery or lifestyle changes may reduce their risk of EC. Physical activity may be an effective EC risk reduction strategy, particularly for overweight or obese women. (Grade A)

EC ranks highest amongst all cancers in its association with obesity, with every 5 kg/m2 increase in BMI conferring an extra 1.6-fold increased risk of EC. In the ASTEC trial, a ramdomised controlled trial (RCT) of more than 1400 women with early stage EC, 80% of women with type I EC were overweight and 50% were obese [13]. While an average woman has a 3% lifetime risk of EC, obese women have a lifetime risk as high as 9–10%. In Europe,

excess weight has been estimated to account for 60% of all new EC cases per year [14].

Maintaining a healthy BMI is likely to reduce the risk of EC. Women who had a lower BMI in later life compared to their BMI at age 20 were 50% less likely to develop EC compared with those whose BMI had remained constant or increased slightly [15]. Additionally, women who sustained weight loss for five years of more had a 25% lower risk of developing EC than those who had no weight loss [16].

Bariatric surgery (gastric bypass or banding to reduce stomach capacity) can result in 10–15% excess body weight loss by six weeks after surgery with continued weight loss up to about one-year post-surgery [17].

A prospective Swedish study of morbidly obese patients undergoing bariatric surgery or medical weight loss management reported a 38% reduction in cancer incidence in women who sustained weight loss of 20 kg for 10 years or more [18]. A retrospective case-control study found a 38% decrease in cancer incidence, including EC, in the bariatric surgery group compared with controls that were obese [19]. Bariatric surgery also resulted in a seven-fold reduction in incident endometrial cancer risk (14/6596 bariatric surgery patients versus 98/9442 controls who were obese, HR 0.22, $p < 0.0001$) in another retrospective study [20].

The World Cancer Research Fund/American Institute for Cancer Research review concluded that increased physical activity probably reduces EC risk (WCRF/AICR, 2007). A meta-analysis found that moderate physical activity reduces the risk of EC, particularly for obese or overweight women, when compared with low physical activity (OR 0.62, 95% CI 0.44–0.88).

2.3 Prevention in high-risk groups

Risk reducing surgery is an effective means of preventing EC in high risk women. (Grade C)

2.3.1 Supporting evidence

Prophylactic hysterectomy and bilateral salpingo-oophorectomy when fertility is no longer required is an effective strategy for preventing endometrial and ovarian cancer in high-risk women [21]. Women with Lynch syndrome have a 40–60% lifetime risk of EC. A case-control study compared women with documented germ-line mutations associated with Lynch syndrome who had undergone prophylactic hysterectomy with those who had not. There were no occurrences of EC among women who had undergone prophylactic surgery compared with 33% of the control group, yielding a prevented fraction of 100% (95% CI 90–100%) (Schmeler et al., 2006). But surgery is challenging in obese women with increased risk of intraoperative complications and post-operative morbidity.

Alternative approaches which need further investigation include the levonorgestrol intrauterine system and weight loss interventions.

3 Diagnosis of endometrial cancer

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 [22].

3.1 Presenting symptoms

Women with endometrial cancer classically present with 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 endometrial cancer in women presenting with PMB is 5–10% [23], but the chances increase with age and risk factors. Premenopausal and perimenopausal women may present with intermenstrual or prolonged bleeding, often with a background of irregular, dysfunctional menstruation that suggests anovulation.

3.2 Diagnostic methods

3.2.1 Current guidance

In the UK, recommendations for diagnosis and referral are based on guidance from NICE [22,24].

3.2.2 History and examination

Women presenting with PMB, unscheduled bleeding on HRT, persistent prolonged or intermenstrual bleeding should receive an abdominal, speculum and pelvic examination at their clinical assessment. Women with menorrhagia over 45 years, or those with irregular bleeding or failure of treatment over 45, need endometrial sampling. (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 [22]. The clinician should obtain a detailed account of the presenting symptoms, a full drug history (including use of HRT, oral contraceptive pill, tamoxifen), and a gynaecological history (early menarche/late menopause, known endometrial hyperplasia, parity). Medical, family and surgical history may be relevant (obesity, treatment for breast cancer, diabetes mellitus, hypertension, and Lynch syndrome).

3.2.3 Referral pathway

When women not on HRT present with PMB, general practitioners in the UK should refer them to a rapid access gynaecology clinic to be seen within two weeks [22]. Likewise, when a woman who has stopped HRT for at least six weeks previously and then presents with persistent or unexplained bleeding, an urgent referral should be made [22]. Similarly, an urgent referral should also be considered in a patient with postmenopausal bleeding on tamoxifen treatment and those having intermenstrual bleeding with a negative pelvic examination [22].

3.2.4 Investigations

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

The best diagnostic strategy in patients with suspected endometrial cancer still remains controversial. There is a range of investigations available for investigating suspected endometrial cancer and include the TVS, hysteroscopy and endometrial biopsy. The strategy with TVS followed by endometrial biopsy if abnormality is detected is the most cost-effective for the UK population in which the prevalence of endometrial carcinoma is lower than 15% [25]. Adnexal pathology identified at ultrasound should be documented in the ultrasound report and investigated as appropriate.

3.2.5 Accuracy of TVS and cut off for endometrial thickness

Double layer endometrial thickness measurements on TVS with a cut off of $\geq$4 mm should be investigated. In the absence of any irregularity of the endometrial profile, and an endometrial thickness of $<$4 mm, no further investigations are required unless there is recurrent PMB. (Grade B)

TVS is an accurate and precise diagnostic method for endometrial cancer. A comparative study found that calculating endometrial thickness was easier with transvaginal ultrasound than with transabdominal ultrasound [26]. A recent study concludes that the first step in the diagnostic pathway should be the measurement

of endometrial thickness followed by endometrial sampling. Sensitivities of 98%, 95% and 90% to exclude endometrial cancer are seen with cut-off levels of 3 mm, 4 mm and 5 mm of endometrial thickness respectively [24,27,28]. TVS also reliably identifies postmenopausal women with vaginal bleeding who were unlikely to have cancer (thickness of 3 mm or less), which would mean that unnecessary endometrial sampling could be avoided [27]. In postmenopausal women on HRT or tamoxifen and in premenopausal women measurement of the endometrial thickness alone is not diagnostically useful. The upper endometrial thickness limit for postmenopausal women on HRT is 8 mm if asymptomatic [29], but if vaginal bleeding is present a biopsy should be taken if the thickness is greater than 5 mm. The 5 mm cut-off has also been suggested for postmenopausal women on tamoxifen [21]. However, the definitive diagnosis of endometrial cancer is by histological sampling. If the TVS is suggestive of cancer, or if ultrasound is not available, an urgent referral should be made [22].

3.2.6 Endometrial biopsy

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

The Pipelle and Vabra aspirator devices used for endometrial sampling are very sensitive techniques for the detection of endometrial carcinoma [30]. A sample of endometrial tissue should be obtained in the gynaecology outpatient setting. A systematic review of 13 diagnostic evaluations showed that a Pipelle biopsy leads to a high overall diagnostic accuracy when an adequate specimen is obtained (post-test probability of endometrial cancer of 81.7% for a positive test and 0.9% for a negative test), but is also acceptable when an insufficient sample is obtained provided the device was inserted more than 4 cm through the cervical canal [30]. However, further evaluation is warranted in cases of persistent abnormal vaginal bleeding despite negative biopsy.

3.2.7 Hysteroscopy

Hysteroscopy should only be carried out if outpatient endometrial biopsy is not feasible or for women with ultrasound irregularities and at high risk of endometrial cancer. (Grade B)

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

Hysteroscopy tends to be reserved for patients at high risk for endometrial cancer and patients in whom outpatient biopsy was inadequate. It is used with regional or general anaesthesia for those who cannot tolerate outpatient examination and biopsy, and for patients with cervical stenosis which cannot be managed in the outpatient setting. Hysteroscopy also has the added benefit in detecting ultrasound irregularities, such as endometrial polyps. 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 [31]. A positive hysteroscopy result (likelihood ratio 60.9) increased the probability of cancer to 71.8% from a pre-test probability of 3.9%, whereas a negative hysteroscopy result (likelihood ratio 0.15) reduced the probability of cancer to 0.6%.

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

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

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.

4 Pathways for management of endometrial cancer

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 1A endometrioid cancer, G1 or G2, may undergo surgery by a gynaecologist at a Diagnostic Centre who is a core member of an SMDT. (Grade D)

Women with papillary serous, clear cell, carcinosarcoma, endometrioid G3 or FIGO 1 B (≥50% myometrial invasion on MRI) or above should undergo surgery at a Cancer Centre by specialised surgeons who are core members of an SMDT. Women requiring radiotherapy or chemotherapy 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)

The NHS Cancer Action Plan in 2002 set target Cancer Wait Times including the 14, 31 and 62 day targets to see and treat patients who may have a diagnosis of cancer. These were updated in the 2010 document "Going Further on Cancer Wait Times". Women suspected of having endometrial cancer should be referred urgently and seen within two weeks 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).

Providers should analyse data on their local pathways to adjust pathways and capacity to plan treatment in time to achieve these targets [32]. Where investigation is initiated in primary care, TVS should be performed within two weeks of being requested. Existing guidelines for the UK recommend referral to gynaecologist to exclude endometrial cancer.

4.1 Where women are treated

The Improving Outcomes document recommended treatment of endometrial cancer grade 1/grade 2, FIGO Ia in diagnostic centres (cancer units) and of endometrial cancers FIGO Ib or above or grade 3 of any stage will be treated in a cancer centre [33]. The SMDT is now central to planning cancer care in the UK and the 2013/14 NHS Standard Contract for Cancer: Gynaecological (Section B Part 1 – Service Specifications) states that "it is essential that all patients with a suspected gynaecological tumour are discussed at an expert multi-disciplinary team". The SMDT provides the opportunity for peer review of pathology, radiology and clinical decision making, providing quality assurance and support to treating clinicians.

4.2 After treatment

Supportive care and follow up are described in other sections. 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. They should also inform women what to look out for and critically who to contact if they experience problems that suggest

recurrence or side effects or 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.

4.3 Failsafe

Failsafe mechanisms are required to ensure that women needing investigation and treatment negotiate the healthcare system reliably. These mechanisms should encompass all steps along the diagnostic and treatment pathway including appointments and admissions.

Providers should have in place failsafe mechanisms to ensure that women with thickened endometrium undergo proper assessment (biopsy or hysteroscopy) and that all biopsies demonstrating malignancy or atypical hyperplasia 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.

5 Investigations – imaging and pre-operative work-up

Women with endometrial cancer who require elective surgery in the NHS should have access to a holistic assessment with a nurse specialist or key worker. (Grade D)

Qualitative surveys suggest that nurses save money [34], increase service efficiency [35] and patient satisfaction with their cancer journey [36]. Expert opinion and current UK service provision mandate that all women in the NHS with a new diagnosis of endometrial cancer should have access to a nurse specialist as part of surgical preparation.

Some form of pre-operative surgical assessment is needed to assess the appropriateness and route of surgery. (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.

CA125 estimation occasionally may direct investigations toward detecting unexpected metastatic disease. (Grade D)

CA125 is often raised non-specifically in the presence of bulky metastatic disease. Its place has not been tested in any randomised trial but 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 mandatory routine practice.

5.1 Imaging

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

Imaging of the chest and pelvis 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 and may spare women with chest metastasis from undergoing unnecessary surgery.

Women with high risk histology types (for example grade 3 endometrioid endometrial cancer, uterine serous cancer, clear cell cancer) should be recommended to be undergo further imaging by abdomino-pelvic MRI or CT scan. MRI is optional in women with low risk histology types. (Grade D)

All women with a high risk of potential metastases should have a CT of the chest abdomen and pelvis preoperatively to help plan surgery or potentially avoid upfront surgery if metastatic disease is found. The yield from CT scanning in low risk disease is very small, is very unlikely to alter the ultimate outcome and is not mandatory. (Grade D)

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. (Grade D)

See Appendix for FIGO staging and stratification of endometrial cancer by risk categories. A review of 702 women with primary endometrial carcinoma, showed that pre-operative CT findings altered treatment plans in only six patients [37]. 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 [38]. 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 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 can provide useful information on depth of myometrial infiltration, which can be used to triage patients into surgery at cancer units or centres.

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

A systematic review of 18 studies (693 women) with endometrial cancer found that MRI is the most accurate tool to determine the lymph node status of patients [39]. MRI scanning should be performed to set protocols of imaging and should ideally be interpreted by radiologists with expertise in gynaecological cancer.

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

There is no reliable data to support the routine use of preoperative PET staging in endometrial cancer.

6 Pathology of uterine cancer

Uterine cancer is broadly classified into endometrioid and non-endometrioid histological types. A further classification based on FIGO staging and prognosis is detailed in the appendix.

These guidelines are based on the RCPath guidelines for reporting endometrial carcinomas. The diagnosis and management of endometrial carcinoma is based on robust pathological input. Correct typing and grading of endometrial carcinomas determine the type of surgical management. After hysterectomy, certain features of endometrial carcinoma, such as the type and grade of carcinoma, the presence of cervical involvement, depth of myometrial invasion, serosal breach and lymph node involvement will determine whether adjuvant therapy will be administered and the choice of adjuvant therapy. In addition, accurate typing of endometrial cancers will allow epidemiological information to be collected with regard to cancer subtypes and their association with genetic syndromes. This is now mandatory for enrolment of patients into trials. Use of a structured pathology reporting with a data set in the report allows easy extraction of the necessary information [40].

6.1 Clinical information required on the specimen request form

Provision of accurate clinical details assists diagnosis of pathology in biopsy and hysterectomy specimens. Clinical details should include patient demographic details, clinical presentation, results of previous biopsies and radiological investigations for

tumour staging, and details of the surgical procedure especially the type of hysterectomy performed. It is desirable to include details of any family history of cancer and relevant hormonal therapy. The nature of surgical specimens from multiple sites should be carefully recorded and the specimen pots should be labelled to correspond to the specimen details on the request form and appropriately labelled as to site of origin.

6.2 Reporting of small biopsy specimens

Most endometrial carcinomas are diagnosed on biopsies that are obtained by either an outpatient sampling procedure or endometrial curettage under anaesthesia. In some cases, formal curettage may be required to obtain sufficient tissue for tumour diagnosis, typing and grading. When handling endometrial biopsy specimens, all of 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 but correlation for tumour type is good. 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 [41]. 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.

6.3 Reporting of frozen sections

In most institutions in the UK, intra-operative frozen sections are rarely performed in patients with endometrial carcinoma. Frozen sections may be performed occasionally to confirm endometrial carcinoma when there is no preoperative diagnosis, determine the nature of unexpected and clinically suspicious extra-uterine lesions at surgery for endometrial carcinoma, evaluate depth of myometrial invasion and look for metastasis in suspicious lymph nodes. It is important that clinicians who request frozen sections are cautioned about the potential limitations of the technique.

6.4 Testing for mismatch repair proteins

Lynch syndrome occurs due to a germline mutation in one of a family of DNA 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. For Lynch syndrome, ancillary tests of immunohistochemistry for mismatch repair proteins (MMR) and PCR-based microsatellite instability (MSI) analysis are emerging as key components of the clinical evaluation of this syndrome. Routine testing for mismatch repair proteins may need to be incorporated into standard care in the UK NHS in the near future.

7 Endometrial cancer –surgery at presentation

7.1 Early disease (FIGO stage I and II)

Surgery may be limited to hysterectomy and bilateral salpingo-oophorectomy in those patients with grade 1 or 2 endometrioid adenocarcinoma which appears confined to the uterus. However, there will be a proportion of women who may require further surgery or adjuvant treatment using this approach due to underestimation of histological grade on pre-operative biopsy or the presence of other risk factors on final histological examination. (Grade D)

Lymphadenectomy in this instance does not improve survival or reduce the risk of disease recurrence. There is no evidence to support routine lymphadenectomy in low risk endometrial cancers. (Grade A)

A recent Cochrane review [42] identified two large RCTs randomising women with pre-operative clinical stage I endometrial cancer to either pelvic lymphadenectomy or palpation and removal of enlarged nodes at the surgeons' discretion. This included the multinational ASTEC study by Kitchener et al. [43], which enrolled women with disease of all histological types and the smaller trial by Benedetti-Panici et al. [44] which included only those with at least stage Ib or high grade endometrioid or adenosquamous carcinoma. The latter study compared outcomes following systematic pelvic lymphadenectomy of at least 20 lymph nodes to removal of enlarged nodes only. The meta-analysis, based on the results of 1851 participants, showed no statistically significant difference in the risk of death (HR = 1.07, 95% CI 0.81–1.43) or disease recurrence (HR = 1.23, 95% CI 0.96–1.58) in women undergoing lymphadenectomy compared to those who had not, after adjusting for age and tumour grade. Indeed, women who had lymphadenectomy performed were more likely to suffer from surgically related systemic morbidity, namely lymphoedema and lymphocysts (RR 8.39, 95% CI 4.06–17.33).

The concordance between pre and post-operative histology has been variably quoted at 52–96% in prospective and retrospective studies [45,46]. A Canadian group found only moderate concordance between pre and post-surgical histology and this was affected by grade of endometrial cancer with grade 1 tumours having 73% concordance compared with 52% and 53% in grade 2 and 3 disease [46]. The incidence of pelvic lymph node metastases increases with grade of tumour and degree of myometrial invasion [47]. Of women with grade 3 and clinical stage I disease with outer myometrial invasion, 28% were subsequently found to have lymph node involvement. Accurate prediction of myometrial invasion and grade of histology are, therefore, required pre-operatively to ensure that patients receive appropriate surgical treatment.

There are no randomised controlled trials comparing pelvic and para-aortic lymphadenectomy with either pelvic lymphadenectomy alone or no lymphadenectomy.

Sentinel lymph node biopsy appears to have good diagnostic performance, is likely to provide a useful balance between achieving adequate staging whilst minimising morbidity and may be a useful service development for centres to undertake. Currently more evidence is required to support its inclusion in routine clinical practice. (Grade B)

A multicentre observational study carried out by Ballester et al. in nine French centres reported a sensitivity of 84% (95% CI 62–95%) and negative predictive value of 97% (95% CI 91–99%) for the detection of lymph node metastases using sentinel lymph node biopsy in women with presumed stage I–II endometrial cancer of differing histological types. Indeed 11% of low risk and 15% of intermediate risk endometrial cancers were associated with positive lymph node metastases that would otherwise not have been detected if lymphadenectomy had not been performed (see Appendix iii, stratification of endometrial cancer risk of recurrence). As 50% of high risk endometrial cancers (type I endometrial cancer, grade 3 stage Ib and type II tumours) had metastases, sentinel lymph node biopsy could not be recommended routinely in this group [48]. A meta-analysis performed by Kang et al. prior to the publication of the French study reported a similar sensitivity 93% (95% CI 87–100%) but noted that the included studies were

small in number and had significant heterogeneity [49]. The impact of sentinel lymph node biopsy on adjuvant treatment use, overall and disease free survival has yet to be determined, limiting its clinical applicability.

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

Laparoscopic surgery is not associated with a significant adverse impact on disease recurrence and overall survival. (Grade A)

A Cochrane review identified eight RCTs which evaluated the role of total laparoscopic hysterectomy (TLH) or laparoscopic assisted vaginal hysterectomy (LAVH) in 3644 women with early stage disease compared to conventional total abdominal hysterectomy. Details of specific adverse events were lacking but there appeared to be a reduction in severe post-operative complications in the laparoscopy arm (RR 0.58, 95% CI 0.37 to 0.91) and an average shorter hospital stay [50].

The meta-analysis of available data showed no difference in overall survival or the risk of disease recurrence between the two groups (HR 1.14, 95% CI 0.62–2.10, HR 1.13, 95% CI 0.9–1.42, respectively). However, the authors were unable to include outcome data from the largest GOG trial LAP 2 as it had yet to be published [51]. This latter study did not confirm non-inferiority of laparoscopic surgery in comparison to laparotomy with recurrence rates at three years of 11.4% in the laparoscopy arm compared to 10.2% in the open surgery group (HR for laparoscopy 1.14, 95% CI 0.92–1.46). This should be interpreted in the light of a recurrence rate that was lower than anticipated and that recurrence and survival were not included as end points in the original study design leading to almost a quarter of participants being lost to follow-up. This trial does not, however, exclude the possibility that laparoscopic surgery may be associated with a small increase in recurrence. Nevertheless, NICE have not revised their original guidance and have continued to endorse the use of TLH and LAVH for the treatment of early stage endometrial cancer [52].

Robotic surgery appears to be non-inferior to laparoscopy for the treatment of endometrial cancer, but has a higher cost association. (Grade C)

There are no RCTs comparing robotic assisted surgery for gynaecological cancer with open or laparoscopic surgery. The limited data available supports the non-inferiority of robotic surgery compared with laparoscopy for the management of endometrial cancer in terms of both short term morbidity (intra-operative complications 4% vs. 3%, $p = 0.18$; surgical site complications 1.8% vs. 2.9%, $p = 0.08$) and survival [53,54]. The use of a robot, even in large centres, was associated with an additional cost of $818 per case [53]. Longer term survival and recurrence data would be needed to establish the role of robotic surgery in this area, though these data are likely to be difficult to obtain in randomised studies.

A study comparing outcomes for obese and morbidly obese women undergoing total robotic hysterectomy with a retrospective cohort who underwent laparoscopic hysterectomy demonstrated a significantly shorter operating time (189 mins vs. 215 mins, $p = 0.0004$), estimated blood loss (50 mls vs. 150 mls, $p < 0.0001$), mean hospital stay (1.02 days vs. 1.27 days, $p = 0.0119$) and fewer operative complications (6.5% vs. 17.3%) [55]. There was no difference in conversion rate to laparotomy between the two groups. Whilst these data are based on fewer than 50 women in each group it suggests that robotic surgery may have a role to play in the treatment of endometrial cancer in obese women.

A Cochrane review reported limited evidence on the effectiveness and safety of robotic surgery compared with conventional laparoscopic surgery or open surgery for surgical procedures performed for gynaecological cancer [56].

Radical hysterectomy is an alternative to simple hysterectomy and adjuvant radiotherapy for patients with overt stage II disease. Radicality should be limited to provide clear tumour margins from surgery. (Grade B)

There are no randomised data comparing radical hysterectomy with simple hysterectomy for the treatment of stage II disease but the results of several small series [57–60] support data from three large retrospective studies [61–63] which suggest that patients with stage II disease appear to have similar survival with either simple hysterectomy and adjuvant radiotherapy or radical hysterectomy alone. Patients treated with simple hysterectomy and no adjuvant treatment, however, have a poorer prognosis than those treated with simple hysterectomy and adjuvant radiotherapy or radical hysterectomy alone. Operative complications appear to be similar between the two groups, however, longer term morbidity data in relation to the addition of radiotherapy treatment in those undergoing simple hysterectomy was not documented [64].

Surgical staging, including pelvic and para-aortic lymphadenectomy and omental biopsy, may be appropriate for women with high grade disease and non-endometrioid endometrial cancers. (Grade C)

These patients should be operated on in a cancer centre. (Grade D)

Minimal access surgery can be used for these patients. (Grade A)

Recruitment of patients with high grade disease and non-endometrioid endometrial cancers into trials investigating lymphadenectomy and/or sentinel node surgery is strongly recommended. (Grade C)

There are limited data available on the management of non-endometrioid endometrial cancers due to their relative rarity. Non-endometrioid tumours were included in the ASTEC randomised trial by Kitchener et al. and there was no demonstrable benefit to the addition of lymphadenectomy in these cases. Numbers were small, with type II cancers comprising less than 10% of the study population. Lymphadenectomy was also limited to pelvic node dissection rather than pelvic and para aortic node dissection. For these reasons lymphadenectomy continues to be practiced by many. Work is now required to establish patterns of lymph node involvement in these tumours, the accuracy of sentinel node assessment and whether lymphadenectomy can be used to direct adjuvant therapy by allowing the omission of adjuvant treatment in women who are node negative. Wherever possible, patients with non-endometrioid tumours should be recruited to ongoing clinical trials.

7.2 Late disease (FIGO stage III and IV)

Complete surgical resection of all visible disease in advanced endometrial cancer may be considered in selected patients who are fit to undergo surgery as limited evidence shows this may prolong survival. (Grade C)

A meta-analysis performed by Barlin et al. included 14 small retrospective non-randomised analyses evaluating the role of surgery in the setting of advanced and recurrent endometrial cancer [65]. A range of histological subtypes, adjuvant treatments and definitions of 'optimal' surgical treatment were included in the analysis. The limited number of studies available made multivariate analysis impossible. For each 10% increase in the proportion of patients undergoing complete surgical resection of the disease there was an associated 9.3-month increase in survival ($p = 0.04$). Increasing the proportion of women having 'optimal' (variably defined) surgical resection was associated with a prolongation in survival that did not reach statistical significance (change in median survival 16 months, $p = 0.05$). Complete surgical resection was possible in 18–75% of cases. Similarly, Eto et al. demonstrated a

15-month increase in overall survival when complete resection of intra-abdominal metastases was performed in patients with stage IVb endometrial cancer (median overall survival 48 months complete resection vs. 23 months 'optimal' resection vs. 14 months 'suboptimal' resection) [66]. The presence of intra-abdominal residual disease remained an independent prognostic factor.

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

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 [44].

Complete resection of macroscopic nodal disease may be associated with an improvement disease specific survival but data are at high risk of bias. (Grade C)

A retrospective observational study of 41 patients with Stage IIIc endometrial cancer found a significantly longer disease specific survival time in those patients with complete resection of macroscopic nodal disease compared with those with residual gross disease (37.5 months vs. 8 months, $p = 0.006$) [67]. 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 [68].

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

The use of neoadjuvant chemotherapy in the context of treating advanced endometrial cancer has not been formally assessed in randomised controlled trials and is addressed separately (see chapter 9).

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

There is limited evidence regarding the role of palliative surgery in endometrial cancer. Hysterectomy can 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 [69]. Decisions regarding the role of surgery in this setting should be made on an individual basis taking into consideration patient wishes and symptoms within the MDT setting. A national register of patients undergoing neaoadjuvant chemotherapy for endometrial cancer is an aspiration.

8 Adjuvant treatment of endometrioid endometrial cancer

This section provides evidence-based information on the adjuvant options after hysterectomy for endometrioid endometrial cancer. In this setting, it describes non-medical therapy, hormonal therapy, radiotherapy, chemotherapy and concomitant chemo-radiotherapy after a hysterectomy for early (stage I or II) uterine adenocarcinoma and may also have relevance in stage III but completely resected disease. The purpose is to improve the chance of cure, prolong life or change the pattern of recurrent disease.

High-dose progesterone must always be avoided. (Grade A)

Routine use of adjuvant progesterone is not recommended as it may cause side effects, may increase the risk of death from cardiovascular disease and there is no evidence that routine use will affect the outcome. (Grade A)

There is no role for adjuvant progesterone in early stage endometrial cancer outside of a clinical trial. (Grade A)

8.1 Progesterone therapy

Seven randomised trials [70–76] involving 4556 women showed that the routine use of hormone therapy after hysterectomy does not improve cure rates, recurrence rates or the pattern of recurrent disease [77]. Progesterone in hormone replacement therapy has been shown to increase the risk of death, myocardial infarction, stroke, thrombosis, breast cancer [78] and other data suggests it may affect mood adversely and increase water retention. This is consistent with other established knowledge about progesterone biology and physiology. Furthermore, even in advanced cancer, data from six randomised trials [79] involving 542 women found that hormonal treatment does not improve survival.

For low risk endometrioid endometrial cancer, there is no improvement in survival and additional harm and mortality from routine adjuvant radiotherapy and it is not recommended. (Grade A)

For intermediate risk endometrial cancer, in the absence of risk factors such as lymphovascular invasion (LVSI), external beam radiotherapy has no overall survival benefit over vaginal brachytherapy. External beam radiation reduces the risk of local relapse but has a negative impact on quality of life in patients. Patients with intermediate risk endometrioid endometrial cancer must therefore make fully informed decisions about adjuvant radiotherapy in this setting. (Grade A)

For high risk endometrioid endometrial cancer, expert opinion and observational studies support the use of adjuvant pelvic external beam radiotherapy, pending the results from randomised controlled trials. This is because of the possibility of a survival advantage and the proven reduction of risk from suffering pelvic recurrence. Women have to balance these advantages against the long term reduction in quality of life caused by pelvic radiotherapy. (Grade A)

In patients with high risk endometrial cancer who have undergone lymphadenectomy, there is no role for adjuvant radiotherapy in patients with proven node negative status. (Grade C)

(see Appendix iii for risk stratification in endometrial cancer)

8.2 External beam radiotherapy

Level 1a evidence from meta-analysis of seven randomised trials involving 3628 women shows that radiotherapy does not improve overall survival rates nor survival duration significantly [80,81]. Adjuvant radiotherapy delays the onset of recurrence in the pelvis and alters the pattern of recurrence to that of distant metastases [82]. Five randomised trials show no survival advantage from radiotherapy and there is evidence of harm [83–90]. However, a meta-analysis found a significant benefit of about 10% improved OS for external beam radiotherapy with FIGO Ib, grade 3 tumours [91]. Randomised trials restricted to low risk cancers show a significantly higher death rate in women allocated radiotherapy. Only the GOG99 [92] and a small unpublished preliminary abstract report (but probably still reliable) [93] support external beam pelvic radiotherapy. These trials examined high risk stage I cancer but even this combined data of 334 women has a non-significant improved hazard ratio HR 0.91 (0.60 to 1.39) for overall survival duration. The suggestion that there may be a survival advantage was refuted by a subgroup analysis of the ASTEC data.

Some centres use pelvic and para-aortic lymph node histology to triage patients for adjuvant external beam radiotherapy. However, there is no evidence that delivering external beam radiotherapy after lymph node dissection will add anything to pelvic disease control. Isolated pelvic recurrence can be salvaged in

the majority of women with radiotherapy [94] or chemoradiotherapy. In PORTEC-1 the majority of the locoregional relapses were located in the vagina, mainly in the vaginal vault. Of the 714 women who were evaluated, 39 had isolated vaginal relapse, 35 (87%) were treated with curative intent, usually with external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT), and surgery in some. A complete remission was obtained in 31 of the 35 (89%), and 24 (77%) were still in complete remission after further follow-up. Five subsequently developed distant metastases, and two had a second vaginal recurrence. The three-year survival after vaginal relapse was 73%. At five years, the survival after vaginal relapse was 65% making an observation programme an attractive alternative to a policy of routine radiotherapy.

Long term follow-up of women in the PORTEC 2 trial [87] shows that late toxicity from EBRT compared with VBT is highly significant. Women who received EBRT had significantly 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" ($P = 0.009$).

Modern radiation techniques with intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) are expected to lead to a significant reduction in late toxicity.

The greatest benefit from adjuvant radiotherapy is linked to a reduced risk of local recurrence. It follows that radiotherapy for stage II endometrial cancer might have a greater role than in stage I cancer. However, there are no randomised trials to guide us and observational studies do not support radiotherapy. For example, the SEER database [61] suggests that the five-year cumulative survival rate for women with stage II uterine corpus adenocarcinoma who received surgery alone as primary therapy was 84.4% with simple hysterectomy and 93.0% with radical hysterectomy ($P < 0.05$). Survival after radiation and surgery was 82.9% with simple hysterectomy and 88.0% with radical hysterectomy ($P < 0.05$) implying no significant survival difference for radiation versus no radiation in either surgical group. Observational studies have limited value as women selected for more aggressive therapy will have less co-morbidities and a greater expected survival. Nevertheless, other observational studies also fail to support radiotherapy for uterine cancer extending to the cervix [95].

Vaginal brachytherapy can reduce the small risk of vaginal vault recurrence after surgery for endometrial cancer. However, women have to understand that vaginal brachytherapy does not confer a survival advantage. (Grade A)

8.3 Brachytherapy (vaginal vault radiotherapy)

Adjuvant treatment will only avoid a small number of women having to undergo more radical therapy should they suffer an isolated vault relapse. Only one randomised trial [96] has compared brachytherapy with no additional treatment and this was confined to low-risk women. There was no survival advantage from VBT but there is a non-significant reduction in loco-regional recurrence in the VBT group (RR 0.39, 95% CI 0.14 to 1.09). Observational studies and expert opinion support this reduction. Survival is not affected because isolated tumours that only recur in the vaginal vault with no distant metastases can be salvaged [94].

The above sections are condensed below and provide guidance in adequately staged patients with early stage endometrioid endometrial cancer (modified from ESGO guidelines[2]).

Low risk	FIGO grade 1, Stage Ia, Ib, no LVSI FIGO grade 2, Stage Ia, no LVSI	No adjuvant treatment
Intermediate risk	FIGO grade 2, Stage Ib, no LVSI FIGO grade 3, Stage Ia, no LVSI	Vaginal brachytherapy
High-intermediate risk	FIGO grade 3, Stage 1a, regardless of LVSI FIGO grade 1, grade 2, LVSI unequivocally positive, regardless of depth of invasion	Consider external beam radiation versus vaginal brachytherapy if nodal status unknown. Consider adjuvant brachytherapy versus no adjuvant therapy if node negative
High risk	FIGO grade 3, Stage Ib	Consider external beam radiation versus vaginal brachytherapy. Consider adjuvant chemotherapy.

8.4 For late stage disease

Recent ASCO/ASTRO guidelines for endometrial cancer have been published [97]. ASTRO recommends radiation therapy without chemotherapy for patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder or rectum, ASCO also recommends the use of chemotherapy. ASTRO endorsed concurrent chemoradiation followed by adjuvant chemotherapy for patients with positive nodes. ASCO noted that this recommendation is based on expert opinion and limited data, clinical trials are underway to provide more insight in this area.

8.5 Chemotherapy

Postoperative platinum-based chemotherapy is associated with a small benefit in progression-free survival and overall survival irrespective of radiotherapy treatment. It can be recommended as an option for well-informed women with high risk endometrioid adenocarcinoma and minimal comorbidities but they should be realistic in accepting the toxicity and small potential survival advantage. (Grade B)

There are nine randomised trials [98–105] examining the role of adjuvant chemotherapy for high risk, high grade endometrial carcinomas; however all have 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 2197 women shows a small but statistically significant overall survival advantage from adjuvant chemotherapy [106] (RR 0.88 (95% CI 0.79–0.99)). Sensitivity analysis focused on trials of modern platinum based chemotherapy regimens and found the relative risk of death to be 0.85 (95% CI 0.76–0.96); number needed to treat for an additional beneficial outcome (NNT) was 25 and an absolute risk reduction of 4% (1%–8%)). The HR for overall survival was 0.74 (0.64–0.89), significantly favouring the addition of postoperative platinum-based chemotherapy. The HR for progression-free survival was 0.75 (0.64–0.89). This means that chemotherapy reduces the risk of being dead at any censorship by a quarter. Chemotherapy reduces the risk of developing the first recurrence outside the pelvis (RR = 0.79 (0.68–0.92), 5% absolute risk reduction; NNT was 20). The analysis of pelvic recurrence rates was underpowered but the trend suggests that chemotherapy may be less effective than radiotherapy in a direct comparison (RR 1.28 (0.97–1.68)) but it may have added value when used with radiotherapy (RR 0.48 (0.20–1.18)).

Despite the statistics quoted, the precise survival advantage is difficult to quantify because the studies are heterogeneous. Clearly

a 4% survival advantage to someone over the age of 70 is relatively trivial compared to the toxicity of additional treatment. Nevertheless, it remains an option for younger women with minimal co-morbidities. Many of the trials use doxorubicin and a platinum agent. There is no evidence in the adjuvant setting that one regime is better than another. One popular and reasonable modern trend is to use the untested regimen of carboplatin combined with paclitaxel (four doses).

Chemotherapy contrasts with radiotherapy. The immediate toxicities are different and depend on the chemotherapy regime used. As no particular regime has any obvious advantage, the therapy can be tailored to the individual's preference. The lack of significant long term toxicity is one advantage of chemotherapy over radiotherapy.

Concomitant chemotherapy and radiotherapy should be used only in the context of a clinical trial. (Grade D)

There is no randomised data to support the use of chemo-radiation (giving chemotherapy together with radiation therapy). There are data from other tumour groups that chemoradiation is more toxic but more effective than radiotherapy alone. However, endometrioid cancer has relatively low recurrence rates and at the current time, chemoradiation is still experimental. PORTEC-3 evaluates this and results are awaited with interest.

9 Neoadjuvant chemotherapy in endometrial cancer

For more advanced cases where there is evidence of extra-uterine spread or significant lymph node metastases at time of primary diagnosis, there is a considerable controversy about the optimal management and in some centres primary surgery is offered. Despierre et al. in 2006 first reported the use of neoadjuvant chemotherapy (NACT) in uterine cancer [107].

NACT and delayed primary surgery may be an alternative approach in the treatment of selected patients with advanced endometrial cancer who are considered poor candidates for upfront surgery. Generally, NACT would be reserved for patients where it would be expected that primary debulking surgery would not achieve complete macroscopic resection. Recruitment into trials investigating this approach is strongly recommended. (Grade D)

NACT may be considered in selected cases with evidence of disease breaching through the serosa and where there is evidence of significant pelvic and para-aortic nodal spread after careful discussion at the SMDT. Evidence for NACT is limited to a small number of case reports and case series who were not candidates for primary debulking surgery. With this approach, Despierre reported in a series of 24 patients that 22 (92%) had complete cytoreduction (no residual tumour), and two (8%) had optimal cytoreduction [107].

In uterine corpus cancer, there has been increasing adoption of the use of NACT in selected cases but to date there have been no randomised clinical trials which have substantiated its place. Nevertheless, it is reasonable for individual cases to be discussed at the SMDT to determine whether neoadjuvant chemotherapy may be considered.

The choice of chemotherapy will usually be carboplatin and paclitaxel. The optimal chemotherapy schedule of carboplatin and paclitaxel (CP) is derived from the similar responses of endometrial cancer to epithelial ovarian cancer. (Grade D)

This is clearly superior to cisplatin and doxorubicin in terms of its reduced toxicity and deliverability. It is debatable whether there would be justification to carry out a clinical trial of these regimes.

10 Management of unfit patients with endometrial cancer

Women who are unfit for standard treatment for endometrial endometrioid disease (i.e. hysterectomy and bilateral salpingo-oophorectomy under general anaesthesia) either due to morbid obesity or intercurrent medical conditions may be considered for vaginal hysterectomy, definitive pelvic radiotherapy or conservative management with progestogens/aromatase inhibitors. The choice of treatment will be influenced by patient characteristics and local preferences. (Grade D)

Vaginal hysterectomy is likely to offer good palliation in women with non-endometrioid cancer who are less likely to respond to alternative management such as progestogens. (Grade D)

10.1 Vaginal hysterectomy

Women who are unfit for standard treatment may undergo simple vaginal hysterectomy, with removal of ovaries where possible under regional analgesia. This might be curative for the majority of stage I disease [108] or might act as palliation for symptoms. A pre-operative MRI or CT scan will determine if there is any bulky lymphadenopathy or metastatic disease present. For some patients, regional anaesthesia will be equally problematic and if surgery under any form of analgesia is contra-indicated, then the choices are either radiotherapy or progestogen therapy in women with endometrioid disease. Patients with extreme co-morbidities might not be suitable for intracavitary treatment as this requires either general or regional anaesthesia to correctly position the radiotherapy sources.

10.2 Radiotherapy

Endometrial cancer is radiosensitive and radiotherapy may be used as a sole treatment modality. Although there have been no direct comparisons of primary radiotherapy with surgery in women with local disease and significant co-morbidities, early case series suggest that primary radiotherapy has inferior survival rates compared to hysterectomy, with the risk of intrauterine recurrence. Radiotherapy as primary treatment of endometrial cancer is only considered in exceptional cases, recurrence rates of up to 18% have been reported in these patients in a recent retrospective study [109].

Radiotherapy is administered either as a combination of EBRT and VBT or VBT alone [109]. The justification for using EBRT is that some patients have occult pelvic sidewall disease particularly with high grade tumours and its inclusion might improve outcomes. The inclusion of EBRT might be considered over-treatment in early stage low grade disease and reports suggest a 5–20% rate of late radiation toxicity when combining external beam and intracavitary radiotherapy [110]. However, if imaging suggests more advanced stage uterine tumours this combined approach might be justifiable.

External beam radiotherapy of the pelvis in obese patients is also complicated by anatomical changes in these patients. The target organ may shift resulting in a reduced dose that is delivered to it. Higher failures with radiotherapy to pelvic cancers have been reported in prostate cancer for obese patients [111]. Image guided planning and treatment may overcome some of these problems.

The majority of early publications report on low-dose-rate (LDR) brachytherapy which is no longer used in the UK, with later studies reporting on high-dose-rate (HDR) brachytherapy. HDR offers the benefit of shorter treatment times. These case series tend to include women who are unfit for surgery due to medical co-morbidities including significant obesity and the majority of published case series were conducted prior to computerised radio-planning. In these case reports, death rates due to intercurrent disease were high but reported disease specific five-year survival rates [109] were similar to surgical cure rates.

10.3 Progestogens

There are no large case series reporting on the outcome of such medical management as a primary treatment and the long-term outcome of such management is unclear.

Most case series have relatively short duration of follow-up. Women with endometrioid endometrial cancer with morbid obesity and/or co-morbidities that prevent them having curative surgery or radiotherapy may be considered for progestogen therapy. The levonorgestrel-releasing intra-uterine system (IUS) has the advantage of good compliance and reduced side effects compared to oral progestogen therapy. However, the vast majority of published data are retrospective non randomised observational studies which have evaluated the response to oral progestogens, particularly in young women wishing to retain their reproductive function. There is limited robust evidence on regression and relapse rates in older women with endometrioid endometrial cancer treated by either IUS or oral progestogens. Similarly, there are no large case series reporting on the outcome of such medical management as a primary treatment and the long-term outcome of such management is unclear as most case series have a relatively short duration of follow-up.

Generally, the recommended oral progestogens are megestrol (160 mg daily), or medroxyprogesterone acetate (200 mg/400 mg daily). However as stated above, a much lower dose is likely to be equally effective and in patients with a history of cardiac failure so being less problematic with respect to fluid retention. Aromatase inhibitors may be an alternative in such patients. The comparative efficacy of progestogens and aromatase inhibitors has never been investigated in a randomised controlled trial.

The Australian FEMME trial randomizes such patients to the IUS, IUS with weight loss or the IUS and metformin. Results of this trial are currently awaited.

11 Management of women wishing to preserve their fertility

Current evidence suggests that conservative management of endometrial cancer may be safe in the short term in selected women with grade 1 endometrial cancer and with superficial myometrial invasion. (Grade C)

Women with endometrial cancer desiring fertility should be counselled carefully about the current known response rates on progestogens and progression risk. (Grade D) SMDT should involve specialist gynae-pathology review, MRI imaging to exclude >50% myometrial invasion, adnexal or nodal involvement, follow-up with regular endometrial sampling and individualised care in their management. (Grade D)

Less than 5% of endometrioid endometrial cancers occur in women under 45 years of age. Some of these women will not have had children and will want to preserve their reproductive potential. Present evidence suggests that progestogens can be a primary treatment for selected patients. These women will need to be carefully discussed within a multidisciplinary forum, ideally at centres with expertise in this approach. The initial diagnostic pathology will require expert peer review and ideally an MRI scan should be organised whatever the grade of disease. The SMDT will have to determine if imaging and pathological characteristics suggest that the disease is low grade and confined to the endometrium (or with only superficial myometrial invasion). Such patients will have a minimal risk of metastatic disease or local invasion and therefore a higher chance of regression or cure of disease with progestogens. Synchronous ovarian cancers have been reported in up to 25% of young women with uterine disease. Careful evaluation of ovarian cysts found on imaging need to be assessed by expert review and need to carefully managed.

The majority of published case series have only included grade 1 endometrioid endometrial disease. Patients with higher grades should be excluded. There are currently only three published studies that have evaluated the outcomes after IUS administration and in contrast over 30 studies have assessed outcomes after oral progestogens for six to 12-month duration for administration. Initial reports suggest similar outcomes with IUS with better compliance. Pooled outcomes from case series suggest a regression rate of 76%, a relapse rate of 26% and live birth rate of 26% [112].

Patients should be informed of the need for future hysterectomy in case of failure of the treatment and/or after pregnancies. Medroxyprogesterone acetate (400–600 mg/day) or megestrol (160–320 mg/day) are the recommended treatments [113,114]. However, treatment with the IUS with or without gonadotropin releasing hormone analogues can also be considered.

Most authorities recommend regular endometrial biopsy in the first year and twice yearly subsequently. After successful pregnancy, particularly if predisposing factors persist such as obesity or diabetes, hysterectomy should be considered.

These women should be offered genetic counselling and investigation to exclude hereditary non-polyposis colorectal cancer (HNPCC). The Australian FEMME trial may address management of young women wishing to retain their fertility.

12 Non – endometrioid cancer: uterine serous carcinoma

Although uterine serous carcinoma (USC) comprises only 10% of the cases of endometrial cancer, it is highly aggressive and disproportionally accounts for 39% of all deaths from endometrial cancer. Clinically, USC behaves more like high grade serous ovarian cancer than the endometrial cancer with high rates of extra-uterine and intra-abdominal disease spread [115,116]. USC is associated with a high rate of recurrent disease and a high mortality rate at recurrence [117,118].

Accurate surgical staging including peritoneal cytology, hysterectomy, bilateral salpingo-oopherectomy, omental, peritoneal biopsies, is necessary to identify or exclude the presence of extrauterine disease and adequately define the FIGO stage. (Grade C)

In case of peritoneal tumor dissemination, optimal cytoreduction with maximal surgical effort to obtain minimal residual disease may confer survival benefit. (Grade C)

Systematic pelvic and para-aortic lymph node dissection may be appropriate. Recruitment into trials investigating lymphadenectomy and possible sentinel node surgery in this group is strongly recommended. (Grade C)

Although the depth of myometrial invasion or presence of lymphovascular invasion has been historically recognised as adverse prognostic features of endometrioid endometrial cancer, presence of metastatic disease in USC patients has been frequently reported even in the absence of the above features [119–124]. High rates of extra-uterine disease spread have been reported in 37–63% of USC patients with no evidence of myometrial invasion [121,123,124]. Surgical staging is therefore mandated and should include total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings and cytology, retroperitoneal lymph node sampling and biopsy of any suspicious lesion [125].

Although two RCTs; ASTEC and Benedetti-Panici et al. have categorically demonstrated that lymphadenectomy does not improve survival in endometrial cancer, neither was powered to detect a survival difference in high risk poor prognosis histology types. There were 35 USC patients in the retrospective SEPAL study which investigated pelvic versus pelvic and para-aortic lymphadenectomy in 671 women with intermediate or high risk endometrial cancer. There was an overall survival benefit in favour

of pelvic and para-aortic lymphadenectomy cohort (HR 0.53, 95% CI 0.38–0.76; p = 0.0005) [126].

Multiple studies have also demonstrated that optimal cytoreductive surgery in advanced metastatic USC is associated with improved recurrence free and overall survival [127–130].

For stage I surgically staged USC, vaginal brachytherapy (VBT) is recommended. Addition of external beam radiotherapy (EBRT) is not associated with reduction in the rate of distant disease spread and does not improve the recurrence free or overall survival. (Grade B)

There is no consensus on the use of adjuvant therapy in stage Ia surgically staged USC. However due to the high risk or recurrence and extra-uterine metastatic disease with early stage USC, adjuvant therapy either as wider field radiotherapy or systemic chemotherapy are increasingly administered.

Multiple retrospective small studies have investigated the association between abdominal and pelvic radiotherapy and the risk of recurrence [131–134]. Lim et al. studied 43 clinical stage I USC cases treated with whole abdominal radiotherapy and pelvic boost and showed that 70% of recurrences occurred in the irradiated field [135]. Also in a study by Huh et al., of 60 surgically staged stage I USC patients, 40% received no adjuvant therapy, 20% received adjuvant radiotherapy and 12% adjuvant chemotherapy. No difference in recurrence was seen between patients who had received adjuvant radiotherapy alone or no adjuvant therapy at all [133].

ASTEC and EN5 studies investigated the adjuvant external beam radiotherapy (EBRT) in patient with early stage endometrial cancer and pathological features suggestive of intermediate or high risk of recurrence and death (high risk defined as all papillary serous and clear cell subtypes, all other subtypes in Ic (grade 3) and IIa (grade 3), and all patients with stage IIb disease; pre 2009 FIGO staging) [84]. In this study 905 patients were assigned to adjuvant external beam radiotherapy (452) or observation (453). After 58 months of follow up, the risk of local recurrence was lower in the EBRT group (HR: 0.46 (95% CI, 0.24 to 0.89; p = 0.02). However, there was no difference in the rate of distant metastasis (8% in the observation group and 9% in the EBRT group), recurrence-free survival (HR: 0.93 (95% CI, 0.66–1.31; p = 0.68) or overall survival between the two groups (HR: 1.05 (95% CI, 0.75 to 1.48; p = 0.77). The rate of acute toxicities was higher in the radiotherapy group compared with the observation group (43% vs. 27% respectively).

A Cochrane review of eight randomized trials of adjuvant radiotherapy (EBRT, VBT or both) in early stage endometrial cancer did not show any improvement in survival of high risk stage I endometrial cancer who were treated with pelvic radiotherapy [80]. The authors of the review concluded that in patients with stage I disease "For the intermediate to high-intermediate risk group, VBT alone appears to be adequate in ensuring vaginal control compared to EBRT".

There is no consensus on the use of adjuvant chemotherapy in stage Ia surgically staged USC. Patients with stage Ia USC with no residual disease in surgical specimen or USC confined to a polyp should be advised about the extremely low risk of recurrence. (Grade C)

Two randomised trials have shown no overall survival benefit from the addition of cisplatin and doxorubicin chemotherapy to external beam radiotherapy alone in surgically operated FIGO stage I–III endometrial cancer with no residual disease and poor prognostic factors. (Grade A)

Of note, however, there was no survival benefit in the subgroup of USC or clear cell cancer and the benefit of additional chemotherapy seemed to be confined to the endometrioid group alone [105].

Adjuvant platinum-based chemotherapy may be considered in stage Ib, and II–IV USC after patients have been adequately counselled about the evidence base for this and pending results from ongoing trials. (Grade B)

Two randomised studies have evaluated sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – the NSCGO/EORTC/MaNGO trials randomised 540 patients with operated endometrial cancer FIGO stage I–III with no residual tumour and prognostic factors implying high risk to adjuvant radiotherapy with or without sequential cisplatin plus doxorubicin. They found that addition of adjuvant chemotherapy to radiation improves progression-free survival but neither study showed significant differences in overall survival. In combined analysis, overall survival was not significant (HR 0.69, CI 0.46–1.03; p = 0.07) but cancer-specific survival was significant (HR 0.55, CI 0.35– 0.88; p = 0.01). There was also a 36% reduction in the risk of relapse (HR: 0.64, 95% CI: 0.41–0.99, p = 0.04) in the patients treated with sequential chemotherapy and radiation [105]. However, neither trial showed a benefit in the subgroup of uterine serous cancers. Due to the rarity of USC, there is lack of evidence from prospective randomised clinical trials to direct the decision making in treatment of early stage disease. Multiple retrospective studies have demonstrated the improved outcome of USC patients with early stage disease who were treated with platinum-based chemotherapy compared with those who had no adjuvant treatment or were treated by radiotherapy alone [131–134,136].

For late stage disease several studies have reported improvement in progression free survival of USC patient with adjuvant chemotherapy. Many of these studies included USC patients as part of advanced stage endometrial carcinoma. In a study of adjuvant cisplatin, adriamycin and cyclophosphamide in 62 patients with high-risk endometrial cancer (21% with UPSC or clear cell carcinoma), Burke et al. reported three-year survival of 82% in patients with no extra-uterine disease. A phase III trial of cisplatin and adriamycin versus cisplatin, adriamycin and paclitaxel (TAP) in advanced stage endometrial cancer (GOG 177) showed an overall survival benefit in the cohort treated with TAP chemotherapy. The GOG 209, a phase III study is currently investigating the chemotherapy with TAP vs paclitaxel/carboplatin.

In a recent phase II pilot study patients with stage I–IV USC of pelvic radiotherapy 'sandwiched' between platinum/taxane-based chemotherapy investigators demonstrated antitumor activity and a favourable toxicity profile for this approach but the majority of patients with advanced disease recurred during the three-year study period [137].

PORTEC-3 trial is currently investigating pelvic radiotherapy versus pelvic radiotherapy with concurrent chemotherapy followed by adjuvant chemotherapy.

NACT and interval debulking surgery (IDS) is an alternative approach in the treatment of patient with advanced stage USC who are considered poor candidates for upfront surgery. (Grade D)

Evidence for neoadjuvant chemotherapy (NACT) in USC is limited to a small number of case reports and case series in selected cases who were not candidates for primary debulking surgery [107,138–140]. In one study 30 patients with stage IV endometrial cancer (including 27 USC patients (90%)) were treated with three or four cycles of NACT followed by IDS [140]. A total of 24 patients (80%) had optimal cytoreduction described as to less than one cm and six patients (20%) either had progressive disease during NACT or were inoperable after NACT. Both case reports achieved high rates of optimal cytoreduction. However, there is insufficient data to inform management of USC specifically.

12.1 Treatment of recurrent USC

There is no evidence base on the use of second line chemotherapy in recurrent USC. This is covered in greater detail

in the section on management of relapsed cancer. Referral of patients into early phase clinical trials with newer targeted agents should be encouraged.

13 Non-endometrioid carcinoma: uterine clear cell carcinoma

Endometrial clear cell cancer (ECCC) is classified together with the serous-papillary subtype to type II endometrial cancers (EC). Even though type II cancers account for <15% of all ECs, they are mainly responsible for the EC-related mortality, since they are biologically more aggressive and usually associated with a poorer outcome than the most common type I cancers.

ECCC tend to show higher rates of myometrial and lympho-vascular invasion, intraperitoneal and extra-abdominal spread including the upper abdomen, explaining the higher stages of the disease at its initial presentation [141,142]. At least from the standpoint of gene expression, they appear more similar to clear cell cancers arising in other organs (e.g. the kidney) than to other uterine cancers, including those of the papillary serous variety [143]. For the definition of ECCC 25–50% clear cell features are required to classify a tumour as such. Interestingly, patients with pure clear cell cancers and mixed clear cell cancers with endometrioid components have the same survival as those whose clear cell cancers contain less histologically favourable components [144].

In a large series presented by Hamilton et al. [145] the clinical course of more than 4000 women was analysed according to the histologic subtype: 4180 women with high risk EC subtypes reported to the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 2001; 1473 had a serous-papillary histology, 391 had clear cell, and 2316 had grade three endometrioid ECs [145]. ECCC patients had higher rates of stage III or IV disease than did grade 3endometrioid ECs (36% versus 26%, respectively). For early stage disease, five-year survival for uterine serous papillary (USC), ECCC and grade three endometrial cancer were 74, 82, and 86%; $P < 0.0001$) and stage III–IV disease (33, 40, and 54%; $P < 0.0001$). Moreover, although serous papillary, clear cell and grade 3 endometrioid tumours accounted for 10%, 3% and 15% of all endometrial cancers, they were responsible for 39%, 8%, and 27% of all deaths, respectively. Retrospective data indicate that patients with ECCC confined to the uterus and without extension to the cervix present a better prognosis than those with a tumour of serous papillary histology and of equivalent stage [141,146].

Accurate surgical staging including peritoneal cytology, hysterectomy, bilateral salpingo-oophorectomy, omental, peritoneal biopsies is necessary to identify or exclude the presence of extrauterine disease and adequately define the FIGO stage. (Grade C)

In case of peritoneal tumor dissemination, optimal cytoreduction with maximal surgical effort to obtain minimal residual disease may confer survival benefit. (Grade C)

Optimal cytoreduction is an important component of surgical treatment with the amount of residual disease following surgery being the strongest predictor of overall survival in advanced disease, but high quality data are lacking [147–149]. The best available evidence is a meta-analysis of 14 retrospective case series that included 10 studies of primary disease and four studies of recurrent disease, patients had both endometrioid and non-endometrioid histology types [65]. A higher proportion of women with complete cytoreduction was found to be significantly associated with longer median survival. For women with primary disease, overall survival rates were related to: complete cytoreduction (30 to 51%) and optimal cytoreduction, defined in individual studies as ≤1 or ≤2 cm (15 to 51%); however, confidence limits were wide. Similar to epithelial ovarian cancer surgery these patients may be considered for referral to specialized centres with high surgical experience, since the strongest predictor of overall survival is the amount of postoperative residual disease [127,129].

Systematic pelvic and para-aortic lymph node (LN) dissection has a higher diagnostic accuracy than palpation and removal of enlarged LN's or LN sampling. (Grade A)

Non randomised evidence suggests that systematic pelvic and para-aortic lymphadenectomy maybe appropriate for high grade disease and non-endometrioid endometrial cancers. Recruitment into trials investigating lymphadenectomy including sentinel node surgery is strongly recommended. (Grade C)

There is no prospectively randomized trial so far demonstrating any therapeutic value of systematic lymph node dissection (LND) in ECCC, and the value of lymphadenectomy lies mainly on the accurate staging revealing occult disease and hence to determine the optimal adjuvant treatment for the affected patients.

In a prospectively randomized study, Benedetti-Panici et al. demonstrated a four-fold increase in the rate of detection of LN metastases when systematic lymphadenectomy was performed in comparison to the removal of enlarged nodes only [44]. Another prospective randomized study in early epithelial ovarian cancer comparing LN-sampling versus systematic LND showed that 13% of the positive LN were missed in the only sampling group compared to the systematic LND arm. This means that 13% of the apparently early stage disease had an occult stage III disease and were under staged by inaccurate staging [150].

Para-aortic LND up to the renal veins is more accurate to detect para-aortic LN-metastases. (Grade C)

Through numerous mapping studies, it has been demonstrated that if EC has extended to a para-aortic node, the majority of metastases are in the area between the renal veins and inferior mesenteric artery (IMA) [151–156]. Mariani et al. found in a prospective assessment of over 400 EC patients, that 77% of the patients with para-aortic lymphatic spread had positive LN in the area above the IMA [153]. Therefore, para-aortic LND up to the level of the IMA would leave higher positive para-aortic LN undetected.

If adequately staged, then patients with early stage ECCC derive no benefit from adjuvant systemic chemotherapy or external beam radiation. (Grade C)

Adjuvant therapy of early-stage USC and ECCC is controversial. Many trials of prospective and retrospective design have been conducted to evaluate outcomes of patients with early or later stage disease to define the optimal treatment after complete surgical staging [157–159]. Rauh et al. [158] evaluated all patients with FIGO stage I ECCC after comprehensive surgical staging in a 10-year period to compare the outcome with and without adjuvant radiation therapy. Twenty-five patients with stage I ECCC were identified of whom 13 (52%) received no adjuvant therapy and 12 (48%) received adjuvant radiation therapy. The five-year disease-free survival and overall survival rates for the observation and the radiotherapy groups were 78% and 75%, (p = 0.7) and 85% and 82% (p = 0.1), respectively. When compared to controls, the five-year disease-free survival rates and overall survival rates of patients with stage I ECCC were not significantly different, 77% vs 75% (p = 0.8) and 84% vs 88% (p = 0.5) respectively. The authors concluded that in patients with stage I ECCC tumors there was no clear benefit to adjuvant radiation given the absence of improvement in recurrence risk or any survival benefit. A further study by Kwon et al. [159] showed that adjuvant therapy may not be necessary for stage Ia and Ib (pre-2009 FIGO staging) serous papillary and ECCC after adequate surgical staging. From 2000 to 2006, they evaluated all consecutive patients (n = 22) with stage Ia/Ib serous papillary or ECCC who had surgical staging by a gynecological oncologist at the London Health Sciences Centre in Canada. Only one patient recurred (stage Ib UPSC, isolated vault recurrence 10 months after surgery), but she was well nine months

after receiving pelvic radiotherapy and vault brachytherapy. Two-year disease-free survival was 95%.

Platinum based systemic chemotherapy may be appropriate for adjuvant therapy for ECCC patients with advanced stage III or IV disease. (Grade C)

There are controversies about the optimal chemotherapeutical regimen. Several platinum-based combination chemotherapy regimens have been evaluated in clinical trials, including carboplatin plus paclitaxel, doxorubicin plus cisplatin (AP), and AP plus paclitaxel (TAP). Most current European guidelines, including the UK, recommend combination chemotherapy in preference to single agent platinum, historically platinum with doxorubicin. However increasingly, treating physicians tend to choose paclitaxel and carboplatin due to its more favourable toxicity profile.

Trials presented below contained a mixture of histology types.

The combination approach of carboplatin plus paclitaxel in the adjuvant setting has been further reinforced by the results of GOG 209, which were presented at the 2012 Society of Gynecologic Oncology Annual Meeting [160]. This trial compared carboplatin plus paclitaxel to TAP in 1300 women with chemotherapy naïve advanced EC, including women with stage III disease, and demonstrated that carboplatin and paclitaxel results in an equivalent overall response rate, similar progression-free survival, but is also less toxic. The currently ongoing GOG 258 trial will evaluate the use of chemotherapy alone (six cycles of carboplatin plus paclitaxel) versus volume-directed pelvic radiotherapy (RT) with concomitant cisplatin followed by chemotherapy (four cycles of carboplatin plus paclitaxel) in patients with optimally debulked FIGO stage III or IVa EC, including clear cell and serous papillary and undifferentiated carcinomas. Also PORTEC 3 is comparing patients with high risk stage I (including women with USC and ECCC), stage II and III EC to treatment with adjuvant RT alone to RT with concomitant cisplatin followed by four cycles of carboplatin plus paclitaxel.

External beam radiotherapy (EBRT) has not been demonstrated to improve the overall survival in ECCC and is equally effective in preventing local recurrence to vaginal brachytherapy (VBT) but with higher toxicity. (Grade C)

In ECCC the risk of recurrence is not only locally but also as multifocal peritoneal disease. Therefore, achieving local control is not as important a goal as for endometrioid ECs.

The PORTEC-2-trial [89] in high and intermediate risk endometrioid endometrial cancer has clearly shown in a prospective randomized design that VBT is equally effective to EBRT in ensuring vaginal control, with fewer gastrointestinal toxic effects than with EBRT. A total of 427 women were randomly assigned treatment with VBT or EBRT. At 45 months there were no statistically significant differences between VBT and pelvic RT in terms of: locoregional recurrence (5% vs. 3% percent for VBT and pelvic RT, respectively), distant metastases (8% vs. 6%, respectively), five-year disease free survival (83% vs. 78%, respectively) and overall survival (85% vs. 80%, respectively). VBT was however associated with a significantly lower rate of treatment-related diarrhoea and other bowel symptoms (13% vs. 54%, respectively).

This evidence is corroborated specifically for USC and ECCC in two retrospective series [161,162].

There is also little evidence to support the utility of whole abdominal irradiation (WART) in patients with ECCC, particularly those with early stage disease. To date no prospective, randomized phase III clinical trials have been conducted evaluating the role of WART especially just for ECCC, so that its true benefit remains undefined but is unlikely to be any more successful than EBRT given that the dose to the whole abdomen is likely to be lower.

14 Non–endometrioid cancer: uterine carcinosarcoma

Uterine carcinosarcomas comprise between three to 8% of uterine cancers. The incidence has risen in the course of the last 20 years. It is unclear whether this is due to improved histopathological and immunocytochemical techniques which now identify carcinosarcomas which were previously called poorly differentiated carcinomas or whether this may be due to the greater availability of subspecialty expertise from gynae-pathologists. Whatever the reason this has now become a more common tumour and clinicians are faced with the practicalities of managing these patients.

However, there is now increasing evidence that carcinosarcomas as opposed to leiomyosarcomas and endometrial stromal sarcomas are not sarcomas at all, and from the use of molecular markers and profiling that these are poorly differentiated endometrial carcinomas. Patterns of spread almost always show that metastases are epithelial showing the carcinomatous component and not the sarcomatous component. It sometimes appears confusing when mixed tumours are seen which contain poorly differentiated carcinomatous components, serous or clear cell but nevertheless it is increasingly being recognised that these fit into the type II endometrial carcinoma spectrum.

The consequence of this is given that they are similar to type II endometrial carcinomas, they should probably be managed in similar manner. This means that this is one of the indications where patients should be considered for referral to the specialist gynae-oncology centres for surgical management. There is a stronger feeling that pelvic lymph node dissection is more important in this group of patients. The GOG study reported by Major et al. in 1993 showed that around 15–20% of patients with carcinosarcomas had positive lymph nodes. This is significantly higher than leiomyosarcomas and well differentiated endometrial carcinomas. This also has significant implications for adjuvant treatment.

Patients with the initial endometrial biopsy suggestive of carcinosarcoma should be discussed at the SMDT and would normally be recommended to undergo additional scanning with an MRI of the pelvis and CT of chest and abdomen. Following initial management, histology should be reviewed by centre gynaecological pathologist. (Grade C)

The higher risk of pelvic lymph node metastasis justifies the recommendation that patients should be considered for pelvic and possible para-aortic lymphadenectomy in addition to hysterectomy and bilateral salpingo-oophorectomy (BSO) if patients are fit to undergo the procedure. (Grade C)

Recruitment into trials investigating lymphadenectomy including sentinel node surgery is strongly recommended. (Grade C)

Many of these patients do have significant co-morbidity such as obesity, diabetes, hypertension and may not be good candidates for more aggressive surgical approaches but nevertheless a strong case can be made for referring these patients for central surgery where they will undergo total hysterectomy, BSO, omentectomy and pelvic lymph node dissection and discussion of para-aortic lymph node dissection. It remains unclear whether lymphadenectomy in general has a therapeutic benefit but certainly the information gained from the additional staging procedure will help tailoring adjuvant treatment. Following surgery patients should have their cases discussed again at the SMDT so that specialist pathology can be obtained with a full multidisciplinary discussion regarding the place of adjuvant treatment.

Adjuvant treatments should be individualised and should be discussed at the SMDT. The combination of systemic chemotherapy followed by vaginal brachytherapy is a reasonable post-operative approach to the management of carcinosarcomas, pending the outcome of large trials. (Grade C)

In general, the three adjuvant treatments are radiotherapy, chemotherapy and hormonal therapy and perhaps in the next five years the new targeted agents will become established but these are not yet of proven value. There remains no reason to recommend the routine use of adjuvant hormonal therapy in the adjuvant setting.

The EORTC Gynaecological Cancer Group initiated a clinical trial randomising patients with all types of uterine sarcomas of stage I and II who received appropriate surgical staging to undergo either adjuvant radiotherapy or no additional treatment. This trial was reported in 2008 and showed that although there was a significant reduction in local recurrence, there was no overall survival benefit and similar to studies in endometrial carcinomas there was a tendency to worse overall survival in those who received adjuvant radiation treatment [163]. Therefore, it cannot be recommended to routinely use adjuvant radiotherapy in this group of patients.

External beam radiotherapy has not been shown to be of any benefit in overall survival although may reduce the risk of local recurrence. Vaginal brachytherapy may help to reduce local relapse rate and may be optionally selected. There may be individual cases where there is residual disease or where excised nodes are positive where one may wish to consider adjuvant radiation but this again should be discussed at the SMDT. The role of vaginal brachytherapy is more contentious as there is no evidence base to support or refute its use. Nevertheless, many centres do consider the use of vaginal brachytherapy in view of its reported reduction in the risk of local recurrence.

This leaves adjuvant chemotherapy as an option. The place of adjuvant chemotherapy in high risk endometrial carcinomas is again controversial. The NSGO/EORTC/ILIAD study did show improvement in progression free survival and a trend towards improvement in overall survival from the combined analysis, and this approach is being further investigated by the PORTEC 3 study [105]. However, given that adjuvant radiotherapy has no impact on overall survival and simply reduces the risk of local relapse, it may be argued that these patients are at greater risk of developing distant metastases and therefore systemic treatment would be more likely to have an impact. Increasingly systemic adjuvant chemotherapy is being used in these patients and in many centres four to six cycles of adjuvant chemotherapy with carboplatin and paclitaxel is used with or without the use of adjuvant brachytherapy.

Recurrent disease is usually shown to be carcinomatous rather than sarcomatous. ER and PR status are usually negative so of limited value but should be checked as the occasional patient shows positivity. (Grade C)

For patients with no symptoms, who have hormone receptor positive tumours, endocrine therapy may be a good approach. Most patients will have symptomatic disease and thus will require chemotherapy. Anthracyclines, platinum, ifosfamide and taxanes have been the most active agents. Carboplatin is active and effective and has generally replaced the combination of cisplatin and doxorubicin which are poorly tolerated. If prior chemotherapy has been used and the time interval is less than 12 months, it is likely that the tumour will be platinum resistant (as in ovarian cancer). Second line schedules have poor response. Doxorubicin either alone or in combination with ifosfamide may be used. The GOG study of ifosfamide and paclitaxel was superior to ifosfamide alone but ifosfamide is a drug with a higher toxicity profile and is infrequently chosen by oncologists.

Following this, there is no established third line regime and patients should be considered for phase one trials if fit. Other options which are unproven include weekly paclitaxel. Drugs like Caelyx (PLDH) and topotecan have disappointing activity in carcinosarcoma. To date the targeted molecular agents have no proven role but will be investigated further over the next few years as we enter the era of personalised medical care. Molecular profiling will help to identify when these agents can be used.

15 Management of uterine sarcomas

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

Oophorectomy is indicated for endometrial stromal sarcoma. These patients 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 by specialist multidisciplinary teams. (Grade D)

Gynaecological sarcomas are rare accounting for only 2% of all gynaecological malignancies, hence there is a great paucity of high quality evidence to guide management of these patients. Evidence from trials and guidelines for soft tissue sarcomas is often adopted.

The WHO classification of uterine sarcomas (WHO):

A. Mesenchymal tumours

- Leiomyosarcoma (LMS)
- Endometrial stromal tumours
  - low-grade endometrial stromal sarcoma (LG-ESS)
- high-grade endometrial stromal sarcoma (HG-ESS)
- undifferentiated uterine sarcoma
- Miscellaneous
  - rhabdomyosarcoma
- perivascular epithelioid cell tumour

B. *Mixed tumours*

- Adenosarcoma
- Carcinosarcoma – regarded an epithelial tumour and should be treated as such (see Section 14).

15.1 Uterine leiomyosarcoma

Recommendations

- The cornerstone of management of early LMS is total hysterectomy with bilateral salpingectomy
- Oophorectomy in young women is not mandatory
- Routine pelvic lymphadenectomy is not recommended
- Morcellation of fibroids should be avoided in peri- and postmenopausal women
- There is no data on the benefit of adjuvant chemotherapy or radiotherapy
- Patients with advanced or recurrent LMS are usually offered chemotherapy unless complete surgical resection is possible
- Management of patients with primary or recurrent leiomyosarcoma requires a multidisciplinary team approach preferably with discussion with the regional sarcoma team.

Leiomyosarcomas (LMS) account for 1% of all uterine cancers and 35–40% of all uterine sarcomas, and therefore are the most common gynaecological sarcomas [164,165]. Although rapidly growing pelvic mass 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 LMS out of 371 women [166]. Leiomyosarcoma of the uterus is most commonly reported as an incidental finding in hysterectomy specimens.

Leiomyosarcoma has a poor prognosis with recurrence rate of up to 70% and overall 5-year survival for all stages of 39% [167]. 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 [168]. Mitotic index, age are also important prognostic factors [169].

15.2 Early stage leiomyosarcoma

15.2.1 Surgery

Leiomyosarcoma is usually a postoperative diagnosis after hysterectomy or myomectomy, in 0.5% of the cases [170]. If the diagnosis is known or suspected prior to surgery, *en bloc* total hysterectomy is the cornerstone of the management. Ovarian metastasis is uncommon (2%) in early stage (I–II), therefore oophorectomy in young women is not mandatory [171,172]. Independent predictors of disease specific survival in patients with uterine LMS 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 [172].

Systematic pelvic lymphadenectomy is not routinely recommended, as the incidence of lymph node involvement is 6.6% [172]. Lymphadenectomy has been shown to provide no survival benefit in a GOG study, however, patients with uterine carcinosarcoma were also included in the study [167]. Debulking of enlarged lymph nodes is recommended for staging and treatment planning purposes.

15.2.2 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 [173]. The US Food and Drug Administration (FDA) in their review found the risk of incidental uterine leiomyosarcoma in patients undergoing hysterectomy or myomectomy for presumed benign fibroids one in 498 (one in 352 for all uterine sarcomas) [174]. 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%) [175]. For peri- and postmenopausal women, the FDA does not support the use of laparoscopic power morcellators for myomectomy [174].

Exceptionally, fertility preservation can be considered if the LMS is discovered in a pedunculated tumour, if all surgical margins were clear and if no morcellation was performed. Close follow-up is recommended, with clinical examination, regular ultrasound and hysteroscopy, six-monthly CT/MRI and completion surgery when achieved fertility goals [176].

15.3 Adjuvant treatment for early uterine leiomyosarcoma

15.3.1 Radiotherapy

The EORTC 55874 trial which included 103 patients with stage I/II LMS randomised patients between observation and pelvic radiotherapy after hysterectomy. The results showed no improved local control, disease-free survival or overall survival in the radiotherapy arm [163]. The routine use of postoperative radiotherapy is not recommended in this patient group, however it may be considered for selected high-risk cases such as those with positive surgical excision margins.

15.3.2 Chemotherapy

There is no evidence that adjuvant chemotherapy would improve survival for early, completely resected uterine LMS [177,178]. The SARC005 phase two study on patient with uterine LMS limited to uterus investigated an adjuvant chemotherapy regime of four cycles of gemcitabine/docetaxel followed by four cycles of doxorubicin, and demonstrated superior outcome when compared with external controls [179]. The prospective phase three trial using this protocol is ongoing.

15.4 Advanced stage or recurrent leiomyosarcoma

15.4.1 Surgery

Cytoreductive surgery even with complete resection of all visible disease does not seem to improve overall survival [180]. In exceptional cases, the resection of pulmonary metastasis can be considered if the primary disease is completely resected [181].

15.4.2 Chemotherapy

The following chemotherapy agents demonstrated response in patients with unresectable, metastatic or recurrent soft tissue sarcomas: doxorubicin, gemcitabine, gemcitabine with docetaxel, ifosfamide have been investigated with a response rate up to 50% [177,182–184].

Combination chemotherapy when compared with monotherapy did not improve overall survival and resulted in more grade three to four complications [185]. However, a randomised phase two trial comparing single agent gemcitabine with the combination of gemcitabine and docetaxel in the treatment of patients with recurrent or progressive soft tissue sarcoma demonstrated improved disease-free and overall survival for the gemcitabine combination [186].

Trabectedin is indicated for patients with recurrent soft-tissue sarcomas after failure of treatment with anthracyclines and ifosfamide [187].

15.4.3 Hormonal treatment

Oestrogen receptors (ER) and progesterone receptors (PR) are expressed in approximately half of the patients with LMS [188,189]. Some low and intermediate grade tumours may be sensitive to oestrogen deprivation and therefore it is reasonable to check ER/PR expression to consider aromatase inhibitors or progestogens [190,191].

15.5 Management of patients with endometrial stromal sarcoma

Low-grade ESSs are relatively indolent tumours with good prognosis and a propensity for late recurrences, and are characterised by special molecular features (chromosomal translocation (7;17) with JAZF1-SUZ12, EPC1-PHF1 or JAZF1-PHF1 transcripts [192]. A subset of ESS patients with specific cytogenetic features (translocation (10;17), with YWHAE-FAM22 transcript) is distinguished by their aggressive behaviour and poor prognosis; this group is called high-grade ESS. They are more likely to present in more advanced stage and their response to hormonal treatment is limited [193].

15.6 Early stage endometrial stromal sarcoma

15.6.1 Surgical treatment

Surgical treatment with total hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of the treatment, and in view of the hormone responsiveness of ESS, oophorectomy is always recommended even in pre-menopausal women.

There is 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 [194].

The role of lymphadenectomy is unclear; the incidence of lymph node involvement is around 10% [195]. The lymph node status has prognostic significance and may guide adjuvant treatment but there is no evidence that it would improve survival.

15.6.2 Adjuvant treatment

There is no data supporting adjuvant treatment (chemotherapy, radiotherapy, hormonal therapy) for early stage ESS with complete resection. In view of the high rate of expression of ER/PR in low-grade ESS, oestrogen or tamoxifen treatment is not advised [196].

15.7 Advanced or recurrent endometrial stromal sarcoma

15.7.1 Surgical treatment

Surgical resection may be considered in completely resectable cases [197].

15.7.2 Systemic treatment

In disseminated or recurrent cases aromatase inhibitors (letrezol, anastrazol), progestogens (medroxyprogesterone or megestrol) or GnRH analogues (for premenopausal patients) have been demonstrated to provide patients with long-term control of disease [197]. Tamoxifen is contraindicated due to possible agonist activity [198]. In hormonal therapy resistant cases, ifosfamide chemotherapy can be considered [199].

15.7.3 Uterine adenosarcoma

Uterine adenosarcomas are mixed tumours, composed of benign glandular and low grade sarcomatous stromal components. The majority of these cases present in an early stage (80% stage I) with good prognosis [200].

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) [200].

Due to its low prevalence, there are no established treatment strategies available for adenosarcomas, but for early stage disease, total hysterectomy with bilateral salpingo-oophorectomy is usually performed with no adjuvant treatment [201].

16 Follow-up for endometrial cancer

Individualised follow-up strategies should be prescribed by the multidisciplinary team once treatment is complete. These should stratify patients by anticipated risks of recurrence, side effects of treatment and take into account patient or local factors. (Grade D)

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 medical attention, for example vaginal bleeding and discharge. (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)

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 A)

There is currently no evidence to 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 endometrial cancer treatment. The package of care should be designed to screen for recurrent disease and manage the consequences of cancer and treatment.

The traditional follow-up of gynaecological cancer follows the same clinical pathway based in secondary care with clinical examinations every three months for the first three years and annually for the subsequent two years. These visits allow hospitals to audit their outcomes, provide holistic survivorship care and screen for recurrent disease. Patients may suffer anxiety or enjoy the reassurance from a clinical examination. They may have an opportunity to discuss holistic needs with specialist nurses or keyworkers. Holistic survivorship care addresses cancer treatment sequelae and these consults can be conveniently combined with follow-up clinics.

Guidelines relating to follow-up of endometrial cancer treatment should focus on the screening for asymptomatic recurrent disease with individualised survivorship care managed separately, although this could be in the same clinic. All follow-up programmes should aim to identify asymptomatic isolated pelvic recurrence or vaginal vault recurrence. Some women with multiple co-morbidities may not be suitable for any further treatment on grounds of fitness; it is reasonable for these women to be discharged from routine follow-up and an individualised care plan put in place.

One RCT comparing hospital and telephone follow-up for women treated for endometrial cancer (ENDCAT: Endometrial Cancer Telephone follow-up trial) showed that telephone follow-up was not inferior to hospital follow-up in terms of psychological morbidity [202].

16.1 Technique

Identifying vaginal vault disease requires visual inspection of the vagina. Tumour breaching the vagina will be visible and can be detected by any trained health care practitioner. There is no prodromal atypia and therefore vault cytology is inappropriate. 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 make the case that this is why they should be involved in all follow-up programmes. Pelvic side wall and central recurrent disease can be identified by bimanual vaginal examination, rectal examination or ultrasound.

16.2 Frequency of visits

For women with low risk endometrioid endometrial cancers, it is reasonable to restrict follow-up to a limited number of infrequent visits for the first two years. Alternatively, patients with low risk endometrial cancer can be discharged to patient initiated follow-up. Such patients should receive written instructions on when to seek medical input and re- referral and their GP should be informed of this. (Grade D)

For women with high risk endometrial cancers, it is reasonable to use a more rigorous follow-up schedule, with more frequent visits in the first two years, up to five years. (Grade D)

The data is not robust enough to allow us to calculate the utility of follow-up with precision but women with low risk endometrial cancer should be reassured that failure to attend at a follow-up clinic is extremely unlikely to be detrimental to their survival prospects. (Grade D)

The current practice of seeing all women at three monthly clinic intervals for three years followed by annual visit seems illogical when different cancers have different recurrence risks. Follow-up intervals should depend on the threshold for detection, the incidence of any abnormal findings and the benefit derived from early detection. Most of the evidence on the pattern of recurrence of disease is from the era of high rates of adjuvant radiotherapy. Many studies were small and the current pattern of recurrence might be different to historical studies. 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. In 2008–2009, there were over 80,000 gynaecology oncology follow-up hospital appointments in England, compared to 10,000 in 2005–2006 [203] yet there is no hard evidence that early detection of recurrent disease improves survival [204–206].

A systematic review [207] designed to inform the Canadian healthcare system on optimum follow-up strategies for endometrial cancer reviewed 16 non comparative observational studies. Survival graphs show that most of the deaths from high grade disease occur within the first two years but well differentiated tumours and adjuvant radiotherapy are associated with much longer remission intervals. The risk of recurrence is also very different varying from 0% to 50% depending on the pathology of the tumour. This implies that follow-up appointments should be most frequent in the first 24 months for high grade tumours and much less frequent but for longer in other cases. It also implies that there may be some cases where the risk of recurrence falls below the threshold for any follow-up. There is no systematic review that allows us to calculate individualised recurrence rates, sites and timing based on all the risk factors of age, lymphovascular invasion, node status, and adjuvant therapy. Until this is available, we can only estimate the value of follow-up for each individual.

In the absence of clinical trials comparing outcomes of intensive secondary care follow-up and no follow-up, clinical teams have to base judgments on follow-up management based on risk of recurrence, and the clinical combined with psychological benefits of traditional follow-up. Potential options for follow-up based on risk stratification are

- immediate discharge following initial treatment,
- clinic based follow-up with traditional frequency of visits over five years in
  - Traditional secondary care gynaecology doctor led clinics
- Secondary care gynaecology nurse led clinics:
- Nurse led telephone follow-up
- Primary care follow-up

- individualised programmes based on the need for psychological survivorship support, management of late radiation toxicity, oestrogen deficiency and the individualised risk of recurrence.

16.3 Eliciting symptoms at follow-up

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 but not mandatory 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).

16.4 Follow-up for endometrial sarcomas

There is no evidence on the optimal follow up strategy for patient with uterine sarcoma. 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 examinations [198].

17 Supportive care – addressing patient needs

This section provides information on supportive care and aims to signpost the reader to agencies that provide supportive resources for the endometrial cancer patient and her family.

All patients should have a named keyworker to co-ordinate treatment and their care pathway. For the vast majority of patients this will be the clinical nurse specialist. Contact details of keyworker should be given to the patient in a format they can use. (Grade D)

17.1 Background

The National Cancer Survivorship Initiative (NCSI), originating from the Cancer Reform Strategy (DH 2007) is a collaboration between NHS England and Macmillan Cancer Support. The aim is to ensure that those living with and beyond cancer get the care and support they need to lead as healthy and active life as possible, for as long as possible. More information is available on the concise links:

http://www.ncsi.org.uk

http://www.ncsi.org.uk/what-we-are-doing/the-recovery-package/.

The Recovery Package comprises the following domains of care;

- Structured holistic needs assessment and care planning; suggested responsible clinician, keyworker, generally the clinical nurse specialist
- End of treatment summaries and cancer care reviews; suggested responsible clinician; treating oncologist and GP respectively
- Patient education and support events (Health and Wellbeing Clinic) provided by the responsible clinician, clinical nurse specialist and charitable organisations. To incorporate advice and access to schemes that support physical, psychosocial and psychological needs.

NCSI programmes of care related to the endometrial cancer patient via these links cover the following topics

- Assessment and Care Planning

- Health and Wellbeing Clinics
- Managing Active and Advanced Disease
- Supported Self Management
- Consequences of Cancer and its Treatment
- Work and Finance
- Vocational Rehabilitation
- Physical Activity

18 Management of relapsed endometrial carcinoma

All patients with disease recurrence should be managed in a multi-disciplinary team consisting of surgeons, medical and clinical oncologists, radiologists, palliative care physicians, and clinical psychologists. (Grade D)

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. This recommendation already exists as a NICE clinical guideline for breast cancer [208].

Patients who have not received prior radiotherapy should be considered for radical radiotherapy as treatment for localised or pelvic recurrence. (Grade B)

Isolated vaginal recurrence in patients who have not received prior external beam radiotherapy can effectively be treated with salvage radiotherapy. Long-term follow-up of stage 1 patients with mostly adenocarcinoma in the PORTEC I trial showed that in the observation only arm, radiotherapy achieved an 89% complete response rate and a 65% five-year survival. This compares to a five-year survival rate of 43% in previously irradiated patients, which was no different to those patients who experienced distant metastases [94]. In retrospective series, size of tumour at recurrence may help select patients more suited to salvage radiotherapy, with the most commonly suggested cut-off being 2 cm. At five years, this translates into local control of 80% and overall survival of 50–55% [209,210].

Isolated abdomino-pelvic disease that appears resectable, with no evidence of further distant metastases can be considered for surgery with the aim of an R0 resection (total macroscopic clearance). Caution should be exercised in older patients and those with early disease recurrence. (Grade D)

Sometimes NACT or hormonal treatment prior to resection of metastatic disease allows the identification of hormone responders who are more likely to benefit long term. Surgery may be a useful modality in patients with good performance status, isolated disease and with long disease free intervals.

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

In a retrospective series of 61 patients with recurrent endometrial carcinoma, 35 were treated with salvage surgery, usually those who had received prior radiotherapy; about two thirds had endometrioid carcinoma. Patients undergoing surgery achieved a median overall survival of 28 months, and 39 months if complete cytoreduction was achieved. This compares to an overall survival of 13 and 13.5 months if residual disease was present after surgery or radiotherapy alone, respectively. These differences were statistically highly significant even after adjustment for multiple testing [211]. In another retrospective series of 62 patients, those who had pelvic exenteration had a five-year overall survival of 52%; factors adversely affecting prognosis were age greater than 69 years, recurrence within three years of the original diagnosis, persistent tumour after surgery, and positive resection margins [212]. Lastly, based on a prospective case series of 75 patients, those with central vaginal relapse experienced superior outcomes, with 42% surviving five years compared to patients with 'extended abdominal' disease (five-year overall survival 17%). Patients with abdominal carcinomatosis at relapse are not candidates for surgery, with no patient surviving beyond 13 months in this series [213]. For patients who have received prior radiotherapy, pelvic exenteration, while highly morbid, achieves five-year overall survival rates of 20–50% [214,215]. However, in general, there is a much smaller role for exenteration in recurrent endometrial cancer than in other gynaecological cancers.

Patients being considered for radical pelvic surgery or radiotherapy should be imaged staged using PET/CT to exclude distant metastases, prior to surgery. (Grade B)

Based on a recent meta-analysis, PET/CT has a sensitivity of 95.8% (95% CI 92.2–98.1), and specificity of 92.5% (95% CI 89.3–94.9) in this setting [216] and has been reported to change the management plan in up to 22% of patients with recurrent endometrioid adenocarcinoma [217]. The meta-analysis included 541 patients with adenocarcinoma; it is not clear if PET/CT is equally sensitive and specific in all subtypes [216].

Following local surgical therapy for recurrence, further 'adjuvant' chemotherapy can be considered although as in first line treatment, there is no clear evidence to support this approach. (Grade D)

For patients with an R1 resection or who have had incomplete cytoreduction for vaginal or pelvic recurrence, post-operative radiotherapy or brachytherapy should be considered if normal tissue tolerance allows (Grade D)

In a prospective trial of 75 consecutive patients with recurrent endometrial cancer who underwent salvage surgery, those patients who received post-operative chemotherapy at the discretion of the treating physician had significantly better outcomes than those who did not. There was a mixture of regimens employed, and 20% had prior chemotherapy, while 37% of patients had prior radiotherapy. It is not possible to draw conclusions regarding the interaction of these factors and outcome [213]. There are no good data to support the use of radiotherapy as consolidation therapy for R1 margins however this practice seems sensible given the poorer prognosis conferred by the R1 resection margin [212].

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

Fit patients with disseminated recurrent disease can be offered primary systemic therapy such as carboplatin and paclitaxel. Several other agents have shown useful activity in this setting (doxorubicin, cisplatin, cyclophosphamide) [218]. A trial in 281 patients comparing doxorubicin to doxorubicin with cisplatin showed improved response rates (42% vs. 25%), and prolonged progression-free survival HR = 0.736 (95% CI, 0.58–0.94; P = 0.014), translating in a median progression-free survival gain of 1.9 months for the combination. Overall survival was not significantly different between the treatment arms [219]. The results of this US trial were mirrored by those of the EORTC study in 177 chemotherapy naïve patients using the same chemotherapy arms [220]. There is some evidence for a modest (up to three months) improvement in overall survival with a more intense three drug regimen (doxorubicin, cisplatin, paclitaxel), but at the cost of markedly increased toxicity, leading to 24% of patients discontinuing the experimental three drug arm [221].

The GOG 209 study, a non-inferiority randomized study of carboplatin AUC6 and paclitaxel 175 mg/m^2 compared to doxorubicin, cisplatin and paclitaxel with G-CSF support has reported in abstract form, showing that the carboplatin and paclitaxel combination is non-inferior with significantly less toxicity in patients with relapsed endometrial adenocarcinoma [222]. Pegylated liposomal doxorubicin can be combined with carboplatin in

fit patients, and has also been used followed by carboplatin/paclitaxel with acceptable toxicity. This may be particularly suited to patients with carcinosarcoma [223].

Second line chemotherapy can be considered in fit patients as either a re-challenge with carboplatin and paclitaxel if the treatment free-interval is more than six months, or single agent chemotherapy if less than six months or less fit patients. (Grade D)

For second line chemotherapy or relapse within six months of adjuvant carboplatin and paclitaxel, response rates are disappointing, but pegylated liposomal doxorubicin has been used with good palliation in some patients even if the response rate (9.5%) and overall survival (8.4 months) are modest [224]. Topotecan 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 four neutropaenia [225]. The use of weekly paclitaxel is only supported by anecdotal evidence; but based on its useful activity in ovarian cancer and tolerability, it is an option for selected patients.

Patients not fit for chemotherapy may benefit from a trial of a progestin. Selected cases with long disease free interval, well-differentiated tumours, lung only metastases and high oestrogen or progesterone receptor expression in the tumour may be candidates for primary hormonal therapy. However, there is no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival [79]. (Grade C)

For some patients, hormonal therapy may be a more appropriate option than chemotherapy. Response rates are in the order of 20–25%, and higher responses are seen in those with progesterone receptor positive tumours [226,227]. It has been suggested that patients with a long treatment-free interval between the initial diagnosis and disease recurrence, and those with lung only metastases, appear to benefit more. Attempts to improve on the initial trials using dose-escalation did not show any benefit from higher doses of medroxyprogesterone (MPA) but underlined the importance of progesterone receptor expression in the tumour with an overall survival of 11.1 months; a dose of MPA 200 mg/d orally is recommended [228]. Trials with tamoxifen showed similar survival (8.8 months) but lower response rates (10.3%) [229]. Likewise, aromatase inhibitors have disappointing response rates (9%), the overall survival for letrozole and anastrozole are of a similar magnitude as for other hormonal agents, with 8.8 months and 6 months, respectively [230,231]. The ongoing PARAGON trial of Anastrazole in recurrent endometrioid cancer will provide further evidence as to the efficacy of aromatase inhibitors in this setting, which for patients with cardiac comorbidities may well be advantageous.

An alternating regime of megestrol acetate (MA) 80 mg twice daily for three weeks followed by tamoxifen 20 mg twice daily for three weeks orally 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 [232].

One Cochrane review investigating the role of hormonal therapy in advanced or recurrent endometrial cancer found six trials (542 participants) that met the inclusion criteria. These trials assessed the effectiveness of hormonal therapy in women with advanced or recurrent endometrial cancer as a single agent, as part of combination therapy and as low versus high dose. This systematic review found no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival [79].

19 Areas of future research/developments

- Routine testing of patients with endometrial cancer for genetic predisposition syndromes
- Registry for patients receiving neoadjuvant chemotherapy for uterine cancer
- Novel radiation techniques for adjuvant therapy in uterine cancer
- Debulking surgery for advanced stage uterine cancer
- Primary care testing and development of diagnostic algorithms for women with symptoms of endometrial cancer in primary care

Appendix A. i – Evidence level and grades of recommendation for standards of care

i – Evidence level and grades of recommendation for standards of care

Evidence level

1+	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias align="<span class="
1–	Meta-analyses, systematic reviews of RCTs or RCTs 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

RCT = randomised controlled trial

Grades of recommendations

Strength	
A	At least one meta-analysis, systematic reviews or RCT's 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+

ii – FIGO staging of endometrial cancer and uterine sarcomas

Carcinoma of the Endometrium

Ia Tumour confined to the uterus, no or $< {}^{1}/_{2}$ myometrial invasion

Ib Tumour confined to the uterus, $\geq {}^{1}/_{2}$ myometrial invasion

II Cervical stromal invasion, but not beyond uterus

IIIa Tumour invades serosa or adnexa

IIIb Vaginal and/or parametrial involvement

IIIc1 Pelvic node involvement

IIIc2 Para-aortic involvement

IVa Tumour invasion bladder and/or bowel mucosa

IVb Distant metastases including abdominal metastases and/or inguinal lymph nodes

Uterine Sarcomas (Leiomyosarcoma, Endometrial Stromal Sarcoma, and Adenosarcoma)

Ia Tumour limited to uterus $\leq$5 cm

Ib Tumour limited to uterus >5 cm
IIa Tumour extends to the pelvis, adnexal involvement
IIb Tumour extends to other uterine pelvic tissue
IIIa Tumour invades abdominal tissues, one site
IIIb More than one site
IIIc Metastasis to pelvic and/or para-aortic lymph nodes
IVa Tumour invades bladder and/or rectum
IVb Distant metastasis
Adenosarcoma Stage I Differs from Other Uterine Sarcomas
Ia Tumour limited to endometrium/endocervix
Ib Invasion to $\leq 1/2$ myometrium
Ic Invasion to $> 1/2$ myometrium
Refs:

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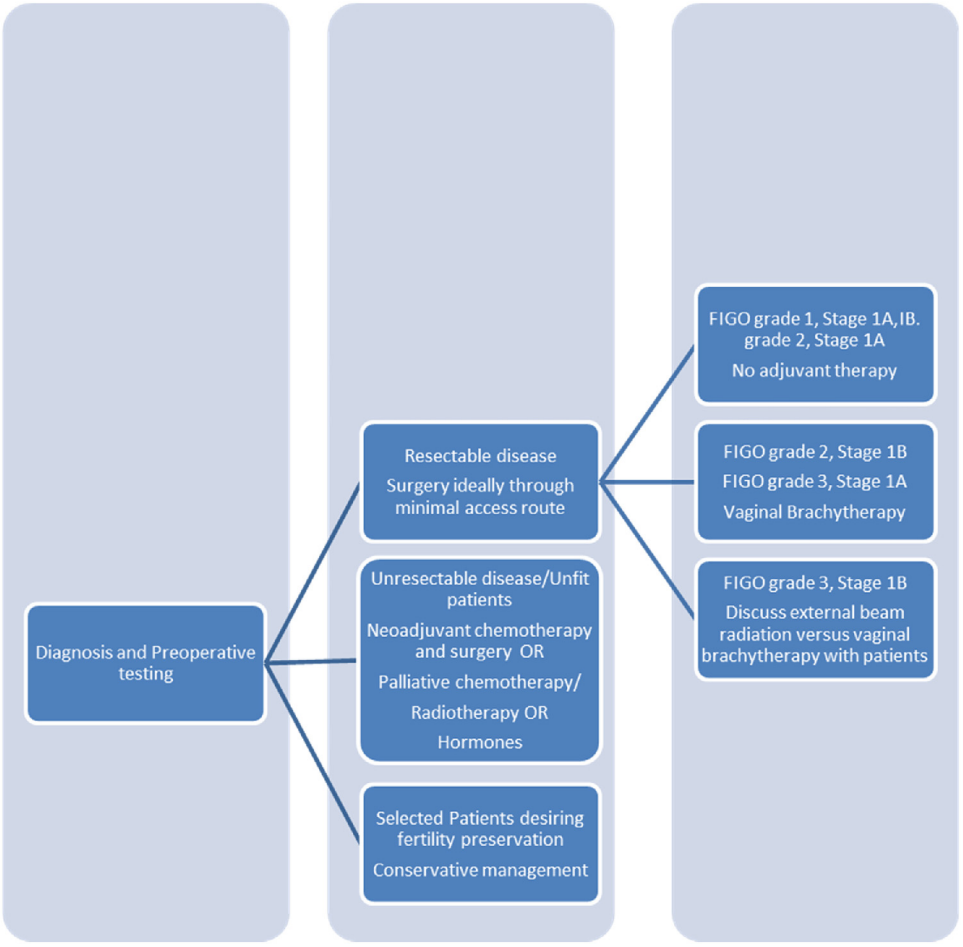
iii – Stratification of endometrial cancer risk of recurrence

Low risk	FIGO grade 1, Stage Ia, Ib FIGO grade 2, Stage Ia
Intermediate risk	FIGO grade 2, Stage Ib FIGO grade 3, Stage Ia
High risk	FIGO grade 3, Stage Ib Non endometrioid cancer

iv – Flowchart for management of endometrioid endometrial cancer



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