Anglia Gynae Cancer Networks
Network Guidelines

Current version
July 2019
Combined guidelines

Chair: Helen Bolton

Document contains AGCN guidelines for endometrial, ovarian, vulval and cervical cancer

Anglia Cancer Network Guidelines 2018

Gynaecological Cancers

Endometrial Cancer

Anglia Cancer Network have agreed to follow published guidelines where available, with local modifications, which have been annotated in this summary document. Local modifications have been agreed by consensus meeting, following local hospitals review and feedback to the Network for comments. All hospitals were invited to be involved in face-to-face discussion of the guidelines at the September 2017 meeting.

Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

Document contains:

1. A summary of recommendations from the published guidelines alongside the Network Modifications. Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

2. A full copy of the published guidelines (see below)

Endometrial Cancer guidelines are based on both the following published guidelines:

- 2017 – BGCS Uterine Cancer Guidelines: Recommendations for Practice

BGCS Uterine Cancer Guidelines: Recommendations for Practice

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

1. 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)

2. 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)

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

4. 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)

5. 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)

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

Diagnosis of endometrial cancer

7. 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)

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

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

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

11. 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)

    Disagree – changed statement to reflect Cambridge policy of offering outpatient hysteroscopy to all requiring endometrial assessment and biopsy. Hysteroscopy is gold standard. Suggest changing statement to *'Hysteroscopy may be offered to women requiring outpatient biopsy, and is the test of choice for all women with ultrasound irregularities and at high risk of endometrial cancer'.*

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

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

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

Pathways for management of endometrial cancer

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

15. 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)

16. Women with papillary serous, clear cell, carcinosarcoma, endometrioid G3 or FIGO 1B (≥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)

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

18. 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)

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

20. 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)

Investigations – Imaging and pre-operative work-up

21. 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)

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

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

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

Disagree - there is insufficient evidence that routine chest imaging is necessary in low risk, early stage disease. Suggest change to 'Chest radiology with either CT or plain X-ray is part of staging and should be performed in all women with high risk or advanced endometrial cancer. (Grade D) Low risk, early stage women do not require routine chest imaging, unless required for pre-operative assessment'

25. 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)

26. 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)

We agree with BCGS guidance that high risk histology should undergo CT. This is also in line with ESGO. Low risk patients should have an MRI to guide the need for lymphadenectomy (as per ESGO). In addition the BGCS guidelines are contradictory as guidance number 28 suggests that MRI is useful to identify nodal metastases.

Would suggest guideline should read "MRI pelvis is indicated in all patients not undergoing CT, to help stratify into pathways of care".

Disagree – MRI pelvis is indicated in all patients to help stratify into pathways of care

27. 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)

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

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

Pathology of uterine cancer

Endometrial cancer –surgery at presentation

Early disease (FIGO Stage I and II)

30. 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)

31. 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)

32. 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)

33. 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)

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

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

36. 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)

    We disagree with BGCS statement. There is insufficient data to suggest radical hysterectomy is superior, in terms of morbidity or survival, compared with routine hysterectomy and radiotherapy.

37. 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)

    This is a very contentious issue, as the BGCS guidance uses the term “may be appropriate”, this leaves the options of open and allows variation in centre and individual practice. Therefore I don’t think additional wording is needed as the guidance is not suggesting mandatory use of PA or pelvic lymphadenectomy.

    Staging pelvic lymphadenectomy, and its role in guiding adjuvant treatment, will be discussed with patients on a decision made on a case-by-case basis. Clarified that we may be discussing pelvic lymphadenectomy in relevant patients, but not para-aortic.

38. 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)

Late Disease (FIGO Stage III and IV)

39. 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)

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

    Disagree in relation to advanced disease, the Benedetti reference relates to early stage disease. So we agree with the comment in relation to surgical staging in early disease but this does not apply in advanced/ debulking scenarios where the aim is to remove macroscopic disease be it in nodes or elsewhere. There is no data to support routine lymphadenectomy in advanced endometrial cancer (or indeed ovarian cancer ref LIONS trial).

    Disagree – we will consider debulking of enlarged nodes, either on palpation or on pre-operative imaging in patients with stage III or IV disease. There is no role for systematic lymphadenectomy in these patients.

41. 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)

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

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

Adjuvant treatment of endometrioid endometrial cancer

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

45. 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)

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

47. 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)

48. 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)

49. 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)

50. 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)

51. 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)

Low risk	FIGO grade 1, Stage Ia, Ib, 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.

For late stage disease

52. 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.

Chemotherapy

53. 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)

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

In fully staged patients, those with stage III disease have a significant survival benefit from chemotherapy (PORTEC III).

In an unstaged population, we plan to discuss the pros and cons of chemotherapy in high grade uterine cancers as per our proposed chart

Stage	G1 G2	G3 endometrioid	Serous papillary adenocarcinoma	Clear cell carcinoma	Carcinosarcoma
Ia - polyp only	No	No	No	No	No
Ia - no myometrial invasion	No	No	Discuss	No	Discuss
Ia - myometrial invasion	No	No	Discuss	No	Discuss
Ib	No	Discuss	Discuss	No	Discuss
II	No	Discuss	Discuss	No	Discuss
III	Recommend	Recommend	Recommend	Recommend	Recommend

Neoadjuvant chemotherapy in endometrial cancer

55. 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)

56. 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)

Management of unfit patients with endometrial cancer.

57. 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)

58. 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)

Management of Women Wishing to Preserve their Fertility

59. 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)

60. Women with endometrioid 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)

A referral to specialist fertility services should be offered to women wishing to preserve their fertility.

Non – endometrioid cancer: uterine serous carcinoma

61. 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)

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

63. 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)

64. 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)

65. 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)

66. 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)

6 7 . 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)

68. 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)

Patients with uterine serous carcinoma presenting to the Cambridge MDM will be offered genetic testing for BRCA mutation, and a referral to Clinical Genetics will be generated at the time of first MDT discussion.

Non-endometrioid carcinoma: uterine clear cell carcinoma

69. 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)

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

71. 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)

72. 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)

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

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

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

76. 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)

Non–endometrioid cancer: uterine carcinosarcoma

77. 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)

78. 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)

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

80. 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)

81. 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)

Management of uterine sarcomas

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

83. 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)

84. 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)

85. 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)

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

87. Patients with sarcoma should be treated by specialist multidisciplinary teams. (Grade D)

88. 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.

Follow-up for endometrial cancer

89. 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)

90. 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)

91. Women should receive information on symptoms that should prompt medical attention, for example vaginal bleeding and discharge. (Grade D)

92. 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)

93. 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)

94. 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)

95. There is currently no evidence to support the use of routine imaging or biochemical testing in follow-up for endometrial cancer. (Grade D)

96. 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)

97. 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)

98. 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)

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

100. 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)

Supportive care – addressing patient needs

101. 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)

Management of relapsed endometrial carcinoma

102. 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)

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

104. 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)

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

106. 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)

107. 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)

108. 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)

109. 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)

110. 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)

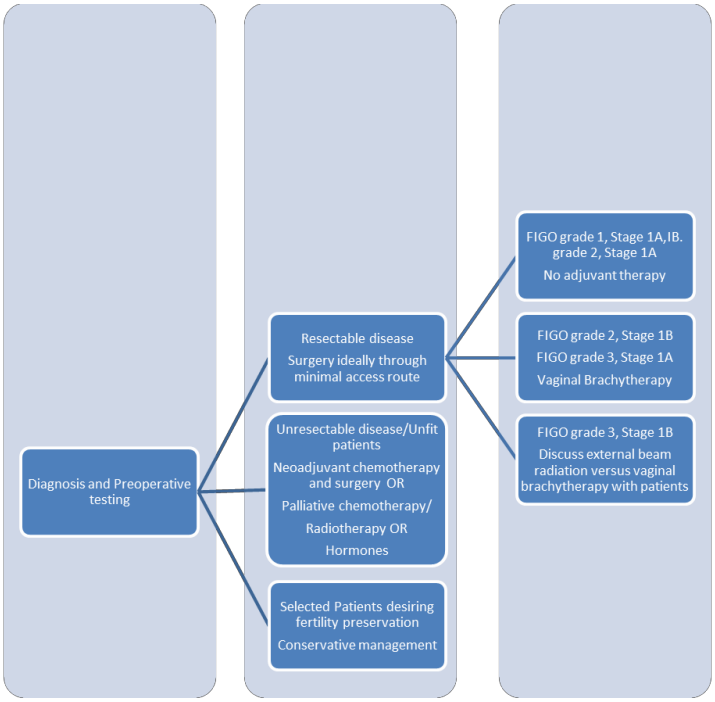
111. Patients not fit for chemotherapy may benefit from a trial of a progestin. Selected cases with long disease free interval, well-differentiated tumours, lung only metastases and high oestrogen or progesterone receptor expression in the tumour may be candidates for primary hormonal therapy. However,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

Appendices

- 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

- Flowchart for management of endometrioid endometrial cancer



BGCS Uterine Cancer Guidelines: Recommendations for Practice

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

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

1) These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
2) The guideline development process is detailed below
    a. Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic
    b. Lead then identified a team called the guideline team (GT) to develop the 1st draft
    c. 1st draft was submitted to the GC
    d. GC approved draft and recommended changes
    e. Changes were accepted by the GT who produced the guidelines
    f. 2nd draft was then submitted to council members and officers
    g. Council and officers approved 2nd draft and recommended changes
    h. Changes were then accepted by GC and GT
    i. 3rd draft was sent to national and international peer review
    j. GC and GT then made changes based on peer review comments
    k. 4th draft was sent back to council for approval
    l. 4th draft was sent to BGCS members for feedback
    m. GC and GT then made changes based on members' feedback
    n. 5th draft was sent to public consultation including patient support groups
    o. GC and GT then made changes based on non-members' feedback
    p. Final draft was approved by council and officers.

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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 8,475 women in 2011 and causing 2,025 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 ≤4mm 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.

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 10mm (12), and a low positive predictive value in this group.

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 5kg/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 1,400 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 20kg 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 (14/6,596 bariatric surgery patients versus 98/9,442 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).

Prevention in high-risk groups

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

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).

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.

Diagnostic methods

Current guidance

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

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).

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).

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.

Accuracy of TVS and cut off for endometrial thickness

Double layer endometrial thickness measurements on TVS with a cut off of ≥4 mm should be investigated. In the absence of any irregularity of the endometrial profile, and an endometrial thickness of <4mm, 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 3mm, 4mm 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 3mm 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 8mm if asymptomatic (29), but if vaginal bleeding is present a biopsy should be taken if the thickness is greater than 5mm. The 5mm 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).

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 4cm through the cervical canal (30). However, further evaluation is warranted in cases of persistent abnormal vaginal bleeding despite negative biopsy.

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 1B (≥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.

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.

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.

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.

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).

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.

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.

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.

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

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 1,851 participants, showed no statistically significant difference in the risk of death (HR=1.07, 95% CI 0.81 to 1.43) or disease recurrence (HR=1.23, 95% CI 0.96 to 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 to 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 3,644 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 to 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 (50mls

vs. 150mls, 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.

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 chemoradiotherapy 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)

Progesterone therapy

Seven randomised trials (70-76) involving 4,556 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)

External beam radiotherapy

Level 1a evidence from meta-analysis of seven randomised trials involving 3,628 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).

V**aginal 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)**

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.

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.

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 2,197 women shows a small but statistically significant overall survival advantage from adjuvant chemotherapy (106) (RR 0.88 (95% CI 0.79 to 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 to 0.96); number needed to treat for an additional beneficial outcome (NNT) was 25 and an absolute risk reduction of 4% (1% to 8%)). The HR for overall survival was 0.74 (0.64 to 0.89), significantly favouring the addition of postoperative platinum-based chemotherapy. The HR for progression-free survival was 0.75 (0.64 to 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 to 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 to 1.68)) but it may have added value when used with radiotherapy (RR 0.48 (0.20 to 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 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 chemoradiation (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)

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.

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.

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 (160mg daily), or medroxyprogesterone acetate (200mg/ 400mg 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 to 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 to 1.03; p = 0.07) but cancer-specific survival was significant (HR 0.55, CI 0.35 to 0.88; p=0.01). There was also a 36% reduction in the risk of relapse (HR: 0.64, 95% CI: 0.41 to 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.

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 lymphovascular 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., (2006) the clinical course of more than 4,000 women was analysed according to the histologic subtype: 4,180 women with high risk EC subtypes reported to the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 2001; 1,473 had a serous-papillary histology, 391 had clear cell, and 2,316 had grade three endometrioid ECs (145). ECCC patients had higher rates of stage III or IV disease than did grade 3 endometrioid 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 ≤2cm (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 1,300 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

1. Leiomyosarcoma (LMS)
2. Endometrial stromal tumours
    a. low-grade endometrial stromal sarcoma (LG-ESS)

b. high-grade endometrial stromal sarcoma (HG-ESS)
c. undifferentiated uterine sarcoma

3. Miscellaneous
    a. rhabdomyosarcoma
    b. perivascular epithelioid cell tumour

B. Mixed tumours

1. Adenosarcoma
2. Carcinosarcoma – regarded an epithelial tumour and should be treated as such (see section 14).

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).

Early stage leiomyosarcoma

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.

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).

Adjuvant treatment for early uterine leiomyosarcoma

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.

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.

Advanced stage or recurrent leiomyosarcoma

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).

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).

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).

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).

Early stage endometrial stromal sarcoma

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.

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).

Advanced or recurrent endometrial stromal sarcoma

Surgical treatment

Surgical resection may be considered in completely resectable cases (197).

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).

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).

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.

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

1) immediate discharge following initial treatment,
2) clinic based follow-up with traditional frequency of visits over five years in
    a) Traditional secondary care gynaecology doctor led clinics
    b) Secondary care gynaecology nurse led clinics:
    c) Nurse led telephone follow-up
    d) Primary care follow-up
3) individualised programmes based on the need for psychological survivorship support, management of late radiation toxicity, oestrogen deficiency and the individualised risk of recurrence.

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).

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)

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

1. Assessment and Care Planning
2. Health and Wellbeing Clinics
3. Managing Active and Advanced Disease

4. Supported Self Management
5. Consequences of Cancer and its Treatment
6. Work and Finance
7. Vocational Rehabilitation
8. 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 2cm. 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 to 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 175mg/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

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

20. Bibliography

(1) Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2014;4(3):137-144.

(2) Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016;27(1):16-41.

(3) Evans T, Sany O, Pearmain P, Ganesan R, Blann A, Sundar S. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. Br J Cancer 2011 26 April;104(9):1505-1510.

(4) Smith-Bindman R, Kerlikowske K, Feldstein Vea. Endovaginal ultrasound to exclude endometrial cancer and other abnormalities. JAMA 1998;89(8):1765-1772.

(5) Jacobs I, Gentry-Maharaj A, Burnell Mea. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case control study within the UKCTOCS cohort. Lancet Oncol 2011;12:38-48.

(6) Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol 2004;24(5):558-565.

(7) Archer D, McIntyre-Seltman K, Wilborn Jr, WW. et al. Endometrial morphology in asymptomatic postmenopausal women. Am J Obstet Gynecol 1991;165(2):317-320.

(8) Meyer L, Broaddus R, Lu K. Endometrial Cancer and Lynch Syndrome: clinical and pathologic considerations. Cancer Control 2009;16(1):14-22.

(9) Helder-Woolderlink J, De Bock G, Sijmons Rea. The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome. Gynecol Oncol 2013;131(2):304-308.

(10) Fisher B, Constantino J, Wickerham Dea. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel ProjectP-1 Study. J Natl Cancer Inst 1998;90:1371-1388.

(11) Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol 2014;32(21):2255-2269.

(12) Gerber B, Krause A, Muller Hea. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol 2000;18(20):3464-3470.

(13) Crosbie E, Roberts C, Qian Wea. Body mass index does not influence post treatment survival in early stage endometrial cancer: results from the MRC ASTEC trial. Eur J Cancer 2012;48:853-864.

(14) Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19(12):3119-3130.

(15) Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. J Natl Cancer Inst 2004;96(21):1635-1638.

(16) Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA.
Weight change and risk of endometrial cancer. Int J Epidemiol 2006;35(1):151-158.

(17) Mackintosh ML, Crosbie EJ. Obesity-driven endometrial cancer: is weight loss the answer? BJOG 2013;120(7):791-794.

(18) Sjöström L, Gummesson A, Sjöström CD, Narbro K, Crosbie EJ, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009;10(7):653-662.
(19) McCawley GM, Ferriss JS, Geffel D, Northup CJ, Modesitt SC. Cancer in obese women: potential protective impact of bariatric surgery. J Am Coll Surg 2009;208(6):1093-1098.
(20) Adams TD, Hunt SC. Cancer and obesity: effect of bariatric surgery. World J Surg 2009;33(10):2028-2033.
(21) Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013;62(6):812-823.
(22) National Institute for Health and Care Excellence. NICE guidelines (NG12) Suspected cancer: recognition and referral. June 2015; Available at: https://www.nice.org.uk/guidance/ng12, 2016.
(23) Gredmark T, Kvint S, Havel G, Mattson L. Histopathological findings in women with postmenopausal bleeding. BJOG 1995;102:133-136.
(24) Scottish Intercollegiate Guidelines Network. Investigation of Post-Menopausal Bleeding. Edinburgh: SIGN; 2002.
(25) Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. Cost-effectiveness of the use of transvaginal sonography in the evaluation of postmenopausal bleeding. Maturitas 2003;45:275-282.
(26) Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilatation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol 2003;188:401-408.
(27) Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol 2010;116:160-167.
(28) Gupta JK, Chien PFW, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: A meta-analysis. Acta Obstet Gynecol 2002;81:799-816.
(29) Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 1998;280:1510-1517.
(30) Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 2002;109:313-321.
(31) Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA 2002;288:1610-1621.
(32) Health Service Circular. Cancer Waiting Times: Guidance on Making and Tracking Progress on Cancer Waiting Times. 005th ed.: HSC; 2002.
(33) Improving Outcomes Guidance. Improving Outcomes in Gynaecological Cancers. 1999; Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4083846.pdf, 2016.
(34) Royal College of Nursing. Specialist nurses; Changing lives, saving money. 2010; Available at: http://www.rcn.org.uk/__data/assets/pdf_file/0008/302489/003581.pdf, 2016.
(35) Target Ovarian Cancer. The Pathfinder Study. 2012; Available at: http://www.targetovariancancer.org.uk/core/core_picker/download.asp?id=1354&filetitle=Target+Ovarian+Cancer%27s+Pathfinder+Study, 2016.

(36) National Cancer Action Team. Quality in Nursing Excellence in Cancer Quality in Nursing Excellence in Cancer Care: The Contribution of the Clinical Nurse Specialist. National Cancer Programme 2010.
(37) Connor JP, Andrews JI, Anderson B, Buller RE. Computed tomography in endometrial carcinoma. Obstet Gynecol 2000;95(5):692-696.
(38) Milam MR, Java J, Walker JL, Metzinger DS, Parker LP, Coleman RL. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012;119(2):286-292.
(39) Selman TJ, Mann CH, Zamora J, Khan KS. A systematic review of tests for lymph node status in primary endometrial cancer. BMC Womens Health 2008:doi: 10.1186/1472-6874-8-8.
(40) Ganesan R, Singh N, McCluggage WG. Standards and datasets for reporting cancers: Dataset for histological reporting of endometrial cancer. 2014; Available at: https://www.rcpath.org/asset/4E78C04D-8536-4554-80E0A3ECECADEE34/. Accessed 7 Nov, 2016.
(41) Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006;106(4):812-819.
(42) Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database of Systematic Reviews 2015(9):Art. No.: CD007585. DOI: 10.1002/14651858.CD007585.pub3.
(43) Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373(9658):125-136.
(44) Benedetti-Panici P, Basile S, Maneschi F, Lissoni AA, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy in early-stage endometrial carcinoma: randomised clinical trial. J Natl Cancer Inst 2008;100(23):1707-1716.
(45) Traen K, Holund B, Mogensen O. Accuracy of preoperative tumour grade and intraoperative gross examination of myometrial invasion in patients with endometrial cancer. Acta Obstet Gynecol Scand 2007;86(6):739-741.
(46) Francis JA, Weir MM, Ettler HC, Qiu F, Kwon JS. Should preoperative pathology be used to selects patients for surgical staging in endometrial cancer? Int J Gynecol Cancer 2009;19(3):380-384.
(47) Chi DS, Barakat RR, Palayekar MJ, Levine DA, Sonoda Y, Alektiar K, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometroid histology. Int J Gynecol Cancer 2008;18(2):269-273.
(48) Ballester M, Dubernard G, Lécuru F, Heitz D, Mathevet P, Marret H, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multi-centre study (SENTI-ENDO). Lancet Oncol 2011;12(5):469-476.
(49) Kang S, Yoo HJ, Hwang JH, Lim M, Seo S, Park S. Sentinel lymph node biopsy in endometrial cancer: Meta-analysis of 26 studies. Gynecol Oncol 2011;123(3):522-527.
(50) Galaal K, Bryant A, Fisher AD, Al-Khaduri M, Kew F, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev 2012;12(9):CD006655. doi: 10.1002/14651858.CD006655.pub2.
(51) Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, et al. Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group LAP2 Study. J Clin Oncol 2012;30(7):695-700.
(52) National Institute for Health and Clinical Excellence. IPG356 Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer. London: NICE; 2010.

(53) Wright JD, Burke WM, Wilde ET, Lewin SN, Charles AS, Kim JH, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. J Clin Oncol 2012;30(8):783-791.
(54) Kilgore JE, Jackson AL, Ko EM, Soper JT, Van Le L, Gehrig PA, et al. Recurrence-free and 5-year survival following robotic assisted surgical staging for endometrial carcinoma. Gynecol Oncol 2013;129(1):49-53.
(55) Gehrig PA, Cantrell LA, Shafer A, Abaid LN, Mendivil A, Boggess JF. What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? Gynecol Oncol 2008;111:41-45.
(56) Hongqian L, Theresa AL, DongHao L, Huan S, Boggess JF. Robot-assisted surgery in gynaecology. Cochrane Database Syst Rev 2014(12):Art. No.: CD011422. DOI: 10.1002/14651858.CD011422.
(57) Tebes SJ, Cardosi RJ, Hoffman MS, Grendys EC. Radical Hysterectomy Versus Extrafascial Hysterectomy in the Management of Stage II Endometrial Carcinoma. J Gynecol Surg 2005;21(3):111-116.
(58) Eltabbakh GH, Moore AD. Survival of women with surgical stage II endometrial cancer. Gynecol Oncol 1999;74(1):80-85.
(59) Mariani A, Webb MJ, Keeney GL, Calori G, Podratz KC. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. Gynecol Oncol 2001;83(1):72-80.
(60) Wright JD, Fiorelli J, Kansler AL, Burke WM, Schiff PB, Cohen CJ, et al. Optimizing the management of stage II endometrial cancer: the role of radical hysterectomy and radiation. Am J Obstet Gynecol 2009:200(4):419.e1-7. doi: 10.1016/j.ajog.2008.11.003.
(61) Cornelison TL, Trimble EL, Kosary CL. SEER data, corpus uteri cancer: treatment trends versus survival for FIGO stage II, 1988-1994. Gynecol Oncol 1999;74(3):350-355.
(62) Sartori E, Gadducci A, Landoni F, Lissoni A, Maggino T, Zola P, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. Int J Gynecol Cancer 2001;11(6):430-437.
(63) Boente MP, Yordan ELJ, McIntosh DG, Grendys ECJ, Orandi YA, Davies S, et al. Prognostic factors and long-term survival in endometrial adenocarcinoma with cervical involvement. Gynecol Oncol 1993;51(3):316-322.
(64) Ayhan A, Taskiran C, Celik C, Yuce K. The long-term survival of women with surgical stage II endometrioid type endometrial cancer. Gynecol Oncol 2004;93:9-13.
(65) Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: A meta-analysis. Gynecol Oncol 2010;118:14-18.
(66) Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol 2012;127(2):338-344.
(67) Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, Montz FJ. FIGO Stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer 2003;13(5):664-672.
(68) Havrilesky LJ, Cragun JM, Calingaert B, Synan I, Secord AA, Soper JT, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. Gynecol Oncol 2005;99(3):689-695.
(69) Guimara˜es GC, Baiocchi G, Ferreira FO, Kumagai LY, Fallopa CC, Aguiar S, et al. Palliative pelvic exenteration for patients with gynaecological malignancies. Arch Gynecol Obstet 2011;283(5):1107-1112.
(70) COSA-NZ-UK Endometrial Cancer Groups. Adjuvant medroxyprogesterone acetate in high-risk endometrial cancer. Int J Gynecol Cancer 1998;8:387-391.
(71) DePalo G, Mangioni C, Periti P, Del Vecchio M, Marubini E. Treatment of FIGO (1971) stage 1 endometrial carcinoma with intensive surgery, radiotherapy and hormonotherapy according to

pathological prognostic groups. Long term results of a randomised multicentre trial. Eur J Cancer 1993;29a:1133-1140.
(72) Lewis GC, Slack NH, Mortel R, Bross I. Adjuvant progestagen therapy in the definitive treatment of endometrial cancer. Gynecol Oncol 1974;2:368-376.
(73) MacDonald RR, Thorogood J, Mason MK. A randomised trial of progestagens in the primary treatment of endometrial carcinoma. BJOG 1988;95:166-174.
(74) Malkasian G, Decker D. Aduvant progesterone therapy for stage 1 endometrial cancer. Int J Gynaecol Obstet 1978;16:48-49.
(75) Urbanski K, Karolewski K, Kojs Z, Klimek M, Dyba T. Adjuvant progestagen therapy improves survival in patients with endometrial cancer after hysterectomy. results of one-institutional prospective clinical trial. Eur J Gynaecol Oncol 1993;14 suppl:98-104.
(76) Vergote I, Kjorstad K, Abeler V, Kolstad P. A randomised trial of adjuvant progestagens in early endometrial cancer. Cancer 1989;64:1011-1016.
(77) Martin-Hirsch PPL, Bryant A, Keep SL, Kitchener HC, Lilford R. Adjuvant progestagens for endometrial cancer. Cochrane Database Syst Rev 2011(6):Art. No.: CD001040. DOI: 10.1002/14651858.CD001040.pub2.
(78) Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2009(2):CD004143. doi: 10.1002/14651858.CD004143.pub3.
(79) Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev 2010(12):CD007926. DOI: 10.1002/14651858.CD007926.pub2.
(80) Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev 2012(4):CD003916. DOI: 10.1002/14651858.CD003916.pub4.
(81) Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. J Natl Cancer Inst 2012;104(21):1625-1634.
(82) Reed N. Endometrial cancer: adjuvant treatment of endometrial cancer—radiotherapy, chemotherapy or both. Eur Soc Med Oncology 2008;19(Supplement 7):vii67-vii69.
(83) Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56(4):419-427.
(84) ASTEC/EN.5 Study Group. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373(9658):137-146.
(85) PORTEC-1 Study Group. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;15(81):e631-638.
(86) Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355(9213):1404-1411.
(87) Nout RA, van de Poll-Franse LV, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol 2011;29(13):1692-1700.
(88) Nout RA, Putter H, Ju¨rgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, van der Steen-Banasik EM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009;27(21):3547-3556.
(89) Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer

of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial.. Lancet 2010;375(9717):816-823.
(90) Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma - a prospective randomised study. Int J Radiat Oncol Biol Phys 2011;82(3):1249-1255.
(91) Johnson N, Cornes P. Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. Br J Obstet Gynaecol 2007;114:1313-1320.
(92) Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92(3):744-751.
(93) Soderini A, Anchezar JP, Sardi JE. Role of adjuvant radiotherapy (RT) in intermediate risk (1b G2-3-1C) endometrioid carcinoma (EC) after extended staging surgery (ESS). Preliminary reports of a randomised trial. . Int J Gynaecol Cancer 2003;13(Supp 1):Abstract P0147:78.
(94) Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial.. Gynecol Oncol 2003;89(2):201-209.
(95) Straughn JM, Numnum TM, Kilgore LC, Partridge EE, Phillips JL, Markman M, et al. The use of adjuvant radiation therapy in patients with intermediate-risk Stages IC and II uterine corpus cancer: A patient care evaluation study from the American College of Surgeons National Cancer Data Base. Gynecol Oncol 2005;99(3):530-535.
(96) Sorbe B, Nordström B, Mäenpää J, Kuhelj J, Kuhelj D, Okkan S, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynaecol Cancer 2009;19(5):873-878.
(97) Meyer LA, Bohlke K, Powell MA, Fader AN, Franklin GE, Lee LJ, et al. Postoperative Radiation Therapy for Endometrial Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. J Clin Oncol 2015;33(26):2908-2913.
(98) Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer 2006;95(3):266-271.
(99) Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24(1):36-44.
(100) Watkins Bruner D, Barsevick A, Tian C, Randall M, Mannel R, Cohn D. Quality of life trade-off to incremental gain in survival on Gynecologic Oncology Group (GOG) Protocol 122: Whole abdominal irradiation (WAI) vs. doxorubicin-platinum (AP) chemotherapy in advanced endometrial cancer. American Society of Clinical Oncology 2003;22:449-Abstract 1803.
(101) Wolfson AH, Brady MF, Rocereto T, Mannel RS, Lee YC, Futoran RJ, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus.. Gynecol Oncol 2007;107(2):177-185.
(102) Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. Gynecol Oncol 1990;36(2):166-171.
(103) Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with

intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 2008;108(1):226-233.
(104) Kuoppala T, Mäenpää J, Tomas E, Puistola U, Salmi T, Grenman S, et al. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecol Oncol 2008;110(2):190-195.
(105) Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46(13):2422-2431.
(106) Johnson N, Bryant A, Miles T, Hogberg T, Cornes P. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev 2011(10):Art. No.: CD003175. DOI: 10.1002/14651858.CD003175.pub2.
(107) Despierre E, Moerman P, Vergote I, Amant F. Is there a role for neoadjuvant chemotherapy in the treatment of stage IV serous endometrial carcinoma? Int J Gynaecol Cancer 2006;16(Suppl 1):273-277.
(108) Peters WA, Andersen WA, Thornton WNJ, Morley GW. The selective use of vaginal hysterectomy in the management of adenocarcinoma of the endometrium. Am J Obstet Gynecol 1983;146(3):285-289.
(109) Podzielinski I, Randall ME, Breheny PJ, Escobar PF, Cohn DE, Quick AM, et al. Primary radiation therapy for medically inoperable patients with clinical stage I and II endometrial carcinoma. Gynecol Oncol 2012;124:36-41.
(110) Inciura A, Atkocius V, Juozaityte E, Vaitkiene D. Long-term results of high-dose-rate brachytherapy and external-beam radiotherapy in the primary treatment of endometrial cancer. J Radiat Res 2010;51:675-681.
(111) Wong JR, Gao Z, Merrick S, Wilson P, Uematsu M, Woo K, et al. Potential for higher treatment failure in obese patients: correlation of elevated body mass index and increased daily prostate deviations from the radiation beam isocenters in an analysis of 1,465 computed tomographic images. Int J Radiat Oncol Biol Phys 2009;75(1):49-55.
(112) Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2012;207(4):266e1-12.
(113) Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, et al. Long-term oncologic outcomes after fertility-sparing managementusing oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer 2013;49(4):868-874.
(114) Laurelli G, Di Vagno G, Scaffa C, Losito S, Del Giudice M, Greggi S. Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecol Oncol 2011;120(1):43-46.
(115) del Carmen MG, Birrer M, Schorge JO. Uterine papillary serous cancer: a review of the literature. Gynecol Oncol 2012;127(3):651-661.
(116) Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol 2010;22(1):21-29.
(117) Nicklin JL, Copeland LJ. Endometrial papillary serous carcinoma: patterns of spread and treatment. Clin Obstet Gynecol 1996;39(3):686-695.
(118) Rosenberg P, Risberg B, Askmalm L, Simonsen E. The prognosis in early endometrial carcinoma. The importance of uterine papillary serous carcinoma (UPSC), age, FIGO grade and nuclear grade. Acta Obstet Gynecol Scand 1989;68(2):157-163.
(119) Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. Gynecol Oncol 1992;47(3):298-305.
(120) Chan JK, Loizzi V, Youssef M, Osann K, Rutgers J, Vasilev SA, et al. Significance of comprehensive surgical staging in noninvasive papillary serous carcinoma of the endometrium. Gynecol Oncol 2003;90(1):181-185.

(121) Gehrig PA, Groben PA, Fowler WCJ, Walton LA, Van Le L. Noninvasive papillary serous carcinoma of the endometrium. Obstet Gynecol 2001;97(1):153-157.
(122) Goff BA, Kato D, Schmidt RA, Ek M, Ferry JA, Muntz HG, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol 1994;54(3):264-268.
(123) Hui P, Kelly M, O'Malley DM, Tavassoli F, Schwartz PE. Minimal uterine serous carcinoma: a clinicopathological study of 40 cases. Mod Pathol 2005;18(1):75-82.
(124) Slomovitz BM, Burke TW, Eifel PJ, Ramondetta LM, Silva EG, Jhingran A, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol 2003;91(3):463-469.
(125) DG M. The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas. Gynecol Oncol 2009(115):325-328.
(126) Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375(9721):1165-1172.
(127) Bristow RE, Duska LR, Montz FJ. The role of cytoreductive surgery in the management of stage IV uterine papillary serous carcinoma. Gynecol Oncol 2001;81(1):92-99.
(128) Memarzadeh S, Holschneider CH, Bristow RE, Jones NL, Fu YS, Karlan BY, et al. FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. Int J Gynecol Cancer 2002;12(5):454-458.
(129) Moller KA, Gehrig PA, Van Le L, Secord AA, Schorge J. The role of optimal debulking in advanced stage serous carcinoma of the uterus. Gynecol Oncol 2004;94(1):170-174.
(130) Thomas MB, Mariani A, Cliby WA, Keeney GL, Podratz KC, Dowdy SC. Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. Gynecol Oncol 2007;107(2):190-193.
(131) Dietrich CS, Modesitt SC, DePriest PD, Ueland FR, Wilder J, Reedy MB, et al. The efficacy of adjuvant platinum-based chemotherapy in Stage I uterine papillary serous carcinoma (UPSC). Gynecol Oncol 2005;99(3):557-563.
(132) Fader AN, Drake RD, O'Malley DM, Gibbons HE, Huh WK, Havrilesky LJ, et al. Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. Cancer 2009;115(10):2119-2127.
(133) Huh WK, Powell M, Leath CA, Straughn JMJ, Cohn DE, Gold MA, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical Stage I patients with and without adjuvant therapy. Gynecol Oncol 2003;91(3):470-475.
(134) Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley H, Lee RB, et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2006;100(2):349-354.
(135) Lim P, Al Kushi A, Gilks B, Wong F, Aquino-Parsons C. Early stage uterine papillary serous carcinoma of the endometrium: effect of adjuvant whole abdominal radiotherapy and pathologic parameters on outcome. Cancer 2001;91(4):752-757.
(136) Kelly MG, O'malley DM, Hui P, McAlpine J, Yu H, Rutherford TJ, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. Gynecol Oncol 2005;98(3):353-359.
(137) Fields AL, Einstein MH, Novetsky AP, Gebb J, Goldberg GL. Pilot phase II trial of radiation "sandwiched" between combination paclitaxel/platinum chemotherapy in patients with uterine papillary serous carcinoma (UPSC). Gynecol Oncol 2008;108(1):201-206.
(138) Le TD, Yamada SD, Rutgers JL, DiSaia PJ. Complete response of a stage IV uterine papillary serous carcinoma to neoadjuvant chemotherapy with Taxol and carboplatin. Gynecol Oncol 1999;73(3):461-463.
(139) Price FV, Amin RM, Sumkin J. Complete clinical responses to neoadjuvant chemotherapy for uterine serous carcinoma. Gynecol Oncol 1999;73(1):140-144.
(140) Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, Neven P, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial

cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer 2009;101(2):244-249.
(141) Abeler VM, Vergote IB, Kjørstad KE, Tropé CG. Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. Cancer 1996;78:1740.
(142) Lindahl B, Persson J, Ranstam J, Willén R. Long-term survival in uterine clear cell carcinoma and uterine papillary serous carcinoma. Anticancer Res 2010;30(9):3727-3730.
(143) Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, et al. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res 2005;11:6422.
(144) Cirisano FDJ, Robboy SJ, Dodge RK, Bentley RC, Krigman HR, Synan IS, et al. The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecol Oncol 2000;77(1):55-65.
(145) Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006;94(5):642-646.
(146) Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat 2001;6(1):47-86.
(147) Thomas M, Mariani A, Wright JD, Madarek EO, Powell MA, Mutch DG, et al. Surgical management and adjuvant therapy for patients with uterine clear cell carcinoma: a multi-institutional review. Gynecol Oncol 2008;108(2):293-297.
(148) Patsavas K, Woessner J, Gielda B, Rotmensch J, Yordan E, Bitterman P, et al. Optimal surgical debulking in uterine papillary serous carcinoma affects survival. Gynecol Oncol 2011;121(3):581-585.
(149) Rauh-Hain JA, Growdon WB, Schorge JO, Goodman AK, Boruta DM, McCann C, et al. Prognostic determinants in patients with stage IIIC and IV uterine papillary serous carcinoma. Gynecol Oncol 2010;119(2):299-304.
(150) Maggioni A, Benedetti Panici P, Dell'Anna T, Landoni F, Lissoni A, Pellegrino A, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer 2008;95(6):699-704.
(151) Yaegashi N, Ito K, Niikura H. Lymphadenectomy for endometrial cancer: is paraaortic lymphadenectomy necessary? Int J Clin Oncol 2007;12(3):176-180.
(152) Abu-Rustum NR, Gomez JD, Alektiar KM, Soslow RA, Hensley ML, Leitao MMJ, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. Gynecol Oncol 2009;115(2):236-238.
(153) Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109(1):11-18.
(154) Walsh CS, Karlan BY. Lymphadenectomy's role in early endometrial cancer: prognostic or therapeutic? J Natl Cancer Inst 2008;100(23):1660-1661.
(155) Mariani A, Dowdy SC, Podratz KC. New surgical staging of endometrial cancer: 20 years later. Int J Gynaecol Obstet 2009;105(2):110-111.
(156) Fotopoulou C, El-Balat A, du Bois A, Sehouli J, Harter P, Muallem MZ, et al. Systematic pelvic and paraaortic lymphadenectomy in early high-risk or advanced endometrial cancer. Arch Gynecol Obstet 2015;292(6):1321-1327.
(157) Shechter-Maor G, Bruchim I, Ben-Harim Z, Altaras M, Fishman A. Combined chemotherapy regimen of carboplatin and paclitaxel as adjuvant treatment for papillary serous and clear cell endometrial cancer. Int J Gynecol Cancer 2009;19(4):662-664.
(158) Rauh-Hain JA, Costaaggini I, Olawaiye AB, Growdon WB, Horowitz NS, del Carmen MG. A comparison of outcome in patients with stage 1 clear cell and grade 3 endometrioid adenocarcinoma of the endometrium with and without adjuvant therapy. Eur J Gynaecol Oncol 2010;31(3):284-287.

(159) Kwon JS, Abrams J, Sugimoto A, Carey MS. Is adjuvant therapy necessary for stage IA and IB uterine papillary serous carcinoma and clear cell carcinoma after surgical staging? Int J Gynecol Cancer 2008;18(4):820-824.
(160) Miller DS, Filiaci G, Mannel R, Cohn D, Matsumoto T, Tewari K, et al. Randomized Phase III Noninferiority Trial of First Line Chemotherapy for Metastatic or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study. Presented at the 2012 Society of Gynecologic Oncology Annual Meeting, Austin, TX 2012.
(161) Barney BM, Petersen IA, Mariani A, Dowdy SC, Bakkum-Gamez JN, Haddock MG. The role of vaginal brachytherapy in the treatment of surgical stage I papillary serous or clear cell endometrial cancer. Int J Radiat Oncol Biol Phys 2013;85(1):109-115.
(162) Townamchai K, Berkowitz R, Bhagwat M, Damato AL, Friesen S, Lee LJ, et al. Vaginal brachytherapy for early stage uterine papillary serous and clear cell endometrial cancer. Gynecol Oncol 2013;129(1):18-21.
(163) Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008;44(6):808-818.
(164) Francis M, Dennis NL, Hirschowitz L, Grimer R, Poole J, Lawrence G, et al. Incidence and survival of gynecologic sarcomas in England. Int J Gynaecol Cancer 2015;25(5):850-857.
(165) Grimer R, Judson I, Peake D, Seddon B. Guidelines for the Management of Soft Tissue Sarcomas. Sarcoma 2010;Article ID 506182.
(166) Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol 1994;83(3):414-418.
(167) Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer 1993;71(4 Suppl):1702-1709.
(168) Zivanovic O, Leitao MM, Iasonos A, Jacks LM, Zhou Q, Abu-Rustum NR, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the international Federation of gynecology and obstetrics and american joint committee on cancer staging systems. J Clin Oncol 2009;27(12):2066-2072.
(169) Iasonos A, Keung EZ, Zivanovic O, Mancari R, Peiretti M, Nucci M, et al. External validation of a prognostic nomogram for overall survival in women with uterine leiomyosarcoma. Cancer 2013;119(10):1816-1822.
(170) Leibsohn S, d'Ablaing G, Mishell DRJ, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol 1990;162(4):968-976.
(171) Leitao MM, Sonoda Y, Brennan MF, Barakat RR, Chi DS. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. Gynecol Oncol 2003;91(1):209-212.
(172) Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer 2008;112(4):820-830.
(173) Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, et al. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. JAMA 2014;312(12):1253-1255.
(174) FDA. Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy: FDA Safety Communication. April 17, 2014; Available at: www.fda.gov, 2016.
(175) Bogani G, Cliby WA, Aletti GD. Impact of morcellation on survival outcomes of patients with unexpected uterine leiomyosarcoma: a systematic review and meta-analysis. Gynecol Oncol 2015;137(1):167-172.
(176) Lissoni A, Cormio G, Bonazzi C, Perego P, Lomonico S, Gabriele A, et al. Fertility-sparing surgery in uterine leiomyosarcoma. Gynecol Oncol 1998;70(3):348-350.

(177) Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. J Clin Oncol 1985;3(9):1240-1245.
(178) Giuntoli RL, Metzinger DS, DiMarco CS, Cha SS, Sloan JA, Keeney GL, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89(3):460-469.
(179) Hensley ML, Wathen JK, Maki RG, Araujo DM, Sutton G, Priebat DA, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer 2013;119(8):1555-1561.
(180) Leitao MMJ, Zivanovic O, Chi DS, Hensley ML, O'Cearbhaill R, Soslow RA, et al. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. Gynecol Oncol 2012;125(2):409-413.
(181) Blackmon SH, Shah N, Roth JA, Correa AM, Vaporciyan AA, Rice DC, et al. Resection of pulmonary and extrapulmonary sarcomatous metastases is associated with long-term survival. Ann Thorac Surg 2009;88(3):877-884.
(182) Look KY, Sandler A, Blessing JA, Lucci JA, Rose PG, Gynecologic Oncology Group (GOG) Study. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. Gynecol Oncol 2004;92(2):644-647.
(183) Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20(12):2824-2831.
(184) Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008;109(3):329-334.
(185) Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014;15(4):415-423.
(186) Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007;25(9):2755-2763.
(187) National Institute for Health and Care Excellence. NICE Trabectedin for the treatment of advanced soft tissue sarcoma. NICE technology appraisal guidance [TA185] 2010 Feb 2010.
(188) Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Leodolter S, Mayerhofer K. Estrogen and progesterone receptor expression in patients with uterine leiomyosarcoma and correlation with different clinicopathological parameters. Anticancer Res 2003;23(1B):729-732.
(189) Leitao MM, Hensley ML, Barakat RR, Aghajanian C, Gardner GJ, Jewell EL, et al. Immunohistochemical expression of estrogen and progesterone receptors and outcomes in patients with newly diagnosed uterine leiomyosarcoma. Gynecol Oncol 2012;124(3):558-562.
(190) O'Cearbhaill R, Zhou Q, Iasonos A, Soslow RA, Leitao MM, Aghajanian C, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. Gynecol Oncol 2010;116(3):424-429.
(191) George S, Feng Y, Manola J, Nucci MR, Butrynski JE, Morgan JA, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer 2014;120(5):738-743.
(192) Rauh-Hain JA, Goodman A, Boruta DM, Schorge JO, Horowitz NS, del Carmen MG. Endometrial stromal sarcoma: a clinicopathologic study of 29 patients. J Reprod Med 2014;59(11-12):547-552.
(193) Lee CH, Mariño-Enriquez A, Ou W, Zhu M, Ali RH, Chiang S, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. Am J Surg Pathol 2012;36(5):641-653.

(194) Laurelli G, Falcone F, Scaffa C, Messalli EM, Del Giudice M, Losito S, et al. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature. Eur J Obstet Gynecol Reprod Biol 2015;195:61-66.
(195) Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer 2008;99(8):1210-1215.
(196) Pink D, Lindner T, Mrozek A, Kretzschmar A, Thuss-Patience PC, Dörken B, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. Gynecol Oncol 2006;101(3):464-469.
(197) Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systematic review. Obstet Gynecol 2013;122(3):676-683.
(198) The ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii102-iii112.
(199) Sutton G, Blessing JA, Park R, DiSaia PJ, Rosenshein N. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. Obstet Gynecol 1996;87(5 Pt 1):747-750.
(200) Carroll A, Ramirez PT, Westin SN, Soliman PT, Munsell MF, Nick AM, et al. Uterine adenosarcoma: an analysis on management, outcomes, and risk factors for recurrence. Gynecol Oncol 2014;135(3):455-461.
(201) Tanner EJ, Toussaint T, Leitao MMJ, Hensley ML, Soslow RA, Gardner GJ, et al. Management of uterine adenosarcomas with and without sarcomatous overgrowth. Gynecol Oncol 2013;129(1):140-144.
(202) Beaver K, Williamson S, Sutton C, Hollingworth W, Gardner A, Allton B, et al. Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): a randomised, multicentre, non-inferiority trial. BJOG 2017;124(1):150-160.
(203) Department of Health. Hospital Episodes Statistics. 2010; Available at: http://www.hesonline.nhs.uk, 2016.
(204) Kew FM, Roberts AP, Cruickshank DJ. The role of routine follow up after gynaecological malignancy. Int J Gynaecol Cancer 2005;15(3):413-419.
(205) Baekelandt MM, Castiglione M, on behalf of the ESMO Guidelines Working Group. Endometrial carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2009;20(Suppl 4):iv29-31.
(206) Tjalma WAA, Van Dam PA, Markar AP, Cruikshank DJ. The clinical value and the cost-effectiveness of follow up in endometrial cancer patients. Int J Gynaecol Oncol 2004;14(5):931-937.
(207) Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol 2006;101(3):520-529.
(208) National Institute for Health and Care Excellence. NICE clinical guideline 81. Advanced breast cancer: Diagnosis and treatment. 2014; Available at: www.guidance.nice.org.uk/cg81, 2016.
(209) Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol 2003;56(5):1366-1372.
(210) Wylie J, Irwin C, Pintilie M, Levin W, Manchul L, Milosevic M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecol Oncol 2000;77(1):66-72.
(211) Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol 2006;103(1):281-287.
(212) Shepherd JH, Ngan HYS, Neven P, Fryatt I, Woodhouse CRJ, Hendry WF. Multivariate analysis of factors affecting survival in pelvic exenteration. Int J Gynecol Cancer 1994;4(6):361-370.
(213) Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Visentin MC, Martella L, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer 2004;100(1):89-96.

(214) Morris M, Alvarez RD, Kinney WK, Wilson TO. Treatment of recurrent adenocarcinoma of the endometrium with pelvic exenteration. Gynecol Oncol 1996;60(2):288-291.
(215) Barakat RR, Goldman N, Patel D, Venkatraman ES, Curtin JP. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol 1999;75(1):99-102.
(216) Kadkhodayan S, Shahriari S, Treglia G, Yousefi Z, Sadeghi R. Accuracy of 18-F-FDG PET imaging in the follow up of endometrial cancer patients: systematic review and meta-analysis of the literature. Gynecol Oncol 2013;128(2):397-404.
(217) Chung HH, Kang WJ, Kim JW, Park NH, Song YS, Chung JK, et al. The clinical impact of [(18)F]FDG PET/CT for the management of recurrent endometrial cancer: correlation with clinical and histological findings. Eur J Nucl Med Mol Imaging 2008;35(6):1081-1088.
(218) Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol 2007;18(3):409-420.
(219) Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 2004;22(19):3902-3908.
(220) Aapro MS. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol 2003;14(3):441-448.
(221) Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2004;22(11):2159-2166.
(222) Miller DS, Filiaci G, Mannel R, Cohn D, Matsumoto T, Tewari K, et al. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2012;125(3):771.
(223) Ang JE, Shah RN, Everard M, Keyzor C, Coombes I, Jenkins A, et al. A feasibility study of sequential doublet chemotherapy comprising carboplatin–doxorubicin and carboplatin–paclitaxel for advanced endometrial adenocarcinoma and carcinosarcoma. Ann Oncol 2009;20(11):1787-1793.
(224) Muggia FM. Phase II Trial of the Pegylated Liposomal Doxorubicin in Previously Treated Metastatic Endometrial Cancer: A Gynecologic Oncology Group Study. J Clin Oncol 2002;20(9):2360-2364.
(225) Miller DS, Blessing J, Lentz SS, Waggoner SE. A Phase II Trial of Topotecan in Patients with Advanced, Persistent, or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol 2002;87(3):247-251.
(226) Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 1996;14(2):357-361.
(227) Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol 1989;28(4):561-566.
(228) Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 1999;17(6):1736-1744.
(229) Thigpen JT, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2001;19(2):364-367.
(230) Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2000;78(2):212-216.

(231) Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers--a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynaecol Cancer 2004;14(4):650-658.
(232) Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92(1):10-14.

20. Appendices

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
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 < ½ myometrial invasion
Ib Tumour confined to the uterus, ≥ ½ 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 ≤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 ≤½ myometrium
Ic Invasion to >½ myometrium

Refs:

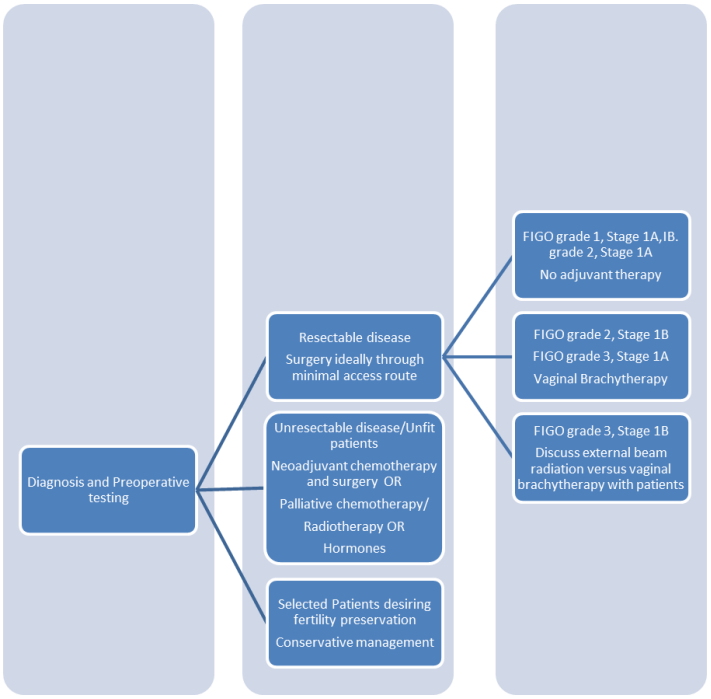
Pecorelli S. FIGO committee on gynecologic oncology: revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Int J Gynecol Oncol 2009;105(2):103-4.

Corrigendum to “FIGO staging for uterine sarcomas” [International Journal of Gynecology and Obstetrics (2009) 104:179]. Int J Gynecol Obstet 2009;106:277.

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



Anglia Cancer Network Guidelines 2018

Gynaecological Cancers

Ovarian / Fallopian Tube / Primary Peritoneal Cancers

Anglia Cancer Network have agreed to follow published guidelines where available, with local modifications, which have been annotated in this summary document. Local modifications have been agreed by consensus meeting, following local hospitals review and feedback to the Network for comments. All hospitals were invited to be involved in face-to-face discussion of the guidelines at the September 2017 meeting.

Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

Document contains:

1. A summary of recommendations from the published guidelines alongside the Network Modifications. Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

2. A full copy of the published guidelines (see below)

Ovarian / Fallopian Tube / Primary Peritoneal Cancers guidelines are based on both the following published guidelines:

- 2017 – British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice

British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube Primary Peritoneal Cancer Guidelines: Recommendations for Practice

Primary care

1. CA125 and pelvic ultrasound scan (+/- TVS as indicated) should be considered the initial investigations for post-menopausal women presenting with signs or symptoms of ovarian cancer (Grade B).

2. Women with an RMI of ≥250 should have further investigations and be referred to the specialist gynaecological centre MDT (Grade B).

3. There is currently no role for organized screening programmes in women considered at low risk of development of ovarian cancer (Grade A)

4. The role of ovarian cancer screening in women at high risk of ovarian cancer has yet to be established (Grade B)

5. Risk-reducing salpingo-oophorectomy (RRSO) prevents development of epithelial ovarian cancer and reduces mortality in women at high risk for epithelial ovarian cancer (Grade B).

Tumour markers and Malignancy Indices

Secondary care and initial pre- treatment assessment

6. In women below 40 years of age with suspected ovarian cancer, measure alpha fetoprotein (AFP), and hCG (human Chorionic Gonadotropin), in addition to CA125, to identify women with non epithelial ovarian lesions (Grade C) .

7. Inhibin should be measured at a presumed diagnosis of a granulosa cell tumor, even though logistically it takes potentially longer to access the results.

   - ***Cambridge modification – Inhibin currently impractical therefore not routinely recommended. AMH may be considered in selected cases.***

8. Where CA125 is elevated, a preoperative CA125/CEA ratio < 25 , especially in combination with an elevated CA19-9, may indicate peritoneal carcinomatosis from a gastrointestinal tumour and bi- directional gastrointestinal endoscopy should be considered prior to upfront primary debulking surgery.[Grade B]**. All patients (stage I-IV) undergoing primary surgery for suspected ovarian malignancy should have the CEA measured prior to surgery. This should be carried out by the referring hospital, together with CA125, and be available for MDT discussion prior to planning surgery. Patients having a biopsy confirming ovarian origin do not need to have CEA measured.**

- *Clarified that all patients having primary surgery should have this assessed, and that this is the responsibility of the referring hospital.*

Advised examinations prior to deciding treatment

9. In patients with presumed ovarian cancer, **radiological staging by CT chest/abdo/pelvis** will provide further information about the extent of disease and potential distant metastases or secondary cancers. (Grade C)

- ***Clarified that in Cambridge our radiological staging will be with CT chest, abdomen and pelvis***

10. CT prediction of suboptimal cytoreduction is not sufficiently reliable and in the absence of favourable data from larger, prospective trials should not be used alone to decide management. (Grade B). **All cases will be discussed at the MDT with the results of imaging and clinical information, and a recommended plan agreed. In selected cases, such as those with extensive disease at presentation, or doubtful response on CT after chemotherapy, a laparoscopic assessment may be considered to aid in management planning.**

- ***We have expanded on this recommendation to included discussion at MDT to aid with surgical planning and the role laparoscopic assessment in selected cases***

11. MRI should not be routinely used for assessing women with suspected ovarian cancer outside of clinical trials, but can be useful where the results of the USS are not helpful in confirming diagnosis, especially in young women with a solitary pelvic mass who want a fertility sparing approach. (Grade B)

12. PET CT is not recommended for routine preoperative staging in the NHS outside a clinical

trial. (Grade C)

13. CT has significant value in excluding distant macroscopic disease spread, including intraparenchymal liver or lung metastases and retroperitoneal node involvement, and in excluding synchronous cancers from other sites or thromboembolic events that may alter management. (Grade B)

Cytological/Histological Diagnosis

14. If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer first obtain a confirmed tissue diagnosis by histology in all but exceptional cases. (Grade C)

15. Only commence cytotoxic chemotherapy for suspected advanced ovarian cancer on the basis of positive cytology alone and imaging and without histological confirmation in exceptional cases and where obtaining a tissue sample would be inappropriate. A discussion of such cases at the multidisciplinary team meeting including a careful consideration of the risks and benefits should be documented (Grade C).

16. If ascites is sent for cytological analysis, the absence of malignant cells does not exclude ovarian malignancy, especially in the presence of inflammation (Grade B).(23, 24)

17. Where upfront cytotoxic chemotherapy is offered to women with suspected advanced ovarian cancer, histological tissue diagnosis via image guided biopsy or laparoscopy is mandatory in all but exceptional cases. Cytology alone, together with a CA125/CEA ratio of >25:1 may be sufficient in patients with poor performance status (PS 3,4) and where biopsy is not feasible. (Grade C)

18. The routine use of laparoscopy to obtain pre-treatment histology and to assess the operability of disease is not recommended. (Grade B)

Pathology and genetics

19. The provision of a minimum set of clinical information on the histopathology request form is crucial to ensure a histopathology report of high enough quality for the accurate diagnosis and appropriate management. (Grade D) **In Cambridge the ICCR protocol will be used for primary site assignment, and the report will include the presence or absence of STIC lesions, including their site of origin (fimbrial or non –fimbrial).**

20. Frozen section may be performed, if the result will alter the intra-operative management although there are limitations to the technique. (Grade B)

21. Women with HGSC or G3 endometrioid ovarian adenocarcinoma have >10% risk of an underlying BRCA mutation and should be offered clinical genetics counselling and testing. (GRADE C).). **In Cambridge, eligible women will be referred to genetics via the GTEOC pathway.**

Surgical treatment

Suspected or Confirmed Early Stage Disease

22. Women with suspected epithelial ovarian cancer should undergo surgery at a cancer centre by specialised surgeons who are core members of a specialist MDT. (Grade B)

23. Women requiring chemotherapy should be treated by a medical or clinical oncologist who is a core member of a specialist MDT. (Grade D)

24. Affected women should have an identified key worker and responsible clinician. (Grade D)

25. 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)

26. The aim of surgery for early ovarian cancer (stage I and II) is complete macroscopic tumour resection and adequate surgical staging. (Grade A)

27. Patients suitable for fertility-sparing surgery should be identified by the MDT and the pros and cons of this discussed with them, so that they can make an informed choice. (Grade D). **Where patients require specialist advice or support, a referral to specialist fertility services should be offered.**

28. Early stage disease may be an unexpected post-operative histological finding in cases that have been managed as a benign condition. A re-staging procedure by a gynaecological oncologist **should be considered prior to commencing chemotherapy**, to establish stage and possibly define type or necessity of adjuvant treatment (Grade B).
    - ***Added 'prior to chemotherapy' to reflect that 'completion surgery' (surgical staging) followed by adjuvant treatment is the standard management approach, unless there are patient-specific factors where adjuvant chemotherapy would be preferable***

29. Adequate (non fertility-sparing) primary surgery for apparent early stage ovarian cancer consists of peritoneal washings/ascitic sampling taken prior to manipulation of the tumour, bilateral salpingo- oophorectomy, total hysterectomy, multiple peritoneal biopsies from the

para-colic spaces, and the sub-diaphragmatic spaces bilaterally, omentectomy.

- ***Removed a pelvic and bilateral para-aortic lymph node assessment up to the level of the insertion of the ovarian vessels in the absence of peritoneal dissemination. (Grade B)***

- ***Cambridge consensus is to follow 2011 NICE guidelines [CG122] regarding lymph node approach:***

1.3 Management of suspected early (stage I) ovarian cancer

1.3.1 The role of systematic retroperitoneal lymphadenectomy

1.3.1.1Perform retroperitoneal lymph node assessment **(imaging / palpation)** [10] as part of optimal surgical staging[5] in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

1.3.1.2Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

30. The rate of positive lymph nodes in mucinous tumours is very low and lymph node dissection is therefore not warranted. However, appendicetomy should be performed where a mucinous tumour is suspected. (GRADE B)

Surgical management of primary advanced ovarian cancer

31. Surgery after three cycles of chemotherapy following initial low effort or diagnostic-only surgery significantly lengthens progression-free and overall survival in patients with advanced disease compared to no further surgery. (Grade A)

32. A "second look" operation with cytoreductive attempt after neo-adjuvant chemotherapy following upfront debulking surgery with residual disease despite maximal effort has no survival benefit and is not recommended (Grade A).

33. The aim of cytoreductive surgery in the management of advanced stage ovarian cancer is surgical resection of all visible disease in patients fit enough to undergo this procedure, as this has been shown to be associated with an improved progression-free and overall survival. (Grade B)

34. Neo-adjuvant chemotherapy with interval debulking surgery after three cycles of platinum

based chemotherapy is non-inferior to primary upfront debulking surgery and adjuvant platinum-based chemotherapy and has reduced morbidity in patient cohorts with significant disease burden and low complete macroscopic tumour clearance rates or in situations where the is uncertainty about the possiblity of optimal removal of tumour (Grade A)

35. Women with advanced disease should have their treatment planned by a specialist MDT at cancer centres having the infrastructure to support maximal surgical effort debulking with the aim of no macroscopic residual disease. (Grade D)

36. Bulky lymph nodes in advanced disease should be removed, if this will complete macroscopic clearance, as this has been shown to significantly prolong survival and is part of the debulking. (Grade A)

Systemic treatment of ovarian cancer

Systemic treatment of early stage ovarian cancer (FIGO I-II)

37. Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of early ovarian cancer apart from low grade stage Ia/Ib. (Grade A)

38. There is a lack of evidence supporting an additional value of targeted therapies such as bevacizumab, other VEGF inhibitors including nintedanib and cediranib, tyrosine kinase inhibitors or PARP inhibitors in early stage ovarian cancer treatment and show they should not be offered outside clinical trials. (Grade D)

First line treatment of advanced ovarian cancer (FIGO III-IV)

Neoadjuvant chemotherapy

39. Primary debulking surgery is the standard of care where complete or optimal cytoreduction appears achievable in patients with good performance status. Where this is not achievable two randomised trials have showed non-inferiority of the neo-adjuvant chemotherapy (NAC) followed by interval debulking surgery. Both trials demonstrated reduction in morbidity in the NAC arm and an equal quality of life in both arms. (Grade A)

Intra-peritoneal chemotherapy

Intra-peritoneal (IP) chemotherapy can be offered within clinical trials where appropriate expertise and resources exist.

Post operative cytotoxic chemotherapy

40. The current standard of care in advanced disease is carboplatin (AUC5/6) and

paclitaxel (175mg/m^2) three-weekly for 6 cycles. (Grade A)

41. The addition of a third cytotoxic agent or more than six cycles has failed to show any survival benefit in prospectively randomised trials and is not recommended. (Grade A)

42. For those patients who develop allergy to or do not tolerate paclitaxel, the combination of protein- bound paclitaxel (Abraxane)-carboplatin or pegylated liposomal doxorubicin-carboplatin could be considered as alternatives. (Grade B)

Anti-angiogenics in adjuvant first-line treatment of ovarian cancer

43. Targeted therapies, in addition to the conventional first line cytotoxic chemotherapy, have been shown to increase PFS, but not OS, when given as maintenance therapy. The addition of anti- angiogenic therapy increases toxicity. (Grade A)

First-line chemotherapy in non-serous histological subtypes

44. Currently no evidence to support the use of drugs other than platinum-taxane for non-serous histological subtypes (Grade A)

Follow-up

45. A careful history, assessment of new and potentially tumour-related symptoms and clinical examination is essential at follow up visits. (Grade C)

46. CA125 measurement is not mandatory and has not been proven to be of survival benefit. (Grade A) **However, increases in CA125 may herald progressive disease, and recurrences may be detected before symptoms arise. Although longer term results from DESKTOP III are still awaited, the findings suggest that CA125 may be helpful in planning treatment in patients suitable for secondary cytoreduction.**
    - ***Changed text to reflect the results of the DESKTOP III trial.***

47. Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms. (Grade D)

Management of recurrent disease

Surgical treatment of recurrent disease

48. Cytoreductive surgery could be offered **as a treatment option to selected** patients with platinum-sensitive ovarian cancer relapse where the disease appears completely **resectable in patients with a positive AGO score (ascites < 500ml, good performance status, complete**

resection at initial surgery), as this has been shown to be associated with a clinically meaningful increase in progression free survival, and time to start of first subsequent therapy, provided complete cytoreduction to R0 is achieved (Grade A). Imaging modalities to determine sites of recurrence, and treatment approaches should be reviewed on a case-by-case basis at the MDT.

- ***Changed text to reflect the results of the DESKTOP III trial. Data on the primary endpoint of overall survival is awaited***

49. Palliative surgery for bowel obstruction could be discussed after failure of conservative treatment and after careful consideration of the patient's overall prognosis, quality of life, previous treatments, future therapeutic options and co-morbidities. Iatrogenic induced short bowel syndrome with the necessity of long life total parenteral nutrition should be avoided and plans for surgery should be agreed within a specialist MDT. (Grade C)

Systemic treatment of recurrent disease

50. In patients with longer treatment free intervals (TFI) (> 6 months), combination therapies with platinum re-challenge are recommended. (Grade A)

51. In patients with short TFIs (<6months) single agent therapy is equally effective and less toxic than combination therapies. (Grade A)

Other epithelial histological subtypes

Low Grade Serous Ovarian Cancer (LGSOC)

52. Surgery is the most effective management for LGSOC, which has a lower response rate to chemotherapy than HGSOC. (Grade B)

53. There is a 25% response rate seen with a platinum-taxane regimen in LGSOC and given the lack of a superior alternative chemotherapy regimen, this can be offered in patients with advanced disease.(Grade B)

Mucinous carcinoma of the ovary

54. True advanced mucinous tumours of primary ovarian origin are rare and effective systemic management / treatment strategies are limited. (Grade B).

55. Ovarian metastases from primary mucinous tumours of other organs such as GI tract should be excluded. (Grade B)

Borderline ovarian tumours (BOT)

56. Complete surgical resection and adequate peritoneal surgical staging has been shown to

be associated with a longer PFS in patients with Borderline tumours. (Grade B)

57. Borderline ovarian tumours with "invasive" peritoneal implants are reclassified as low grade ovarian cancers under the new FIGO classification of 2014.

58. Pelvic and para-aortic lymph node sampling to stage cases of BOT is not recommended in the absence of bulky lymph nodes. (Grade B)

59. It is safe for young patients with BOT to receive fertility sparing surgery but given the higher risk of relapse within any remaining ovarian tissue, regular **radiological** follow up is recommended **with the modality and frequency to be agreed at the post-operative MDT meeting** . (Grade B)
    - ***Changed text slightly (sonographic to radiological), and clarified an individually agreed approach via MDT review***

60. There is no evidence-based indication for cytotoxic chemotherapy in BOT. (Grade B)

Clinical management of borderline ovarian tumours

61. Complete macroscopic tumour resection should be the aim of all surgery for BOT, with adequate surgical staging especially in apparent stage 1 disease including peritoneal biopsies, cytology and omentectomy (with appendicectomy for mucinous tumours). [Grade B]

Support needs for women with ovarian cancer

62. Women with EOC who require elective surgery in the NHS should have access to a holistic assessment by a clinical nurse specialist (Grade D).

Appendix B

Establishing the diagnosis in secondary care (modified from NICE CG122)

Appendix D

Risk of Malignancy Index I (RMI I) calculation

RMI I combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI I is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml). (31)

RMI I = U x M x CA125

The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions.

U = 0 (for an ultrasound score of 0)

U = 1 (for an ultrasound score of 1)

U = 3 (for an ultrasound score of 2–5)

The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal.

The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.

Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units.

British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice

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International reviewers: David Cibula, Robert Coleman, Nicoletta Colombo, Michael Friedlander, Denis Querleu

The remit of this guideline is to collate and propose evidence-based guidelines for the management of epithelial ovarian-type cancers (ovary, fallopian tube or peritoneal origin) and borderline tumours. This document covers all epithelial cancers with any histological subtype.

Grades of recommendations

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/en/guidelines-research-services/guidelines/clinical-governance-advice-1a/

See appendix for more details.

Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2010, Issue 3), 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.

Guideline development process

1) These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
2) The guideline development process is detailed below:
    a. Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;
    b. Lead then identified a team called the guideline team (GT) to develop the 1st draft;
    c. 1st draft was submitted to the GC;
    d. GC approved draft and recommended changes;
    e. Changes were accepted by the GT who produced the guidelines;
    f. 2nd draft was then submitted to council members and officers;
    g. Council and officers approved 2nd draft and recommended changes;
    h. Changes were then accepted by GC and GT;
    i. 3rd draft was sent to national and international peer review;
    j. GC and GT then made changes based on peer review comments;
    k. 4th draft was sent back to council for approval;
    l. 4th draft was sent to BGCS members for feedback;
    m. GC and GT then made changes based on members' feedback;
    n. 5th draft was sent to public consultation including patient support groups;
    o. GC and GT then made changes based on non-members' feedback;
    p. Final draft approved by council and officers.

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1. Introduction

Incidence, prevalence and clinical presentation

Epithelial ovarian cancer (EOC) is the 6th most common cancer among women in the UK (2014) and accounts for 4% of all new cases of cancer in females: it has the highest mortality of all gynaecological cancers, accounting for 6% of all cancer deaths in women (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer - heading-Zero). A total of 7,378 new cases were reported in the UK in 2014 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer - heading-Zero). The crude incidence rate is 23 new ovarian cancer cases for every 100,000 females in the UK, with higher rates in Wales and lower rates in Northern Ireland compared with England. EOC occurs predominantly in post-menopausal women, peaking in the 60-64 years' age group.

Despite the improvements in cancer detection, through increased use of imaging and CA125 measurement, more than 70% of patients with newly diagnosed EOC will present with extra-pelvic, and therefore advanced, disease (FIGO stage-III or IV). Approximately one third of EOC-patients in England presented as an emergency before 2006, with up to 74% of these patients not subsequently receiving any active cancer treatment. (http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis). However, rates of emergency presentations have fallen (from 31% in 2006 to 26% in 2013) and two week wait (TWW) referrals have increased significantly (from 22% in 2006 to 31% in 2013). Overall, 36% of EOC patients die within the first year of presentation.(1)

Diagnosis

Presenting symptoms

Symptoms associated with ovarian cancer (particularly when present for more than a year and occurring more than 12 times per month) are persistent abdominal distension, abdominal bloating, early satiety and/or loss of appetite, pelvic or abdominal pain, and increased urinary urgency and/or frequency. Other symptoms may include: postmenopausal bleeding; unexplained weight loss; fatigue or changes in bowel habit.(2)

A number of case–control studies investigating symptoms in women with ovarian cancer and comparing them to symptoms in women without ovarian cancer demonstrate that patients with ovarian cancer are symptomatic for a variable period before diagnosis and challenge the perception of ovarian cancer as the "silent killer".(3)

Diagnostic methods - Current guidance

Sequential testing with CA125 and ultrasound in women presenting to primary care with symptoms suggestive of ovarian cancer is recommended. This is especially so in women over the age of 50. Urgent referral to secondary care is indicated, if both tests are abnormal, or if women present to primary care with a pelvic or abdominal mass.(2)

In the UK, recommendations for diagnosis and referral are based on National Institute for Health and Clinical Excellence (NICE) guidelines on the Recognition and Initial Management of Ovarian Cancer (2) and the Scottish Intercollegiate Guidelines Network guidelines on epithelial ovarian cancer.(3)

The prospective Canadian Diagnosing Ovarian Cancer Early (DOVE) study investigated whether open-access assessment would increase the rate of early-stage diagnosis of ovarian cancer.(4)The analysis of 1455 women demonstrated that DOVE patients presented with less tumour burden than the general population of patients, had significantly lower CA125 levels and attained significantly higher complete tumour resection rates (due to the lower tumour burden) even though no stage shift *per se* was noted. The investigators concluded that because the development of most (high grade serous) ovarian cancers is thought to be extra-ovarian, early diagnosis programmes should ideally aim to identify low-volume disease, rather than early-stage disease, and that diagnostic approaches should be modified accordingly.

2. Screening and prevention

Risk Stratification

Protective factors include combined oral contraceptive pill use, pregnancy, sterilization/tubal ligation and hysterectomy. Factors associated with increased risk include family history associated with mutations in the *BRCA1*, *BRCA2* or mismatch repair genes (Lynch Syndrome), nulliparity or first birth after age 35 years, early menarche, and late menopause.

Primary care

CA125 and pelvic ultrasound scan (+/- TVS as indicated) should be considered the initial investigations for post-menopausal women presenting with signs or symptoms of ovarian cancer (Grade B).

Women with an RMI of ≥250 should have further investigations and be referred to the specialist gynaecological centre MDT (Grade B).

There is currently no role for organized screening programmes in women considered at low risk of development of ovarian cancer (Grade A)

The role of ovarian cancer screening in women at high risk of ovarian cancer has yet to be established (Grade B)

Clinical examination and serum CA125 measurement should be considered in women with symptoms suggestive of ovarian cancer. If the CA125 is ≥35 IU/ml, or if a pelvic mass or other abnormality is identified at examination, an ultrasound scan of the abdomen and pelvis should be considered. For women with a normal CA125 <35 IU/ml, or a CA125 ≥35 IU/ml associated with a normal ultrasound, careful clinical assessment for other causes for their symptoms is required. Women in this group should return to their GP, if their symptoms become more frequent and/or persistent. (2)

The American Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomised Controlled Trial demonstrated that screening asymptomatic postmenopausal women with a single threshold value of CA125 does not result in reduction of mortality, despite 13 years of long term follow up. Diagnostic evaluation following a false-positive screening test result was associated with complications.(5, 6).

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial randomised 202,000 women to observation alone, multimodal screening (MMS), with an algorithm based on serial values of CA125 and follow on transvaginal ultrasound scanning (TVS) for abnormal results, or serial TVS alone. The results showed no reduction in mortality in the primary analysis, but a possible reduction in mortality after exclusion of prevalent cases after 7 years of follow-up. Long-term data and cost-effectiveness data are awaited.(7)

Approximately 1.3% of women in the general population will develop ovarian cancer in their lifetime (4). By contrast, according to the most recent estimates 39% of women who inherit a harmful *BRCA1* mutation (5, 6) and 11-17% of women who inherit a harmful *BRCA2* mutation will develop ovarian cancer by age 70. (8, 9) The UK Familial Ovarian Cancer Screening Study (UKFOCCS) study evaluated a strategy of annual ultrasound and CA125 measurement in 3,653 women considered at >10% risk of development of ovarian cancer and who declined risk-reducing salpingo-oophorectomy (RRSO). The positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100), respectively. This study is still on-going and work up to 2018 will evaluate a 4-monthly screening strategy with CA125 and ultrasound in this group.(10) RCOG guidelines (2015) did not recommend routine screening in these women (https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip48.pdf).

Risk-reducing salpingo-oophorectomy (RRSO) prevents development of epithelial ovarian cancer and reduces mortality in women at high risk for epithelial ovarian cancer (Grade B).

Prospective multicentre cohort studies have demonstrated that risk-reducing salpingo-oophorectomy (RRSO) is associated with a lower risk of EOC, first diagnosis of breast cancer, all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality in BRCA1- and BRCA2-mutation carriers, although there still is a residual risk for peritoneal cancer.(11, 12) On-going studies are evaluating the role of opportunistic salpingectomy in the prevention of ovarian cancer in low risk women.(13)

Tumour markers and Malignancy Indices

Tumour markers are not diagnostic tests, but may be helpful in establishing diagnosis and providing baseline values that may be of use during follow up.(14)

Prospectively acquired evidence from the United Kingdom Collaborative Trial of Ovarian Cancer Screening Cancer (UKCTOCS) - with 46,237 women triaged using MMS in whom serial CA-125 measurements were interpreted via the risk of ovarian cancer algorithm (ROCA®) - has shown that screening by using ROCA® doubles the number of screen-detected EOC compared with a fixed cut off of 35 IU/ml.

Caution must be exercised in reassuring women with a single normal CA125 measurement and a focus more on interpreting trends, along with the clinical picture and imaging findings, is likely to define the standard of care in the future.(15)

3. Secondary care and initial pre- treatment assessment

In women below 40 years of age with suspected ovarian cancer, measure alpha fetoprotein (AFP), and hCG (human Chorionic Gonadotropin), in addition to CA125, to identify women with non epithelial ovarian lesions (Grade C) . Inhibin should be measured at a presumed diagnosis of a granulosa cell tumor, even though logistically it takes potentially longer to access the results.

Secondary care

Following referral of a patient with a mass suspicious of ovarian cancer to secondary care, an expansion of the tumour marker panel may facilitate diagnosis.

Where CA125 is elevated, a preoperative CA125/CEA ratio < 25 , especially in combination with an elevated CA19-9, may indicate peritoneal carcinomatosis from a gastrointestinal tumour and bi-directional gastrointestinal endoscopy should be considered prior to upfront primary debulking surgery.[Grade B]

HE4 (human epididymis protein 4) has shown promising diagnostic and prognostic value in triaging younger women, with HE4 not raised in cases of pelvic inflammatory disease and endometriosis despite CA125 elevation being observed. (16-18)

Large prospective studies from the International Ovarian Tumour Analysis consortium (IOTA) suggest that using simple “M”(malignant) and “B” (benign) ultrasonographic rules to characterise ovarian masses is highly accurate. Using these simple rules, the reported sensitivity for malignancy was 95%, specificity 91%, positive likelihood ratio 10.37, and negative likelihood ratio 0.06. (19) The accuracy of the IOTA ultrasonographic rules has been demonstrated in secondary care, predominantly with specialists in ultrasonography and their wider use remains under evaluation in the UK (http://www.birmingham.ac.uk/rockets). Results from an on-going study to evaluate the best serum diagnostic tests and ultrasound models to detect ovarian cancer are awaited.

Advised examinations prior to deciding treatment

In patients with presumed ovarian cancer, radiological staging will provide further information about the extent of disease and potential distant metastases or secondary cancers. (Grade C)

CT prediction of suboptimal cytoreduction is not sufficiently reliable and in the absence of favourable data from larger, prospective trials should not be used alone to decide management. (Grade B)

MRI should not be routinely used for assessing women with suspected ovarian cancer outside of clinical trials, but can be useful where the results of the USS are not helpful in confirming a

diagnosis, especially in young women with a solitary pelvic mass who want a fertility sparing approach. (Grade B)

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

CT imaging of the thorax, abdomen and pelvis is recommended to help define the extent of disease and to aid in surgical planning. However, retrospective data have shown that CT cannot accurately predict fine nodule peritoneal carcinomatosis, and therefore mitigate against suboptimal cytoreduction, and that it is not always reliable and reproducible.(2, 20) Current prospective imaging trials are underway to prospectively assess the predictive value of novel imaging techniques in determining operability.

CT has significant value in excluding distant macroscopic disease spread, including intraparenchymal liver or lung metastases and retroperitoneal node involvement, and in excluding synchronous cancers from other sites or thromboembolic events that may alter management. (Grade B)

Current national guidance recommends that MRI should not routinely be used for assessing women with suspected ovarian cancer, but may be used as a problem-solving tool and adjunct to other imaging modalities. There is also no evidence based value in the routine use of specialized imaging techniques such as positron emission tomography–computed tomography (PET CT), although it may be useful as a problem-solving tool in highly specialised situations (for example in the evaluation of thoracic/mediastinal lymph nodes where secondary intra-abdominal debulking for relapsed disease is under consideration).(21)

Diffusion weighted MRI may have a future role in the description of tumour dissemination patterns and assessment of operability, but prospective evidence data for that are warranted.(22)

Cytological/Histological Diagnosis

If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer first obtain a confirmed tissue diagnosis by histology in all but exceptional cases. (Grade C)(2)

Only commence cytotoxic chemotherapy for suspected advanced ovarian cancer on the basis of positive cytology alone and imaging and without histological confirmation in exceptional cases and where obtaining a tissue sample would be inappropriate. A discussion of such cases at the multidisciplinary team meeting including a careful consideration of the risks and benefits should be documented (Grade C).

All patients with histology / cytology showing suspected or actual carcinoma of gynaecological origin should be reviewed at a gynaecology multidisciplinary team (MDT) meeting.

Histological diagnosis is not mandatory prior to upfront debulking surgery if the clinical picture, imaging and tumour marker profile are highly suggestive of epithelial ovarian cancer (CA125:CEA ratio >25:1).

If ascites is sent for cytological analysis, the absence of malignant cells does not exclude ovarian malignancy, especially in the presence of inflammation (Grade B).(23, 24)

The use of immunohistochemistry on a cell block can be of help in such cases if sufficient atypical cells are present to allow for separation from background cells and interpretation of patterns of staining. This is of high value to aid tissue diagnosis in mixed or undifferentiated tumours.

Where upfront cytotoxic chemotherapy is offered to women with suspected advanced ovarian cancer, histological tissue diagnosis via image guided biopsy or laparoscopy is mandatory in all but exceptional cases. Cytology alone, together with a CA125/CEA ratio of >25:1 may be sufficient in patients with poor performance status (PS 3,4) and where biopsy is not feasible. (Grade C)

In the majority of the cases tissue can be safely obtained through image guided biopsy. The value of laparoscopy in the assessment of operability and impact on overall surgical and clinical outcome of advanced ovarian cancer has not been established in prospective randomised trials . Emerging research protocols utilize laparoscopically obtained multiple intra-abdominal biopsies to define molecular biological profile of each individual patient but the survival benefit of this approach has not been proven in any prospective randomised trials.

The routine use of laparoscopy to obtain pre-treatment histology and to assess the operability of disease is not recommended. (Grade B)

Data to support laparoscopic assessment to determine tumour resectability is limited and suffers from verification bias.(2) In a Cochrane review, assessing the accuracy of laparoscopy to determine tumour resectability in ovarian cancer, only two studies performed laparoscopy and laparotomy in all patients. (25) The other studies only performed a laparotomy when it was thought that an optimal result was feasible. It is therefore not possible to draw definitive conclusions about the sensitivity of laparoscopy. Three studies developed or validated a prediction model including laparoscopy. Using a prediction model did not increase the sensitivity and resulted in more patients undergoing suboptimal surgery**.**

A multidisciplinary discussion within a quorate MDT as constituted along national guidelines is fundamental to the appropriate management of each individual patient and should be documented prior to a decision to operate, offering chemotherapy or palliative treatment in all but exceptional cases, such as emergency presentations between meetings, and the management of these cases should be agreed and described in a departmental gynaecological cancer operational document.

Significance and caveats of cytology

In about two thirds of patients with known ovarian carcinoma, malignant cells are seen in the ascitic fluid. However, there are strong reservations about using peritoneal or ascitic cytology without

histological confirmation in the primary diagnosis of ovarian cancer. Cytological preparations lack architectural patterns and false positive tests may be obtained from serous borderline tumours and from exfoliation of other cells, such as epithelial cells from Müllerian rests and reactive mesothelial cells, which may be mistaken for carcinoma. This problem may be partially resolved through constructing cell blocks and performing appropriate immunohistochemistry, but despite this, the use of cytology in the diagnosis of ovarian carcinoma has a high false negative rate and is operator dependent.

Histological confirmation is recommended prior to treatment with chemotherapy. In exceptional cases, where obtaining material for histology is not possible or is associated with a high risk due to the poor performance status or co-morbidities of the patient, cytology may be used alone in establishing a pre-chemotherapy diagnosis.

In women with pleural effusions, aspiration and examination for malignant cells and cytology should be considered to confirm staging (preferably with immunohistochemistry on cell block). (23, 24).

When used in trial settings, cytological preparations are suboptimal for archiving, tissue microarrays and some molecular testing.

4. Pathology and genetics

The provision of a minimum set of clinical information on the histopathology request form is crucial to ensure a histopathology report of high enough quality for the accurate diagnosis and appropriate management. (Grade D)

Frozen section may be performed, if the result will alter the intra-operative management although there are limitations to the technique. (Grade B)

Clinical information required on the specimen request form

The Royal College of Pathology guidelines for reporting ovarian carcinomas mandate the provision of minimum clinical details to include demographics, clinical presentation, results of previous biopsies, radiological investigations for tumour staging, and details of the surgical procedures 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 labelled to correspond to the specimen details on the request form and appropriately labelled as to site of origin.

Primary site assignment

The origin of high-grade serous ovarian carcinoma (HGSC) has been the subject of intense study. The distal fallopian tube has emerged as the likely site of origin for most HGSC. (26) This observation is, in great part, attributable to the use of sampling protocols that thoroughly examine the distal fallopian tube and also due to the greater number of specialist pathologists with a sub-specialty interest in gynaecological pathology. The discovery of serous tubal intraepithelial carcinoma (STIC) in women with BRCA1 or BRCA2 mutations following risk-reducing salpingo-oophorectomies (RRSO) and in women with advanced ovarian carcinoma lead to the hypothesis that the natural history of pelvic

HGSC might involve an origin in most cases of the distal fimbria of the fallopian tube. Identification of STIC in 18% to 60% of cases of advanced/symptomatic HGSC supports this assertion. STIC lesions are characterized by DNA damage, TP53 mutation, and progressive molecular abnormalities that are also seen in high-grade serous carcinoma. An origin from epithelial inclusion cysts in the ovary has been proposed as a potential explanation as site of origin in the cases where complete examination of the fallopian tube does not reveal STIC. A consensus statement on primary site assignment in tubo-ovarian HGSC has been made. (27)

Immunohistochemical features of HGSC

HGSC of tubo-ovarian and peritoneal origin have similar morphological and immunohistochemical features. HGSC can be arranged in papillary, glandular or solid architecture. HGSC exhibits moderate to marked nuclear atypia and greater than 12 mitoses per 10 high power fields. Necrosis and multinucleate cells are often present. The distinction between low-grade and high-grade serous carcinoma is based on cytological, not architectural, features. On immunohistochemistry, HGSC of tubo-ovarian and peritoneal origin are typically positive for CK7, WT1, PAX8, oestrogen receptor and CA125. They do not stain for CK20, CEA and CDX2. P53 shows aberrant expression, characterized by either diffuse strong positive staining in greater than 75% of cells or by complete lack of staining.

Genetics

Women with HGSC or G3 endometrioid ovarian adenocarcinoma have >10% risk of an underlying BRCA mutation and should be offered clinical genetics counselling and testing. (GRADE C)

Recently it has been shown that ~18% (much higher in certain groups such as Ashkenazi Jews) of the population of women presenting with high grade serous or G3 endometrioid ovarian adenocarcinoma carry a germline BRCA mutation, 44% of whom have no positive family history.(28) Every patient with a current or past histological diagnosis of HGSC or G3 endometrioid ovarian carcinoma therefore qualifies for BRCA counselling and testing, as advised by NICE, which should be discussed and offered .(29) The advantages of BRCA testing include:

- Prognostic information, as this group is likely to have longer remission periods;
- Predictive genetic testing and advice for other family members who are at risk of inheriting BRCA, about screening and risk-reducing surgery to minimise their chance of developing cancers;
- PARP inhibitor treatment may offer longer-term remission and response for some BRCA-mutation carriers. (30) Olaparib is an option for treating women with relapsed, platinum-sensitive ovarian cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy, if they have had 3 or more courses of platinum-based chemotherapy. (31)

Special histological features of different subtypes

Endometrioid Carcinoma of ovary

These represent the second most common form of ovarian EOC and account for 10 – 15% of ovarian EOC. A significant number are associated with endometriosis in the ovary, or elsewhere in the pelvis,

and about 15% of cases have synchronous endometrial carcinomas. (32, 33) Endometrioid carcinomas of the ovary can show a variety of patterns of which an adenofibromatous pattern and squamous metaplasia are amongst the confirmatory endometrioid features. The clinical management of G3 endometrioid ovarian cancers corresponds to that described for high-grade serous cancer (HGSC).

Clear cell carcinoma

Clear cell carcinoma is the subtype most frequently associated with pelvic endometriosis, paraneoplastic hypercalcaemia and venous thromboembolism. The tumour is composed of clear, or hobnail, cells arranged in papillary, glandular or solid patterns in a hyaline stroma. The cells are typically WT1-/p53 wild type and show staining with napsin A. They mostly lack expression of oestrogen and progesterone receptors.(34) Clear cell carcinoma of the ovary is managed in an identical manner to HGSC, but is less responsive to chemotherapy than serous and endometrioid histological subtypes.

Carcinosarcoma

Carcinosarcoma is a rare gynecological neoplasm that may arise in any region of the gynaecological tract and which accounts for 1% to 3% of ovarian cancers. It belongs to the category of mixed Müllerian tumours, with both epithelial and mesenchymal components being malignant. They were previously called malignant mixed Müllerian tumours (MMMT). Recent immunohistochemical and molecular findings support the hypothesis that gynecological carcinosarcomas represent metaplastic carcinomas. Cell lines established from carcinosarcomas are able to differentiate into epithelial or mesenchymal components, or a combination of the two, (35) and immunohistochemistry demonstrates the expression of epithelial markers in the sarcomatous component of carcinosarcoma. Clonality patterns, genomic analysis, and loss of heterozygosity studies have shown that carcinomatous and sarcomatous components of these tumours share common genetic alterations, including aberrant p53 expression and occasionally germline mutation of BRCA2.(36, 37) The transformation of a carcinoma to a sarcoma in these tumours may represent a transdifferentiation, as seen in epithelial-to-mesenchymal transition phenomena. (38)
Overall, the prognosis for carcinomosarcoma is worse than for high-grade ovarian carcinoma of a similar FIGO stage (39). Most (90%) present with advanced disease. At present they should be managed in the same way as HGSC.

5. Surgical treatment

Suspected or Confirmed Early Stage Disease

Women with suspected epithelial ovarian cancer should undergo surgery at a cancer centre by specialised surgeons who are core members of a specialist MDT. (Grade B)

Women requiring chemotherapy should be treated by a medical or clinical oncologist who is a core member of a specialist MDT. (Grade D)

Affected 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)

The aim of surgery for early ovarian cancer (stage I and II) is complete macroscopic tumour resection and adequate surgical staging. (Grade A)

Patients suitable for fertility-sparing surgery should be identified by the MDT and the pros and cons of this discussed with them, so that they can make an informed choice. (Grade D)

Early stage disease may be an unexpected post-operative histological finding in cases that have been managed as a benign condition. A re-staging procedure by a gynaecological oncologist could be advised to establish stage and possibly define type or necessity of adjuvant treatment (Grade B).

Adequate (non fertility-sparing) primary surgery for apparent early stage ovarian cancer consists of peritoneal washings/ascitic sampling taken prior to manipulation of the tumour, bilateral salpingo-oophorectomy, total hysterectomy, multiple peritoneal biopsies from the para-colic spaces, and the sub-diaphragmatic spaces bilaterally, omentectomy, and pelvic and bilateral para-aortic lymph node assessment up to the level of the insertion of the ovarian vessels in the absence of peritoneal dissemination. (Grade B)

The rate of positive lymph nodes in mucinous tumours is very low and lymph node dissection is therefore not warranted. However, appendicetomy should be performed where a mucinous tumour is suspected. (GRADE B)

Women with suspected ovarian cancer should be referred to gynaecological oncology centres for treatment. A meta-analysis of retrospective studies assessing over 9000 women suggested that treatment of women in institutions with gynaecological oncologists on site may prolong survival, compared to community or general hospitals (HR 0.90; 95% CI 0.82 to 0.99)(40) This supports guidelines in the UK on Improving Outcomes in Gynaecological Cancers (41, 42).

Full surgical staging provides useful prognostic information and may affect subsequent treatment. The survival value of full surgical staging in apparent stage I ovarian cancer is extrapolated from data from RCTs assessing the benefit of adjuvant chemotherapy in early stage disease (43,44).

Depending on the histological grade and subtype, up to 30% of the patients with apparently early epithelial ovarian cancer will be upstaged after comprehensive surgical staging. (46, 47) Cass and colleagues showed in 96 patients with grade 3 tumours and gross disease confined to one ovary, that 15% had microscopically positive lymph nodes. (48) Among these patients, 50% had positive pelvic nodes, 36% had positive para-aortic node and both were positive in 14% of the cases. Maggioni and colleagues reported on a prospective randomised trial of systematic lymphadenectomy in patients with ovarian cancer macroscopically confined to the pelvis. Positive nodes were detected in 22% of patients undergoing systematic lymphadenectomy compared to only 9% of patients who underwent merely a sampling (p=0.007). Although a trend for improved PFS and OS was observed for the lymphadenectomy group compared to control, the study lacked the statistical power. (49) Increasing evidence shows that the rate of positive lymph nodes in stage I mucinous cancer is extremely low

(near 0%), and there is no value in performing this given the potential morbidity of such the procedure. (50-52)

When young women are affected by early stage epithelial ovarian cancer, fertility-sparing surgery can be considered following thorough discussion with the patient about the potential risk of recurrent epithelial ovarian cancer. Patients with grade 1 or 2 mucinous, serous, endometrioid, or mixed histology and FIGO stage IA or stage IC with unilateral ovarian involvement may be eligible for uterus/contra-lateral ovary preserving surgery, in combination with surgical staging of the remaining peritoneal surfaces +/- retroperitoneal lymph node chains (dependent upon histological subtype). In a large retrospective analysis, women with G3 disease or stage IC3 with clear cell histology had a higher risk of recurrence, but mainly related to the higher incidence of extra-ovarian spread observed in grade 3 tumours, rather than to a higher relapse rate in the preserved ovary.(53) Therefore, these patients should be carefully informed about their prognosis, to enable them to make a personalized and informed choice. Retrospective evidence reveals that 3.5%-11% of the women with unilateral disease will have contra-lateral pelvic lymph node metastases, despite negative ipsilateral nodes. (54, 55)

Surgical management of primary advanced ovarian cancer

Surgery after three cycles of chemotherapy following initial low effort or diagnostic-only surgery significantly lengthens progression-free and overall survival in patients with advanced disease compared to no further surgery. (Grade A)

A "second look" operation with cytoreductive attempt after neo-adjuvant chemotherapy following upfront debulking surgery with residual disease despite maximal effort has no survival benefit and is not recommended (Grade A).
The aim of cytoreductive surgery in the management of advanced stage ovarian cancer is surgical resection of all visible disease in patients fit enough to undergo this procedure, as this has been shown to be associated with an improved progression-free and overall survival. (Grade B)

Neo-adjuvant chemotherapy with interval debulking surgery after three cycles of platinum based chemotherapy is non-inferior to primary upfront debulking surgery and adjuvant platinum-based chemotherapy and has reduced morbidity in patient cohorts with significant disease burden and low complete macroscopic tumour clearance rates or in situations where the is uncertainty about the possiblity of optimal removal of tumour (Grade A)

Women with advanced disease should have their treatment planned by a specialist MDT at cancer centres having the infrastructure to support maximal surgical effort debulking with the aim of no macroscopic residual disease. (Grade D)

Bulky lymph nodes in advanced disease should be removed, if this will complete macroscopic clearance, as this has been shown to significantly prolong survival and is part of the debulking. (Grade A)

In advanced epithelial ovarian cancer the aim is complete cytoreduction of all macroscopically visible disease, since this has been shown to be associated with a significantly increased overall and progression-free survival in numerous prospective and retrospective trials. (56-58)
It is unclear whether this association is causal or whether resectable tumours are intrinsically biologically more chemosensitive and less likely to recur quickly.(59-61) The only evidence comparing maximal effort debulking surgery versus no further surgery is in the setting of interval debulking surgery. The EORTC trial by van der Burg et al, which randomised 319 patients to further surgery versus no surgery followoing three cycles of platinum-based chemotherapy after initial surgery by a non-gynaecological oncologist or diagnostic surgery only.(57) The study, and subsequent Cochrane review which included three studies, showed that interval debulking surgery lengthened progression-free and overall survival only in those who had not had maximal effort at initial surgery. (62) The risk of death was reduced by one third in this subgroup, after adjustment for a variety of prognostic factors (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%).(62)

In order to achieve macroscopic tumour clearance in peritoneally disseminated disease, maximal surgical effort is required, potentially including multi-visceral resection techniques such as peritoneal stripping, diaphragmatic resection, removal of bulky pelvic/ para-aortic lymph nodes, splenectomy, liver and/or liver capsule resection and bowel resection. Retrospective data suggest that additional surgical procedures do result in improved rates of cytoreduction. This requires specialist training and surgical expertise, as well as co-ordinated institutional effort to safely deliver.(63) Therefore women with advanced disease should ideally undergo such surgery in specialized centres with adequate infrastructure, staff and training. (64) These centres should consider keeping prospective records of the surgical and non-surgical management of all patients, the surgical procedures performed, the amount and location of any residual disease and associated morbidity and mortality. Surgery should be ideally performed within 2-4 weeks of decision to operate, depending on patients' wishes, co-morbidities and prior history.

The Chief Medical officer has emphasised the need for specialist surgical training and the need for a national audit in ovarian cancer to improve outcomes. (65) The on-going SOQCER2 study should give further information about the quality of life after debulking surgery.
(https://clinicaltrials.gov/ct2/show/NCT02569983).

Complete macroscopic cytoreduction is defined as macroscopic tumour clearance with no residual visible disease, as documented by a comprehensive visual assessment of all the areas of the abdomen. When complete macroscopic cytoreduction is not achievable at the time of laparotomy, attempts should be made to achieve near-optimal cytoreduction (<1cm residual disease) as meta-analysis suggests that patients in whom <1cm residual disease remains have a greater overall survival than those with >1cm residual disease, if associated morbidity seems acceptable and depending on the constitution of the patient. (56)

The value of systematic pelvic and para-aortic lymphadenectomy in advanced disease in the absence of bulky lymph nodes has not been prospectively proven to influence overall survival**.** A large prospectively randomised trial that randomised patients with residual disease <1cm to removal of bulky lymph nodes only versus systematic pelvic and para-aortic LND showed that 5-year PFS could

be improved in the systematic LND arm; from 21.6% to 31.2% with a median of an additional seven months. (66) The study failed to show any overall survival benefit from a systematic LND. A large multicentre prospectively randomised trial of systematic pelvic and para-aortic lymphadenectomy extending up to the renal vessels in tumour free operated patients with advanced disease and without bulky lymph nodes has completed accrual (LION Trial, AGO-OVAR OP.3 [NCT00712218]) and the results are awaited in ASCO 2017.

There is no proven value or survival benefit in second look cytoreductive surgery after three cycles of chemotherapy to clear any disease remaining after primary surgery performed with maximal surgical effort unless this paradigm was not employed upfront. (62) Similarly, a "second look" diagnostic laparoscopy or laparotomy after completion of treatment to assess intra-peritoneal status should not be routinely performed, except in the context of pertinent clinical trials, as its impact on survival has not been demonstrated. (67)

6. Systemic treatment of early stage ovarian cancer (FIGO I-II)

Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of early ovarian cancer apart from low grade stage Ia/Ib. (Grade A)

Two randomised, prospective trials examined the value of chemotherapy after surgery in early stage ovarian cancer. The ACTION and ICON1 trials included early stage cases, with grade 2/3 stage IA/B and all stage IC/IIA eligible. The primary analysis of ICON1, with a median follow-up of four-years, demonstrated a significant improvement in both relapse-free survival (RFS) (Hazard Ratio (HR)=0.65, 95%CI=0.46-0.91, p=0.01) and overall survival (OS) (HR=0.66,95%CI=0.45-0.97,p=0.03) in favour of adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6). (68) Similar findings were reported in the ACTION trial in which the majority of patients received platinum-based combination chemotherapy. (69)

A Cochrane meta-analysis of five large prospective clinical trials concluded that chemotherapy is more beneficial than observation in patients with early stage ovarian cancer. (70) Patients who received platinum-based adjuvant chemotherapy had a better OS (hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment. Approximately two thirds of the cases were sub-optimally staged and 30% of women with presumed stage 1 disease may have had undetected stage 3 disease. One interpretation is that the observed effect is due to the overuse of chemotherapy in cases unlikely to benefit compensating for the lack of complete surgical staging. However, due to concerns with outcome reporting bias, the Cochrane review performed an analysis of 10-year data from ACTION and ICON1, which suggested that the difference between optimally and sub-optimally staged subgroups, in terms of deaths from ovarian cancer, was not significant (Test for subgroup differences: Chi^2 test = 2.75, df = 1, P = 0.10). Benefit for chemotherapy, even in optimally staged patients, could not be excluded. Adjuvant chemotherapy should be discussed with all patients with high risk early stage ovary cancer.

There is a lack of evidence supporting an additional value of targeted therapies such as bevacizumab, other VEGF inhibitors including nintedanib and cediranib, tyrosine kinase inhibitors or PARP inhibitors in early stage ovarian cancer treatment and show they should not be offered outside clinical trials. (Grade D)

The response rate to chemotherapy in patients with non-serous epithelial ovarian carcinoma, including clear cell and mucinous tumours, is poor and the effectiveness of adjuvant chemotherapy in early stage disease in these groups may be less than HGSC. However, as patients with non-HGSC subtypes were not excluded from previous studies and, since there are currently no evidence-based alternatives for women with non-HGSC subtypes, it is remains reasonable to offer treatment as per HGSC. Women with non-HGSC should be encouraged to participate in histological subtype specific studies, where these exist.

7. First-line chemotherapy for advanced disease (FIGO II – IV)

Neoadjuvant chemotherapy

Primary debulking surgery is the standard of care where complete or optimal cytoreduction appears achievable in patients with good performance status. Where this is not achievable two randomised trials have showed non-inferiority of the neo-adjuvant chemotherapy (NAC) followed by interval debulking surgery. Both trials demonstrated reduction in morbidity in the NAC arm and an equal quality of life in both arms. (Grade A)

Two prospectively randomised trials have shown that treating patients with advanced ovarian cancer with NAC followed by interval surgery after three cycles is no worse than first-line surgery. (58,72), especially in cases where performance status and/or resection is unlikely to result in an optimal debulking procedure and that this strategy is associated with lower surgical morbidity and mortality in this context. The limiting factor of both studies was that for many atients entered there was uncertainty about the ablity to resect tumour. 'Ability' to optimally resect disease relies in general not just on the actual surgical skills, but also the overall infrastructure, team effort, anesthetic cover and institutional expertise. Both options –upfront surgery and NAC- may be discussed with patients with advanced disease and treatment decisions made based on the patient's performance status, symptoms, co-morbidities, patient preference and quality assured institutional expertise.

A Chemotherapy Response Score (CRS), based on pathological evaluation material prior to NAC and following it has been developed in a single centre but not yet validated in a prospective multicentre setting. The three-tier CRS system applied to omental samples from this initial single centre study showed high reproducibility (kappa, 0.67) and predicted PFS. The score also predicted sensitivity to first-line platinum therapy. Until validation studies are completed and the clinical benefit of the CRS is defined, no recommendation of its routine can be made. (74)

Intra-peritoneal chemotherapy

Intra-peritoneal (IP) chemotherapy can be offered within clinical trials where appropriate expertise and resources exist.

A Cochrane review of IP versus intravenous (IV) chemotherapy demonstrated an improved overall survival if women received an IP component to chemotherapy (eight studies, 2026 women; HR = 0.81; 95% confidence interval (CI): 0.72 to 0.90). Intraperitoneal chemotherapy prolonged the DFI (five studies, 1311 women; HR = 0.78; 95% CI: 0.70 to 0.86). However, there was greater serious toxicity with regard to gastrointestinal effects, pain, fever and infection, but less ototoxicity with the IP than the IV route. (75) The improved survival with IP chemotherapy impact has been shown to extend even beyond 10 years. (76) However, because of concerns over potential toxicity, due to the increased dose of chemotherapy given in some of the IP arms and IP catheter-related complications, it has not been widely adopted in Europe and is currently the subject of on-going trials the results of which are eagerly awaited. Meta-analysis of the current trial data suggests that research is still needed to determine the optimal agent, dose and scheduling and also the value of IP therapy in the era of targeted maintenance tretaments. (77)

Post operative cytotoxic chemotherapy

The current standard of care in advanced disease is carboplatin (AUC5/6) and paclitaxel (175mg/m^2) three-weekly for 6 cycles. (Grade A)

Following surgery, all patients with FIGO stage II-IV ovarian cancer should be offered platinum based chemotherapy +/- paclitaxel, depending on fitness. The interpretation of the results of trials that added paclitaxel to platinum-based drugs during the 1990s generated some controversy, but a meta-analysis showed superiority of the combination of platinum-paclitaxel to platinum-based drugs (79). Carboplatin is less toxic than cisplatin and equally effective. The standard of care is three-weekly carboplatin (AUC5/6) and paclitaxel (175mg/m^2) for six cycles.

Dose-dense scheduling of the paclitaxel (80 mg/m^2 days 1, 8, 15 every 21 days, with carboplatin AUC 5/6 on day 1) has been shown to improve overall survival in a Japanese population. (80) A European phase III trial (MITO7), which randomised patients to standard dose three-weekly carboplatin /paclitaxel or weekly carboplatin (AUC 2) and paclitaxel (60 mg/m^2), showed no difference in PFS or OS, although weekly treatment was better tolerated. (81) An absence of benefit of dose-dense therapy may have been due to the lower dose of paclitaxel (60 mg/m^2 as opposed to 80 mg/m^2 weekly) used in this study. The ICON 8 trial, currently in follow up, has randomised over 1500 patients to receive either three-weekly carboplatin / paclitaxel, three-weekly carboplatin and weekly paclitaxel (80mg/m^2), or weekly carboplatin (AUC 2) and weekly paclitaxel (80mg/m^2) with results expected during 2017.

The addition of a third cytotoxic agent or more than six cycles has failed to show any survival benefit in prospectively randomised trials and is not recommended. (Grade A) (82, 83)

For those patients who develop allergy to or do not tolerate paclitaxel, the combination of protein-bound paclitaxel (Abraxane)-carboplatin or pegylated liposomal doxorubicin-carboplatin could be considered as alternatives. (Grade B) (84, 85)

Hypersenstivity to carboplatin may occur, in which case desensitisation regimens can be useful**,** or the equally efficacious, but potentially more toxic, agent cisplatin can be used as an alternative. Cross-hypersensitivity to cisplatin may occasionally occur.(86)

Anti-angiogenics in adjuvant first-line treatment of ovarian cancer

Targeted therapies, in addition to the conventional first line cytotoxic chemotherapy, have been shown to increase PFS, but not OS, when given as maintenance therapy. The addition of anti-angiogenic therapy increases toxicity. (Grade A)

Giving bevacizumab plus chemotherapy and then alone as maintenance for up to 12 months (ICON 7) (87) or for 15 months (GOG 218) (88) following cytotoxic chemotherapy has been shown to prolong PFS in patients with advanced disease. The three-arm randomised ICON8B trial opened in 2015, building on the ICON8 trial (NCT01654146) to explore the interaction between three-weekly chemotherapy with bevacizumab (ICON7), carboplatin and weekly paclitaxel, and the addition of bevacizumab to weekly paclitaxel.

The addition of other anti-angiogenic agents, including the oral tyrosine kinase inhibitors pazopanib and nintedanib, has also been shown to increase PFS, but not OS. Pazopanib maintenance therapy provided a median improvement in PFS of 5.6 months (HR 0.77; 95% CI 0.64 to 0.91; P = .0021; median, 17.9 v 12.3 months) in patients with advanced ovarian cancer who had not progressed after first-line chemotherapy in a large multicentre phase III study, but with increased treatment-related Grade 3 or 4 adverse events. The schedule has not been submitted for EMA licensing. (90) Nintedanib in combination with carboplatin and paclitaxel has also been demonstrated to be an active first-line treatment that increases PFS in a recent large multicentre phase III trial, but is associated with more gastrointestinal adverse events. (91)

First-line chemotherapy in non-serous histological subtypes

Currently no evidence to support the use of drugs other than platinum-taxane for non-serous histological subtypes (Grade A)

The efficacy of conventional chemotherapy in rarer histological subtypes, including low-grade endometrioid and mucinous subtypes, has been shown to be less effective.(92) Nevertheless, all large phase III randomised chemotherapy trials so far have included all histological subtypes. It has been difficult to conduct randomised trials in rarer histological subtypes. However, a Japanese-led trial in clear cell cancer has recently been published, showing no difference between standard chemotherapy and cisplatin-irinotecan. (93)

In mucinous tumours, an even rarer subtype, an international randomised trial was abandoned due to poor accrual. Currently there is no evidence to support the use of drugs other than carboplatin/paclitaxel in these histological subtypes. Furthermore the role of adjuvant conventional chemotherapy in early stage tumours with rare histological subtypes remains unclear. Currently, decision-making is often based on larger trials that contain patients with these subtype tumours.

The national prospective observational study of rare neoplasias of gynaecological origin (RANGO) will allow the collection of information about tumours in the future. In time, this project will link in with an international Gynaecological Cancer Inter-Group mega-database initiative.

8. Follow-up

A careful history, assessment of new and potentially tumour-related symptoms and clinical examination is essential at follow up visits. (Grade C)

CA125 measurement is not mandatory and has not been proven to be of survival benefit. (Grade A)

Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms. (Grade D)

Follow-up along a traditional hospital-based model provides opportunities to assess the risk and/or presence of recurrence and to assess patients holistically for the presence of on-going physical, psychological, emotional, financial and sexual survivorship issues related to their cancer treatment.

The intervals between follow-up visits vary according to local practice, but the most common schedule through convention is every 3 months for the first 2 years and then every 6 months up to 5 years after end of treatment, despite a lack of randomised trial data illustrating a benefit of strict follow-up protocols over an individualized patient- and symptom-led approach.

Increases in CA125 may herald progressive disease in patients who achieve a normal CA125. A prospectively randomised MRC/EORTC trial demonstrated no difference in overall survival after a median follow-up of 56.9 months (HR 0.98, 95% CI 0.80 to 1.20; P = 0.85) between patients who received chemotherapy based on a rising CA125 and those who did not receive chemotherapy until they were symptomatic. Treatment based on an abnormal CA125 led to early treatment by a median of 4.8 months. (94), (95). Interestingly, those in the arm where treatment was initiated on CA125 rise had a shorter interval to deterioration in global health score or death (HR 0.71, 95% CI 0.58 to 0.88; P value < 0.01). This finding led to many questioning the clinical and cost-effectiveness of routine CA125 measurements in follow-up. Despite this, some patients may wish to know what might lie ahead and for some a rise in CA125 might indicate surgically-resectable disease recurrence, while for others it may trigger imaging that will determine timing and value of further treatment (96). In addition, participation in first-line trials normally requires regular post-treatment CA125 measurements for trial end points. However, it is now accepted that a rising CA125 alone, without clinical or radiographic evidence of recurrence, should not be routinely be used as an indication to commence systemic chemotherapy**.**

The results of the prospectively randomised DESKTOP III (NCT01166737) and GOG 0213 (NCT00565851) trials may potentially change current follow up recommendations, if secondary debulking surgery is shown to be associated with improved survival and becomes a standard of care. Emerging maintenance therapies such as immunotherapy may also require changes in current follow up arrangements in the future.

9. Management of recurrent disease

Surgical treatment of recurrent disease

Cytoreductive surgery could be offered to patients with platinum-sensitive ovarian cancer relapse where the disease appears completely resectable in patients with a good performance status, as this has shown to be associated with improved OS and PFS in retrospective studies and meta-analyses; patients should however be aware that the disease will remain chronic, and that no prospective trials have yet proven a survival benefit. (Grade C)

Palliative surgery for bowel obstruction could be discussed after failure of conservative treatment and after careful consideration of the patient's overall prognosis, quality of life, previous treatments, future therapeutic options and co-morbidities. Iatrogenic induced short bowel syndrome with the necessity of long life total parenteral nutrition should be avoided and plans for surgery should be agreed within a specialist MDT. (Grade C)

The value of surgery for relapsed ovarian cancer on overall survival in patients with EOC has not yet been established in prospectively randomised trials, but when complete tumor removal can be achieved, retrospective studies have shown a significantly longer OS and PFS when compared to women with residual disease following surgery for relapse. This survival benefit persists even in multifocal relapse and peritoneal carcinosis as long as complete tumor clearance is achieved (97-100).

Careful consideration of cases within a specialist MDT can identify individuals whose disease may benefit from a surgical approach. In a large, retrospective, systematic trial (DESKTOP I), patients with two out of three of complete resection at first surgery, good performance status and absence of ascites, had an improved survival. (97) No RCT-level data were identified in systematic reviews. (101, 102) Four prospective multicentre randomised trials evaluating the value of surgery at relapse are now underway: DESKTOP III [NCT01166737] used the selection criteria detailed above and is in follow up, GOG 213 [NCT00565851] incorporates the addition of bevacizumab to chemotherapy, SOC1 [NCT01611766] from the Shanghai Gynecologic Oncology Group, and the SOCceR from the Netherlands [NTR3337]. The results of these prospective trials will define the value of cytoreductive surgery at relapse.

EOC patients often present with symptoms of acute or sub-acute bowel obstruction at relapse, often attributable to diffuse peritoneal dissemination of recurrent tumour rather than a single point of obstruction. The implementation of novel targeted therapies with anti-angiogenic potential may favour fistula formation or intestinal perforation and so recurrent EOC, with the potential to be complicated by such severe and acute events, constitutes a therapeutic dilemma.(103) No RCTs exist comparing surgical and medical management, and evidence that showed a benefit to surgery over octreotide was of low quality. (104) In a retrospective review of 90 patients who underwent surgery for bowel obstruction in relapsed ovarian cancer, the median OS was 90.5 days (range, <1 day-6 years). (105) Palliative surgery in patients with gastrointestinal and other symptoms of ovarian cancer recurrence therefore requires multidisciplinary consideration.(100, 105) Any perceived benefits should be carefully balanced against the risks for each individual patient and factors such as

co-morbidities, baseline quality of life, previous response to chemotherapy, length of treatment intervals and patient wishes are likely to be crucial. The management of these cases should be led by specialist gynaecological multidisciplinary teams, including palliative care input at an early stage. If surgery is planned, intra-operative input from gynaecological oncologists is important, so that likelihood of chemotherapy responses after palliative surgery is considered when making intra-operative decisions.

Endoscopic techniques, such as placement of intestinal stents and percutaneous endoscopic gastrostomy (PEG), may allow the palliation of gastrointestinal symptoms with reduced procedure-related morbidity in selected patients.

Surgical intervention should be restricted to cases where there is a distal mechanical bowel obstruction and where the formation of a proximal high output small bowel stoma is not likely to be necessary, as such high output stomas significantly reduce quality of life and require permanent total parenteral nutrition (TPN). Pre-operative imaging demonstrating the most proximal point of bowel obstruction should be used to identify patients with a level of obstruction at high risk of iatrogenic short bowel syndrome. Management of patients with bowel obstruction should ideally happen within multi-disciplinary teams with experience in managing such cases. (106)

Systemic treatment of recurrent disease

In patients with longer treatment free intervals (TFI) (> 6 months), combination therapies with platinum re-challenge are recommended. (Grade A)

In patients with short TFIs (<6months) single agent therapy is equally effective and less toxic than combination therapies. (Grade A)

Along with patient factors, including patient choice and performance status, residual toxicities and prior hypersensitivity reactions, the most important factors that inform the choice of chemotherapy for relapsed ovarian cancer are the TFI and platinum-free interval (PFI). The conventional definition of platinum sensitivity is a PFI of greater than six months after cessation of the last platinum-based chemotherapy course and was based on the likelihood of disease response to platinum re-treatment in older studies. (107, 108) However**,** in an era of more accurate imaging techniques and maintenance regimens, this definition is more complex with the conventional definition of platinum-sensitive disease becoming less useful clinically (Table 1). (109)

Table 1 The Gynecologic Cancer Intergroup (GCIG) (162) categorisation of patients based on the length of remission following platinum-based chemotherapy. The platinum-free interval is however somewhat theoretical and in real-life exists as a spectrum

Classification	Definition
Platinum Sensitive (PS)	Progress with an interval of > 12 months after completion of chemotherapy
Partially PS (pPS)	Progress with an interval of between 6-12 months after completion of chemotherapy
Platinum Resistant (PR)	Progress with an interval of less than 6 months after completion of chemotherapy
Platinum Refractory (PRef)	Progress during, or within 4 weeks after completion of chemotherapy

While the duration of response to platinum is important, retrospective data also suggest that seeking to extend the platinum-free interval itself may also help improve the patient's subsequent response to platinum re-treatment and there are now several studies supporting this concept.(110, 111) In patients with platinum-sensitive or partially platinum-sensitive ovarian cancer recurrence (6-12 months PFI) published clinical evidence reports response rates to second-line therapy ranging between 27% and 33%, regardless of whether platinum-based or non-platinum drugs are used. However, response rates can be a poor measure of benefit, which is better expressed in terms of PFS and combination therapy (such as carboplatin / paclitaxel, carboplatin / liposomal doxorubicin or carboplatin / gemcitabine) would be recommended as this improves PFS and OS in this group of patients. (107, 112, 113) Trabectedin and pegylated liposomal doxorubicin (PLD) have been shown to be more beneficial compared with PLD alone, especially in the group of patients with partially platinum-sensitive disease. The addition of bevacizumab to relapse chemotherapy in the platinum sensitive setting and as maintenance afterwards also increases PFS compared with combination carboplatin / gemcitabine alone (85, 114).

In the platinum refractory / resistant setting there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. In the platinum-resistant setting, second-line single-agent chemotherapy with non-platinum drugs (such as PLD, weekly paclitaxel, etoposide or topotecan) results in short-lived response rates of approximately 10% to 25% and PFS of 4-5 months and OS of 12-13 months (96). However, the addition of bevacizumab to conventional chemotherapy has been shown to increase PFS to 6.7 months, with OS of 16.6 months compared to monotherapy (PLD, weekly paclitaxel or topotecan) and improved patient-related outcomes in a carefully selected population (115). If the patient cannot tolerate chemotherapy and/or symptoms are not requiring a rapid response to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited. (116, 117)

Palliative radiation may have a role in highly selected situations.

10. Other epithelial histological subtypes

Low Grade Serous Ovarian Cancer (LGSOC)

Surgery is the most effective management for LGSOC, which has a lower response rate to chemotherapy than HGSOC. (Grade B)

There is a 25% response rate seen with a platinum-taxane regimen in LGSOC and given the lack of a superior alternative chemotherapy regimen, this can be offered in patients with advanced disease.(Grade B)

LGSOC constitutes about 5% of all serous carcinomas, occurs in younger women and is characterised by a uniform population of cells arranged typically in papillary clusters and showing sparse mitotic activity (118). Neither necrosis nor P53 mutation are features of LGSOC. (119)

The management of LGSOC is predominantly surgical. Primary surgery aims to remove all visible disease and may be considered again at relapse. A large meta-analysis showed a response rate to platinum based chemotherapy of approximately 24% in patients with advanced primary low grade advanced ovarian cancer after upfront surgery, and hence lower than for their high grade serous counterparts (120). The authors concluded that HGSOC and LGSOC differ with respect to chemosensitivity, chemotherapy being of considerably less benefit in patients with LGSOC than patients with HGSOC, growth pattern and outcome following surgery. Hormonal maintenance strategies in LGSOC after completion of platinum based chemotherapy seem to have a survival benefit in retrospective series (121).

International multicentre studies are urgently needed and recruitment to these is important, as is registration of cases onto rare tumour databases to facilitate the study of this rare condition**. (122)**

Mucinous carcinoma of the ovary

True advanced mucinous tumours of primary ovarian origin are rare and effective systemic management / treatment strategies are limited. (Grade B).

Ovarian metastases from primary mucinous tumours of other organs such as GI tract should be excluded. (Grade B)

Mucinous histologies account for 3 – 5% of all ovarian carcinomas. They are typically confined to the ovary at presentation, are large and show a continuum of architectural features including benign, borderline and malignant areas. Confluent and expansile patterns of invasion are often seen, but when an infiltrative pattern is present, the pathologist must be alert to the possibility of a metastatic carcinoma from another site. Invasive mucinous carcinoma with an infiltrative pattern has a more aggressive course than mucinous carcinoma with an expansile pattern. Mucinous carcinomas of the ovary usually exhibit a CK7+/CK20-/CDX2- immunoprofile.

Advanced mucinous tumours, with intra-peritoneal involvement, are unlikely to be of ovarian origin as these are rare. (123) Many of these are Krukenberg tumours or arise from other organs, such as

the appendix. Ovarian tumours metastatic from appendiceal primaries may have morphological features of mucinous borderline tumours and the presence of dissecting mucin in the peritoneal cavity (psuedomyxoma peritonei) favours this diagnosis. Rarely advanced mucinous tumours can arise from an ovarian teratoma.

Surgery with adequate peritoneal staging is the standard treatment for the majority of primary mucinous ovarian tumours. Fertility-sparing surgery should be considered in young women with unilateral disease. The management of advanced true primary ovarian mucinous tumours is challenging, as they are not particularly chemo-responsive. The collection of pathological and clinical data from patients with these rare tumours is vital to allow progress to be made in determining appropriate therapeutic strategies. (124) Patients with advanced disease are usually treated with carboplatin and paclitaxel, although these tumours respond less well to this combination than the more common non-mucinous tumours. mEOC (NCT01081262), a randomised trial comparing carboplatin and paclitaxel, oxaliplatin and capecitabine +/- bevacizumab (a regimen used in gastrointestinal tract cancers) closed early due to poor recruitment.

Where metastasis from the gastro-intestinal (GI) tract must be excluded, bidirectional GI endoscopy should be performed and referral to a GI MDT should be considered.

Other subtypes

Rarer carcinoma subtypes include malignant Brenner tumour, sero-mucinous carcinoma and undifferentiated carcinoma, and transitional cell carcinomas. (125) Mesenchymal tumours that occur in ovaries include endometrial stromal sarcomas and various other sarcomas. In addition, multiple different histological subtypes of cancer can also arise from within mature teratomas, such as squamous cell carcinoma (126) and carcinoid tumours. (127)

Mixed epithelial and mesenchymal tumours

Adenosarcoma is a rare biphasic tumour of the ovary composed of malignant mesenchymal and benign epithelial elements.

Carcinosarcoma is a more common neoplasm, composed of malignant epithelial and mesenchymal elements. Molecular studies indicate that the sarcomatous components of the neoplasms arise from carcinomatous components. High-grade serous carcinomas and carcinosarcomas share several molecular abnormalities including aberrant P53 expression and occasional germline mutation of BRCA2. (36, 37)

Wolffian tumour

Previously termed female adnexal tumour of Wolffian origin (FATWO), this is an uncommon tumour that is presumed to arise from the Wolffian remnants in the adnexal region. The tumour is usually benign and composed of cysts of varying size with sieve like areas admixed with solid and spindled areas.

Small cell carcinoma of the ovary (SCCO)

Four types of small cell carcinoma of the ovary are recognised: hypercalcaemic and pulmonary subtypes (SCCOHT and SCCOPT), as well as a large cell variant, which can be difficult to distinguish from the other two, and the classical carcinoid. Overall these are rare and highly malignant tumours that typically occur in young women. The tumours are usually unilateral with extra-ovarian spread in nearly 75% of cases at the time of presentation. (128) Yong and colleagues found that only 33% of women presenting with stage I SCCO were alive and disease free at an average of 5.7 years' follow up and no patients with advanced disease survived. (129) A diffuse growth pattern, with foci of follicle-like spaces, is typical. The lining cells are monotonous, showing high grade atypia, brisk mitotic activity and necrosis. On immunohistochemistry (IHC), the cells stain positive for WT1 with focal staining for epithelial markers. It has been shown very recently that the cells in SCCOHT are characterised by inactivation of the SMARCA4 gene (encoding the BRG1 protein) resulting in a loss of BRG1 protein expression on IHC. (130) This means that a cohort of the patients with so-called "ovarian" small cell carcinoma have a malignant rhabdoid tumour and maybe a strategy for identifying SCCOHT from SCCOPT and larger cell variants. (131) It is accepted that the patients with small cell ovarian cancer have a dismal prognosis. There maybe some evidence for considering pelvic radiotherapy (RT) for those with early stage disease following surgery but this has not been validated in prospective randomised trials. (132) For those with advanced disease or relapse, chemotherapy schedules are generally extrapolated from those used in small cell lung cancer and generally include a platinum-based agent and etoposide, although more intense treatment strategies have also been investigated. (133) (134)

All of the above more unusual subtypes of ovarian cancers tend to be managed in the same way as serous epithelial ovarian carcinoma, earlier stages clearly benefiting from surgery in the first instance. The introduction of a national rare gynaecological tumour database to assimilate the treatments and outcomes of these patients prospectively will be integral to any progress in managing these rarer malignancies.

Metastatic carcinoma including Krukenberg tumours

Metastasis to the ovary is not an uncommon phenomenon where it may represent the clinical sentinel site of a metastatic cancer. Gross features suggesting metastases are small size, bilaterality, nodular appearance and involvement of the ovarian surface. Microscopic features favouring metastases are an infiltrative growth pattern, stromal desmoplasia, necrosis, hilar and vascular involvement and IHC may assist in determining the primary site of a metastatic mucinous carcinoma. The commonest primary cancer sources (other than from the endometrium or cervix) are colorectal, gastric, pancreaticobiliary and appendicular adenocarcinomas (the appendix may also be the primary site of a borderline mucinous tumour, which progresses rarely to pseudomyxoma peritoneii). Krukenberg tumours are particular ovarian metastases, characterised by bilateral solid ovarian masses, microscopically demonstrating replacement of the ovarian stroma by signet ring, mucinous cells. The primary site is most often gastric or breast, where similar signet ring mucinous cells are seen.

11. Borderline ovarian tumours (BOT)

Complete surgical resection and adequate peritoneal surgical staging has been shown to be associated with a longer PFS in patients with Borderline tumours. (Grade B)

Borderline ovarian tumours with "invasive" peritoneal implants are reclassified as low grade ovarian cancers under the new FIGO classification of 2014.

Pelvic and para-aortic lymph node sampling to stage cases of BOT is not recommended in the absence of bulky lymph nodes. (Grade B)

It is safe for young patients with BOT to receive fertility sparing surgery but given the higher risk of relapse within any remaining ovarian tissue, regular sonographic follow up is recommended. (Grade B)

There is no evidence-based indication for cytotoxic chemotherapy in BOT. (Grade B)

Ovarian epithelial tumour classification is characterised by its unique category of borderline tumours. Although the morphology of these tumours includes no invasive characteristics, clinically their behaviour is not always entirely benign. While borderline endometrioid, clear cell, Brenner tumours and correctly diagnosed mucinous borderline tumours usually behave in benign fashion, the serous and sero-mucinous have a distinct behaviour, which is not always benign.

Serous borderline tumours (SBTs)

These tumours show a typical hierarchical branching pattern lined by cells that show low grade nuclear atypia. When clusters of cells less than 5 mm in greatest dimension, typically with a surrounding clear space, are seen in the stroma, the term microinvasion is applied. Microinvasion is seen more commonly in pregnant patients but the presence of microinvasion does not alter the outcome. (135) Women with stage I disease have the same outcome as the general population, irrespective of microinvasion. (136)

SBTs can also be associated with peritoneal lesions that are termed implants. When the implants are confined to peritoneal/ mesothelial lined surfaces and lack invasion of underlying tissue, they are termed non-invasive implants. Where there is invasion of the underlying fat or muscle, the term invasive implants is used. In some instances, unequivocal invasion is not demonstrable, but the lesion displays the cytological features of invasive implants. (137) The WHO 2014 classification recommends that because these lesions with invasive implants may behave like LGSOC, they should be designated as such. Finally SBTs with micropapillary and microacinar architecture have a greater association with extra-ovarian disease and a higher incidence of recurrence and death from disease than typical SBTs. (138) Morphologically, micropapillae typically lack stromal cores and hierarchical branching. They are composed of cells that are cuboidal, have a high nuclear cytoplasmic ratio and form finger like protrusions that are at least five times longer than broad.

Mucinous borderline tumours (MBTs)

MBTs typically present as large unilateral masses that are confined to the ovary. There are no well-documented cases of MBTs with implants. Adequate sampling of these tumours is crucial, since they are typically heterogenous and can harbour occult foci of carcinoma. (139) MBTs are lined by mucinous epithelium with varying degrees of stratification, tufting and papillary formation. When the lining cells are markedly atypical the term MBT with intraepithelial carcinoma is used. MBT with microinvasion is defined as small foci of microinvasion less than 5 mm in greatest linear dimension. (140) These features do not appear to affect prognosis adversely in stage 1 tumours. (141)

Non-ovarian mucinous tumours, including metastatic ovarian mucinous tumours associated with pseudomyxoma peritonei and metastatic mucinous carcinomas (Krunkenberg tumours) with a deceptive pattern of invasion, are recognized as tumours that can simulate primary MBTs. (142)

Clinical management of borderline ovarian tumours

Complete macroscopic tumour resection should be the aim of all surgery for BOT, with adequate surgical staging especially in apparent stage 1 disease including peritoneal biopsies, cytology and omentectomy (with appendicectomy for mucinous tumours). [Grade B]

A fertility sparing approach in young patients does not preclude adequate peritoneal staging since, even in the presence of peritoneal implants, peritonectomies with preservation of at least one ovary and tube and uterus, can be performed. Adequate surgical staging at initial presentation of the BOT is a defining factor predicting progression-free and overall survival. However, the diagnosis is often made retrospectively following surgery by a non-gynaecological oncologist. Two large retrospective series of women with BOT showed that, higher stage, incomplete staging, residual tumour, and fertility-sparing surgery were independent prognostic factors for recurrence. (136, 143, 144) Patients should be informed about the risks and benefits of completion staging after simple cystectomy or unilateral salpingo-oopherectomy with an incidental finding of BOT. Simple cystectomy in an ovary with BOT carries a risk of relapse and so should be considered mainly for fertility-sparing reasons and after thorough informed consent. (145) Longer-term, the risk of malignant transformation was low overall (~2%), but was found in 30% of those with relapsed disease, although was much less frequent in women under 40 years of age at original diagnosis, compared to those aged over 40 years (12.0% versus 66.7%, $P < 0.001$). Completion surgery could be discussed with women once they have competed their families, even though there are no data to support this having any impact on OS or PFS.

In early stages, with small volume masses and in the absence of extensive peritoneal implants, laparoscopic management is as safe as laparotomy from an oncological point of view. Hysterectomy has no value in complete staging of a patient with BOT. Hysterectomy should be considered if the patient wishes, or for cytoreduction if the uterus is involved with invasive disease. (143)

There is no value in lymph node sampling or dissection in BOT and this should therefore not be routinely performed, although, if bulky lymph nodes are present they should be removed. There is no proven value of cytotoxic chemotherapy in patients with BOT. (143, 146) BOT can relapse decades after the initial diagnosis, and is uncommon in those who have had both ovaries removed. The most

significant risk factor for relapse was the presence of invasive peritoneal implants, however since this group of patients now belongs to the ones with low grade ovarian cancer, the remaining BOT group is prognostically very favourable. For that reason value of follow up in patients with early disease and after bilateral BSO remains unscertain. However, follow up is essential in patients after fertility-sparing surgery since they have a significantly higher risk of relapse in the remaining ovaries. There is no value in the routine CA125 based follow up for BOT patients (143). Relapse of borderline disease should be mainly treated surgically, if disease seems operable, since response to chemotherapy is poor.

12. Support needs for women with ovarian cancer

Women with EOC who require elective surgery in the NHS should have access to a holistic assessment by a clinical nurse specialist (Grade D).

The ovarian cancer pathway is a complex process that includes recognizing abnormal symptoms, worrying that you may have cancer, developing acute symptoms, having tests and investigations, been told that you may have cancer, having cancer confirmed, treatments that include extensive surgery, multiple chemotherapy agents and courses, the potential shortening of ones life, carrying a gene that may affect children and grandchildren, and facing death. Women with ovarian cancer have some or all of these experiences and other related experiences. Women with ovarian cancer report the significant physical and emotional impact of the disease on quality of life (147-151) and the needs of cancer patients often go unmet. (151-153)

Supporting women effectively during the diagnostic, treatment and post treatment phases involves managing the physical, psychological and social impact of the disease and its treatment.

In line with NICE guidelines (2) , women with ovarian cancer should be offered information about their disease (including the stage of the disease, treatment options and prognosis, management of side effects, sexuality, fertility, menopause management, signs and symptoms of recurrence, genetic information, self-help strategies, and dealing with emotions). This should include the amount of detail they want and are able to deal with in a suitable format, including written.

Assessing individual patient need is the cornerstone of patient-centred care. The information and support provided should enable women to make decisions about their care and how it will affect their lives from the time of suspected cancer and diagnosis. Decisions made during this time will impact on immediate treatment and side effects, quality of life and post-treatment consequences.

The National Cancer Survivorship Initiative (NCSI) in England was set up to improve cancer care from the point of diagnosis and recommended the provision of a Holistic Needs Assessment (HNA) for all cancer patients at least at the time of diagnosis and end of treatment. (154) This should include a care plan tailored to individual need. Effectively assessing individual needs and concerns can lead to early interventions and open up communication based on partnership, empowering the patient towards self-management, and the confidence and permission to access available help and support.

The HNA should be a formal process, best led by a framework or tool to ensure that physical, psychological, spiritual, emotional and social domains are considered, and documented to develop an individualised care plan that can be shared with other healthcare professionals, as appropriate. (154) The HNA, together with a treatment summary, a cancer care review and a health and wellbeing

event are key elements of the Recovery Package which, when delivered together, can improve outcomes for people living with and beyond cancer. (155)

Women undergoing surgery may also benefit from being treated within an Enhanced Recovery Programme (ERP), a multimodal perioperative care enhancement protocol designed to improve patient outcomes and speed recovery. (156) There is qualitative evidence to support ERP in women with gynaecological cancer but no evidence to date from high-quality studies specific to gynaecological oncology surgery(157-159), however, data from a colorectal surgery RCT support this approach. (160) The ERP focuses on making sure that patients are active participants in their own recovery process and focuses on four elements:

- Pre-operative assessment, planning and preparation before admission
- Reducing the physical stress of the operation
- Structured approach to immediate post-operative and during (perioperative) management, including pain relief
- Early mobilisation

Effective supportive care involves patient involvement in the care process, and identification and management of individual supportive care needs, to maximise quality of life. Focusing on these needs is a key function of the cancer Clinical Nurse Specialist (CNS). The high-level activities of the cancer CNS can be separated into four main areas; having technical knowledge to oversee and co-ordinate services to personalise the cancer pathway for individual patients, being the key accessible professional for the multidisciplinary team, assessing and alleviating psychosocial suffering including referral as necessary and ensuring services are responsive to patient need. Access to a cancer CNS has been shown to improve patient experience.

13. Appendices

Appendix A

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 2+ studies directly applicable to the patient population or extrapolated evidence from studies rated at 2++.
D	Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+.

Appendix B

Establishing the diagnosis in secondary care (modified from NICE CG122)

Appendix C

***2014 FIGO ovarian, fallopian tube, and peritoneal cancer staging system and corresponding TNM* (161)**

Stage I. Tumour confined to ovaries or fallopian tube(s)

FIGO staging 2009	**TNM staging**	**Description**
FIGO IA	**T1a-N0-M0**	Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IB	**T1b-N0-M0**	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IC1	**T1c N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with surgical spill
FIGO IC2	**T1c-N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
FIGO IC3	**T1c-N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with malignant cells in the ascites or peritoneal washings

Stage II. Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

FIGO IIA	**T2a-N0-M0**	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
FIGO IIB	**T2b-N0-M0**	Extension to other pelvic intraperitoneal tissues

Stage III. Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.

FIGO IIIA1 FIGO IIIA1(i) FIGO IIIA1(ii)	**T1/T2-N1-M0**	Positive retroperitoneal lymph nodes only (cytologically or histologically proven) Metastasis up to 10 mm Metastasis more than 10 mm
FIGO IIIA2	**T3a2-N0/N1-M0**	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
FIGO IIIB	**T3b-N0/N1-M0**	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
FIGO IIIC	**T3c-N0/N1-M0**	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)

Stage IV. Distant metastasis excluding peritoneal metastases

FIGO IVA	Any T, any N, M1	Pleural effusion with positive cytology
FIGO IVB	Any T, any N, M1	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Appendix D

Risk of Malignancy Index I (RMI I) calculation

RMI I combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI I is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml). (31)

RMI I = U x M x CA125

The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions.

U = 0 (for an ultrasound score of 0)

U = 1 (for an ultrasound score of 1)

U = 3 (for an ultrasound score of 2–5)

The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal.

The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.

Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units.

14. References

(1) Barclay M, Gildea C, Poole J, Hirschowitz L, Menon U, Nordin A. Factors Affecting Short-term Mortality in Women With Ovarian, Tubal, or Primary Peritoneal Cancer: Population-Based Cohort Analysis of English National Cancer Registration Data. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2016 Jan;26(1):56-65. PubMed PMID: 26509852.

(2) Redman C, Duffy S, Bromham N, Francis K, Guideline Development G. Recognition and initial management of ovarian cancer: summary of NICE guidance. BMJ. 2011;342:d2073. PubMed PMID: 21511784.

(3) Network SIG. Management of epithelial ovarian cancer. SIGN Publication No 135. Edinburg: SIGN; 2013.

(4) Gilbert L, Basso O, Sampalis J, Karp I, Martins C, Feng J, et al. Assessment of symptomatic women for early diagnosis of ovarian cancer: results from the prospective DOvE pilot project. Lancet Oncol. 2012 Mar;13(3):285-91. PubMed PMID: 22257524.

(5) Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011 Jun 8;305(22):2295-303. PubMed PMID: 21642681.

(6) Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012 Jan 18;104(2):125-32. PubMed PMID: 22228146. Pubmed Central PMCID: PMC3260132.

(7) Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016 Mar 5;387(10022):945-56. PubMed PMID: 26707054. Pubmed Central PMCID: PMC4779792.

(8) Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet. 1995 Jan;56(1):265-71. PubMed PMID: 7825587. Pubmed Central PMCID: PMC1801337.

(9) Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998 Mar;62(3):676-89. PubMed PMID: 9497246.

(10) Rosenthal AN, Fraser L, Manchanda R, Badman P, Philpott S, Mozersky J, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol. 2013 Jan 1;31(1):49-57. PubMed PMID: 23213100. Pubmed Central PMCID: PMC3530690.

(11) Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006 Jul 12;296(2):185-92. PubMed PMID: 16835424.

(12) Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010 Sep 1;304(9):967-75. PubMed PMID: 20810374. Pubmed Central PMCID: PMC2948529.

(13) Hanley GE, McAlpine JN, Kwon JS, Mitchell G. Opportunistic salpingectomy for ovarian cancer prevention. Gynecol Oncol Res Pract. 2015;2:5. PubMed PMID: 27231565. Pubmed Central PMCID: PMC4881168.

(14) Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol. 1990 Oct;97(10):922-9. PubMed PMID: 2223684.

(15) Menon U, Ryan A, Kalsi J, Gentry-Maharaj A, Dawnay A, Habib M, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015 Jun 20;33(18):2062-71. PubMed PMID: 25964255. Pubmed Central PMCID: PMC4463475.
(16) Wu L, Dai ZY, Qian YH, Shi Y, Liu FJ, Yang C. Diagnostic value of serum human epididymis protein 4 (HE4) in ovarian carcinoma: a systematic review and meta-analysis. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2012 Sep;22(7):1106-12. PubMed PMID: 22854652.
(17) Braicu EI, Fotopoulou C, Van Gorp T, Richter R, Chekerov R, Hall C, et al. Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients: results from the OVCAD study. Gynecologic oncology. 2013 Feb;128(2):245-51. PubMed PMID: 23178313.
(18) Braicu EI, Chekerov R, Richter R, Pop C, Nassir M, Loefgren H, et al. HE4 expression in plasma correlates with surgical outcome and overall survival in patients with first ovarian cancer relapse. Ann Surg Oncol. 2014 Mar;21(3):955-62. PubMed PMID: 24217786.
(19) Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839. PubMed PMID: 21156740. Pubmed Central PMCID: PMC3001703.
(20) MacKintosh ML, Rahim R, Rajashanker B, Swindell R, Kirmani BH, Hunt J, et al. CT scan does not predict optimal debulking in stage III-IV epithelial ovarian cancer: a multicentre validation study. J Obstet Gynaecol. 2014 Jul;34(5):424-8. PubMed PMID: 24725017.
(21) Mapelli P, Incerti E, Fallanca F, Gianolli L, Picchio M. Imaging biomarkers in ovarian cancer: the role of (1)(8)F-FDG PET/CT. Q J Nucl Med Mol Imaging. 2016 Jun;60(2):93-102. PubMed PMID: 26859083.
(22) deSouza NM, Rockall A, Freeman S. Functional MR Imaging in Gynecologic Cancer. Magn Reson Imaging Clin N Am. 2016 Feb;24(1):205-22. PubMed PMID: 26613882.
(23) Shen-Gunther J, Mannel RS. Ascites as a predictor of ovarian malignancy. Gynecologic oncology. 2002 Oct;87(1):77-83. PubMed PMID: 12468346.
(24) Allen VA, Takashima Y, Nayak S, Manahan KJ, Geisler JP. Assessment of False-negative Ascites Cytology in Epithelial Ovarian Carcinoma: A Study of 313 Patients. Am J Clin Oncol. 2014 Sep 05. PubMed PMID: 25198110.
(25) Rutten MJ, Leeflang MMG, Kenter GG, Mol BWJ, Buist M. Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. Cochrane Database of Systematic Reviews. 2014 (2). PubMed PMID: CD009786.
(26) Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG : an international journal of obstetrics and gynaecology. 2011 Jun;118(7):814-24. PubMed PMID: 21392246.
(27) Singh N, Gilks CB, Hirschowitz L, Kehoe S, McNeish IA, Miller D, et al. Primary site assignment in tubo-ovarian high-grade serous carcinoma: Consensus statement on unifying practice worldwide. Gynecologic oncology. 2016 May;141(2):195-8. PubMed PMID: 26827965.
(28) Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 30;474(7353):609-15. PubMed PMID: 21720365. Pubmed Central PMCID: PMC3163504.
(29) NICE. Clinical Guideline CG164: Familial Breast Cancer: Classification and Care of People at Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer2013.
(30) Wiggans AJ, Cass GK, Bryant A, Lawrie TA, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2015 May 20(5):CD007929. PubMed PMID: 25991068.

(31) NICE. Technology Appraisal guidance TA381. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy2016.
(32) Van Gorp T, Amant F, Neven P, Vergote I, Moerman P. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. Best Pract Res Clin Obstet Gynaecol. 2004 Apr;18(2):349-71. PubMed PMID: 15157647.
(33) Zaino RJ, Unger ER, Whitney C. Synchronous carcinomas of the uterine corpus and ovary. Gynecologic oncology. 1984 Nov;19(3):329-35. PubMed PMID: 6500375.
(34) Iwamoto M, Nakatani Y, Fugo K, Kishimoto T, Kiyokawa T. Napsin A is frequently expressed in clear cell carcinoma of the ovary and endometrium. Hum Pathol. 2015 Jul;46(7):957-62. PubMed PMID: 25971546.
(35) Sreenan JJ, Hart WR. Carcinosarcomas of the female genital tract. A pathologic study of 29 metastatic tumors: further evidence for the dominant role of the epithelial component and the conversion theory of histogenesis. Am J Surg Pathol. 1995 Jun;19(6):666-74. PubMed PMID: 7755153.
(36) Jin Z, Ogata S, Tamura G, Katayama Y, Fukase M, Yajima M, et al. Carcinosarcomas (malignant mullerian mixed tumors) of the uterus and ovary: a genetic study with special reference to histogenesis. Int J Gynecol Pathol. 2003 Oct;22(4):368-73. PubMed PMID: 14501818.
(37) Fujii H, Yoshida M, Gong ZX, Matsumoto T, Hamano Y, Fukunaga M, et al. Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity. Cancer Res. 2000 Jan 1;60(1):114-20. PubMed PMID: 10646862.
(38) Amant F, Vloeberghs V, Woestenborghs H, Moerman P, Vergote I. Transition of epithelial toward mesenchymal differentiation during ovarian carcinosarcoma tumorigenesis. Gynecologic oncology. 2003 Aug;90(2):372-7. PubMed PMID: 12893202.
(39) Rauh-Hain JA, Growdon WB, Rodriguez N, Goodman AK, Boruta DM, 2nd, Schorge JO, et al. Carcinosarcoma of the ovary: a case-control study. Gynecologic oncology. 2011 Jun 1;121(3):477-81. PubMed PMID: 21420726.
(40) Woo YL, Kyrgiou M, Bryant A, Everett T, Dickinson HO. Centralisation of services for gynaecological cancer. Cochrane Database Syst Rev. 2012 Mar 14(3):CD007945. PubMed PMID: 22419327. Pubmed Central PMCID: 4020155.
(41) Haward RA. Guidance on Commissioning Cancer Services. Improving Outcomes in Gynaecological Cancers. The Manual.: NHS Executive; 1999
(42) Health Do. Improving Outcomes in Gynaecological Cancers. The Research Evidence. Guidance on Commissioning Cancer Services. Wetherby: Department of Health; 1999.
(43) Timmers PJ, Zwinderman K, Coens C, Vergote I, Trimbos JB. Lymph node sampling and taking of blind biopsies are important elements of the surgical staging of early ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2010 Oct;20(7):1142-7. PubMed PMID: 21495216.
(44) Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst. 2003 Jan 15;95(2):105-12. PubMed PMID: 12529343.
(45) Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2015 (12). PubMed PMID: CD004706.
(46) Timmers PJ, Zwinderman AH, Coens C, Vergote I, Trimbos JB. Understanding the problem of inadequately staging early ovarian cancer. Eur J Cancer. 2010 Mar;46(5):880-4. PubMed PMID: 20074933.
(47) Garcia-Soto AE, Boren T, Wingo SN, Heffernen T, Miller DS. Is comprehensive surgical staging needed for thorough evaluation of early-stage ovarian carcinoma? Am J Obstet Gynecol. 2012 Mar;206(3):242 e1-5. PubMed PMID: 22055337.

(48) Cass I, Li AJ, Runowicz CD, Fields AL, Goldberg GL, Leuchter RS, et al. Pattern of lymph node metastases in clinically unilateral stage I invasive epithelial ovarian carcinomas. Gynecologic oncology. 2001 Jan;80(1):56-61. PubMed PMID: 11136570.
(49) Maggioni A, Benedetti Panici P, Dell'Anna T, Landoni F, Lissoni A, Pellegrino A, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer. 2006 Sep 18;95(6):699-704. PubMed PMID: 16940979. Pubmed Central PMCID: PMC2360519.
(50) Kleppe M, Wang T, Van Gorp T, Slangen BF, Kruse AJ, Kruitwagen RF. Lymph node metastasis in stages I and II ovarian cancer: a review. Gynecologic oncology. 2011 Dec;123(3):610-4. PubMed PMID: 21982047.
(51) Schmeler KM, Tao X, Frumovitz M, Deavers MT, Sun CC, Sood AK, et al. Prevalence of lymph node metastasis in primary mucinous carcinoma of the ovary. Obstet Gynecol. 2010 Aug;116(2 Pt 1):269-73. PubMed PMID: 20664385. Pubmed Central PMCID: PMC4163054.
(52) Powless CA, Aletti GD, Bakkum-Gamez JN, Cliby WA. Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: implications for surgical staging. Gynecologic oncology. 2011 Sep;122(3):536-40. PubMed PMID: 21636114.
(53) Fruscio R, Corso S, Ceppi L, Garavaglia D, Garbi A, Floriani I, et al. Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol. 2013 Jan;24(1):138-44. PubMed PMID: 22945381.
(54) Suzuki M, Ohwada M, Yamada T, Kohno T, Sekiguchi I, Sato I. Lymph node metastasis in stage I epithelial ovarian cancer. Gynecologic oncology. 2000 Nov;79(2):305-8. PubMed PMID: 11063662.
(55) Nomura H, Tsuda H, Susumu N, Fujii T, Banno K, Kataoka F, et al. Lymph node metastasis in grossly apparent stages I and II epithelial ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2010 Apr;20(3):341-5. PubMed PMID: 20375794.
(56) du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009 Mar 15;115(6):1234-44. PubMed PMID: 19189349.
(57) van der Burg ME, van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med. 1995 Mar 9;332(10):629-34. PubMed PMID: 7845426.
(58) Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010 Sep 2;363(10):943-53. PubMed PMID: 20818904.
(59) Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet. 2014 Oct 11;384(9951):1376-88. PubMed PMID: 24767708.
(60) Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev. 2011 Aug 10(8):CD007565. PubMed PMID: 21833960.
(61) Ang C, Chan KK, Bryant A, Naik R, Dickinson HO. Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer. Cochrane Database Syst Rev. 2011 Apr 13(4):CD007697. PubMed PMID: 21491400. Pubmed Central PMCID: PMC4028614.
(62) Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. . Cochrane Database Syst Rev 2016 (1):Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub7.

(63) Aletti GD, Gostout BS, Podratz KC, Cliby WA. Ovarian cancer surgical resectability: relative impact of disease, patient status, and surgeon. Gynecologic oncology. 2006 Jan;100(1):33-7. PubMed PMID: 16153692.
(64) NICE. Interventional Procedures Guidance Ultra Radical (Extensive) Surgery for Advanced Ovarian Cancer IPG470. 2013.
(65) Annual Report of the Chief Medical Officer, 2014 - The Health of the 51%: Women: Department of Health; 2014.
(66) Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. J Natl Cancer Inst. 2005 Apr 20;97(8):560-6. PubMed PMID: 15840878.
(67) Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med. 2004 Dec 09;351(24):2489-97. PubMed PMID: 15590951.
(68) Colombo N, Guthrie D, Chiari S, Parmar M, Qian W, Swart AM, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. J Natl Cancer Inst. 2003 Jan 15;95(2):125-32. PubMed PMID: 12529345.
(69) Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst. 2003 Jan 15;95(2):113-25. PubMed PMID: 12529344.
(70) Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database Syst Rev. 2009 (3):CD004706. PubMed PMID: 19588360.
(71) Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol. 2006 Dec;103(3):1070-6. PubMed PMID: 16875720.
(72) Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015 Jul 18;386(9990):249-57. PubMed PMID: 26002111.
(73) Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. 20160801(1879-0852 (Electronic)). eng.
(74) Bohm S, Faruqi A, Said I, Lockley M, Brockbank E, Jeyarajah A, et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. J Clin Oncol. 2015 Aug 1;33(22):2457-63. PubMed PMID: 26124480.
(75) Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev. 2016;1:CD005340. PubMed PMID: 26755441.
(76) Tewari D, Java JJ, Salani R, Armstrong DK, Markman M, Herzog T, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2015 May 1;33(13):1460-6. PubMed PMID: 25800756. Pubmed Central PMCID: PMC4404424.
(77) Elit L, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, et al. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer. 2007 Feb 15;109(4):692-702. PubMed PMID: 17238181.

(78) Gore M, du Bois A, Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. J Clin Oncol. 2006 Oct 1;24(28):4528-30. PubMed PMID: 17008689.
(79) Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M, Johnston M. Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer. Gynecologic oncology. 2002 Apr;85(1):71-80. PubMed PMID: 11925123.
(80) Katsumata N, Yasuda M, Isonishi S, Takahashi F, Michimae H, Kimura E, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol. 2013 Sep;14(10):1020-6. PubMed PMID: 23948349.
(81) Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, De Placido S, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2014 Apr;15(4):396-405. PubMed PMID: 24582486.
(82) Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol. 2009 Mar 20;27(9):1419-25. PubMed PMID: 19224846. Pubmed Central PMCID: PMC2668552.
(83) Lambert HE, Rustin GJ, Gregory WM, Nelstrop AE. A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. Ann Oncol. 1997 Apr;8(4):327-33. PubMed PMID: 9209661.
(84) Pignata S, Scambia G, Ferrandina G, Savarese A, Sorio R, Breda E, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J Clin Oncol. 2011 Sep 20;29(27):3628-35. PubMed PMID: 21844495.
(85) Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst. 2004 Nov 17;96(22):1682-91. PubMed PMID: 15547181.
(86) Li Q, Cohn D, Waller A, Backes F, Copeland L, Fowler J, et al. Outpatient rapid 4-step desensitization for gynecologic oncology patients with mild to low-risk, moderate hypersensitivity reactions to carboplatin/cisplatin. Gynecologic oncology. 2014 Oct;135(1):90-4. PubMed PMID: 25110329.
(87) Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2484-96. PubMed PMID: 22204725.
(88) Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2473-83. PubMed PMID: 22204724. Epub 2011/12/30.
(89) Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, Walker JL, et al. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. N Engl J Med. 2016 Feb 25;374(8):738-48. PubMed PMID: 26933849.
(90) du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol. 2014 Oct 20;32(30):3374-82. PubMed PMID: 25225436.
(91) du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, et al. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2016 Jan;17(1):78-89. PubMed PMID: 26590673.
(92) Mackay HJ, Brady MF, Oza AM, Reuss A, Pujade-Lauraine E, Swart AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer.

International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2010 Aug;20(6):945-52. PubMed PMID: 20683400.
(93) Sugiyama T, Okamoto A, Enomoto T, Hamano T, Aotani E, Terao Y, et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial. J Clin Oncol. 2016 Aug 20;34(24):2881-7. PubMed PMID: 27400948.
(94) Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010 Oct 2;376(9747):1155-63. PubMed PMID: 20888993.
(95) Clarke T, Galaal K, Bryant A, Naik R. Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment. Cochrane Database Syst Rev. 2014 Sep 08(9):CD006119. PubMed PMID: 25198378.
(96) Hall M, Rustin G. Recurrent ovarian cancer: when and how to treat. Curr Oncol Rep. 2011 Dec;13(6):459-71. PubMed PMID: 22045509.
(97) Harter P, Hahmann M, Lueck HJ, Poelcher M, Wimberger P, Ortmann O, et al. Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis: exploratory analysis of the DESKTOP I Trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis. Ann Surg Oncol. 2009 May;16(5):1324-30. PubMed PMID: 19225844.
(98) Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2011 Feb;21(2):289-95. PubMed PMID: 21270612.
(99) Zang RY, Harter P, Chi DS, Sehouli J, Jiang R, Trope CG, et al. Predictors of survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery based on the pooled analysis of an international collaborative cohort. Br J Cancer. 2011 Sep 27;105(7):890-6. PubMed PMID: 21878937. Pubmed Central PMCID: PMC3185944.
(100) Fotopoulou C, Zang R, Gultekin M, Cibula D, Ayhan A, Liu D, et al. Value of tertiary cytoreductive surgery in epithelial ovarian cancer: an international multicenter evaluation. Ann Surg Oncol. 2013 Apr;20(4):1348-54. PubMed PMID: 23054114.
(101) Al Rawahi T, Lopes AD, Bristow RE, Bryant A, Elattar A, Chattopadhyay S, et al. Surgical cytoreduction for recurrent epithelial ovarian cancer. Cochrane Database Syst Rev. 2013 Feb 28(2):CD008765. PubMed PMID: 23450588.
(102) Galaal K, Naik R, Bristow RE, Patel A, Bryant A, Dickinson HO. Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer. Cochrane Database Syst Rev. 2010 Jun 16(6):CD007822. PubMed PMID: 20556785. Pubmed Central PMCID: 4170993.
(103) Burger RA, Brady MF, Bookman MA, Monk BJ, Walker JL, Homesley HD, et al. Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol. 2014 Apr 20;32(12):1210-7. PubMed PMID: 24637999. Pubmed Central PMCID: PMC3986384.
(104) Kucukmetin A, Naik R, Galaal K, Bryant A, Dickinson HO. Palliative surgery versus medical management for bowel obstruction in ovarian cancer. Cochrane Database Syst Rev. 2010 Jul 07(7):CD007792. PubMed PMID: 20614464. Pubmed Central PMCID: PMC4170995.
(105) Kolomainen DF, Daponte A, Barton DP, Pennert K, Ind TE, Bridges JE, et al. Outcomes of surgical management of bowel obstruction in relapsed epithelial ovarian cancer (EOC). Gynecologic oncology. 2012 Apr;125(1):31-6. PubMed PMID: 22082991.
(106) Fotopoulou C, Braicu EI, Kwee SL, Kuhberg M, Richter R, Pietzner K, et al. Salvage surgery due to bowel obstruction in advanced or relapsed ovarian cancer resulting in short bowel syndrome and long-life total parenteral nutrition: surgical and clinical outcome. International journal of

gynecological cancer : official journal of the International Gynecological Cancer Society. 2013 Oct;23(8):1495-500. PubMed PMID: 24189059.
(107) Blackledge G, Lawton F, Redman C, Kelly K. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer. 1989 Apr;59(4):650-3. PubMed PMID: 2713253. Pubmed Central PMCID: PMC2247161.
(108) Stuart GC, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, et al. 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2011 May;21(4):750-5. PubMed PMID: 21543936.
(109) Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: Recurrent Disease. Ann Oncol. 2016 Dec 19. PubMed PMID: 27993805.
(110) Tanguay JS, Ansari J, Buckley L, Fernando I. Epithelial ovarian cancer: role of pegylated liposomal Doxorubicin in prolonging the platinum-free interval and cancer antigen 125 trends during treatment. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2009 Apr;19(3):361-6. PubMed PMID: 19407560.
(111) Colombo N. Efficacy of trabectedin in platinum-sensitive-relapsed ovarian cancer: new data from the randomized OVA-301 study. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2011 May;21 Suppl 1:S12-6. PubMed PMID: 21540666.
(112) Lawrie TA, Bryant A, Cameron A, Gray E, Morrison J. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. Cochrane Database Syst Rev. 2013 Jul 09(7):CD006910. PubMed PMID: 23835762.
(113) Raja FA, Counsell N, Colombo N, Pfisterer J, du Bois A, Parmar MK, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. Ann Oncol. 2013 Dec;24(12):3028-34. PubMed PMID: 24190964.
(114) Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45. PubMed PMID: 22529265. Pubmed Central PMCID: 3646321. Epub 2012/04/25.
(115) Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014 May 1;32(13):1302-8. PubMed PMID: 24637997. Stockler MR, Hilpert F, Friedlander M, King MT, Wenzel L, Lee CK, Joly F, de Gregorio N, Arranz JA, Mirza MR, Sorio R, Freudensprung U, Sneller V, Hales G, Pujade-Lauraine E. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. Journal of Clinical Oncology. 2014;32(13):1309-16.
(116) Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev. 2010 Dec 08(12):CD007926. PubMed PMID: 21154390. Pubmed Central PMCID: 4164823.
(117) Wuntakal R, Seshadri S, Montes A, Lane G. Luteinising hormone releasing hormone (LHRH) agonists for the treatment of relapsed epithelial ovarian cancer. Cochrane Database Syst Rev. 2016 Jun 29(6):CD011322. PubMed PMID: 27356090.
(118) Kobel M, Kalloger SE, Huntsman DG, Santos JL, Swenerton KD, Seidman JD, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol. 2010 May;29(3):203-11. PubMed PMID: 20407318.
(119) Altman AD, Nelson GS, Ghatage P, McIntyre JB, Capper D, Chu P, et al. The diagnostic utility of TP53 and CDKN2A to distinguish ovarian high-grade serous carcinoma from low-grade serous ovarian tumors. Mod Pathol. 2013 Sep;26(9):1255-63. PubMed PMID: 23558569.

(120) Grabowski JP, Harter P, Heitz F, Pujade-Lauraine E, Reuss A, Kristensen G, et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase. Gynecologic oncology. 2016 Mar;140(3):457-62. PubMed PMID: 26807488.
(121) Gershenson DMB, D.C.; Coleman, R.L.; Lu, K.H.; Malpica, A.; Sun, C.C. Hormonal maintenance therapy for women with low grade serous carcinoma of the ovary or peritoneum. J Clin Oncol 2016;34(Suppl; abstr):5502.
(122) Gourley C, Farley J, Provencher DM, Pignata S, Mileshkin L, Harter P, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian and primary peritoneal low-grade serous carcinomas. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Nov;24(9 Suppl 3):S9-13. PubMed PMID: 25341587.
(123) Zaino RJ, Brady MF, Lele SM, Michael H, Greer B, Bookman MA. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal: a Gynecologic Oncology Group study. Cancer. 2011 Feb 1;117(3):554-62. PubMed PMID: 20862744. Pubmed Central PMCID: PMC3010456.
(124) Ledermann JA, Luvero D, Shafer A, O'Connor D, Mangili G, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Nov;24(9 Suppl 3):S14-9. PubMed PMID: 25341574.
(125) Kurman RJ, International Agency for Research on Cancer., World Health Organization. WHO classification of tumours of female reproductive organs. 4th ed. Lyon: International Agency for Research on Cancer; 2014. 307 p. p.
(126) Glasspool RM, Gonzalez Martin A, Millan D, Lorusso D, Avall-Lundqvist E, Hurteau JA, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for squamous cell carcinoma of the ovary. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Nov;24(9 Suppl 3):S26-9. PubMed PMID: 25126954.
(127) Reed NS, Gomez-Garcia E, Gallardo-Rincon D, Barrette B, Baumann K, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for carcinoid tumors of the ovary. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Nov;24(9 Suppl 3):S35-41. PubMed PMID: 25341578.
(128) Reed NS, Pautier P, Avall-Lundqvist E, Choi CH, du Bois A, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian small cell cancers. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Nov;24(9 Suppl 3):S30-4. PubMed PMID: 25341577.
(129) Young RH, Oliva E, Scully RE. Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases. Am J Surg Pathol. 1994 Nov;18(11):1102-16. PubMed PMID: 7943531.
(130) Foulkes WD, Clarke BA, Hasselblatt M, Majewski J, Albrecht S, McCluggage WG. No small surprise - small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour. J Pathol. 2014 Jul;233(3):209-14. PubMed PMID: 24752781.
(131) Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, Hendricks WP, et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. 20140428 DCOM- 20140616(1546-1718 (Electronic)). eng.
(132) Harrison ML, Hoskins P Fau - du Bois A, du Bois A Fau - Quinn M, Quinn M Fau - Rustin GJS, Rustin Gj Fau - Ledermann JA, Ledermann Ja Fau - Baron-Hay S, et al. Small cell of the ovary, hypercalcemic type -- analysis of combined experience and recommendation for management. A GCIG study. 20060117 DCOM- 20060307(0090-8258 (Print)). eng.
(133) Cheng S, Evans Wk Fau - Stys-Norman D, Stys-Norman D Fau - Shepherd FA, Shepherd FA. Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline. 20070405 DCOM- 20070501(1556-1380 (Electronic)). eng.
(134) Pautier P, Ribrag V Fau - Duvillard P, Duvillard P Fau - Rey A, Rey A Fau - Elghissassi I, Elghissassi I Fau - Sillet-Bach I, Sillet-Bach I Fau - Kerbrat P, et al. Results of a prospective dose-

intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type. 20071217 DCOM- 20080116(1569-8041 (Electronic)). eng.
(135) Mooney J, Silva E, Tornos C, Gershenson D. Unusual features of serous neoplasms of low malignant potential during pregnancy. Gynecologic oncology. 1997 Apr;65(1):30-5. PubMed PMID: 9103387.
(136) Hannibal CG, Vang R, Junge J, Frederiksen K, Kjaerbye-Thygesen A, Andersen KK, et al. A nationwide study of serous "borderline" ovarian tumors in Denmark 1978-2002: centralized pathology review and overall survival compared with the general population. Gynecologic oncology. 2014 Aug;134(2):267-73. PubMed PMID: 24924123. Pubmed Central PMCID: PMC4370179.
(137) Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. Am J Surg Pathol. 2001 Apr;25(4):419-32. PubMed PMID: 11257616.
(138) Seidman JD, Kurman RJ. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol. 2000 May;31(5):539-57. PubMed PMID: 10836293.
(139) McCluggage GWW, N. Datasets for the histopathological reporting of neoplasms of the ovaries and fallopian tubes and primary carcinomas of the peritoneum RCPath; 2010.
(140) Khunamornpong S, Settakorn J, Sukpan K, Suprasert P, Siriaunkgul S. Mucinous tumor of low malignant potential ("borderline" or "atypical proliferative" tumor) of the ovary: a study of 171 cases with the assessment of intraepithelial carcinoma and microinvasion. Int J Gynecol Pathol. 2011 May;30(3):218-30. PubMed PMID: 21464732.
(141) Lee KR, Scully RE. Mucinous tumors of the ovary: a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with 'pseudomyxoma peritonei'. Am J Surg Pathol. 2000 Nov;24(11):1447-64. PubMed PMID: 11075847.
(142) Ronnett BM, Kajdacsy-Balla A, Gilks CB, Merino MJ, Silva E, Werness BA, et al. Mucinous borderline ovarian tumors: points of general agreement and persistent controversies regarding nomenclature, diagnostic criteria, and behavior. Hum Pathol. 2004 Aug;35(8):949-60. PubMed PMID: 15297962.
(143) du Bois A, Ewald-Riegler N, de Gregorio N, Reuss A, Mahner S, Fotopoulou C, et al. Borderline tumours of the ovary: A cohort study of the Arbeitsgmeinschaft Gynakologische Onkologie (AGO) Study Group. Eur J Cancer. 2013 May;49(8):1905-14. PubMed PMID: 23490647.
(144) Hannibal CG, Vang R, Junge J, Frederiksen K, Kurman RJ, Kjaer SK. A nationwide study of ovarian serous borderline tumors in Denmark 1978-2002. Risk of recurrence, and development of ovarian serous carcinoma. Gynecologic oncology. 2017 Jan;144(1):174-80. PubMed PMID: 27836204. Pubmed Central PMCID: 5183562.
(145) Trillsch F, Mahner S, Woelber L, Vettorazzi E, Reuss A, Ewald-Riegler N, et al. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. Ann Oncol. 2014 Jul;25(7):1320-7. PubMed PMID: 24618151.
(146) Faluyi O, Mackean M, Gourley C, Bryant A, Dickinson HO. Interventions for the treatment of borderline ovarian tumours. Cochrane Database Syst Rev. 2010 Sep 08(9):CD007696. PubMed PMID: 20824864. Pubmed Central PMCID: PMC4164822.
(147) Fitch MI, Steele R. Identifying supportive care needs of women with ovarian cancer. 20100624 DCOM- 20100726(1181-912X (Print)). eng.
(148) Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. 20120213 DCOM- 20120430(1095-6859 (Electronic)). eng.
(149) Ahmed-Lecheheb D, Joly F. Ovarian cancer survivors' quality of life: a systematic review. J Cancer Surviv. 2016 Oct;10(5):789-801. PubMed PMID: 26884372.
(150) Watts S, Prescott P, Mason J, McLeod N, Lewith G. Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open. 2015 Nov 30;5(11):e007618. PubMed PMID: 26621509. Pubmed Central PMCID: PMC4679843.

(151) Ozga M, Aghajanian C, Myers-Virtue S, McDonnell G, Jhanwar S, Hichenberg S, et al. A systematic review of ovarian cancer and fear of recurrence. Palliat Support Care. 2015 Dec;13(6):1771-80. PubMed PMID: 25728373. Pubmed Central PMCID: PMC4995592.
(152) Armes J, Crowe M, Colbourne L, Morgan H, Murrells T, Oakley C, et al. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. J Clin Oncol. 2009 Dec 20;27(36):6172-9. PubMed PMID: 19884548.
(153) Beesley V, Eakin E, Steginga S, Aitken J, Dunn J, Battistutta D. Unmet needs of gynaecological cancer survivors: implications for developing community support services. Psychooncology. 2008 Apr;17(4):392-400. PubMed PMID: 17680554.
(154) NCSI. Living with and beyond cancer: taking action to improve outcomes: Department of Health, London; 2013.
(155) Hughes C, Henry R, Richards S, Doyle N. Supporting delivery of the recovery package for people living with and beyond cancer. Cancer Nursing Practice 2014;13(10):30-5.
(156) Paton F, Chambers D, Wilson P, Eastwood A, Craig D, Fox D, et al. Effectiveness and implementation of enhanced recovery after surgery programmes: a rapid evidence synthesis. BMJ Open. 2014 Jul 22;4(7):e005015. PubMed PMID: 25052168. Pubmed Central PMCID: PMC4120402.
(157) Archer S, Montague J, Bali A. Exploring the experience of an enhanced recovery programme for gynaecological cancer patients: a qualitative study. Perioper Med (Lond). 2014 Apr 04;3(1):2. PubMed PMID: 24708824. Pubmed Central PMCID: PMC4746987.
(158) Lu D, Wang X, Shi G. Perioperative enhanced recovery programmes for gynaecological cancer patients. Cochrane Database Syst Rev. 2012 Dec 12;12:CD008239. PubMed PMID: 23235656.
(159) Lu D, Wang X, Shi G. Perioperative enhanced recovery programmes for gynaecological cancer patients. Cochrane Database Syst Rev. 2015 Mar 19(3):CD008239. PubMed PMID: 25789452.
(160) Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Annals of surgery. 2007 Jun;245(6):867-72. PubMed PMID: 17522511. Pubmed Central PMCID: 1876970.
(161) Prat J, Oncology FCoG. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014 Jan;124(1):1-5. PubMed PMID: 24219974. Epub 2013/11/14.
(162) Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, du Bois A, Vergote I, Reuss A, Bacon M. 5th Ovarian Cancer Consensus Conference of the Gynaecologic Cancer InterGroup: Recurrent Disease. Ann Oncol mdw663. DOI: https://doi.org/10.1093/annonc/mdw663. Pub.19/12/2016.
(163) Leary AF, Quinn M, Fujiwara K, Coleman RL, Kohn E, Sugiyama T, Glasspool R, Ray-Coquard I, Colobo N, Bacon, M. 5th Ovarian Cancer Consensus Conference of the Gynaecologic Cancer InterGroup (GCIG): Clinical trial design for rare ovarian tumours. Ann Oncol mdw662. DOI: https://doi.org/10.1093/annonc/mdw662.Pub19/12/2016.
(164) Karam A, Ledermann JA, Kim JW, Sehouli J, Lu K, Gourley C, Katsumata N, Burger RA, Nam BH, Bacon M. 5th Ovarian Cancer Consensus Conference of the Gynaecologic Cancer InterGroup: First Line Interventions. Ann Oncol mdx011. DOI: https://doi.org/10.1093/annonc/mdx011. Pub 21/02/2017.
(165) McGee J, Bookman M, Harter P, Marth C, McNeish I, Moore KN, Poveda A, Hilpert F, Hasegawa K, Bacon M, Gatsonis C, Brand A, Kridelka F, Berek J, Ottevanger N, Levy T, Silverberg S, Kim BG, Hirte H, Okamoto A, Stuart G, Ochiai K. 5th Ovarian Cancer Consensus Conference: Individualized Therapy and Patient Factors. Ann Oncol mdx010. DOI: https://doi.org/10.1093/annonc/mdx010. Pub 24/01/2017.

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Anglia Cancer Network Guidelines 2018

Gynaecological Cancers

Cervical Cancer

Anglia Cancer Network have agreed to follow published guidelines where available, with local modifications, which have been annotated in this summary document. Local modifications have been agreed by consensus meeting, following local hospitals review and feedback to the Network for comments. All hospitals were invited to be involved in face-to-face discussion of the guidelines at the September 2017 meeting.

Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

National guidelines have not yet been published and therefore the current guidelines are based on a review and update of the previous edition of the ACN guidelines.

Document contains:

> A summary of recommendations from the previous guidelines alongside the recent Network Modifications. Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

Amendment before full review (July 2019) – statement on laparoscopic radical hysterectomy for cervical cancer

At the February 2019 ACN business network it was agreed to update guidance on the route of radical hysterectomy in light of published research evidence. In May 2019 the BGCS published a position statement and concluded that the 'BGCS recommends that clinicians and patients exercise caution when considering undergoing minimal access radical hysterectomy for the management of early-stage cervical cancer. We recommend gynaecological oncologists and nurse specialists counsel patients regarding the potential risks and benefits of short term morbidity versus long term survival in surgery for early-stage cervical cancer, to enable women and their families to make a fully informed choice regarding the surgical options'

FIGO staging refers to FIGO 2009 classification and will be updated to reflect 2018 in the next review

CERVICAL SECTION (14-1C-108e)

Introduction

The purpose of these guidelines is to provide a summary guide for the management of patients with cervical cancer.

Cervical cancer occurs with similar frequency in all women over the age of 30. The incidence is highest in Norfolk compared to Cambridgeshire and Suffolk. This differs from the other gynaecology malignancies, particularly ovarian and endometrial cancer, where the incidence increases with age. Although less common than ovarian and endometrial cancer, the latest data indicates there is an incidence rate of 11.9 per 100,000 women (Anglia Network) with a mortality rate of 1.5 per 100,000 (Anglia Network). Infection with the sexually transmitted human papilloma virus is the main risk factor for this disease. Accurate pre-treatment assessment and staging are crucial in ensuring patients with cervical cancer receive appropriate management and treatment.

Population screening has led to a decline in the incidence of cervical cancer from cervical intraepithelial neoplasia, but is much less effective in detecting adenocarcinoma, which historically accounts for approximately 10 – 15% of invasive cervical cancers.

Vaginal cancer is similar in nature to cervical cancer but much less common and once diagnosed should always be referred on to the Cancer Centre for treatment.

A summary of the outcome measures adopted by Addenbrooke's Cancer Centre for audit is provided on page C2 of this document.

http://www.nci.nih.gov/cancertopics/types/cervical

Outcome Measure Summary

Referral:
All patients meeting urgent referral criteria for cervical cancer will be seen by a member of the specialist team within two weeks.

All patients will be referred to gynaecological oncology team within two working days of emergency admission or two working days of definitive diagnosis by another specialist.

All patients meeting urgent referral criteria for cervical cancer will have a definitive diagnosis within four weeks.

Investigations:
All patients will have FIGO staging recorded.

All patients will have an MRI of the pelvis as a minimum. Patients with stages 1B1 and higher should have a CT of the chest and abdomen in addition. (NB: If MRI is contraindicated or found unacceptable by the patient then CT is acceptable).

Patients with stages 1B1 and higher **should have a cross sectional imaging of the chest and upper abdomen in addition, or PET-CT. (NB: If MRI is contraindicated or found unacceptable by the patient then CT is acceptable)**.

- ***We have clarified our imaging protocol***

Treatment:
All patients with a diagnosis of cervical/vaginal cancer will have their treatment plan discussed at a multi-disciplinary meeting.

All patients undergoing radical treatment for cervical cancer should receive appropriate preparation.

Overall mortality for primary cervical cancer surgery (within 1 month of surgery) should be less than 1%.

All patients undergoing elective surgery for cervical / vaginal cancer should receive appropriate preparation.

Radiotherapy:
Patients should commence radiotherapy within 31 days of decision to treat or within 62 days from referral whichever is sooner.

Compensation for unscheduled gaps in radiotherapy should be made for all patients.

The incidence of fistula formation after radical radiotherapy should be less than 5%.

Follow Up:
All patients treated for cervical cancer will have access to follow up.

Follow up occurs as indicated in the guidelines.

Management of Recurrent Disease:
All patients with recurrent disease will be discussed at the multidisciplinary team meeting prior to any treatment.

All recurrences will be referred urgently to the Cancer Centre for assessment and treatment,

Pathology:
See appendix E

Patient Care:
Clear and comprehensive written information on the following will be offered:

- Disease
- Diagnostic procedures
- Treatment options
- Outcomes
- Post-treatment symptoms
- Members of the multidisciplinary team

Access will be available to a named nurse who has specialist knowledge in cervical cancer for all patients / carers.

Access will be available to a specialist gynaecology radiographer for advice and support pre, during and post-radiotherapy.

Patients identified as having lymphoedema will be referred to lymphoedema centre for treatment, support and information

Nurse specialists will be responsible for ensuring that local referral pathways are kept up to date. ➢ ***We have added that this must be kept current***

Practical information and advice regarding sexual function and problems will be discussed at commencement of treatment and where appropriate, patients referred on for specialist advice to psycho-sexual counsellor.

All CNS should have the basic skills and there should be an intermediate level skilled CNS who thenrefers onto to the specialist psycho-sexual practitioner. This pathway is currently under development.

GP Guidelines

Cervical Cancer:

- Patients presenting with symptoms suggestive of cervical carcinoma should be assessed by pelvic examination and referred on directly to the gynaecology assessment service at the Cancer Unit if there is a suspicion of cervical cancer.
- Abnormal cervix on pelvic examination should be referred on to the rapid access clinic using the two week wait system. Cervical smears are not useful in this group of patients and may delay referral. Patients with vaginal carcinoma should be referred on to the Cancer Centre.
- Persistent Post-coital or inter-menstrual bleeding (below 30 years old, please refer to GUM initially)
- Persistent vaginal discharge (patients with persistent vaginal discharge can be referred to GU medicine, who will refer on if a suspicion of cancer is present Abnormal cervix on pelvic examination should be referred on to the rapid access clinic using the two week wait system.
- Abnormal cervix on pelvic examination should be referred on to the rapid access clinic using the two week wait system.
- Patients with moderate Dyskariosis (grade 7), severe Dyskariosis (grade 4), suspicious of invasion (grade 5) and CGIN (grade 6) should be seen within two weeks in the cancer unit for colposcopic and clinical assessment.

Other Referral Route Guidelines

Patients referred from other hospitals: (Referrals from Cancer Unit to Cancer Centre)

The cancer unit will have facilities to assess women with possible cervical cancer rapidly.

Unit to Centre Referral:
Any patient with a confirmed diagnosis of cervical cancer greater than stage Ia1 carcinoma or vaginal cancer should be referred to the gynaecology specialist multi-disciplinary team at the Cancer Centre and relevant histopathology material forwarded to the designated lead pathologist for review.

All cases of cervical cancer including stage 1a1 should be reviewed at the centre at the multi-disciplinary meeting. The patients with stage 1a1 do not need to be physically seen in the centre.

Information should be given to all cervical cancer patients, that there will be a review of their smear history, as per the guidelines in NHSCSP Publication No. 28, December 2006.

Patients wishing to discuss fertility preservation surgery may be referred to the Addenbrooke's MDT. We have removed a single name, to reflect that this is a general service offered by Addenbrooke's, not a single-practitioner led service.

In-patients:
Patients should be referred to the gynaecological oncology team within two working days of their emergency admission or within two working days of a definitive diagnosis.

Other referral routes will include:

- Other surgeons following emergency admission.
- Other clinicians e.g. radiologist, pathologists.
- General Medicine.

Investigations

All patients will have FIGO staging (see Appendix C).

- EUA, in patients undergoing radiation therapy, and biopsy of lesion and any clinically suspicious nodes or other metastases which may alter management.
- FBC.
- U&E.
- Liver function test.
- Group and save or cross match according to local guidelines
- (Prior to surgery clotting screen and cross match two units)
- MRI of pelvis (MRI is now the method of choice for staging Ca Cervix).
- Assess extent of primary tumour.
- Detect lymphadenopathy.
- Detect liver and other metastases.
- Assess upper renal tracts.

Primary Treatment

Patients with a diagnosis of cervical cancer will be discussed prior to treatment at the multi-disciplinary meeting and a treatment plan formulated. This will include the use of pre-operative / post-operative adjuvant therapy and entry into clinical trials where appropriate.

Examination under anaesthetic will be considered and conducted by a

gynaecological oncologist surgeon and clinical oncologist. Where possible, both specialists should be present at staging EUA to decide primary treatment. Patients with apparent stage 1B1 disease on MRI may have a clinical examination avoiding the EUA. A clear documentation of the stage will be made in the notes. **Staging should be recorded using both FIGO and TNM staging systems**

➢ ***We have added the TNM system, due to forthcoming international treatment guidelines that will be using this system***

An EUA may be arranged for these (1B1 <2cm) patients at the discretion of the assessing clinician.

➢ ***We have clarified that tumours should be less than 2cm if no EUA is being considered, larger tumours should be assessed under anaesthesia***

Preparation for Surgery will include:

1. Informed consent
2. Group and save or Cross-matching according to local guidelines
3. Thrombo-embolism prophylaxis
4. Antibiotic infection prophylaxis

Pre-operative:
All patients will be assessed pre-operatively by a consultant gynaecological oncologist.

Patients will have the necessary investigations (CXR, ultrasound, blood tests).

Aim of Cervical Surgery:
Surgical management will be dependent upon stage.

Stage Ia 1	LLETZ, simple hysterectomy.
Stage Ia 2	LLETZ/Trachelectomy; for pelvic node dissection for poor prognosis tumours (G3, LVSI+). If fertility not an issue then consider simple hysterectomy.
Stage Ib1 – IIa (Non bulky)	Radical hysterectomy and pelvic node dissection (this should be open – see 2019 statement above) (Fertility sparing surgery stage Ib - radical Trachelectomy)

Ovaries should be **considered in pre-menopausal women aged less than 45. Beyond 45 the risks and benefits of ovarian preservation should be discussed with the patient as the evidence for preservation is less robust.** Bilateral salpingectomy will be performed in all women having hysterectomy. **Ovarian transposition should be advised in women under the age of 40 years having surgery for tumours > 2cm (1b1) and their position should be marked with surgical clips.**

➢ ***We have added our recommendations on women who should be considered for ovarian preservation, and for those in whom we advise ovarian transposition***

Women experiencing treatment-induced menopause may be considered for HRT

treatment. Transdermal oestrogen is the route of choice. Women who have had a hysterectomy require oestrogen-only HRT.
➢ ***We have added advice on HRT for women with treatment-induced menopause***

Documentation:
Operation notes should be electronically recorded.
Any operation note must provide sufficient information to allow a clear understanding of the operative findings, the procedure carried out and the personnel involved

Post--Operative Radiotherapy

Indications

Patients at higher of local recurrence after surgery **should be offered adjuvant treatment:**

·**Positive lymph nodes**
·**Parametrial disease**
·**Positive surgical margins**

Those with intermediate risk factors should referred for discussion of adjuvant treatment:

- **Two of three of the presence of LVSI, deep stromal invasion or large tumour size (>2cm)**
- **The presence of close vaginal surgical margins (<5mm)**

➢ ***We have altered the criteria women with intermediate risk factors for recurrence who should be considered for adjuvant treatment after surgery***

Non-surgical Therapy:
Radiotherapy and chemotherapy will be managed by a Clinical Oncologist with specialist expertise in the management of gynaecology malignancy.

Radical **chemoradiation** will be considered for all patients with:

- • Stage 1b2
- • **2a (> 4cm)** and above (all histological types)
- Positive lymph nodes

Although age is not related to outcome, consideration will be given for older patients (>60 years) to undergo radical radiotherapy in preference to surgery.

➢ ***We have changed to chemoradiation, and clarified size of IIa disease. We have also removed 'surgically-treated with close surgical margins' (as this is covered in the section above)***

Patients should have their haemoglobin maintained at 12g/dl or greater throughout treatment. ***We disagree with this statement now, as there is evidence from other tumour***

***sites that this is not necessary*.**

Local audit has suggested that debulking of pelvic and/or para-aortic nodes ≥ 2 cm has improved **local control**. This approach is supported by other reports in the literature.

Radical Radiotherapy

Treatment Regime
Radiotherapy will be given according to the EMBRACE II protocol. Full details can be found on the website https://www.embracestudy.dk/About.aspx

- ***This has been updated to reflect current practice***

Chemotherapy

Treatment Regime:
Concomitant chemotherapy will be given according to the EMBRACE II protocol with weekly cisplatin for 5-6 cycles

Palliative chemotherapy – first line is carboplatin, paclitaxel +/- bevacizumab, given three weekly for six cycles. Second line options for palliative chemotherapy may include topotecan / cisplatin, or referral for clinical trials

- ***This has been updated to reflect current practice***

Follow Up and Routine Surveillance of Patients with Cervical / Vaginal Cancer

There is no clinical evidence to support the frequency of follow-up in the guidelines below. The NCG will recommend all cancer units to join the FIGURE study

Long-term follow-up is recommended for this group of patients as they are at increased risk of developing carcinomas elsewhere in the pelvis and genital tract. Patients with local recurrence have a high chance of cure and / or prolonged remission if they are re-treated promptly. Patients with vaginal cancer should be followed up for the first year at the Cancer Centre and thereafter by the gynaecology cancer lead in the Cancer Unit. The follow-up schedule is therefore:

Year 1:	Three monthly
Year 2:	Six monthly
Year 3:	Six monthly
Years 4 and 5:	Yearly
After 5 years:	Patients will be discharged, but asked to return if they develop any symptoms.

- ***We have changed year 2 to six monthly***

Cytology: No need for cytology follow up after radical surgery or radiotherapy.
Patients who have had a trachelectomy may require cytology and / or colposcopy follow-up, as directed by their gynaecological oncologist.

- ***We have added that cervical cytology may be appropriate for patients who have had a trachelectomy***

Stage 1a1 completely excised by LLETZ/cone/hysterectomy – tests at 6 & 12 months, then 9 annuals, then 3-yearly routine. Stop at age 64 or after 10yrs, whichever is later.

Trial Patients:
Follow up intervals and investigations as indicated by protocol.

Management of Recurrent Disease
Surgery may be indicated in patients with recurrence confined to the central pelvic region and radiotherapy can be considered for patients who have not previously received this treatment modality.

Specialist Palliative Care

Common Symptom Control Problems in Carcinoma of the Cervix:
Common symptom control problems in carcinoma of the cervix include bleeding, discharge and pelvic pain.

-Bleeding – Only basic guidance will be given here. Symptom control advice from a specialist in Palliative Care is advised.

- For "large bleeds" the advice of the surgeon oncologist may be sought for local treatment.
- Tran examic acid 1g o qds may be useful in chronic small bleeds.
- Iron therapy will be useful.

-Vaginal Discharges – Discharges can be offensive. Infection needs to be sought actively and treated but other palliative measures may require specialist Palliative Care Unit advice.

-Pelvic Pain - Pelvic pain can be very difficult to treat and is only partially responsive to opioids. Triple therapy with an opioid, a non steroidal and an anti-convulsant/anti-depressant may be necessary, referral to a specialist in palliative care is advised.

-Dysparunia and sexual dysfunction - Referral to Psychosexual counselling would be recommended.

Familial Disease
There is no significant familial element in cervical cancer. There is currently no screening programme for patients with a family history.

Population Screening
Patients will be screened as per the quality assurance guidelines for the NHS Cervical Screening Programme.

http://www.cancerscreening.nhs.uk/cervical/publications/co-03.html

Clinical Trial Overview
Patients should be encouraged to enter clinical trials. This is an ongoing area of focus within the Anglia Cancer Network – there being a dedicated team and plan for improvement in place as part of the AngCN Gynae Network Site Specific Group.

Anglia Cancer Network Guidelines 2018

Gynaecological Cancers

Vulva Cancer

Anglia Cancer Network have agreed to follow published guidelines where available, with local modifications, which have been annotated in this summary document. Local modifications have been agreed by consensus meeting, following local hospitals review and feedback to the Network for comments. All hospitals were invited to be involved in face-to-face discussion of the guidelines at the September 2017 meeting.

Document contains:

1. A summary of recommendations from the published guidelines alongside the Network Modifications. Comments and modifications from Addenbrooke's Hospital are annotated in green font. Those from Norfolk and Norwich are annotated in red.

2. A full copy of the published guidelines (see below)

Vulva Cancer guidelines are based on both the following published guidelines:

- 2014 - BGCS / RCOG – Guidelines for the Diagnosis and Management of Vulval Carcinoma
- 2016 – ESGO – Vulvar Cancer Guidelines

Royal College of Obstetricians & Gynaecologists

2014 Summaryofconsensus statements

1. There is no evidence to support screening an unselected population for vulval cancer.

2. There is no evidence that the follow-up of women with uncomplicated lichen sclerosus needs to be hospital based.

3. Women with high-grade vulval intraepithelial neoplasia (VIN), high-grade VIN with multicentric disease, VIN in the immunosuppressed and those with Paget's disease or melanoma in situ should be followed up in either specialist multidisciplinary vulval clinics or by gynaecological oncologists. This is to provide the full range of surgical treatments, reconstructive surgery, nonsurgical alternatives and colposcopic follow-up. Guidance for the assessment and management of women with vulval disorders is detailed in RCOG Green-top Guideline No. 58.[4]

4. Women with Paget's disease of the vulva should have

   prolonged follow-up. Vulval cytology is not a substitute for

   diagnostic biopsy of suspicious lesions.

5. In women where a vulval cancer is strongly suspected on examination, urgent referral to a cancer centre should not await biopsy.

6. All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy and reviewed by the specialist multidisciplinary team prior to radical treatment.

7. Diagnostic biopsies of suspected vulval cancer should be representative incisional biopsies, avoiding removal of the whole lesion.

8. All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

9. Wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue is often sufficient.

10. Groin node surgery should be undertaken through separate incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is low.

11. In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.

12. In lateral tumours, only ipsilateral groin node surgery need initially be performed. Contralateral lymphadenectomy may be required if ipsilateral nodes are positive.

13. Superficial groin node dissection alone should not be performed, as it is associated with a higher risk of groin node recurrence.

14. Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

15. Preservation of the long saphenous vein may reduce both groin wound and subsequent lower limb problems.

16. Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who cannot be optimised to enable surgery can be treated with primary radiotherapy.

17. Plastic surgery involvement may be required for large defects and when radiotherapy has been used. The vulva is a challenging area for wound healing and faecal and urinary diversion is often required.

18. Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

19. Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.

20. Vulval melanomas need to be jointly managed with the appropriate melanoma MDT.

21. Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

22. Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients.

23. Future development of targeted therapy with drugs such as erlotinib through mutation testing may lead to improvement in vulval cancer

treatment toxicity benefit ratio and provide effective systemic treatment even for the more infirm patients.

ESGO Diagnosis and referral

24. In any patient suspected for vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may obstruct further treatment planning.

25. In patients with multiple vulvar lesions, all lesions should be biopsied separately (with clear documentation of mapping).

26. All patients with vulvar cancer should be referred to a Gynaecological oncology centre (GOC) and treated by a multidisciplinary gynaecological oncology team.

ESGO Staging system

27. Vulvar cancer should be staged according to FIGO and/or TNM classification[1].

ESGO Preoperative investigations

28. Preoperative work-up should at least include clear documentation of clinical exam (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (see below).

29. Evaluation of the cervix/vagina/anus is recommended.

30. Prior to sentinel lymph node biopsy, clinical examination and imaging of the groins (either by ultrasound, (positron emission tomography-)computed tomography ((PET-)CT), or magnetic resonance imaging (MRI)) are required to identify potential lymph node metastases.

Cross-sectional imaging is modality of choice.

31. Suspicious nodes (at palpation and/or imaging) should be analysed by fine-needle aspiration (FNA) or core biopsy when this would alter primary treatment.

32. Further staging with CT thorax/abdomen and pelvis is recommended where there is a clinical suspicion of, or proven (nodal) metastatic disease and/or advanced stage disease.

33. The pathology report on preoperative biopsy should at least include histological type and depth of invasion.

ESGO Surgical management

Local treatment

34. Radical local excision is recommended.

35. Consider additional, more superficial resection of differentiated vulvar intraepithelial neoplasia (d- VIN) in addition to radical local excision of invasive tumours.

36. In multifocal invasive disease radical excision of each lesion as a separate entity may be considered. Vulvectomy may be required in cases with multifocal invasion arising on a background of extensive vulvar dermatosis.

37. The goal of excision is to obtain tumour-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider less wide margins where the tumour lies close to midline structures (clitoris, urethra, anus) and preservation of their function is desired.

38. When invasive disease extends to the pathological excision margins of the primary tumour, reexcision is treatment of choice.

39. Advanced stage patients should be evaluated in a multidisciplinary setting to determine the optimal choice and order of treatment modalities.

Groin treatment

40. Groin treatment should be performed for tumours > pT1a.

41. For unifocal tumours, < 4 cm in diameter, without suspicious groin nodes on clinical examination and imaging (any modality) the sentinel lymph node procedure is recommended.

Tumours eligible for sentinel node biopsy includes all of the following criteria:

- Uni-focal tumours
- < 4cm in diameter

- No suspicious groin nodes on clinical examination & imaging, and pathology
- Tumour not encroaching the urethra, vagina, or anus
- Position of the tumour allows four sites of peri-lesional tracer injection.

42. For tumours ≥ 4 cm and/or in case of multifocal invasive disease inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumours (medial border > 1 cm from midline) ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease.

43. When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed.

44. Preservation of the saphenous vein is recommended.

45. The optimal management of the groin (full inguinofemoral lymphadenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined.

46. Where enlarged (> 2 cm) pelvic nodes are identified, their removal should be considered.

Reconstructive surgery

47. Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease.

ESGO Sentinel lymph node procedure

48. The sentinel lymph node procedure is recommended in patients with unifocal cancers of < 4 cm, without suspicious groin nodes (not enlarged or suspicious on imaging, or disease has been excluded by biopsy or fine needle aspiration).

Referring clinicians are encouraged not to perform excision biopsies or wide local excision where this can be avoided. Where an excision biopsy has been performed SLND may be considered where all of the following criteria are fulfilled:

- The size and location of the primary lesion has been adequately documented, preferably by photograph
- The scar can readily be identified and a representative injection on either side of the scar is possible

49. Use of radioactive tracer is mandatory, use of blue dye is optional.

50. Lymphoscintigram is advised to enable the preoperative identification, location and number of sentinel lymph nodes.

51. Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node can be performed in an attempt to prevent a second surgical procedure. Caution is warranted because of an increased risk of missing micrometastases on final pathology due to the loss of tissue arising from processing for frozen section assessment.

52. When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.

53. Where metastatic disease is identified in the sentinel lymph node (any size): inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph node.

54. For tumours involving the midline: bilateral sentinel lymph node detection is mandatory. Where only unilateral sentinel lymph node detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed.

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

ESGO Radiation therapy

56. Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment.

57. When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed.

58. In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised.

Cases with margins of ≤ 8mm identified at final histology should be considered for re-excision to ensure complete resection. When re-excision would compromise neighbouring anatomy or when the patient does not want re-excision, radiotherapy

is a reasonable alternative. Repeat excision is not suitable for those patients with metastases requiring chemotherapy and/or radiotherapy.

Where the margin is <8mm, and no further options for surgical excision, then the option of adjuvant radiotherapy should be discussed with the patient and treatment decision made on a case-by-case basis.

59. Postoperative radiotherapy to the groin is recommended for cases with > 1 metastatic lymph node and/or presence of extracapsular lymph node involvement.

60. Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are non-suspicious on imaging, the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery.

61. Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.

ESGO Chemoradiation

62. Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.

63. In advanced stage disease neoadjuvant chemoradiation, or chemotherapy alone, should be considered in order to avoid exenterative surgery. Surgery may be considered as an interval procedure after assessment of response to treatment.

64. Radiosensitising chemotherapy, preferably with weekly cisplatin, is recommended.

ESGO Systemic treatment

65. Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting.

In Cambridge the current preferred regime is carboplatin / paclitaxel. Carboplatin

alone may be an option in individual cases.

ESGO Treatment of recurrent disease

Treatment of vulvar recurrence

66. Radical local excision is recommended.

67. For vulvar recurrence with a depth of invasion > 1 mm and previous sentinel lymph node removal only, inguinofemoral lymphadenectomy should be performed.

68. The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease.

Factors that should be considered include disease-free interval, location of the tumour, and the potential for future surgery

Treatment of groin recurrence

69. Restaging by CT (or PET-CT) of the thorax/abdomen/pelvis is recommended.

70. Preferred treatment is radical excision when possible, followed by postoperative radiation in radiotherapy naïve patients.

71. Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of radiosensitising chemotherapy to postoperative radiotherapy should be considered.

72. Definitive chemoradiation when surgical treatment is not possible.

Treatment of distant metastases

73. Systemic (palliative) therapy may be considered in individual patients (see systemic treatment).

ESGO Follow-up

74. The optimal follow-up schedule for vulvar cancer is undetermined.

75. After primary surgical treatment the following follow-up schedule is suggested:

- First follow-up 6-8 weeks postoperative
- First two years every three-four months
- Third and fourth year biannually

- Afterward, long-term follow-up, especially in case of predisposing vulvar disease. Follow-up after surgical treatment should include clinical examination of vulva and groins.

76. After definitive (chemo)radiation the following follow-up schedule is suggested:

- First follow-up visit 10-12 weeks post completion of definitive (chemo)radiation.
- First two years every three-four months
- Third and fourth year biannually
- Afterward, long-term follow-up, especially in case of predisposing vulvar disease.

The first visit should include cross-sectional imaging to document complete response.

77. At first follow-up visit 10-12 weeks post definitive (chemo)radiation CT or PET-CT is recommended to document complete remission.

BRITISH GYNAECOLOGICAL CANCER SOCIETY

Royal College of Obstetricians & Gynaecologists

Guidelines for the Diagnosis and Management of Vulval Carcinoma

May 2014

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Development of the document

This report is an updated version of that published by the Royal College of Obstetricians and Gynaecologists in January 2006.

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Summary of consensus statements

C There is no evidence to support screening an unselected population for vulval cancer.

C There is no evidence that the follow-up of women with uncomplicated lichen sclerosus needs to be hospital based.

C Women with high-grade vulval intraepithelial neoplasia (VIN), high-grade VIN with multicentric disease, VIN in the immunosuppressed and those with Paget's disease or melanoma in situ should be followed up in either specialist multidisciplinary vulval clinics or by gynaecological oncologists. This is to provide the full range of surgical treatments, reconstructive surgery, nonsurgical alternatives and colposcopic follow-up. Guidance for the assessment and management of women with vulval disorders is detailed in RCOG Green-top Guideline No. 58.[4]

C Women with Paget's disease of the vulva should have prolonged follow-up.

C Vulval cytology is not a substitute for diagnostic biopsy of suspicious lesions.

C In women where a vulval cancer is strongly suspected on examination, urgent referral to a cancer centre should not await biopsy.

C All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy and reviewed by the specialist multidisciplinary team prior to radical treatment.

C Diagnostic biopsies of suspected vulval cancer should be representative incisional biopsies, avoiding removal of the whole lesion.

C All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

B Wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue is often sufficient.

B Groin node surgery should be undertaken through separate incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is low.

B In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.

B In lateral tumours, only ipsilateral groin node surgery need initially be performed. Contralateral lymphadenectomy may be required if ipsilateral nodes are positive.

B Superficial groin node dissection alone should not be performed, as it is associated with a higher risk of groin node recurrence.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

C Preservation of the long saphenous vein may reduce both groin wound and subsequent lower limb problems.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who cannot be optimised to enable surgery can be treated with primary radiotherapy.

C Plastic surgery involvement may be required for large defects and when radiotherapy has been used. The vulva is a challenging area for wound healing and faecal and urinary diversion is often required.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

B Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.

C Vulval melanomas need to be jointly managed with the appropriate melanoma MDT.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

C Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients.

C Future development of targeted therapy with drugs such as erlotinib through mutation testing may lead to improvement in vulval cancer treatment toxicity benefit ratio and provide effective systemic treatment even for the more infirm patients.

1. Background

Vulval cancer is rare. In the year 2010, there were 1172 new cases in the UK, giving a crude incidence rate of 3.7/100 000 women. It is ranked as the 20th most common female cancer.[1] The most recent mortality figures (2011) suggest a crude mortality rate of 1.3/100 000 women.[2] By age group, the incidence trend has remained relatively stable over the last three decades, although the incidence in women aged 40–49 years has risen two-fold. This increase has been reflected in reports from other countries and has been ascribed to the effect of increasing human papillomavirus (HPV) infection.[1]

This document covers all invasive vulval cancers of any histological type.

Vulval cancer is a disease affecting predominantly elderly women and is uncommon below the age of 50 years. Comorbidities also increase with age which may prove challenging when planning management.

As there will be occasions when clinical history and examination alone cannot exclude cancer or preinvasive disease, this document addresses issues of referral for investigation and confirmation, diagnostic procedures and management. The questions of follow-up and outcome assessment are also addressed.

1.1 Objectives

This document is intended to fulfil several objectives:

- To promote a uniformly high standard of care for women with vulval cancer
- To define standard approaches to treatment
- To encourage gynaecological oncologists to develop and participate in clinical trials involving new approaches to management
- To establish auditable standards.

1.2 Methodology

The authors have developed this consensus document, with input from British Gynaecological Cancer Society members. The authors have also drawn on the experience of previously published guideline materials and other relevant published texts. The document sets out achievable clinical standards and targets for all health professionals involved in the management of patients with vulval malignancy.

Classification of evidence

To ensure that the statements made in this document are evidence based, the current literature was reviewed and critically appraised. The reliability and quality of the evidence given throughout this document has been graded following the NHS Executive classification system, as follows:

Grade A: Based on randomised controlled trials (RCTs).

Grade B: Based on other robust experimental or good observational studies.

Grade C: More limited evidence but the advice relies on expert opinion and has endorsement of respected authorities.

1.3 Definitions of excision

Incisional biopsy

A biopsy taken with the intent of securing a diagnosis only. This should ideally contain the interface between normal and abnormal epithelium and be large enough for the pathologist to be able to adequately provide evidence of substage (in stage I cases).

Excisional biopsy

A biopsy taken that includes all of the abnormal epithelium but does not provide a tumour-free zone of 1 cm (after fixation) on all dimensions. This would normally be performed in cases of vulval intraepithelial neoplasia (VIN) or when there is a low suspicion of invasive carcinoma and the operator wishes to limit the amount of cosmetic harm.

Radical excision

An excision performed with the intent of achieving clearance of at least 1 cm (after fixation) on all aspect of the tumour(s). Depending on the site and size of the tumour, this could vary from a radical local excision to a radical vulvectomy.

2. Screening, diagnosis and presentation

2.1 Screening

Unselected population

There are no screening tests that have been shown to be of benefit in an unselected population. Self-examination is recommended by organisations such as the Vulval Pain Society, although there is no published evidence on whether this is beneficial or not. Given a common aetiological factor in many cases of vulval cancer is oncogenic HPV infection, some women with vulval cancer may benefit from a shorter cervical screening interval, but there is currently no evidence to support this.

C There is no evidence to support screening an unselected population for vulval cancer.

Women with conditions that predispose to vulval cancer

Lichen sclerosus and infection with high-risk types of HPV are both conditions in which squamous neoplastic change can be seen. There may be an intraepithelial stage seen first (vulval intraepithelial neoplasia, VIN) with either condition. This is known as differentiated VIN when it is associated with lichen sclerosus (d-VIN) and usual, classical or undifferentiated when it is HPV associated. It has been suggested that there is a higher risk of invasion in d-VIN,[3] but the diagnosis is often only made in association with a squamous cancer.[4,5] Typically HPV-related disease is seen in younger women and may be multifocal. Either disease may also be present in the perianal region.

The risk of developing invasive disease in women with lichen sclerosus is approximately 4%. It is not clear whether this risk is reduced by treatment. Women with uncomplicated lichen sclerosus do not require routine hospital-based follow-up, but should be informed of the risks of invasion. Those who have or have had VIN associated with lichen sclerosus should be followed up in the same manner as those with VIN.

C There is no evidence that the follow-up of women with uncomplicated lichen sclerosus needs to be hospital based.

In women with VIN (either lichen sclerosus related or HPV related), colposcopy is useful for localisation but the signs are nonspecific. Diagnosis is by biopsy. Multiple biopsies may be required to exclude invasion. Standard treatment is wide local excision. Medical treatment may be appropriate and consideration should be given to enrolment in an appropriate trial. The risk of recurrence following treatment is high and the risk of invasion approximately 4%. Follow-up should be either in specialist vulval clinics or by gynaecological oncologists.

C Women with high-grade vulval intraepithelial neoplasia (VIN), high-grade VIN with multicentric disease, VIN in the immunosuppressed and those with Paget's disease or melanoma in situ should be followed up in either specialist multidisciplinary vulval clinics or by gynaecological oncologists. This is to provide the full range of surgical treatments, reconstructive surgery, nonsurgical alternatives and colposcopic follow-up. Guidance for the assessment and management of women with vulval disorders is detailed in RCOG Green-top Guideline No. 58.[4]

Other pre-invasive conditions include Paget's disease (adenocarcinoma in situ) and melanoma in situ. These conditions are rare, but have a significant risk of invasion. As there is no large body of evidence on which to base practice, it may be best for them to be followed up in a clinic with a special interest in premalignant vulval disease. Prolonged follow-up for Paget's disease is suggested.[6,7]

C Women with Paget's disease of the vulva should have prolonged follow-up.

HPV testing is not a proven screening tool for vulval cancer and does not aid diagnosis, although it may be used as a research tool. Other aids to diagnosis have been described in women with pre-existing vulval disease, including toluidine blue and exfoliative cytology using scalpel scrapings or Dacron swabs. Results of studies are variable and none of these techniques is a replacement for biopsy of clinically suspicious lesions.[8–11]

C Vulval cytology is not a substitute for diagnostic biopsy of suspicious lesions.

2.2 Presentation

Vulval cancer is most common among women over 65 years old, but may present in women considerably younger. Presentation is often delayed.

Presentation will vary according to stage of disease. Women often have difficulty articulating vulval symptoms to medical practitioners and all women with vulval symptoms should be examined. Presentation usually comes in one of the following categories:

Incidental

Vulval cancers are sometimes diagnosed on examination during another procedure, for example colposcopy or catheterisation. Often these are not asymptomatic, but the women have either not presented for diagnosis, or not been appropriately referred.

During follow-up for pre-existing vulval disease

For example, lichen sclerosus or VIN; see section on screening.

Symptomatic

Symptoms of vulval cancer include vulval itching, irritation or pain. Women may also notice a lump, bleeding or discharge.

2.3 National Institute for Health and Care Excellence (NICE) guidance

The National Institute for Health and Care Excellence (NICE) guidance on referral for suspected vulval cancer (Clinical guideline 27; June 2005)[12] recommends the following:

- When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made (within the 2 week wait schedule).
- Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently (within the 2 week wait schedule).
- Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms and where cancer is not immediately suspected, it is reasonable to use a period of 'treat, watch and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer.

2.4 Diagnosis

The cornerstone of diagnosis is examination and diagnostic biopsy.

While the need to take a full history is self-evident, specific questioning will also be required. Women often self-medicate with over-the-counter topical preparations that can exacerbate the symptoms of vulval cancer. Advice regarding care of the vulva and omitting these medications forms an important part of management.

Clinical features strongly indicating vulval cancer include an irregular, fungating mass, an irregular ulcer or enlarged groin nodes. Such patients should be referred urgently to a cancer centre without awaiting biopsy.

C In women where a vulval cancer is strongly suspected on examination, urgent referral to a cancer centre should not await biopsy.

Any change in the vulval epithelium in a postmenopausal woman warrants a biopsy.

These changes include: a swelling, polyp or lump, an ulcer, colour change (whitening or pigment deposition), elevation or irregularity of the surface contour. Any 'warts' in a postmenopausal woman or persistent 'warts' in the premenopausal woman should be biopsied. In premenopausal women all other vulval signs and symptoms should be managed as for those in postmenopausal woman unless there is a confirmed infection. Lesions should be biopsied rather than excised, as excision may preclude the use of sentinel node biopsy. If cancer is confirmed, the patient should be referred to a gynaecological cancer centre.

2.5 Biopsies

All diagnoses should be based upon a representative biopsy of the tumour that should include the area of epithelium where there is a transition of normal to abnormal tissue. Diagnostic biopsies should be of a sufficient size (greater than 1 mm depth to allow differentiation between superficially invasive and frankly invasive tumours) and orientated to allow quality pathological interpretation. Biopsies should be referred to a pathologist with a specialist interest in gynaecological pathology

(see section 3: Pathology).

There may be exceptions to these rules. If, for instance, an elderly woman with major medical problems and a severely symptomatic lesion presented, a small punch biopsy under local anaesthetic could provide adequate diagnostic information to allow planning of definitive therapy. In certain situations where the clinical diagnosis is apparent and the patient very symptomatic, i.e. heavy bleeding or pain, definitive surgery to the vulval lesion may be performed but biopsy with frozen section is recommended prior to proceeding with any radical procedure.

Although not essential, pre-biopsy photographs are of value in planning treatment, particularly if the diagnostic phase and treatment phases are conducted in separate centres.

When evaluating a vulval lesion, the size and location should be documented. The appearance of the background epithelium should be noted, particularly the presence of changes suggestive of lichen sclerosus, as this will affect postoperative treatment. Residual lichen sclerosus appears to have a significant risk of recurrence for vulval cancer.[13] Any involvement of the vagina, urethra, base of the bladder or anus should be noted. With large tumours, the tumour should be palpated to assess whether it is infiltrating deep to the pubic and ischial bones. The examination may have to be performed under general anaesthesia because of the pain often associated with large tumours. The presence or absence of groin lymphadenopathy should also be noted. Radical treatment of vulval cancer is associated with significant morbidity and therefore biopsy confirmation should be obtained beforehand.

C All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy and reviewed by the specialist multidisciplinary team prior to radical treatment.

C Diagnostic biopsies of suspected vulval cancer should be representative incisional biopsies, avoiding removal of the whole lesion.

3. Pathology

3.1 Microscopic

Ninety percent of all vulval cancers are squamous cell carcinomas, with melanoma, Paget's disease, Bartholin gland tumours, adenocarcinoma and basal cell carcinoma accounting for most of the remaining tumours. The histology is important, as it represents a variable in determining the likelihood of lymph node involvement.

The presence of infiltrative growth patterns, compared with a pushing pattern, is associated with a higher local recurrence rate. Presence of prominent fibromyxoid stroma at the invasive edge is associated with poorer outcome.[14] Lymphovascular space involvement (LVSI) is also associated with an increased local recurrence rate.[15] LVSI has not been associated with an increased risk of groin node metastasis. Both LVSI and infiltrative growth patterns are markers of poor prognosis but these factors do not indicate the need for adjuvant treatment.

Further research is required to establish the influence of these factors on the outcome of this disease.

3.2 Spread

Vulval cancer spreads by direct extension to adjacent structures, embolisation to the inguinal and femoral nodes (the regional lymph nodes) or by haematogenous spread. Overall, about 30% of women with operable disease have nodal spread.

3.3 Staging

Vulval cancer has been staged surgicopathologically using the International Federation of Gynecology and Obstetrics (FIGO) staging system since 1994 and has had various modifications, including a subdivision for stage I in 1994. The FIGO staging has been revised in 2009[16] and there have been four main changes:

- Stage II (> 2 cm) and Ib (< 2 cm) have been combined because these two categories of patients did not appear to differ in survival
- Patients with tumours involving the vagina and/or urethra with negative nodes are now classified as stage II (formerly stage III)
- Patients with positive nodes are still classified as stage III. The number and morphology (size and whether these have intra- or extranodal growth) of the involved nodes are taken into account.
- Bilaterality of positive nodes has been discounted.

The current FIGO staging is presented in Appendix 1.

3.4 Prognosis

The 5-year survival in cases with no lymph node involvement is in excess of 80%. This falls to less than 50% if the inguinal nodes are involved and 10–15% if the iliac or other pelvic nodes are involved. A multifactorial analysis of risk factors in squamous vulval cancer demonstrated that nodal status and primary lesion diameter, when considered together, were the only variables associated with prognosis.[17]

3.5 Histology

All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

3.6 Clinical information

The clinician should provide an accurate description of the site and appearance of the gross lesion. The request should also indicate whether the biopsy was excisional or diagnostic. Ideally, large radical resections should be pinned out on corkboard, kept moist with normal saline and sent as fresh tissue to the pathology department as rapidly as possible. If this is not possible, the specimen should be carefully orientated by means of marker sutures prior to fixation in the usual way.

3.6.1 Reporting the specimens

Squamous cell carcinoma:

This is the most common malignancy of the vulva. The report should describe:

- Vulval intraepithelial neoplasia
  - Classical type grade I, II and III
  - VIN differentiated type.

Assessment of invasion:

- Tumour type according to World Health Organization (WHO) classification
- Tumour differentiation
- Depth or thickness of invasion
- Presence or absence of vascular invasion
- Presence or absence of non-neoplastic epithelial disease.

In case of excision specimens:

- Assessment of margins
- Distance to epithelial resection margin
- Distance to urethral resection margin (if appropriate)
- Distance to vaginal resection margin (if appropriate)
- Distance to anal resection margin (if appropriate)
- Distance to soft tissue (deep) resection margin.

In cases with lymph node dissection, each lymph node must be examined histologically. Resected lymph nodes not involved macroscopically must be examined in their entirety with nodes larger than 5 mm blocked out at 2–3 mm. Nodes smaller than 5 mm are embedded whole. Levels are recommended in all sentinel node samples and in groin lymphadenectomy, if there are suspicious

groups of cells. The report must record total numbers of sampled lymph nodes, presence or absence of lymph node metastases, presence of extranodal spread and whether > 50% of any one node is involved. In the case of examining sentinel lymph nodes, the GROINSS-V II protocol should be followed until such a time as the procedure is endorsed by NICE.

The report must record the following core data items:
- Tumour type according to the WHO classification
- Tumour differentiation
- Tumour size (in at least two dimensions)
- Thickness/depth of invasion
- Presence or absence of lymphovascular invasion
- Status of all resection margins
- Minimum tumour-free margins
- Presence of associated VIN or Paget's disease
- Status of resection margins for VIN or Paget's disease
- Minimum distance to margins for VIN or Paget's disease
- Presence or absence of non-neoplastic epithelial disease
- Presence or absence of lymph nodes metastases
- Presence of extranodal spread
- Whether > 50% of any one node is involved.

3.7 Ancillary studies

3.7.1 Frozen sections

There is little use of frozen sections in surgical treatment of vulval malignancy.

3.7.2 Immunohistochemistry

It has a limited role in diagnosis of squamous cell carcinomas. Immunohistochemistry for broad-spectrum cytokeratins such as AE1/AE3 can be used to reveal micrometastases in sentinel nodes. Presently it is used routinely in research but awaits further evidence before use in routine practice.

Immunohistochemistry is valuable in differential diagnosis of Paget's disease. The neoplastic cells in primary vulval Paget's disease are positive for CAM 5.2, CEA, EMA and CK7. Diffuse CK20 positivity is suggestive of secondary vulval Paget's disease. This results from spread of an internal malignancy, most commonly from an anorectal adenocarcinoma or urothelial carcinoma of the bladder or urethra, to the vulval epithelium. Paget's disease may mimic melanoma on routine stains and immunohistochemistry for melan A, S100 and HMB45 may be used to confirm a melanoma.

Immunohistochemistry can be useful in differential diagnosis of vulval soft tissue lesions.

C All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

4. Treatment of primary disease

The treatment of vulval cancer is primarily by surgery. This has become more individualised and conservative although the need for adequate resection margins (1 cm after tissue fixation) and groin node dissection or evaluation remain important basic principles. The impetus for more conservative approaches stems from the well recognised psychosexual sequelae and from the morbidity associated with groin node dissection.[19,20] Reconstructive surgery has a role in the management of these cancers. Radiotherapy is used in the adjuvant setting and with or without chemotherapy and surgery in advanced disease.

Management may vary considerably from quite simple to very complex. Each case should be considered on its merits and an agreed plan of management devised by the gynaecological cancer team. Factors such as tumour size, location, medical fitness and the wishes of the patient will all influence management. The management of the nodes and the primary tumour should be considered on their own merits. Tumours should be staged using the most recent FIGO or TNM (tumour, nodes and metastases) classifications. FIGO staging is surgical–pathological and not clinical (Appendix 1).

It should be emphasised that these patients are often elderly and have significant comorbidities. As such, they require access to skilled anaesthesia services including an epidural service, high dependency and/or critical care. A key component of patient management is skilled nursing care. All of these services should be available in a cancer centre.

The major developments since the publication of RCOG guidance in 2006 have been the development of targeting groin lymph node biopsies (sentinel lymph node biopsies, SLNB) and a gradual increase in the number of women having some form of reconstructive or plastic surgery input. The latter is covered in an additional section on plastics and reconstruction. The indications for and use of SLNB is now included in this section.

4.1 Surgery

4.1.1 Early-stage disease

Depth of invasion

Lesions less than 2 cm in diameter and confined to the vulva or perineum, with stromal invasion less than or equal to 1.0 mm (FIGO stage Ia) can be managed by wide local excision only, without groin node dissection. This is because the risk of lymph node metastases is negligible.[21]

Dissection of the groin nodes (unilateral or bilateral) should be performed when the depth of invasion is greater than 1 mm (FIGO stage Ib or worse) or the maximum diameter of the tumour is greater than 2 cm.[22] This surgery can often be undertaken through separate groin and vulval incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is very low.[23]

Published evidence suggests that unifocal tumours of less than 4 cm maximum dimension might safely be managed by excision of the sentinel lymph nodes identified in either groin.[24] Appropriate use of the sentinel node technique is covered in the following section on groin node dissection.

Surgery to the primary tumour should be radical enough to remove the tumour with adequate margins. The incidence of vulval recurrence has been shown to be related to the measured disease-free surgical margin, as measured in the fixed histopathological specimen. Given the reduction and contraction of tissues following excision and fixation, this equates to at least a 15 mm margin on the fresh surgical specimen. The risk of recurrence increases as the disease-free margins decrease (> 8.0 mm: 0%; < 8.0 mm, 47%).[15,23] Therefore, wide radical local excision with a minimum margin of 15 mm of disease-free tissue on all margins should be sufficient.

Excision of atypical skin (lichen sclerosus or VIN) affecting the remainder of the vulva should be considered, as these areas might contain separate foci of invasion and pose an increased risk of recurrence.[13] Removal of any lichen sclerosus or VIN (usual type and differentiated VIN) need not be to the same depth as that for invasive disease unless occult invasion is suspected.

A preoperative vulvoscopy and mapping biopsies may help in the planning of surgery.

When the surgical margins are found to be less than 1 cm, it may be appropriate to perform a further local resection, although evidence is lacking that this will result in a reduction in local recurrence. There is insufficient evidence to recommend adjuvant local therapy routinely in patients with close surgical margins.

B Wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue is often sufficient.

B Groin node surgery should be undertaken through separate incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is low.

B In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.

Lateral vulval tumours

Extensive cross-over of lymphatic channels of the vulva may result in nodal involvement of the contralateral groins in addition to the ipsilateral groin nodes. Therefore, bilateral groin node dissection is usually required. A lateralised lesion is defined as one in which wide excision, at least 1 cm beyond the visible tumour edge, would not impinge upon a midline structure (clitoris, urethra, vagina, perineal body, anus). Lymphatic cross-over is less likely in lateral tumours; therefore, only an ipsilateral groin node dissection need initially be performed.[25] If the ipsilateral nodes are subsequently shown to be positive for cancer, the contralateral nodes should also be excised or irradiated, as the nodes are more likely to be positive in this scenario.

A similar concept applies to the use of sentinel lymph nodes. If a sentinel lymph node can only be identified in the ipsilateral groin then the contralateral dissection can be omitted. If the SLNB is negative then no further surgery is necessary. If the SLNB is positive then consideration should be given to completion lymphadenectomy of both groins.

B In lateral tumours, only ipsilateral groin node surgery need initially be performed. Contralateral lymphadenectomy may be required if ipsilateral nodes are positive.

4.1.2 Groin node dissection

The greatest single factor in reducing mortality from vulval cancer is appropriate groin node dissection. However, groin node dissection should be omitted if the patient has stage Ia disease, as the incidence of lymph node metastases is negligible.[21] When a complete lymphadenectomy is indicated, it is recommended that the superficial inguinal nodes, as well as the deep femoral nodes, be removed. Superficial inguinal node dissection alone is associated with a higher risk of groin node recurrence.[22] Preservation of the long saphenous vein is reported to reduce both groin wound and subsequent lower limb problems,[26] although there are data that have not confirmed this and all studies have been observational and uncontrolled. Following inguinofemoral lymphadenectomy, sartorius muscle transposition may be of benefit in preventing subsequent femoral vessel damage, particularly in those women who are thin and in those in whom adjuvant groin radiation therapy is anticipated.[27] There is some suggestion that the number of groin nodes resected per groin is of relevance to groin relapse and this may have implications for surveillance.[28] However, the number of glands in the groin is very variable with fewer being harvested in elderly patients. Furthermore, there are no robust data on the accuracy of surveillance post surgery either clinically or with cross-sectional imaging.

B Superficial groin node dissection alone should not be performed, as it is associated with a higher risk of groin node recurrence.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

C Preservation of the long saphenous vein may reduce both groin wound and subsequent lower limb problems.

4.1.3 Sentinel lymph node biopsy (SLNB)

Dye studies and lymphoscintigraphy may be of value in the detection of sentinel nodes.[29–31] There is a growing body of evidence demonstrating the safety and practicality of this intervention with significant improvements in postoperative morbidity without any significant compromise in accuracy or outcomes in terms of relapse.

As with all new techniques, their introduction should be undertaken with due regard to patient safety and should be audited closely. Ideally, all patients having SLNB should be enrolled in ongoing clinical studies such as GROINSS-V II. All surgeons undertaking these procedures should do so after appropriate training and demonstration of competency. The environments should be fully compliant with radiation protection protocols. Maintenance of skills and the requirement for robust audit would also suggest that such procedures should be limited to centres that have an adequate volume of work.

Eligibility for sentinel lymph node biopsy

The following eligibility criteria are the result of a series of studies culminating in the GROINSS-V I study that identified scenarios where the accuracy of SLNB was either uncertain or unproven. This has resulted in the following eligibility criteria:

- Primary squamous vulval cancers
- Cancers measuring less than 4 cm in maximum dimension
- Macroscopic unifocal cancers
- No clinical or radiological evidence to suspect lymph node metastasis
- No known safety issues for the use of Patent Blue dye and/or technetium-99

- Informed patient consent and acceptance of close follow-up (recommended 2-monthly in the first year).

If a sentinel lymph node cannot be identified following peritumoural injection of technetium-99 and/or Patent Blue dye then the patient should be considered for a complete inguinofemoral lymphadenectomy and should be counselled to this end at the time of consenting.

4.1.4 Advanced vulval cancer

Surgery to the primary lesion

Resection of advanced disease involves careful preoperative planning and, if reconstruction is required, this should be planned jointly with a plastic surgeon. Ideally a joint examination under anaesthesia (EUA) should be performed with the plastic surgeon. The size and location of the tumour will influence the surgical approach. Wide, radical, local excision with a minimum of 15 mm disease-free margin may be used but some tumours will require a radical vulvectomy. If these surgical approaches risk sphincter damage leading to urinary or faecal incontinence, treatment by radiotherapy should be considered, either with curative intent or to reduce tumour volume to permit less destructive surgery. Two studies have suggested that preoperative radiation in advanced vulval cancer reduced the need to perform defunctioning stomas.[32,33] It should be noted that, in this post-radiation setting, surgery can be more complicated and there is increased morbidity. All management options with their risks and benefits should be discussed with each patient.

Reconstructive surgical techniques should be employed to enable primary surgical closure and to reduce morbidity due to scarring. It should be stressed that the published experience of post-radiation surgery is limited and should not be undertaken lightly. Anovulvectomy might still be considered as an option in selected cases. This is an area where further research is vital. Consideration should be given in some cases to performing a diverting stoma 1–2 weeks before the definitive vulval surgery.

Management of clinically suspicious groin nodes

Groin node dissection should be undertaken when there are clinically suspicious groin nodes present. In cases with large primary lesions and clinically suspicious nodes, a radical vulvectomy with 'en bloc' groin node dissection should be considered.[21] In cases with fixed or ulcerated groin nodes, surgery and/or radiotherapy should be considered. There are no data suggesting the superiority of one treatment over the other, although, if surgery is used, it is likely that postoperative radiation will also be required. Pathological assessment of these nodes should be undertaken prior to radiotherapy, preferably by fine-needle aspiration cytology, in order to maximise the chances of maintaining skin integrity and minimising the risk of wound problems.

Multimodality treatment is increasingly used in the management of advanced vulval cancer to allow for sphincter preserving surgery and as an alternative to surgery for histologically proven involved groin lymph nodes. Surgery following groin radiation may, however, be associated with increased morbidity, both in the groin and in the lower limb. Overall, surgery should still be considered the cornerstone of therapy for the groin nodes.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who cannot be optimised to enable surgery can be treated with primary radiotherapy.

4.2 Reconstructive surgery

Reconstructive surgery should be considered for patients where a major resection is planned and there is doubt as to whether direct closure of the wound will be possible. Care should also be taken in patients with recurrent disease who have previously been treated with radiotherapy as the tissues will be less compliant and more prone to wound breakdown. Involvement of a plastic surgeon in these cases is advised.

Vulval reconstruction presents a challenge for several reasons.

- The vulva and surrounding structures present a complex three-dimensional shape which can be difficult to recreate. Flaps can be bulky and skin grafts are prone to graft loss due to shearing forces, contamination and bowstringing.
- The vulva is situated adjacent to the groin creases and subject to constant movement when walking which contributes to the shear stresses associated with poor wound healing.
- The proximity of urine and faeces makes wound contamination inevitable and faecal and urinary diversion should be considered.
- Patients have frequently had previous radiotherapy and surgery leading to scarring and poor wound healing.
- The vulva is a dependant area that is prone to swelling and difficult to dress.
- Patients are often elderly and may be immunosuppressed due to comorbidities or medications.

4.2.1 Reconstructive surgical options

Secondary intention

If tension-free direct wound closure is not possible, smaller defects can be left to heal by secondary intention. This relies on the cooperation of the patient and the nursing staff to undertake regular dressing changes but can result in acceptable outcomes.

Split skin grafts

Skin grafts are usually taken from the buttock or thigh and rely on a healthy blood supply from the wound bed to ‘take’ and so are less reliable following radiotherapy or in a heavily scarred area. They do not provide any bulk and are often tight and unforgiving, which can be uncomfortable and can limit walking and sexual function.

Skin grafts are usually reserved for large areas when there are no flap options to provide adequate soft tissue cover.

Flap coverage

Flaps provide healthy vascularised tissue and do not rely on adequate perfusion from the wound bed to ‘take’ in the same way that skin grafts do. For this reason they are particularly useful in poorly vascularised areas such as in patients who have had radiotherapy to the vulva. Flaps are also thicker than split skin grafts and so give bulk that can be useful if radiotherapy is planned to the area, although they may be cumbersome and lead to discomfort.

Local flaps are taken from areas adjacent to the vulva, such as rhomboid flaps, lotus petal flaps or pudendal thigh flaps. They require less dissection to raise, but are smaller than distant flaps and there is a possibility that the blood supply to a local flap may have been compromised if there has been previous surgery to the region.

Distant flaps, such as the gracilis and rectus abdominis muscle flaps, provide a larger, more bulky reconstruction with a more predictable blood supply. However, the surgery is more complex with increased potential donor site morbidity.

C Plastic surgery involvement may be required for large defects and when radiotherapy has been used. The vulva is a challenging area for wound healing and faecal and urinary diversion is often required.

4.3 Surgical management of nonsquamous vulval cancer

Carcinoma of the Bartholin gland

This is a rare vulval cancer. Histologically, it is usually a squamous carcinoma or adenocarcinoma. The current evidence base is insufficient to suggest different management from squamous tumours. The lesions are often deep-seated or likely to be associated with metastatic disease. The close proximity to the anal sphincter may necessitate partial resection with reconstruction and this may necessitate a defunctioning temporary colostomy.[34,35] Any perimenopausal or postmenopausal woman with a persisting Bartholin abscess or cyst should be suspected of having a possible carcinoma. Appropriate biopsies and histological review should be undertaken. In general these cancers have a poorer prognosis than squamous cell carcinoma of the vulva and often multiple treatment modalities are required.

There are no data regarding the use of selective lymphadenectomy in Bartholin gland carcinoma. These patients will require bilateral inguinofemoral lymphadenectomy (because of the proximity of the gland to the midline).

Basal cell carcinoma and verrucous carcinoma

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

Malignant melanoma

This group of tumours has not been shown to benefit from block dissection of the groin. Wide local excision is preferred. Relapse in this subgroup is high and closely correlates with the depth of invasion. On the vulva (which includes mucosal surfaces) Breslow's classification[36] is more appropriate than Clark's levels. As yet, there are no new strategies to minimise the risk of relapse in malignant melanomas.[37]

Recent evidence suggests there is an increased frequency of *KIT* mutations in vulval melanomas.[38] This may offer the possibility of entry into phase II clinical trials. All vulval melanomas should be discussed at the gynaecology specialist multidisciplinary team (MDT) and the specialist melanoma MDT. Centres should have effective and rapid channels of communication to facilitate inter-MDT discussion on the management of this rare subgroup of patients.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

B Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.

C Vulval melanomas need to be jointly managed with the appropriate melanoma MDT.

4.4 Morbidity related to surgery

The primary objectives of less radical surgery are to reduce morbidity while maintaining high cure rates for early vulval cancers. The complications associated with vulval and inguinal surgery are:

- wound breakdown
- wound infection
- deep vein thrombosis and pulmonary embolism
- pressure sores
- introital stenosis
- urinary incontinence
- rectocele
- faecal incontinence
- inguinal lymphocyst
- lymphoedema
- hernia
- psychosexual complications.

The risk factors for short- and long-term complications following surgery for vulval cancer have been described in a multivariate analysis on a cohort of 164 patients. Older age, diabetes, 'en bloc' surgery and greater drain production on the last day of drain placement were associated with a higher risk of short-term complications, while younger age and lymphocele were risk factors for long-term complications. However, the dissection of a greater number of lymph nodes was found to be protective against long-term complications.[39]

5. Radiotherapy

Clinical oncologists supervising treatment should have specific expertise in the management of gynaecological malignancies. They should manage integrated treatment plans involving radiotherapy with or without concurrent chemotherapy[40] (see section 6).

The factors influencing the need for adjuvant radiotherapy are surgical margins and groin node positivity. There is not enough evidence to recommend adjuvant local therapy routinely in patients with close surgical margins. Adjuvant treatment for positive margins has an improved survival compared with observation alone.[40]

Adjuvant radiotherapy should be considered when either groin has two or more lymph nodes involved with microscopic metastatic disease or there is complete replacement and/or extracapsular spread in any node.[41–44] There is no evidence to show whether adjuvant radiotherapy should be given to both sides or to the involved side only. Treatment should be to the groins and the pelvic nodes.

5.1 Primary treatment

Radiotherapy, with or without chemotherapy, is increasingly used in the management of advanced vulval cancer. Preoperative radiotherapy may allow for sphincter-preserving surgery. Radiotherapy may also be of use in place of surgery for histologically proven involved groin lymph nodes. It is unknown whether post-radiation groin node removal is advantageous in terms of outcome.

The scheduling of combined surgical and radiotherapeutic approaches needs to be individualised. While performing radiotherapy as the primary approach may result in the ability to avoid permanent functional damage,[44,45] surgery and subsequent healing may be compromised by the prior use of radiation. Furthermore, a temporary bowel diversion may be required for patients to be able to tolerate and complete a course of radiation therapy.

Treatment schedules

The majority of schedules are based upon those developed by the Toronto Group.[44] Fraction size is important, with 1.7 Gy being close to tolerance, although it is recognised that some centres may use slightly larger fractions (1.8 Gy). Doses will have to be reduced for radical treatment if fractions greater than 1.7 Gy are employed.

Radical treatment will usually require a prophylactic dose (45–50 Gy) to be delivered to the primary and nodal sites and the tumour is then boosted by a second phase of treatment by electrons, conformal radiotherapy or brachytherapy, to a total dose of 65 Gy. The total prescribed dose is determined by the clinical context.

A Cochrane review has suggested that there is no evidence that prophylactic groin irradiation should be used in preference to surgery.[45]

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

6. Chemotherapy

Overview of chemotherapy for vulval cancer

Squamous cell carcinomas may arise in many primary sites and, in the majority of cases, those of the anogenital region share a common relationship to HPV infection. Squamous cancers of the vulva are uncommon and often occur in elderly unfit women; therefore there are few trials on which to base recommendations for chemotherapy treatment and most of what follows is drawn from observational studies of small series of patients.

Chemotherapy has been used neoadjuvantly to reduce the extent of surgery, and in the adjuvant setting, postoperatively, alone or concomitantly with radiation in node positive disease. Chemotherapy has also been used in recurrent and metastatic disease. Each of these treatment settings will be reviewed in turn.

6.1 Neoadjuvant chemotherapy for invasive squamous cell carcinoma

There are three small phase II trials and a number of case reports on the potential role of primary chemotherapy in patients with locally advanced vulval cancer deemed difficult to operate and requiring extensive surgery (Durrant et al.,[46] Benedetti-Panici et al.,[47] Geisler et al.,[48] Domingues et al.,[49] Tans et al.[50] and Narimatsu et al.[51]) All of the studies suggest that vulval cancer responds to chemotherapy to a variable extent and there is evidence that some cancers can be rendered more operable. Recurrence remains a problem, even after successful surgical removal of residual disease.

6.2 Adjuvant chemotherapy for vulval cancer

While radiotherapy has been the more usual adjuvant treatment and may benefit those at high risk of relapse,[52] only one feasibility study has focused on chemotherapy in this setting. Bellati et al.[53] looked at acute and long-term morbidity, recurrence rate and overall survival in 14 patients with multiple groin lymph node metastases, treated with postoperative cisplatin chemotherapy and no radiotherapy. All patients completed the treatment. At the time of reporting, 12 of the 14 women were still alive with a median follow-up of 57.5 months, a 3-year overall survival of 86% and a progression-free survival of 71%. They concluded that radical surgery followed by chemotherapy, in patients with multiple lymph node metastases, is a feasible strategy.

Ideally further studies, however, are necessary to compare adjuvant chemotherapy to radiotherapy, chemoradiation and best supportive care in patients affected by high-risk disease.

6.3 Chemotherapy for metastatic and recurrent vulval cancer

There are four small studies of chemotherapy for patients with advanced, recurrent or metastatic vulval carcinoma, not amenable to locoregional treatment. Chemotherapy has generally only been used in the salvage setting after surgery and/or radiotherapy, and the type of chemotherapy that was offered depended on the age, performance status and renal function of the patient.

Patients tend to be treated with similar chemotherapy agents, such as cisplatin, fluorouracil (5FU) and bleomycin, to those used in metastatic squamous cell cancers arising from other sites. Deppe et al.[54] performed the first study on the use of chemotherapy in recurrent vulval cancer. They treated four women with recurrent squamous cell carcinoma with Adriamycin in small doses at 3-week intervals. Three women experienced regression of nodal metastases and residual tumour; however the clinical benefit was unclear.

Mitoxantrone was assessed by the Gynecologic Oncology Group.[55] Nineteen patients with advanced vaginal and vulval cancer were treated with mitoxantrone at 3-weekly intervals. There were no responses to treatment and the median survival for the patients with advanced vulval cancer was 3.2 months. It was thus concluded that mitoxantrone displays no activity in patients with advanced carcinoma of the vulva.

In an EORTC (European Organisation for Research and Treatment of Cancer) phase II trial, Witteveen et al.[56] analysed the use of 3-weekly paclitaxel in patients with recurrent, metastatic or locally advanced vulval cancer not amenable to surgery or radiotherapy. Thirty-one women were included, of whom 29 were assessable for response. Women in the study received a median of four cycles, with an overall response of 13.8% with two complete responses. The median follow-up was 24 months and median progression-free survival was 2.6 months.

Cormio et al.[57] evaluated the activity and toxicity of a combined regimen of cisplatin (day 1) and vinorelbine (day 1, day 8) in 16 women with recurrent vulval carcinoma. None had previously been treated with chemotherapy and the median age was 65 years. Nine women had previously received radiotherapy. The recurrence was local (perineum, vagina and/or vulva) in nine women whereas seven had recurrent groin lymph nodes metastases. Responses were recorded in six women (40%), of whom four (27%) achieved a complete remission and two (13%) had a partial response; another four women (27%) had stable disease and five had progressive disease. The overall survival was 19 months.

6.4 Concomitant chemotherapy and radiotherapy

Chemotherapy used concomitantly with radiation (chemo-RT) should be considered analogous to use in cervical cancer and either cisplatin alone or cisplatin plus fluorouracil should be considered. If used alone, cisplatin at 40 mg/m^2 weekly, concomitantly with radiotherapy, would be advised. Alternative regimens may include cisplatin and fluorouracil using the regimen above, or platinum, mitomycin C and bleomycin given on week 1 and week 4 of a prolonged course of radiation. This should be managed by a unit experienced in looking after women with vulval cancer, as reactions and toxicity can be quite significant. Women should be referred to their regional centres where gynaecological surgeons and oncologists work closely in teams. There is some anecdotal evidence that chemo-RT increases skin toxicity and pelvic morbidity.

6.5 Future developments

At present both erlotinib and cetuximab are used in a variety of other squamous cell cancers, e.g. head and neck, and lung, with the aid of mutation analysis to try and target which patients would benefit from these additional therapies. It may very well be that with time, these two drugs, among other biological agents, will prove very useful in women not fit for aggressive chemotherapy in vulval cancer.

C Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients.

C Future development of targeted therapy with drugs such as erlotinib through mutation testing may lead to improvement in vulval cancer treatment toxicity benefit ratio and provide effective systemic treatment even for the more infirm patients.

7. Treatment of recurrent disease

7.1 Recurrence rates and survival

Recurrence rates for invasive squamous cell carcinoma range from 15% to 33%. In a review of the literature, the vulva was found to be the most common site of recurrence (69.5%) with the groin nodes affected in 24.3%, the pelvis in 15.6% and distant metastases in 18.5%.[58]

Survival following regional recurrence is poor so all attempts to prevent it must be made at the time of primary treatment. However, the outcome from local recurrence in vulval cancer is better than that of other gynaecological cancers. Skin bridge recurrence has been reported to be more likely to occur in patients with positive lymph nodes.[59] If the nodes are known or suspected to be positive at the time of primary treatment, an en bloc dissection should be considered to remove the tissue between the vulva and involved nodes.

Clinical oncologists and gynaecological surgeons need to work closely together to manage patients with recurrent disease, which can be challenging. Integrating all treatment modalities (surgery, chemotherapy and radiation) can, however, be highly rewarding.

Treatment and outcome depend on the site and extent of the recurrence.[58] Surgical treatment of the recurrence can result in a 5-year survival rate of 45%, although the prognosis is worse for groin dissection and for women in whom only a biopsy is taken.[60] If excision would impair sphincter function, irradiation should be considered as the first choice. If irradiation has already been given to maximum dose, then excision should be considered. Such cases require careful joint planning with clinical oncologists and plastic and reconstructive surgeons experienced in the treatment of vulval disease.

7.2 Groin recurrence

Groin recurrence has a much poorer prognosis and is difficult to manage. In women who have not been treated previously with groin irradiation, radiotherapy (with or without additional surgery) would be the preferred option. The options are much more limited in those who have already been irradiated and palliation, which may include surgery, should be considered. In women who have had both surgery and radiotherapy to the groins, the palliative care team should become involved soon after the confirmation of groin recurrence.

7.3 Chemotherapy for relapsed disease

Chemotherapy for recurrent disease may be determined by what previous treatments have been offered and also by the age and performance status of the patient. The use of chemotherapy in this context is addressed in section 6.3.

One challenge is that many of these patients are relatively elderly and therefore not good candidates for aggressive novel combinations and this, taken together with their relative rarity, makes clinical trials difficult to perform. Collaboration between the regional UK centres, either through the National Cancer Research Institute or through groups such as the EORTC or the Gynaecological Cancer Group, should be encouraged.

8. Follow-up

The follow-up of most cancers, including vulval cancer, is based on custom and practice and not evidence. Up to a third of vulval cancers will recur even after satisfactory primary treatment. As salvage is largely dependent on either further excision or radiotherapy, recognition of recurrence as early as possible seems logical. For this reason, most centres would adopt a follow-up regimen of every 3 months for the first year, 6-monthly for the second year and yearly thereafter. There are no data to support this approach.

Late recurrence is unusual but is encountered so follow-up may be required for many years. In addition, patients should be advised to bring forward their review if they experience any new symptoms or if the appearances of the residual tissues change in any way. It should be remembered that elderly and frail patients may find self-examination difficult.

References

1. Cancer Research UK. Vulval cancer incidence statistics [http://www.cancerresearchuk.org/cancer-info/cancerstats/types/vulva/incidence/]. Accessed 2014 Apr 23.
2. Cancer Research UK. Vulval cancer mortality statistics [http://www.cancerresearchuk.org/cancer-info/cancerstats/types/vulva/mortality/]. Accessed 2014 Apr 23.
3. Eva LJ, Ganesan R, Chan KK, Honest H, Luesley DM. Differentiated-type vulval intraepithelial neoplasia has a high-risk association with vulval squamous cell carcinoma. *Int J Gynecol Cancer* 2009;19:741–4.
4. Royal College of Obstetricians and Gynaecologists. *The Management of Vulval Skin Disorders*. Green-top Guideline No. 58. London: RCOG; 2011.
5. van de Nieuwenhof HP, Bulten J, Hollema H, Dommerholt RG, Massuger LF, van der Zee AG, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. *Mod Pathol* 2011;24:297–305.
6. Jones IS, Crandon A, Sanday K. Paget's disease of the vulva: Diagnosis and follow-up key to management; a retrospective study of 50 cases from Queensland. *Gynecol Oncol* 2011;122:42–4.
7. Mendivil AA, Abaid L, Epstein HD, Rettenmaier MA, Brown JV 3rd, Micha JP, et al. Paget's disease of the vulva: a clinicopathologic institutional review. *Int J Clin Oncol* 2012;17:569–74.
8. van den Einden LC, Grefte JM, van der Avoort IA, Vedder JE, van Kempen LC, Massuger LF, et al. Cytology of the vulva: feasibility and preliminary results of a new brush. *Br J Cancer* 2012;106:269–73.
9. Bae-Jump VL, Bauer M, Van Le L. Cytological evaluation correlates poorly with histological diagnosis of vulvar neoplasias. *J Low Genit Tract Dis* 2007;11:8–11.
10. Levine TS, Rolfe KJ, Crow J, Styles S, Perrett CW, Maclean AB, et al. The use of cytospin monolayer technique in the cytological diagnosis of vulval and anal disease. *Cytopathology* 2001;12:297–305.
11. Nauth HF, Schilke E. Cytology of the exfoliative layer in normal and diseased vulvar skin: correlation with histology. *Acta Cytol* 1982;26:269–83.
12. National Institute for Health and Clinical Excellence. *Referral guidelines for suspected cancer.* Clinical Guideline 27. London: NICE; 2005.
13. Regauer S. Residual anogenital lichen sclerosus after cancer surgery has a high risk for recurrence: a clinicopathological study of 75 women. *Gynecol Oncol* 2011;123:289–94.
14. Ambros RA, Malfetano JH, Mihm MC Jr. Clinicopathologic features of vulvar squamous cell carcinomas exhibiting prominent fibromyxoid stromal response. *Int J Gynecol Pathol* 1996;15:137–45.
15. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. *Gynecol Oncol* 1990;38:309–14.
16. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103–4.

17. Homesley HD, Bundy BN, Sedlis A, Yordan E, Berek JS, Jahshan A, et al. Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). *Am J Obstet Gynecol* 1991;164:997–1003.
18. Royal College of Pathologists. *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*. London: RCPath; 2010.
19. Andersen BL. Predicting sexual and psychologic morbidity and improving the quality of life for women with gynecologic cancer. *Cancer* 1993;71:1678–90.
20. Andersen BL, Turnquist D, LaPolla J, Turner D. Sexual functioning after treatment of in situ vulvar cancer: preliminary report. *Obstet Gynecol* 1988;71:15–9.
21. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. *Cancer* 1993;71:1673–7.
22. Sedlis A, Homesley H, Bundy BN, Marshall R, Yordan E, Hacker N, et al. Positive groin lymph nodes in superficial squamous cell vulvar cancer. A Gynecologic Oncology Group Study. *Am J Obstet Gynecol* 1987;156:1159–64.
23. Hacker NF, Leuchter RS, Berek JS, Castaldo TW, Lagasse LD. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. *Obstet Gynecol* 1981;58:574–9.
24. Levenback CF, van der Zee AG, Rob L, Plante M, Covens A, Schneider A, et al. Sentinel lymph node biopsy in patients with gynecologic cancers: Expert panel statement from the International Sentinel Node Society Meeting, February 21, 2008. *Gynecol Oncol* 2009;114:151–6.
25. Stehman FB, Bundy BN, Dvoretsky PM, Creasman WT. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the Gynecologic Oncology Group. *Obstet Gynecol* 1992;79:490–7.
26. Zhang SH, Sood AK, Sorosky JI, Anderson B, Buller RE. Preservation of the saphenous vein during inguinal lymphadenectomy decreases morbidity in patients with carcinoma of the vulva. *Cancer* 2000;89:1520–5.
27. Paley PJ, Johnson PR, Adcock LL, Cosin JA, Chen MD, Fowler JM, et al. The effect of sartorius transposition on wound morbidity following inguinal-femoral lymphadenectomy. *Gynecol Oncol* 1997;64:237–41.
28. Butler JS, Milliken DA, Dina R, Eccles SA, Maghami SG, Jameson C, et al. Isolated groin recurrence in vulval squamous cell cancer (VSCC). The importance of node count. *Eur J Gynaecol Oncol* 2010;31:510–3.
29. de Hullu JA, Hollema H, Piers DA, Verheijen RH, van Diest PJ, Mourits MJ, et al. Sentinel lymph node procedure is highly accurate in squamous cell carcinoma of the vulva. *J Clin Oncol* 2000;18:2811–6.
30. Decesare SL, Fiorica JV, Roberts WS, Reintgen D, Arango H, Hoffman MS, et al. A pilot study utilizing intraoperative lymphoscintigraphy for identification of the sentinel lymph nodes in vulvar cancer. *Gynecol Oncol* 1997;66:425–8.
31. Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 2008;26:884–9.
32. Hacker NF, Berek JS, Juillard GJ, Lagasse LD. Preoperative radiation therapy for locally advanced vulvar cancer. *Cancer* 1984;54:2056–61.
33. Rotmensch J, Rubin SJ, Sutton HG, Javaheri G, Halpern HJ, Schwartz JL, et al. Preoperative radiotherapy followed by radical vulvectomy with inguinal lymphadenectomy for advanced vulvar carcinomas. *Gynecol Oncol* 1990;36:181–4.

34. Hoffman MS, LaPolla JP, Roberts WS, Fiorica JV, Cavanagh D. Use of local flaps for primary anal reconstruction following perianal resection for neoplasia. *Gynecol Oncol* 1990;36:348–52.
35. Barton DP, Hoffman MS, Roberts WS, Fiorica JV, Finan MA, Gleeson N, et al. Use of local flaps in the preservation of fecal continence following resection of perianal neoplasias. *Int J Gynecol Cancer* 1993;3:318–23.
36. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970;172:902–8.
37. DeMatos P, Tyler D, Seigler HF. Mucosal melanoma of the female genitalia: a clinicopathologic study of forty-three cases at Duke University Medical Center. *Surgery* 1998;124:38–48.
38. Omholt K, Grafström E, Kanter-Lewensohn L, Hansson J, Ragnarsson-Olding BK. KIT pathway alterations in mucosal melanomas of the vulva and other sites. *Clin Cancer Res* 2011;17:3933–42.
39. Hinten F, van den Einden LC, Hendriks JC, van der Zee AG, Bulten J, Massuger LF, et al. Risk factors for short- and long-term complications after groin surgery in vulvar cancer. *Br J Cancer* 2011;105:1279–87.
40. Faul CM, Mirmow D, Huang Q, Gerszten K, Day R, Jones MW. Adjuvant radiation for vulvar carcinoma: improved local control. *Int J Radiat Oncol Biol Phys* 1997;38:381–9.
41. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol* 1986;68:733–40.
42. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. *Cancer* 1994;74:2491–6.
43. van der Velden J, van Lindert AC, Lammes FB, ten Kate FJ, Sie-Go DM, Oosting H, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. *Cancer* 1995;75:2885–90.
44. Thomas G, Dembo A, DePetrillo A, Pringle J, Ackerman I, Bryson P, et al. Concurrent radiation and chemotherapy in vulvar carcinoma. *Gynecol Oncol* 1989;34:263–7.
45. van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. *Cochrane Database Syst Rev* 2011;(5):CD002224.
46. Durrant KR, Mangioni C, Lacave AJ, George M, van der Burg ME, Guthrie D, et al. Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynaecological Cancer Cooperative Group (GCCG). *Gynecol Oncol* 1990;37:359–62.
47. Benedetti-Panici P, Greggi S, Scambia G, Salerno G, Mancuso S. Cisplatin (P), bleomycin (B), and methotrexate (M) preoperative chemotherapy in locally advanced vulvar carcinoma. *Gynecol Oncol* 1993;50:49–53.
48. Geisler JP, Manahan KJ, Buller RE. Neoadjuvant chemotherapy in vulvar cancer: avoiding primary exenteration. *Gynecol Oncol* 2006;100:53–7.
49. Domingues AP, Mota F, Durão M, Frutuoso C, Amaral N, de Oliveira CF. Neoadjuvant chemotherapy in advanced vulvar cancer. *Int J Gynecol Cancer* 2010;20:294–8.
50. Tans L, Ansink AC, van Rooij PH, Kleijnen C, Mens JW. The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. *Am J Clin Oncol* 2011;34:22–6.
51. Narimatsu A, Okada O. [A case of FIGO stage IV A vulvar cancer successfully treated by neoadjuvant chemotherapy with continuous intra-arterial infusion (cisplatin, 5-fluorouracil)]. *Gan To Kagaku Ryoho* 1997;24:1161–5. Japanese.
52. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol* 2009;114:537–46.

53. Bellati F, Angioli R, Manci N, Angelo Zullo M, Muzii L, Plotti F, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. *Gynecol Oncol* 2005;96:227–31.
54. Deppe G, Bruckner HW, Cohen CJ. Adriamycin treatment of advanced vulvar carcinoma. *Obstet Gynecol* 1977;50(1 Suppl):13s–14s.
55. Muss HB, Bundy BN, Christopherson WA. Mitoxantrone in the treatment of advanced vulvar and vaginal carcinoma. A Gynecologic Oncology Group study. *Am J Clin Oncol* 1989;12:142–4.
56. Witteveen PO, van der Velden J, Vergote I, Guerra C, Scarabeli C, Coens C, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer—Gynaecological Cancer Group). *Ann Oncol* 2009;20:1511–6.
57. Cormio G, Loizzi V, Gissi F, Serrati G, Panzarino M, Carriero C, et al. Cisplatin and vinorelbine chemotherapy in recurrent vulvar carcinoma. *Oncology* 2009;77:281–4.
58. Piura B, Masotina A, Murdoch J, Lopes A, Morgan P, Monaghan J. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. *Gynecol Oncol* 1993;48:189–95.
59. Rose PG. Skin bridge recurrences in vulvar cancer: frequency and management. *Int J Gynecol Cancer* 1999;9:508–11.
60. Weikel W, Schmidt M, Steiner E, Knapstein PG, Koelbl H. Surgical therapy of recurrent vulvar cancer. *Am J Obstet Gynecol* 2006;195:1293–302.

Appendix I. International Federation of Gynecology and Obstetrics (FIGO) staging system

Stage I	**Tumour confined to the vulva**
Stage Ia	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1 mm. No nodal metastasis
Stage Ib	Lesions > 2 cm in size or with stromal invasion > 1 mm confined to the vulva or perineum. No nodal metastasis
Stage II	**Tumour of any size with extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with negative nodes**
Stage III	**Tumour of any size with or without extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with positive inguinofemoral nodes**
Stage IIIa	(i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1–2 lymph node metastasis(es) (< 5 mm)
Stage IIIb	(i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (< 5 mm)
Stage IIIc	With positive nodes with extracapsular spread
Stage IV	**Tumour invades other regional (upper 2/3 urethra; 2/3 vagina) or distant structures**
Stage IVa	Tumour invades any of the following (i) Upper urethral and/or vaginal mucosa; bladder mucosa; rectal mucosa or fixed to pelvic bone, or (ii) Fixed or ulcerated inguinofemoral lymph nodes.
Stage IVb	Any distant metastasis including pelvic lymph nodes

ESGO
European Society of Gynaecological Oncology

VULVAR CANCER GUIDELINES

www.esgo.org

The European Voice of Gynaecological Oncology

The European Society of Gynaecological Oncology (ESGO) developed guidelines covering diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment, reconstructive surgery), sentinel lymph node procedures, radiation therapy, chemoradiation, systemic treatment, treatment of recurrent disease (vulvar recurrence, groin recurrence, distant metastases), and follow-up for patients with vulvar cancer.

A five-step development process followed:

Nomination of multidisciplinary international development group

↓

Identification of scientific evidence

↓

Formulation of recommendations

↓

External evaluation of guidelines (international review)

↓

Integration of international reviewers' comments

The objectives of these guidelines are to improve and to homogenise the management of patients with vulvar cancer. The guidelines are intended for use by gynaecological oncologists, general gynaecologists, surgeons, pathologists, radiotherapists, medical and clinical oncologists, general practitioners, palliative care teams, and allied health professionals.

These guidelines apply to adults over the age of 18 who have squamous cell carcinoma of the vulva. These guidelines do not address patients with other vulvar cancer histologies. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

To ensure that the statements made in this document are evidence-based, the current literature was reviewed and critically appraised. A comprehensive literature review of the studies published between January 1980 and September 2015 was carried out.

The guidelines were retained if they were supported by sufficient high-level scientific evidence and/or when a large consensus among experts was obtained. By default, a clinical approach guideline is defined as being the criterion-standard clinical approach. If an approach is judged to be acceptable but is not unanimously recognized as a criterion-standard clinical approach, indication is given that it is still subject to discussion and/or evaluation.

These guidelines have five different "strengh of guideline" ratings (SIGN grading system[1]):

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
✓	Recommended best practice based on the clinical experience of the guideline development group

1++ high quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias; 1+ well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias; 2++ high quality systematic reviews of case control or cohort studies/high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+ well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 3 non-analytic studies, e.g. case reports, case series; 4 expert opinions.

[1] http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

PREOPERATIVE INVESTIGATIONS

✓ In any patient suspected for vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may obstruct further treatment planning.

✓ In patients with multiple vulvar lesions, all lesions should be biopsied separately (with clear documentation of mapping).

✓ All patients with vulvar cancer should be referred to a Gynaecological Oncology Centre (GOC) and treated by a multidisciplinary gynaecological oncology team.

STAGING SYSTEM

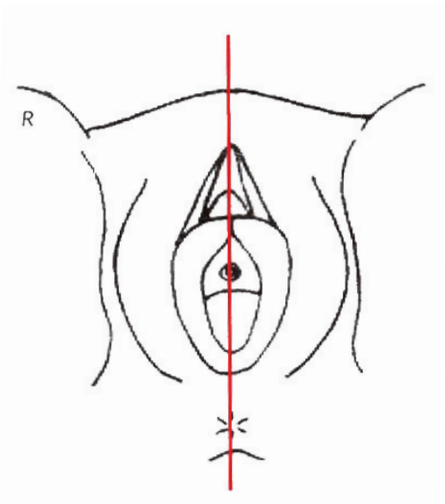
✓ Vulvar cancer should be staged according to FIGO and/or TNM classification[2].

[2] Throughout these recommendations, advanced stage of disease is defined as clinical T3 and/or N3.

PREOPERATIVE INVESTIGATIONS

✓

Preoperative work-up should at least include clear documentation of the clinical exam (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (see below).



✓

Evaluation of the cervix/vagina/anus is recommended.

C

Prior to sentinel lymph node biopsy, clinical examination and imaging of the groins, (either by ultrasound, (positron emission tomography-) computed tomography ((PET-) CT), or magnetic resonance imaging (MRI)) are required to identify potential lymph node metastases.

✓

Suspicious nodes (at palpation and/or imaging) should be analysed by fine-needle aspiration (FNA), or core biopsy when this would alter primary treatment.

✓

Further staging with CT thorax/abdomen and pelvis is recommended where there is a clinical suspicion of, or proven, (nodal) metastatic disease and/or advanced stage disease.

✓

The pathology report on preoperative biopsy should at least include histological type and depth of invasion.

SURGICAL MANAGEMENT

Groin treatment

C	Radical local excision is recommended.
✓	Consider additional, more superficial resection of differentiated vulvar intraepithelial neoplasia (d-VIN) in addition to radical local excision of invasive tumours.
✓	In multifocal invasive disease, radical excision of each lesion as a separate entity may be considered. Vulvectomy may be required in cases with multifocal invasion arising on a background of extensive vulvar dermatosis.
✓	The goal of excision is to obtain tumour-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider narrower margins where the tumour lies close to midline structures (clitoris, urethra, anus), and preservation of their function is desired.
✓	When invasive disease extends to the pathological excision margins of the primary tumour, reexcision is the treatment of choice.
✓	The optimal management of the groin (full inguinofemoral lymphadenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined.

Groin treatment

C	Groin treatment should be performed for tumours > pT1a.
B	For unifocal tumours < 4 cm without suspicious groin nodes on clinical examination and imaging (any modality) the sentinel lymph node procedure is recommended.
C	For tumours ≥ 4 cm and/or in case of multifocal invasive disease, inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumours (medial border > 1 cm from midline), ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease.
D	When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed.
C	Preservation of the saphenous vein is recommended.
✓	The optimal management of the groin (full inguinofemoral lymphadenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined.
✓	Where enlarged (> 2 cm) pelvic nodes are identified, their removal should be considered.

Reconstructive surgery

✓	Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease.

SENTINEL LYMPH NODE PROCEDURE

B	The sentinel lymph node procedure is recommended in patients with unifocal cancers of < 4 cm, without suspicious groin nodes.
B	Use of radioactive tracer is mandatory; use of blue dye is optional.
C	Lymphoscintigram is advised to enable the preoperative identification, location, and number of sentinel lymph nodes.
C	Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node can be performed in an attempt to prevent a second surgical procedure. Caution is warranted because of an increased risk of missing micrometastases on final pathology due to the loss of tissue arising from processing for frozen section assessment.
✓	When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.
C	Where metastatic disease is identified in the sentinel lymph node (any size): inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph node.
✓	For tumours involving the midline: bilateral sentinel lymph node detection is mandatory. Where only unilateral sentinel lymph node detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed.
C	Pathological evaluation of sentinel lymph nodes should include serial sectioning at levels of at least every 200 µm. If the H&E sections are negative, immunohistochemistry should be performed.

RADIATION THERAPY

✓	Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment.
✓	When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed.
✓	In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised.
B	Postoperative radiotherapy to the groin is recommended for cases with > 1 metastatic lymph node and/or the presence of extracapsular lymph node involvement.
✓	Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are non-suspicious on imaging, the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery.
C	Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.

CHEMORADIATION

C	Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.
C	In advanced stage disease, neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery.
C	Radiosensitising chemotherapy, preferably with weekly cisplatin, is recommended.

SYSTEMIC TREATMENT

D	Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting.

TREATMENT OF RECURRENT DISEASE

Treatment of vulvar recurrence

✓ Radical local excision is recommended.

✓ For vulvar recurrence with a depth of invasion > 1 mm and previous sentinel lymph node removal only, inguinofemoral lymphadenectomy should be performed.

✓ The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease.

Treatment of groin recurrence

✓ Restaging by CT (or PET-CT) of the thorax/abdomen/pelvis is recommended.

✓ Preferred treatment is radical excision when possible, followed by postoperative radiation in radiotherapy naïve patients.

✓ Based on evidence from other squamous cell cancers, such as cervical and anal cancer, the addition of radiosensitising chemotherapy to postoperative radiotherapy should be considered.

✓ Definitive chemoradiation when surgical treatment is not possible.

Treatment of distant metastases

✓ Systemic (palliative) therapy may be considered in individual patients (see systemic treatment).

FOLLOW-UP

✓

The optimal follow-up schedule for vulvar cancer is undetermined.

✓

After primary surgical treatment, a follow-up schedule is suggested:

- First follow-up, 6-8 weeks postoperative
- First two years, every 3-4 months
- Third and fourth year, biannually
- Afterward, long-term follow-up, especially in case of predisposing vulvar disease.

Follow-up after surgical treatment should include clinical examination of vulva and groins.[3]

✓

After definitive (chemo)radiation, the following follow-up schedule is suggested:

- First follow-up visit, 10-12 weeks post completion of definitive (chemo)radiation.
- First two years, every three-four months
- Third and fourth year, biannually
- Afterward, long-term follow-up, especially in case of predisposing vulvar disease.

At the first follow-up visit 10-12 weeks post definitive (chemo)radiation, CT or PET-CT is recommended to document complete remission.

[3] Despite the well-recognised low sensitivity of palpation to identify groin recurrences, currently available data do not support routine use of imaging of the groins in follow-up.

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