All Wales Guideline for the Management of Ovarian, Fallopian tube and Primary Peritoneal Cancer

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Date: 1st August 2021	**Date of Review:** August 2024	**Version:** 2.2

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1. Foreword

This guidance document is an update of "Guidelines for the management of ovarian cancer" published in 2011. The aim of this document is to help the decision making of clinicians in Wales who treat women with suspected or proven ovarian, fallopian tube and primary peritoneal cancer, as well as to clarify the patient pathway and processes, in an effort to improve outcomes. Guidance on the detection of ovarian cancer in primary care and its initial management have recently been published by NICE. [1]

This guideline is intended for clinicians in secondary care (i.e. cancer units and centres), however where applicable reference will be made to the NICE guidance as it applies to the secondary care setting.

To support this, an evidence base is provided and important practice points are highlighted.

Improving outcomes for women with ovarian cancer requires a concerted and coordinated effort by all health professionals involved in their care and throughout the document, the role of the gynaecological oncology multidisciplinary team is stressed as a vital component to the success of this strategy.

For the purpose of these guidelines the term ovarian cancer will be used to cover ovarian, fallopian tube and primary peritoneal cancer.

The authors would like to thank the following for their contributions: Dr Gwenllian Davies for Appendix 3 – palliative care, Dr Alison Finall for Appendix 4 – pathology reporting.

2. Introduction

Ovarian cancer is the most common cause of gynaecological cancer death and is the fourth most common cause of cancer deaths of women in Europe. [2] It has the highest fatality-to-case ratio because almost 75% of patients have advanced disease at the time of diagnosis. [3] Incidence increases with age, with a peak rate of ovarian cancer cases between 75 and 79 years of age. [4]

Ovarian cancer is the 6th most common cancer in females in the UK, accounting for 4% of all new cancer cases in females in 2017 and accounting for 5% of all cancer deaths in females in 2018. In 2017, there were 7,309 cases of ovarian cancer diagnosed in UK, with 4,219 patients dying from the disease in 2018. In Wales there were 371 cases of ovarian cancer diagnosed in 2017, with 224 women dying from the disease in 2018. [4]

Ovarian cancer European age-standardised incidence rates for females remained stable in the UK between 1993-1995 and 2015-2017. Over the last decade in the UK (between 2005-2007 and 2015-2017), ovarian cancer age-standardised incidence rates for females decreased by 5%. Ovarian cancer European age-standardised mortality rates for females decreased by 21% in the UK between 1971-1973 and 2016-2018. Over the last decade in the UK (between 2006-2008 and 2016-2018), ovarian cancer age-standardised mortality rates for females decreased by 15%.

The management of ovarian cancer represents a major and complex challenge for healthcare professionals. Improved outcomes can be achieved by centralization of care and a multidisciplinary approach. [5]

3. Background

Approximately 30% of ovarian neoplasms in postmenopausal women are malignant, compared to 7% in premenopausal women. Up to 90% of all primary ovarian malignancies are epithelial. In addition, approximately 75-80% of epithelial cancers are of the serous histological type. Serous carcinomas are now believed to be related aetiologically to fallopian tube and peritoneal cancer. [6] As such, these cancers shall be discussed together while germ cell, non-epithelial and borderline cancers shall be discussed separately.

3.1. Screening and Risk Reduction

Formal guidance on these issues is outside the remit of this guideline. In summary, there is currently no established method of screening for ovarian cancer. There are three randomised controlled trials on ovarian cancer screening in the general population: the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

with 202,546 women, the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial with 78,216 women, and a Japanese study with 41,688 women. [7-11] None have been able to demonstrate conclusively a reduction in mortality from ovarian cancer. With regards women at high risk for ovarian cancers: Familial predisposition accounts for approximately 10% of epithelial ovarian cancer. The UK Familial Ovarian Cancer Screening Study (UKFOCSS) enrolled 4,348 high-risk women from 2007 to 2012 to determine whether or not ovarian cancer can be detected early in women at high risk. [12, 13] Although screening is associated with significantly lower stage disease, it remains unknown whether this strategy would improve survival in the screened high-risk population. Again no definite impact on mortality was reported.

It is recommended that women who appear to be high risk should undergo genetic counselling, and offered genetic testing for BRCA 1, BRCA 2, Lynch Syndrome, RAD51C, RAD51D, and/or BRIP1 if appropriate. Women at high risk may be offered options for risk reduction including surgery. These issues can be quite complex and require careful counselling, which may be best achieved in a joint clinic comprising genetic and gynaecological input. Risk-reducing bilateral salpingo-oophorectomy (BSO) is the 'gold standard' for preventing ovarian cancer in women at increased risk. However, when performed in premenopausal women, it results in premature menopause and associated negative health consequences. This, together with acceptance of the central role of the fallopian tube in etiopathogenesis of high-grade serous carcinoma, has led to risk-reducing early salpingectomy with delayed oophorectomy being proposed as a two-step surgical alternative for premenopausal women. The Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal (PROTECTOR) study is a prospective non-randomised multi-center trial that investigates sexual and endocrine function in three study arms: risk-reducing early salpingectomy with delayed oophorectomy; risk-reducing salpingo-oophorectomy; controls (no surgery). [14] It is estimated recruitment will be completed by 2023 and results will be published by 2027.

3.2. Symptoms, Signs and Diagnosis

Symptoms of ovarian cancer are often vague and non-specific. [1] As the majority of patients with ovarian cancer have advanced disease at presentation, early symptom recognition has attracted much recent interest in an attempt to diagnose disease at an earlier stage. [15] There does appear however to be a significant overlap in the duration and nature of symptoms for both early and advanced disease respectively however. [16] This implies which that early and late stage disease are biologically distinct, thus limiting the prospect of diagnosing disease at an "earlier stage" based on symptoms alone. Nonetheless, early diagnosis is desirable (regardless of stage) as it can lead to prompt referral and specialist care, leading to improved cure rates.

Women may also present with an incidental finding of a pelvic mass detected clinically or at the time of imaging. The possibility of other primary tumours metastatic to the ovary should always be considered. As such, gastrointestinal symptoms should prompt consideration of upper and lower GIT investigations and a complaint of postmenopausal bleeding should prompt investigation of the endometrial cavity. A family history of cancer should be elicited in all cases (especially for breast, ovary and colon cancer). In addition, patients may present acutely with symptoms and signs suggesting torsion/infarction or sub-acute bowel obstruction.

Clinical examination should assess the patient's performance and nutrition status as well as detecting signs of metastatic disease. Breast examination should be considered, especially in the setting of advanced disease. Abdominal and pelvic examination should be routinely performed. The finding of a pelvic mass on clinical examination raises significantly the possibility of an ovarian cancer, especially if found in association with ascites. Rectal examination should be performed to exclude a rectal mass and to help assess resectability.

For further information on detection of ovarian cancer in primary care, please refer to NICE guidance. [1]

CLINICAL PRACTICE POINT 1

The finding of a pelvic mass either on clinical or radiological examination (especially in a postmenopausal patient) is a critical sign, and warrants immediate further investigation to exclude malignancy.

3.3. Investigations

- In primary care an ultrasound scan is the standard investigation if ovarian cancer is suspected [1]
- Tumour markers: CA125 and CEA routinely. A ratio of CA125:CEA of greater than 25 favours the diagnosis of ovarian cancer. [17] If there is a possibility of disseminated upper GI malignancy add CA19-9, and for disseminated breast malignancy add CA 15-3. In the younger patient (age < 40 years), add AFP, HCG and LDH. If a granulosa cell tumour is presumed, add oestradiol and inhibin.
- CT chest, abdomen and pelvis for staging purposes if the pelvic mass is deemed intermediate or high-risk for malignancy, or if the patient presents with advanced disease (MRI is not routinely recommended)
- Full blood count (FBC) and differential, liver and renal function tests
- If ascites or pleural effusion present, consider diagnostic paracentesis or pleural tap respectively

3.4. Differential Diagnosis

Ovarian cancers must be differentiated from benign neoplasms and functional cysts of the ovaries. CA 125 levels on their own are considered unreliable as it is elevated in only 50% of patients with stage 1 ovarian cancer and tends not to be elevated in mucinous carcinomas. [18] Furthermore, interpretation in premenopausal patients is unreliable due to the high incidence of non-neoplastic conditions, which can cause an elevated CA 125. The risk of malignancy index (RMI), first described by Jacobs in 1990 [19] appears to be the best predictor of malignancy. [20] Various modifications of this model have been proposed although it is not entirely clear the optimum cut-off score should be, as alterations of this can affect the sensitivity of the RMI relative to specificity. [21-23] On one extreme, a low cut-off may potentially cause an overburdening of cancer centre resources. On the other, a patient with ovarian cancer might be missed. Most of

the published data regarding RMI uses a cut-off of 200 however [24] and two systematic reviews concluded that a score of 200 or greater gives a sensitivity and specificity for ovarian cancer of 44-73% and 89-95% in premenopausal women and 77-79% and 85-90% in postmenopausal women. [25, 26] However, in the ovarian cancer guidance published by NICE, a cut-off of 250 has been recommended based on a health economics evaluation. [1] Adoption of this cut-off should allow comparison with centres nationwide, and local audit of the referral pathway should be performed to ensure that a significant proportion of ovarian cancers are not being missed using this threshold.

CLINICAL PRACTICE POINT 2
The recommended cut-off for high-risk patients in this guideline is RMI > 250.

The RMI is not the only consideration to be made however. Although the NICE guideline states that there is currently not enough evidence to recommend the routine adoption of other models, the accuracy of the IOTA models has been demonstrated in secondary care, with a sensitivity and specificity for the Simple Rules (classifying all inconclusive cases as malignant) of 94.3% and 73.4% respectively, and for the ADNEX model (at a 30% risk cut-off) of 84.5% and 84.5% respectively. [27] Size of the lesion is also considered to be important, a factor not included in the RMI calculation. [28] As such, it is recommended that asymptomatic, low-risk ovarian cysts < 8cm in diameter are evaluated by the local MDT, where a conservative approach can be considered. The overall clinical picture should always be taken into account and it is the MDT's role to consider this before recommending further management.

It is essential to determine preoperatively whether a patient is high risk for ovarian malignancy or not. This would allow the opportunity for the patient to undergo thorough surgical staging, which is a critical determinant of subsequent treatment and prognosis. Furthermore, optimal debulking at the time of initial surgery is an important determinant of the success of systemic chemotherapy.

CLINICAL PRACTICE POINT 3

Any patient that is being considered for laparotomy to investigate a pelvic mass should have their risk of malignancy assessed pre-operatively under the guidance of the local gynaecological oncology MDT. This risk must take into account all clinical information, including the RMI.

3.5. Referral Pathways

The Single Cancer Pathway (SCP) forms the basis of gynaecological cancer care provision in Wales and clinicians treating these cancers should ensure that they are familiar with them. [29] They aim to establish consistent generic and site specific pathways that describe all routes of entry onto the pathway from the point of suspicion of cancer. The pathways describe good practice diagnostic and treatment pathways and also describe where patients should receive consistent information and support, tailored to meet their needs. The Single Cancer Pathway for ovarian cancer is shown in appendix 2.

CLINICAL PRACTICE POINT 4

The Single Cancer Pathway is the basis of collaboration between the local cancer unit and the cancer centre and essential to prevent delays in diagnosis and delivery of optimum treatment, which can result in poor outcomes. This process should be the subject of continuous audit.

3.6. Confirmation of Diagnosis (Pathology)

This is usually achieved either at laparotomy or, if neo-adjuvant chemotherapy is chosen for treatment, by radiologically guided percutaneous biopsy or laparoscopically when percutaneous biopsy is not feasible. Radiologically guided percutaneous biopsy has been shown to be safe and has high diagnostic accuracy. [30] Occasionally, cytological examination can be used to make a diagnosis, but this shall be discussed in a later section. The importance of a tissue prior to neo-adjuvant chemotherapy has become increasingly important to allow molecular testing while treatment naïve. Currently this is for somatic BRCA testing with HRD testing due to be rolled out imminently.

Serous histology makes up 75% to 80% of epithelial cancers. Less common types are mucinous (10%), endometrioid (10%), clear cell, Brenner and undifferentiated carcinoma. [31] Borderline tumours (tumours of low malignant potential) tend to remain confined to the ovary for long periods of time and are associated with a very good prognosis. Metastatic implants can occur however, which can be divided into invasive and non-invasive. The former group has a higher likelihood of proliferating and progressing within the abdominal cavity, which can lead to intestinal obstruction and death. [32] Primary malignant transformation of the peritoneum is called peritoneal cancer. This has the appearance of "mullerian" cancer and simulates ovarian carcinoma clinically.

The use of perioperative frozen section analysis in apparent early stage disease has been shown to effectively guide surgical staging procedures and has been used in the USA for some time. [33] More recently, routine frozen section analysis has been performed in some centres in the UK with excellent results. [34, 35] Sensitivity and specificity is reduced with borderline tumours, but this is not considered to have any significant clinical impact. [36]

3.7. Genetic Screening

All patients with high grade epithelial ovarian cancer (excluding mucinous) can now be offered germline BRCA testing in line with All Wales Guidance. Patients can be counselled and consent taken by surgical or oncology team and referred to genetics service if BRCA mutation confirmed or a Variant of Uncertain Significance. All patients with Stage III/IV high grade epithelial ovarian cancer (excluding mucinous) should undergo parallel testing of germline and somatic BRCA testing with the addition of HRD testing to guide management for PARP inhibitors.

3.8. FIGO Staging [37]

FIGO stage	Features
Stage I	**Tumour confined to ovaries or fallopian tube(s)**
Stage IA	Tumour limited to 1 ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
Stage IB	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
Stage IC	Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following: **Stage IC1:** surgical spill **Stage IC2:** capsule ruptured before surgery or tumour on ovarian or fallopian tube surface **Stage IC3:**malignant cells in the ascites or peritoneal washings
Stage II	**Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer**
Stage IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
Stage IIB	Extension to other pelvic intraperitoneal tissues
Stage III	**Tumour involves 1 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**
Stage IIIA	**Stage IIIA1**: Positive retroperitoneal lymph nodes only (cytologically or histologically proven): IIIA1(i) Metastasis up to 10 mm in greatest dimension IIIA1(ii) Metastasis more than 10 mm in greatest dimension **Stage IIIA2**: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
Stage IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

Stage IIIC	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**
Stage IVA	Pleural effusion with positive cytology
Stage IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

4. Surgical Treatment

Initial surgery has historically been the standard for treatment of suspected or proven ovarian cancer. Indications for laparotomy include:

- establishment of diagnosis
- accurate staging
- optimal debulking/cytoreduction
- interval/secondary debulking
- palliation

In advanced disease, studies have consistently shown that the volume of residual disease remaining after debulking surgery inversely correlates with survival. [38, 39] Compared to other intra-abdominal carcinomas, this aggressive approach to debulking is unique to ovarian cancer. Optimal debulking is most likely to be achieved under the care of a gynaecological oncologist as evidenced by studies, which have consistently shown that surgical treatment by non-gynaecological oncologists contributes to suboptimal surgical management and shorter median survival. [40-45] Furthermore, there is also the risk of underestimating the stage of disease, as earlier series have shown overall 5-year survival for apparent stage I disease was only 60%. [46] Later studies have shown that with thorough surgical staging that the overall 5-year survival for stage IA or IB disease was reported at 90%. [47]

CLINICAL PRACTICE POINT 5

It is the responsibility of local MDT's to ensure that all patients undergoing laparotomy for evaluation of a pelvic mass or suspected ovarian cancer are discussed preoperatively. The gynaecological oncology MDT should make an assessment of each case individually and ascribe a risk of malignancy. Low risk cases should be managed locally. Intermediate risk cases should be evaluated at the MDT and managed locally if appropriate. All patients deemed high risk should be referred immediately to the cancer centre for treatment.

4.1. Pre-treatment Issues

Patients with ovarian cancer are commonly in the elderly age group and have significant coexisting medical co morbidities. Patients requiring surgery for advanced (stage III-IV) disease are at particularly high risk as there is an added physiological insult due to the extent of disease and associate fluid and electrolyte derangement as a result of ascites and pleural effusions respectively. The requirement of ultra-radical surgical procedures to achieve complete cytoreduction means that it is critical that the surgery is performed in a centre with the requisite infrastructure and expertise to safely manage these patients. Quality indicators for advanced ovarian cancer surgery should be adopted, regularly updated and maintained. [48]

The performance status of the patient should be assessed at the point of suspicion and referral as this will directly influence the ability to perform surgery or administer chemotherapy respectively.

Patient optimisation for treatment should begin as soon as possible and ideally before the patient is seen at the centre. Identification of patients requiring further investigations and medical assessments should be done at the earliest opportunity and nutritional requirements maintained, ideally as part of prehabilitation program if available. Significant effusions (pleural and ascitic) should be completely drained as this will significantly improve the performance status of the patient prior to administration of chemotherapy or surgery respectively. Pre-treatment assessment and optimisation should be performed with minimal delay. [29]

4.1.1 The Role of the Clinical Nurse Specialist (CNS)

All women with a diagnosis of gynaecological cancer should be offered the support of, and have access to, a CNS, in order to facilitate the women's needs throughout the cancer journey, including those of her partner or carer. Within an MDT, the CNS is in an ideal position, frequently as the key worker, to be able to address the often complex and sensitive issues identified and experienced by the patient. Access to self-help, support groups and charitable organisations may also be of significant benefit, allowing women to share experiences and seek support from other women diagnosed and treated for the same condition.

4.1.2 Surgical Considerations

Enhanced recovery programmes should be utilised. Preoperative bowel preparation should be considered where advanced disease is suspected, as the risk of bowel surgery is significant and the rate of infectious complications appears to be lower in patients who receive preoperative bowel preparation. [24] Debilitated patients having bowel preparation are particularly susceptible to intravascular depletion and require careful immediate pre-operative fluid balance and rehydration. The risk of venous thromboembolism (VTE) is particularly high in these patients [49] and VTE thromboprophylaxis is essential. Asymptomatic deep vein thrombosis (usually detected at the time of staging CT) sometimes necessitates placement of an inferior vena cava filter pre-op, which requires specialist interventional radiology expertise. Coexisting pleural effusions and/or ascites may need drainage at the time or just preceding laparotomy. Invasive monitoring is often needed and the laparotomy approach commonly utilizes extended midline incisions, which require epidurals/intrathecal opiates for adequate pain relief. Cell salvage can be utilised if necessary. Cell salvage expertise can reduce the patients' exposure to allogeneic blood transfusion and studies to date have suggested that the technique is safe and that tumour cells are reliably removed by the use of leukocyte depletion filtration. [50] It is cost effective to set up the machine to collect operative blood loss and to only process and retransfuse if clinically indicated.

Postoperatively, fluid balance is a particularly challenging issue and patients with extensive co morbidities are cared for in a high dependency or intensive care setting usually for the first 24 to 48 hours. Adequate fluid and blood product replacement is important, particularly as these patients are likely to need chemotherapy postoperatively. Nursing and physiotherapy requirements can be extensive and specialized. Clinical nurse specialists provide support at the pre-operative phase, which continues throughout the patient journey. The pre-, peri and postoperative care provided to patients with advanced ovarian cancer is a major and complex undertaking, which requires optimal delivery of care to patients who are medically infirm, in an efficient and timely manner. Such a coordinated multidisciplinary effort is one of the main strengths of the cancer centre.

4.2. Low and Intermediate Risk Pelvic Masses (Cancer Unit)

Low risk cases can be managed locally. Intermediate risk cases are evaluated at the MDT. If the MDT decides that an intermediate risk case can be managed locally the procedures to be carried out at laparotomy include the following:

- Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) via a midline incision.
- Peritoneal washings.
- Omental biopsy as well as biopsy of any suspicious peritoneal lesions.
- If fertility preservation is a consideration, a unilateral salpingo-oophorectomy could replace TAH+BSO especially if the contralateral ovary appeared normal.

CLINICAL PRACTICE POINT 6
If the MDT decides that an intermediate risk case can be managed locally, the procedure should include TAH+BSO via a midline incision, omental biopsy and peritoneal washings. Suspicious peritoneal areas should be biopsied.

4.3. High Risk Pelvic Masses (Cancer Centre)

This may be further subdivided into apparent early-stage disease and advanced disease (chapter 5).

4.4 Early Stage Disease

Early stage disease may be suspected preoperatively upon review of imaging at the MDT. As before, a midline approach is recommended.

The advantage of thoroughly staging these patients in addition to providing accurate prognostic information, is the potential avoidance of chemotherapy in patients with histologically confirmed, well differentiated stage IA or 1B disease. [51] One approach is to remove the ovarian tumour intact, if possible and a frozen section histological section obtained as a guide to staging. This approach has been adopted in many centres worldwide and some centres in the UK. The accuracy of frozen section has been analysed, with acceptable sensitivities and very good specificities respectively. [52, 53] Concerns have been raised regarding the accuracy of frozen section when large masses are assessed. [54] Routine implementation of frozen section analysis of adnexal masses in Wales is not currently considered standard practice.

If disease appears to be confined to the pelvis, the following may be performed in addition to TAH+BSO:

- Aspiration of any ascites for cytological examination.
- If no ascites, peritoneal washings should be performed prior to manipulation of the tumour.
- Systematic exploration of all intra-abdominal surfaces and viscera.
- Biopsy of any suspicious peritoneal surfaces or adhesions. If no suspicious areas identified, random peritoneal biopsies can be considered.
- Diaphragmatic surface irregularities should either be biopsied or smeared for cytological evaluation.
- Infracolic omentectomy.
- The appearance of the appendix should be documented if a mucinous tumour is suspected. Appendicectomy should be performed when the appendix is abnormal.

CLINICAL PRACTICE POINT 7

In suspected early stage disease, the procedure should include TAH+BSO via a midline incision, aspiration of ascites or peritoneal washings, systematic exploration of all intra-abdominal surfaces and viscera, biopsies of any

suspicious peritoneal surfaces or adhesions or random biopsies should be considered if no suspicious lesions, and infracolic omentectomy.

CLINICAL PRACTICE POINT 8
The appearance of the appendix should be documented if a mucinous tumour is suspected. Appendicectomy should be performed when the appendix is abnormal.

4.5 Assessment of pelvic and para-aortic nodes

The role of pelvic and para-aortic lymph node sampling is controversial. As many as three in ten patients whose tumour appears confined to the pelvis have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes. [46] In a systematic review on lymph node metastases in apparent clinical stages I and II ovarian cancer, the mean incidence of lymph node metastases was 14.2% (range 6.1–29.6%), which is highly dependent of differentiation grade (grade 1 = 4.0%, grade 2=16.5% and grade 3=20.0%) and histological type (with the highest incidence in the serous subtype (23.3%) and lowest in mucinous subtype (2.6%). [55] The retroperitoneal spaces should be assessed and suspicious nodes should be removed and sent for histological analysis. NICE have recommended sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls if there is a palpable abnormality, or random sampling if there is no palpable abnormality. [1] Systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) should not be included as part of standard surgical treatment in women with suspected ovarian cancer. In a randomised controlled trial comparing systematic lymphadenectomy with lymph node sampling in patients with epithelial ovarian cancer macroscopically confined to the pelvis, a higher proportion of patients with metastatic lymph nodes was detected by systematic lymphadenectomy than lymph node sampling, but this trial lacked power to exclude clinically important effects on progression free and overall survival. [56] In one retrospective review of 721 patients treated for epithelial ovarian cancer (EOC) with apparent early stage disease, no survival differences were noticed between EOC patients who

had negative lymph nodes after surgical staging and did not receive chemotherapy, versus patients who did not have lymphadenectomy but did receive chemotherapy. [57]

The association of lymphadenectomy and survival in stage I ovarian cancer patients was assessed in the SEER database including 6686 patients with stage 1 ovarian cancer (also non-epithelial tumours were included). [58] Lymph nodes were removed in 2862 patients (42.8%) with a median of 9 lymph nodes (range 1–84). The 5-year disease specific survival was 92.6% with lymph node sampling compared to 87.0% without lymph node sampling, which was a significant difference. There was no significant difference in subgroups of patients less than 50 years of ages, germ cell tumours, stroma cell tumours, clear cell carcinoma and grade 1 and 2 tumours. There was a significant difference for non-clear cell epithelial ovarian carcinoma of 93.3% compared to 85.9% ($p<0.001$). Main disadvantage of this large study is that there were no data on adjuvant chemotherapy.

It would appear therefore that the potential under staging of ovarian tumours could be compensated for by overtreatment of patients with chemotherapy (which historically is probably the case in many centres where lymphadenectomy is not routinely performed). In the absence of prospective randomised data to determine the therapeutic effect of systematic lymphadenectomy and until frozen section analysis becomes more widely available, this approach may be acceptable. However, it is recommended that survival outcomes for stage 1 ovarian cancer are assessed locally, to ensure that the observations alluded to above are comparable.

Following complete surgical staging, these women may be further divided prognostically based on high-risk variables, which include: high grade disease, clear cell histological type, tumour growth through capsule, surface excrescences, ascites, malignant cells in fluid, preoperative rupture, dense adherence and aneuploidy. [59, 60]

CLINICAL PRACTICE POINT 9

Systematic lymphadenectomy is not recommended for early stage disease, however enlarged lymph nodes should be removed at the time of surgery.

4.6 Incompletely Staged Ovarian Cancer

This is a very undesirable situation that must be avoided. It can lead to inevitable delays in adequate staging and optimal debulking, which can have an adverse impact on treatment and prognosis. One must also consider the significant morbid physical and psychological impact on the patient of having to undergo a second laparotomy.

A suggested approach to managing these patients is modified from the National Comprehensive Cancer Network (NCCN) guidelines [61]:

- A surgical staging procedure is recommended for all patients with suspected stage IA or IB, grade 1 tumours because, if this stage is confirmed, no further adjuvant therapy is indicated.
- If potentially resectable residual disease is suspected, a completion surgical staging procedure with debulking is recommended for all stages.
- For stages higher than stage IA or IB, grade 1, if no residual disease is suspected; chemotherapy or completion surgical staging may be considered. Observation after careful surgical staging is considered an option for stage IA or IB, grade 2 disease. For patients with stage II-IV disease, consider completion surgery after 3 cycles of chemotherapy followed by postoperative chemotherapy.

Laparoscopic staging can be considered.

CLINICAL PRACTICE POINT 10

Incomplete staging of ovarian cancer must be avoided. In case of incomplete staging, the MDT decides whether restaging or adjuvant chemotherapy without staging is appropriate. Laparoscopic staging can be considered. Completion staging should be performed in the cancer centre.

4.7 Fertility Preservation

There is retrospective data to suggest that fertility conserving procedures in patients with grade 1 and 2 stage 1 non-clear cell epithelial ovarian cancer have excellent long-term survival. [62] The uterus and contralateral ovary can be retained in women wishing to preserve fertility provided they have undergone a thorough staging laparotomy where it was confirmed that there was no disease outside the pelvis. [63] This applies as well to patients with borderline ovarian tumours. [64]

In a recent systematic review, patients with stage 1A or 1B had a recurrence rate of 9.9% with fertility sparing surgery, while stage 1C significantly increased the risk of recurrence to 15.4%. Although the number of available patients for analysis was small, it is important to state that patients with stage 1C3 had a recurrence rate of 38.1% compared to 12% in stage IC1/2. Recurrence rate for high-grade tumours was 25.6% compared to 9.1% in grade 1–2. Given the tendency of ovarian cancer to recur transperitoneally, it is hypothesized that grade and stage, but not fertility sparing surgery, add to the risk of relapse. After fertility sparing surgery, only 44.2% of the patients have a pregnancy wish and 29.5% achieve a pregnancy. Patients should be carefully informed about their prognosis, to enable them to make a personalized and informed choice.

CLINICAL PRACTICE POINT 11

Fertility sparing treatment (preserving uterus and contralateral ovary) can be considered in patients with grade 1 and 2 stage 1 non-clear cell epithelial ovarian cancer. Patients should be carefully informed about their prognosis, to enable them to make a personalized and informed choice.

5. Advanced (metastatic) Disease (Cancer Centre)

There is evidence that survival of women with advanced ovarian cancer is improved when the surgeon is trained to perform cytoreductive surgery [65] and when there is centralisation of care. [5] The treatment aim of laparotomy for advanced disease is to achieve complete cytoreduction. Complete cytoreduction is defined as the removal of all macroscopically visible disease. Optimal debulking

is defined as one or more residual tumour nodules 1-10mm in maximal dimension by the Gynaecologic Oncology Group (GOG).

The benefit of maximal cytoreduction seems clear and women with optimally debulked tumour have on average a 20-month improvement in median survival compared to those with suboptimal resection. [38] There also appears to be benefit in optimal cytoreduction of stage IV disease. [66] However, a growing body of evidence supports the role of cytoreduction to < 1mm or no visible disease with improved survival. An analysis of data of 3,126 women who had primary debulking surgery in three randomised controlled trials on different chemotherapy regimens (AGO-OVAR 3, 5 and 7) showed that median overall survival was significantly higher in women who had complete residual resection (99.1 months) compared to optimal residual resection with residual disease 1-10mm (36.2 months) and incomplete residual resection with residual disease >10mm (29.6 months). [67] Complete residual resection was achieved in 33.5% of women, with stage IIB-IV ovarian cancer. Another retrospective study also showed higher median progression free survival and overall survival in women with complete residual resection at primary debulking surgery (33.0 respectively 71.9 months) compared to optimal residual resection with residual disease 1-10mm (16.8 respectively 42.4 months) and incomplete residual resection with residual disease >10mm (14.1 respectively 35.0 months). [39] All women had stage III ovarian cancer and complete residual resection was achieved in 23.1% of cases. In a retrospective review of 360 women with stage IV ovarian cancer complete residual resection was achieved in 8.1% of cases with median progression free survival and overall survival of 20.1 respectively 64.1 months, compared to 13.0 respectively 28.7 months in case of optimal residual resection with residual disease 1-10mm. [68] These so called ultra-radical procedures may include extensive peritonectomies, resection of subcapsular liver metastases, partial gastrectomy etc. Despite an increased incidence of postoperative morbidity, median survival for these patients is impressive enough to attract much interest in the UK, but this is not considered standard treatment at present. The NICE guideline states that current evidence on the safety and efficacy of ultra-

radical surgery for advanced ovarian cancer is inadequate. Therefore, this procedure should not be done except with special arrangements for clinical governance, consent and audit or research. [69]

CLINICAL PRACTICE POINT 12
The goal standard of debulking surgery is complete cytoreduction.

Exceptions to initial surgical management include [70]:

1. Patients with poor nutritional and performance status in addition to severe medical co morbidity. In these patients, the risk of perioperative morbidity and mortality may be unacceptably high. [71]
2. Patients in whom an extra-ovarian primary tumour is a possibility and has not been excluded.
3. Preoperative assessment of resectability and optimal clearance: This relates to patients who appear to have such a high tumour burden that optimal cytoreduction does not appear to be feasible. Patients are not offered primary surgery if any of the following factors are present [72]:

- Diffuse deep infiltration of the root of small bowel mesentery
- Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 m)
- Diffuse involvement/deep infiltration of stomach/duodenum or head or middle part of pancreas
- Involvement of coeliac trunk, hepatic arteries, left gastric artery
- Central or multisegmental parenchymal liver and/or lung metastases
- Non-resectable lymph nodes
- Brain metastases

Predicting optimal cytoreduction is very difficult and may be related to the following [73]: High preoperative CA125, strong expression of the p53 tumour suppression gene and imaging (CT, CT/PET and MRI). Preoperative CT has shown promise, but caution regarding its use has been advised in a validation study. [74] Efforts to improve the prediction of optimal cytoreduction include the use of

diagnostic laparoscopy, which has been shown to be useful in assessing resectability in advanced disease. [75, 76] Nonetheless, the value of laparoscopy on overall surgical and clinical outcome of advanced ovarian cancer has not been established. [77, 78] Besides that, there is concern regarding the significant risk of port site metastases. [79]

CLINICAL PRACTICE POINT 13
The MDT has the crucial role to decide if there is a reason not to perform primary debulking surgery. This limiting factor should be documented.

The planning and implementation of an efficient cytoreductive surgery service requires advanced operating theatres with highly skilled theatre staff. [48] Involvement of other oncological surgical subspecialists is often required and there is a significant impact on operating time. Such a high demand on specialist resources can only be readily achieved and maintained at the cancer centre.

5.1. Procedure for Cytoreductive Surgery

The aim is to remove the entire primary tumour and all visible macroscopic disease.

As before, a vertical midline approach is recommended, this can be extended if necessary:

- TAH+BSO – this is very seldom straightforward and commonly requires a retroperitoneal approach depending on pelvic anatomy.
- Supracolic and infracolic (total) omentectomy.
- Sampling and drainage of ascites (or washings if no ascites).
- Resection of all macroscopic peritoneal deposits > 1cm in diameter.

The following should be considered especially if it allowed maximal cytoreduction to be achieved:

- Rectosigmoid excision (en bloc with uterus, ovarian masses and pelvic peritoneum - Hudson procedure [80]) or intestinal resection: These procedures may also be considered in the setting of obstruction.
- Appendicectomy
- Splenectomy [81]

- Partial hepatic resection [82]
- Debulking of grossly suspicious lymph nodes
- Diaphragmatic stripping/resection

Factors limiting optimal cytoreduction at the time of surgery include:

- Diffuse encasement of small bowel mesenteric vessels – in this setting, multiple small bowel resections and/or a permanent ileostomy are not advised
- Infiltration of porta hepatis
- Diffuse infiltrative involvement of the right hemi-diaphragm including the suprahepatic inferior vena cava (IVC)
-

5.2 Systematic Lymphadenectomy

The role of systematic pelvic and para-aortic lymph node dissection in patients with completely resected ovarian cancer was ambiguous until recently. An earlier RCT comparing systematic lymphadenectomy with a control arm who did not have lymphadenectomy showed an improvement in progression-free, but not overall survival. [83]. More recently however, the LION trial showed no difference in progression-free or overall survival between the two approaches. [84]. In both studies, complication rates were higher in the systematic lymphadenectomy arm. [83, 84] While resection of grossly suspicious lymph nodes is considered part of the surgical debulking procedure, systemic lymphadenectomy has not been shown to confer a significant survival advantage [83, 84].

CLINICAL PRACTICE POINT 14
Standard systemic lymphadenectomy has no role in debulking surgery. Only grossly suspicious lymph nodes should be resected.

5.3. Interval Debulking Surgery (IDS)

Neoadjuvant chemotherapy followed by surgery (NACT-S) is the term applied to the strategy of primary chemotherapy in surgically resectable cases. There are four large randomised controlled trials comparing primary debulking surgery and adjuvant chemotherapy to NACT-S: EORTC 55971, CHORUS, SCORPION and JCOG0602. The EORTC trial included 670 women with stage IIIC or IV ovarian cancer and had a median follow-up of 9.2 years. [85] The CHORUS trial included

550 women with stage IIIA, IIIB, IIIC or IV ovarian cancer and had a follow-up of 5.9 years. [86] Both studies found no significant difference in overall survival, but there were less grade III and IV adverse events with NACT-S with no difference in quality of life. For women with stage IV ovarian cancer there was a significant improved median disease free survival and overall survival with NACT-S. A comment on these studies was that they had a low percentage of complete resections (EORTC 19% and CHORUS 17% with primary debulking surgery and 51% respectively 43% with interval debulking surgery) and overall survival was low (29 respectively 30 months). [87] In the SCORPION trial 171 women with stage IIIC or IV with a high tumour load visualized with laparoscopy were randomised between primary debulking surgery with adjuvant chemotherapy or NACT-S. [88, 89] While there was a significant difference in complete resections (47.6% with primary debulking compared to 77.0% with interval debulking surgery), there was no significant difference in median progression free survival (15 versus 14 months) or median overall survival (41 versus 43 months). Major postoperative complications were significantly higher with primary debulking surgery (25.9% versus 7.6%). The JCOG0602 trial included 301 women with stage III or IV ovarian cancer. [90, 91] There was no significant difference in median progression free survival (15.1 versus 16.4 months) or median overall survival (49.0 versus 44.3 months). There is another ongoing trial, the Trial on Radical Upfront Surgery in Advanced Ovarian Cancer, of which the survival data are expected in 2023. [92]

Previous studies also supported the concept that primary chemotherapy rendered surgical debulking less morbid and technically easier. [93, 94] A meta-analysis of 17 studies including 3,759 women on morbidity and mortality in primary debulking surgery compared to NACT-S in advanced ovarian cancer showed that primary debulking surgery takes more theatre time, more blood loss, less complete or optimal resection, more Clavien-Dindo grade ≥ 3 morbidity, more infections, thrombotic events, fistulas, more bowel surgery, extended hospital stay, more mortality without 30 days postoperative and no difference in survival. [95]

Percutaneous biopsy should be done to confirm the diagnosis as gold standard to allow molecular testing (sBRCA) while treatment naïve.

If a biopsy specimen is not possible then fine needle aspirate (FNA) showing adenocarcinoma cells may be acceptable under the following conditions:

- Presence of ovarian neoplasm on imaging
- Evidence of extra-pelvic spread> 2cm in size
- Regional lymph node metastases or stage IV disease
- CA 125/CEA ratio > 25. If < 25, consider GI endoscopy and mammography

The preferred standard is that primary treatment should begin within two weeks and no later than three weeks from the date of decision to treat. [29] If neo-adjuvant chemotherapy is chosen, chemotherapy should be initiated no later than three weeks from the date of percutaneous biopsy.

In general, three cycles of chemotherapy are administered and a response to treatment is ascertained by clinical, radiological and biochemical means. If there is a response to chemotherapy (usually after 3 cycles), interval debulking should be offered followed by a further 3 cycles of chemotherapy. No response to chemotherapy is an indication for experimental protocols and/or palliation. Following completion of 6 cycles, the MDT shall discuss the role of maintenance treatment or continued surveillance.

CLINICAL PRACTICE POINT 15
Neo-adjuvant chemotherapy with interval debulking surgery is an alternative when primary debulking surgery is not feasible.

The role of adjuvant intraperitoneal chemotherapy (IPC) postoperatively and hyperthermic intraperitoneal chemotherapy (HIPEC) perioperatively is discussed in section 6.

5.4. Management Following Suboptimal Cytoreduction

Prospective trials have been carried out to assess survival benefit of interval debulking after an initial surgical effort. The evidence is mixed [93, 96-98] and mainly depending on whether a maximum surgical effort was undertaken in the

first attempt. This is especially the case when the initial attempt at debulking was not carried out by a gynaecological oncologist. [93]

Decisions of this nature are complex and should be made at the cancer centre MDT.

CLINICAL PRACTICE POINT 16
Second attempt at primary debulking surgery after suboptimal cytoreduction can be considered if the initial attempt was not carried out by a gynaecological oncologist.

5.5. Secondary Cytoreduction

This may be defined as an attempt at cytoreductive surgery at some stage following completion of first line chemotherapy. It has been suggested that tumour resection under these circumstances should be limited to patients with a long natural history, with a disease-free interval of at least 12 months, with the possibility that all macroscopic disease can be resected. [99]

There are three large randomised controlled trials on secondary debulking surgery in which women with a first recurrence and a platinum free interval of at least 6 months were randomly assigned to surgery with chemotherapy or chemotherapy alone: GOG-213, DESKTOP and SOC-1. [100-102] The GOG-213 included 485 women. The recurrence had to be resectable to no macroscopic residual disease as determined by the investigator. Complete resection was achieved in 67% of cases in the surgery with chemotherapy group. Median progression free and overall survival were not significantly different in both groups (progression free survival 18.9 versus 16.2 months and 50.6 versus 64.6 months). The DESKTOP included 407 women with a good performance score (ECOG 0), complete resection during first line therapy and ascites less than 500ml. Complete resection was achieved in 75.5% of cases in the surgery with chemotherapy group. Median progression free and overall survival were significantly better in the group that had surgery: 18.4 versus 14.0 months for progression free survival, 53.7 versus 46.0 months for overall survival. For women who had complete resection during secondary debulking overall survival was 61.9 months. Quality of life measures through 1 year of follow-up did not differ between the two groups. The SOC-1

included 357 women using a model for eligibility based on FIGO stage, residual disease after primary surgery, platinum-free interval, ECOG performance status, CA 125 at recurrence and presence of ascites at recurrence. Median progression free survival was significantly better in the group that had surgery: 17.4 versus 11.9 months. The interim overall survival was not significantly different: 58.1 versus 53.9 months.

CLINICAL PRACTICE POINT 17

Secondary debulking surgery after first line treatment can be considered in certain circumstances. Reasons for, or against a decision to offer secondary cytoreductive surgery should be clearly documented by the MDT. Only cases that achieve complete cytoreduction have a benefit from secondary debulking surgery.

5.6. Palliative Care

For patients for whom a palliative approach is appropriate, including those who need active treatment such as chemotherapy or surgery with palliative intent, the primary care team and the local MDT will lead on providing that approach. Communication from the MDT to primary care that a palliative approach is being taken is key with clear guidance to primary care that the patient should be put on the palliative care register within the GP practice. Sources of written guidance on symptom control for the non-specialist are available in Appendix 3.

6. Chemotherapy

Inclusion in clinical trials, if available, is recommended for all patients with ovarian cancer who need chemotherapy. Outside clinical trials, the standard recommendations for chemotherapy are outlined here with regards to first-line (adjuvant or neoadjuvant) chemotherapy and treatments for relapsed disease.

6.1. First-line Chemotherapy

6.1.1 Early stage disease (FIGO I-IIa)

Completely debulked and optimally staged patients with FIGO IA grade 1 tumours are at low risk of recurrence and can be managed by follow up only. Chemotherapy should however be considered in sub optimally staged patients.

Patients with risk factors for recurrence (grade >1; bilateral cancers; clear cell histology; capsule ruptured; presence of tumour on ovarian surface; malignant cells in ascites or peritoneal washings) should be offered adjuvant chemotherapy. NICE guidance states that platinum + taxol or platinum alone can be offered as alternatives to these patients; the use of single-agent carboplatin is supported by the ICON1 and ACTION studies. [51]

The recent ESMO-ESGO consensus further updated the recommendations for adjuvant chemotherapy in early-stage ovarian cancer. It was advised that adjuvant chemotherapy should be offered to patients based on stage, grade and histological subtype as per the tables below. It was felt that both carboplatin and carboplatin and paclitaxel are acceptable treatment regimens for early stage disease with 6 cycles recommended for single agent carboplatin and a minimum of 3 cycles of carboplatin and paclitaxel other than those with high grade serous histology or stage 1C (any histological subtype) for whom 6 cycles are recommended as demonstrated in figures below. [103]

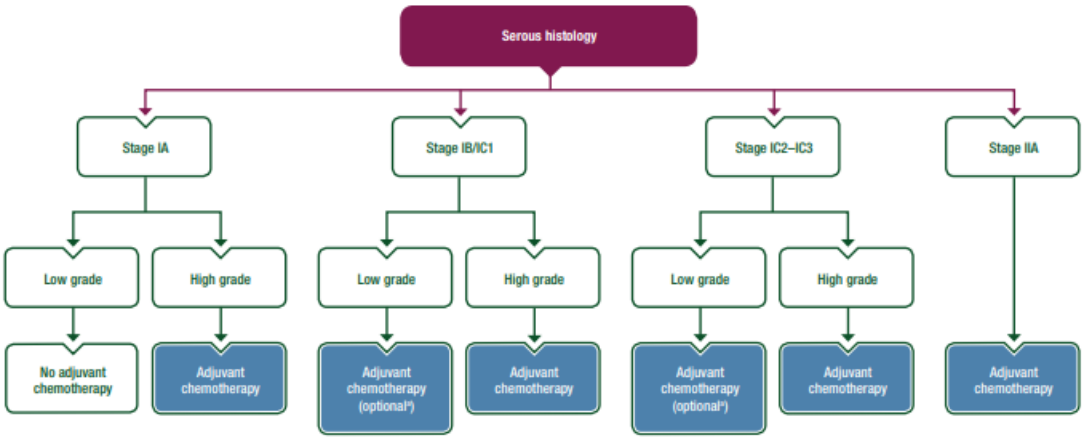


Figure 1. Adjuvant chemotherapy for patients with early-stage serous ovarian cancer (stage I–IIA).
[a]Considered no adjuvant chemotherapy only for patients with complete surgical staging.

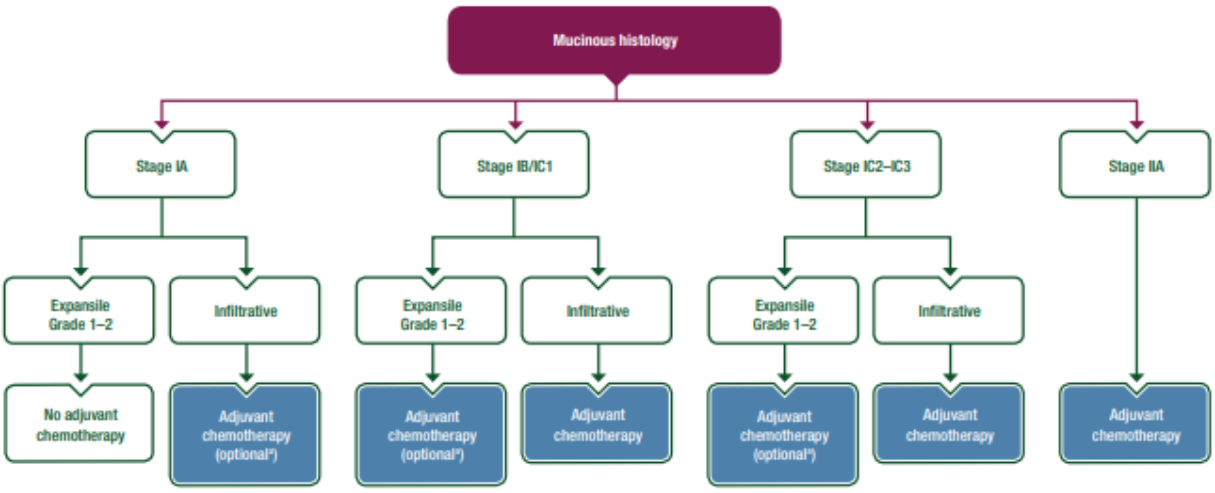


Figure 2. Adjuvant chemotherapy for patients with early-stage mucinous ovarian cancer (stage I–IIA).
[a]Considered no adjuvant chemotherapy only for patients with complete surgical staging.

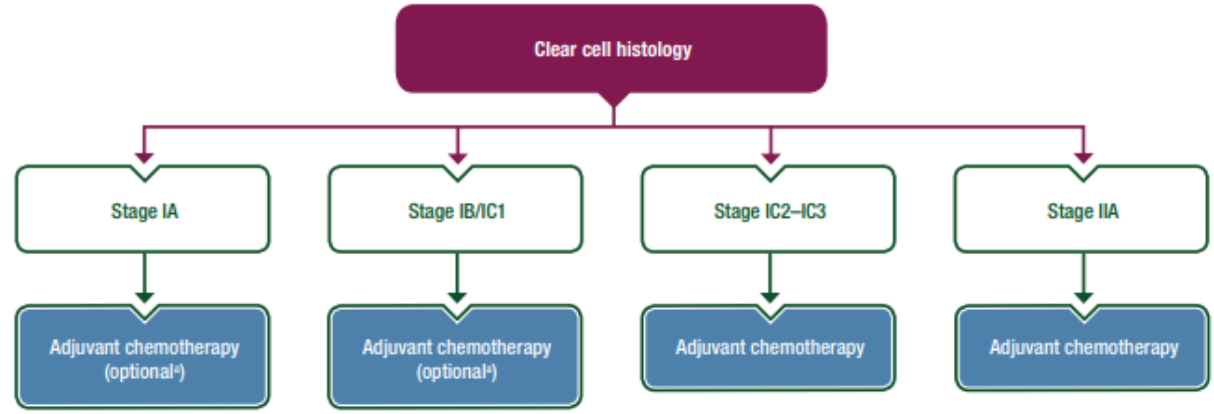


Figure 3. Adjuvant chemotherapy for patients with early-stage clear cell ovarian cancer (stage I–IIA).
[a]Considered no adjuvant chemotherapy only for patients with complete surgical staging.

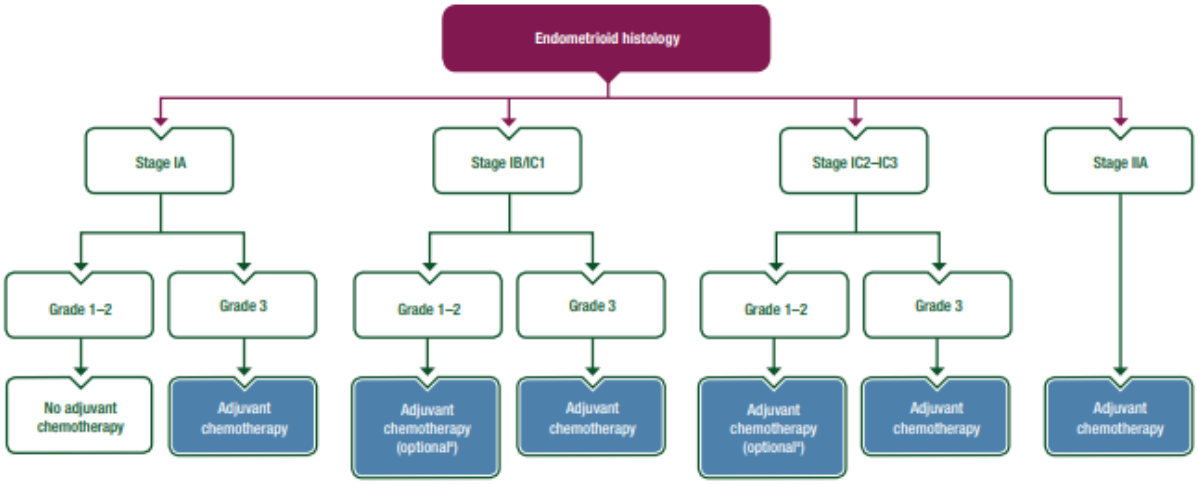


Figure 4. Adjuvant chemotherapy for patients with early-stage endometrioid ovarian cancer (stage I–IIA).
[a]Considered no adjuvant chemotherapy only for patients with complete surgical staging.

6.1.2 Advanced disease (FIGO IIb-IV)

Postoperative chemotherapy

NICE guidance states that platinum + taxol or platinum alone can be offered as alternatives to these patients; however, since all major international guidelines recommend combination therapy for patients with advanced disease, the carboplatin + paclitaxel regimen is considered the optimum treatment:

- Paclitaxel 175mg/m^2 over 3 hours (give paclitaxel first and Carboplatin AUC 5/6 over 30 minutes (see below), repeated every 21 days for 6 cycles
- The Carboplatin doses are calculated according to the Calvert formula:
    - Carboplatin dose in mg = (desired AUC) x (GFR+25)
- The GFR used in the Calvert formula for carboplatin dosing should not exceed 125mls/min.

It is recommended that EDTA clearance is the most accurate method for measuring GFR unless there is significant third space fluid collection (ascites, pleural effusions or gross peripheral oedema) which makes this method inaccurate. If a calculated creatinine clearance is used to calculate the carboplatin dose, then the Wright formula should be used with target carboplatin dose AUC 5 as that formulae has been shown to correspond to directly measured GFR in cancer patients. If the Cockcroft-Gault or Jelliffe formulae are used, then AUC 6 dose of carboplatin should be used as these formulae usually obtain a lower GFR compared to a directly measured GFR. Serum creatinine and weight should be rechecked before each cycle, but only in case of significant variations from baseline (GFR change>25%, or weight change >10%) does the dose need to be recalculated. Actual body weight should be used in the formulae.

These formulae can be inaccurate at the extremes of age and weight and calculated GFR may be falsely high in obese young women and falsely low in thin elderly women and an isotopic GFR should be used instead. If calculated creatinine clearance is <60mls/min then isotope calculation of GFR is also recommended.

Chemotherapy in patients with poor performance score: Weekly chemotherapy can be considered in frail patients who may not tolerate standard three-weekly carboplatin and paclitaxel:

- Paclitaxel 60mg/m^2 over 1 hour (give paclitaxel first) and Carboplatin AUC 2 over 30 minutes. This is given days 1,8 and 15 every 28 days for 6 cycles.
- Single-agent carboplatin (weekly AUC 2 or three-weekly AUC 5-6) is an option for patients who are not suitable for the regimens listed above, or unwilling to accept hair loss.

Maintenance chemotherapy (beyond 6 cycles) may prolong progression free survival but there is no demonstration of overall survival benefit: in view of the additional toxicity, this is not a recommended strategy.

Postoperative chemotherapy should be preceded by a restaging CT scan of abdomen and pelvis. If this shows residual disease, another CT scan should be performed after completion of chemotherapy to document the overall results of treatment and serve as a new baseline if further scans are obtained during follow up.

Ca125 levels must be checked before starting postoperative chemotherapy and monitored during treatment. If CA125 fails to normalize by the end of chemotherapy, the nadir level will be used as baseline to assess biochemical progression during follow up.

6.2. Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy with interval debulking surgery is an option when primary optimal debulking is considered unlikely by the MDT with primary surgery as discussed above (Section 5.2). A meta-analysis demonstrated that neoadjuvant treatment resulted in less morbidity and mortality and improved cytoreduction but did not impart a survival benefit. [95] The treatment protocol should emulate as much as possible the EORTC study [85], with an aim of starting chemotherapy within 3 weeks from biopsy. IDS should be performed after 3 cycles in all non-progressing patients; chemotherapy is restarted no later than 6 weeks after IDS and given for 3 more cycles. [86]

The chemotherapy response score (CRS) has been developed to assess histological effect in ovarian cancer after neoadjuvant chemotherapy. The CRS stratifies patients into complete/near response (CRS 3), partial (CRS 2) and no/minimal (CRS 2) response based on omental examination. A systematic review and meta-analysis confirmed that CRS 3 was significantly associated with an improved progression-free survival and overall survival compared to CRS ½. [104] Recent ESMO-ESGO guidance recommended that the pathological chemotherapy response score (CRS) may provide an objective and reproducible prognostic measure of outcome in high-grade serous ovarian cancer. [103]

6.3. Bevacizumab

Bevacizumab can be given with first-line chemotherapy and as a maintenance therapy afterwards for a total of 18 cycles. The GOG 218 study used adjuvant Bevacizumab at a dose of 15mg/kg for 15 months in those with stage III/IV epithelial ovarian cancer and while in the intent to treat analysis there was no improvement in overall survival, a sub-group analysis demonstrated an improvement in progression-free and overall survival in women with ascites and stage IV disease. [105] The ICON 7 trial in high-risk early stage and advanced epithelial ovarian cancer used Bevacizumab at a dose of 7.5mg/kg for 18 cycles and again there was no survival benefit in the intent to treat population, but a non-planned analysis demonstrated an improvement in progression free and overall survival in patients with stage III disease and residual disease >1cm, inoperable Stage III disease and stage IV. [106]

There is increasing interest in the use of neo-adjuvant bevacizumab and the efficacy and the safety of bevacizumab in addition to carboplatin and paclitaxel has been reviewed in the ANTHALYA trial. This demonstrated that the complete resection was higher in those receiving bevacizumab in addition to chemotherapy with manageable toxicity. [107] Neo-adjuvant bevacizumab is available as below, but it is felt that the results of further clinical trials will help clearly define of the role of bevacizumab in this setting.

The current Cancer drug funded indications for Bevacizumab in EOC administered with carboplatin and paclitaxel combination are: [108]

- FIGO Stage III debulked but residual disease more than 1cm
- Stage III at presentation and requiring neo-adjuvant chemotherapy due to the low likelihood of optimal primary surgical reduction.
- Stage III with contra-indication to debulking surgery
- Stage IV disease

Bevacizumab is generally well tolerated but has a different side effect profile than cytotoxic chemotherapy. In ovarian cancer the main toxicities are hypertension, proteinuria and the potential for bowel perforation so it is important to consider these factors when selecting patients most likely to benefit from the treatment. The risk appears higher in those with significant small bowel disease, bowel symptoms or bowel obstruction and these cases can be reviewed at MDT.

6.4. Maintenance PARP inhibitors in First-line Treatment

The role of BRCA testing for germline or somatic mutations has become increasingly important both for identifying high risk families and to help guide treatment options in gynaecological cancers. PARP inhibitors (Poly-ADP ribose polymerase) are a group of drugs that inhibit the repair of single strand DNA breaks which leads to an increase in double strand DNA repair breaks and failure to repair these due to deficiencies in homologous repair pathways can lead to cell death. Homologous recombination deficiency (HRD) is not limited to tumours with BRCA mutations and is thought to present in approximately 50% of high grade serous ovarian cancers. [109] PARP inhibitors have shown most activity in patients who carry a germline or somatic BRCA mutation but there is increasing evidence for their benefit in patients in those who are BRCA negative but HRD deficient and even in those who are HRD proficient but respond to platinum treatment.

The SOLO 1 trial demonstrated a 70% reduction in risk of progression or death in patients with a BRCA mutation (germline or somatic) and advanced high grade serous or high grade endometrioid cancer of tubo-ovarian origin who had

complete or partial response after platinum chemotherapy with maintenance Olaparib for 2 years versus placebo. The trial data is not yet mature to demonstrate a survival benefit but it demonstrated a 70% reduction in the risk of disease progression or death and at 5 years 48% patients receiving Olaparib were progression-free compared to 21% on placebo. [110] The main toxicities were fatigue, anaemia and low-grade gastro-intestinal toxicity with incidence of AML/myelodysplastic syndrome < 1.5%.

The PRIMA trial compared Niraparib versus placebo for 3 years in patients with advanced tubo-ovarian cancer in all patients responding to platinum-based treatment after surgery and chemotherapy. This trial used the Myriad My choice score to assess for homologous recombination deficiency. This trial demonstrated an improvement in progression-free survival in all groups with greatest benefit seen in those with a BRCA mutated cancer, followed by those who were HRD deficient, but a benefit was still seen in the HRD proficient group and overall intent to treat population. [111] The safety profile was improved with the implementation of the individualised dosing regimen with a start dose of 200mg od for patients with low platelets or body weight <77kg. The toxicities were mainly haematological with low grade nausea and fatigue and hypertension.

The combination of Olaparib and Bevacizumab has recently been approved based on the PAOLA-1 clinical trial which looked at patients with advanced high grade ovarian cancer who were in response after first-line platinum-taxane chemotherapy plus bevacizumab (15 months at a dose of 15mg/kg) and were randomised to the addition of Olaparib versus placebo for 2 years. [112] HRD status was assessed by Myriad test. The overall results in the intent to treat population demonstrated progression-free survival was 22.1 months in the combination arm versus 16.6 months in the Olaparib arm. However, the risk of disease progression or death was 67% lower in patients who were positive for HRD deficiency (including tumours with BRCA mutations), 57% lower in patients who were positive for HRD deficiency (excluding tumours with BRCA mutations) while only 8% lower in patients who were negative for HRD deficiency or unknown status. The overall survival data is immature. Most common adverse events were

anaemia and hypertension with fatal adverse events <1%. There was no significant difference in global quality of life scores between the treatment arms although there was a 20% discontinuation rate in the combination arm versus 6% in the Olaparib only arm.

The current Cancer drug funded indications for PARP inhibitors in first line are:

Niraparib monotherapy as maintenance treatment in patients with high-grade epithelial stage III or IV ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based first line chemotherapy both with and without a somatic or germline mutation. The treatment needs to commence within 12 weeks from the date of the first day of the last cycle of chemotherapy and patient needs to have a WHO performance score 0/1.

Olaparib monotherapy as maintenance treatment in patients with high-grade epithelial stage III or IV ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based first line chemotherapy with a somatic or germline mutation. The treatment needs to commence within 8 weeks from the date of the first day of the last cycle of chemotherapy and patient needs to have a WHO performance score 0/1. If patients had residual disease and are demonstrating an ongoing response to treatment Olaparib can be continued over 2 years.

Olaparib in combination with bevacizumab in patients with high-grade epithelial stage III/IV ovarian, fallopian tube or primary peritoneal cancer who are in response following first line chemotherapy and whose cancer has a positive status for homologous recombination deficiency as defined by the presence of either a deleterious or suspected deleterious BRCA 1 / 2 germline and/or somatic mutation or genomic instability (Myriad test). In this combination bevacizumab is specified as 15mg/kg for a maximum duration of 15 calendar months from the start of bevacizumab-containing treatment whether with chemotherapy or as maintenance. Combination needs to start within 9 weeks from date of last infusion of the last cycle of first line chemotherapy and patients need to have a WHO performance score 0/1.

6.5. Intraperitoneal Chemotherapy (IPC)

Studies have shown (including a systematic review) that IPC is associated with better outcomes than intravenous chemotherapy [113, 114]. This led to a National Cancer Institute announcement in 2006 recommending that women with optimally debulked Stage 3 ovarian cancer be considered for IPC. Serious concerns have been raised however regarding its associated morbidity and technical difficulties. [115] As such it is not recommended as a standard of care in the 2019 ESMO-ESGO consensus and is not seen as standard practice in the UK at present.

6.6. Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

A Dutch study presented in 2018 demonstrated a survival advantage with hyperthermic intraperitoneal chemotherapy in stage III patients undergoing interval cytoreductive surgery after neo-adjuvant chemotherapy but there was concern that the final analysis was based on a very small number of patients which could introduce significant bias (OVHIPEC). [116] A smaller Korean study failed to show a significant difference in 5-year survival so the outcome of further trials are awaited and it is not recommended as a current standard of care within the UK. [117]

6.7. Chemotherapy for Relapsed Disease

The choice of second- and further line chemotherapy traditionally depended on an evaluation of the likelihood of platinum sensitivity which had been defined according to the time since completion of platinum treatment, but this was challenged in the 2019 ESMO-ESGO consensus guidelines it was acknowledged that there are no molecular markers to predict platinum response and therefore the specified time points of <6 months and >6 months to define platinum sensitivity should now be seen more as a continuum. Therefore, platinum sensitivity should be seen as a therapy-orientated definition and treatment should be guided by assessment of platinum progression during platinum therapy or associated/expected response or resistance to platinum based on previous response to platinum and whether early symptomatic relapse. [103]

Factors that should be considered at relapse to guide treatment include tumour histology/biology, number of previous lines of chemotherapy and prior response to treatment, the treatment free interval for platinum, symptoms, persistent toxicity from previous treatment and patient preference. Following the survival benefit seen with DESKTOP 3 surgery may also be considered an option for patients who meet AGO criteria in first relapse as discussed above (Section 5.4)

For patients in whom platinum rechallenge is considered justified this can be as a combination platinum as supported by the ICON4/AGO/OVAR trials, suggesting survival improvement compared to single agent platinum. [118] The ideal platinum-based combination is not known but options include:

- Carboplatin and paclitaxel: Paclitaxel 175mg/m^2 over 3 hours (give paclitaxel first) and Carboplatin AUC 5/6 over 30 minutes, repeated every 21 days for 6 cycles.
- Carboplatin and Liposomal Doxorubicin (Caelyx): Caelyx 30mg/m^2 over 60 minutes and carboplatin AUC 5 over 30 minutes repeated every 28 days for 6 cycles
- Carboplatin and gemcitabine: Carboplatin AUC 4 over 30 minutes and Gemcitabine 1000mg/m2 on days 1 and 8, repeated every 21 days for 6 cycles (not in first relapse)

In platinum-based chemotherapy regimens 6 cycles are recommended as more or fewer cycles have not been shown to be beneficial and consideration should be given to toxicity.

Treatment options for patients in whom platinum is not the best option due to progression on prior platinum treatment, early symptomatic relapse or platinum intolerability should consider single agent non-platinum therapy. In patients with a treatment free interval of less than 6 months the anticipated median overall survival is 10-12 months and therefore the aim of treatment is to improve symptoms with a minimum of side-effects to improve quality of life. Non-platinum regimens should be selected based on toxicity profile and patient preference. The AURELIA study showed the addition of bevacizumab improved

progression-free survival in these patients in combination with caelyx, weekly paclitaxel or topotecan but is not currently available in this setting in the UK. [119]

- Single agent treatment options: Paclitaxel 80 mg/m2 weekly
- Liposomal doxorubicin 40 mg/m2 over 60 minutes every 28 day
- Topotecan 1.25 mg/m2 day 1-5 every 21 days
- Topotecan 4 mg/m2 days 1, 8, 15 every 28 days
- Gemcitabine 1000 mg/m2 days 1, 8, 15 every 28 days
- Oral etoposide 50 mg bd days 1-14 every 21 days
- Oral cyclophosphamide 50mg od, days 1-21 every 28 days

6.8. Maintenance PARP inhibitors in Relapsed Disease

There are 3 PARP inhibitors approved as maintenance in the relapsed disease setting in patients who are in complete or partial response to their platinum-containing regimen for relapsed disease. Olaparib maintenance therapy following platinum-containing regimen demonstrated an improvement in progression free survival for those with a BRCA mutation in Study 19 and SOLO 2 clinical trials. [120, 121] Study 19 also included patients without a BRCA mutation and again demonstrated an improvement in progression-free survival. [121] Study 19 did not demonstrate a survival benefit but a pre-planned final overall survival analysis in SOLO 2 did demonstrate a survival benefit. [122]

The NOVA trial demonstrated an improvement in progression free survival for patients with and without a BRCA germline mutation with the benefit being greatest in those with a BRCA mutation and least in those who were HRD-negative. [123]

The ARIEL 3 trial also demonstrated an improvement in progression-free survival for Rucaparib in patients with high-grade serous or endometrioid cancer in first relapse and demonstrated an improvement in progression-free survival of greatest magnitude in those with BRCA mutation but also in the intent to treat population. [124]

<u>The current Cancer drug funded indications for PARP inhibitors as maintenance in relapsed disease</u>:

Niraparib as a maintenance treatment in patients with high grade epithelial ovarian, fallopian tube or primary peritoneal cancer with and without a germline and/or somatic BRCA mutation who have had a recent first relapse and are in response following a second platinum-based chemotherapy. Niraparib is only approved post second line chemotherapy in those with BRCA mutation but for those who do not have a BRCA mutation it is approved after first or subsequent relapse if patient has not received an earlier PARP inhibitor. Niraparib needs to start within 8 weeks of the last infusion of the last cycle of chemotherapy and patients need to have a WHO performance score 0/1.

Olaparib as a maintenance treatment in patients with high grade epithelial ovarian, fallopian tube or primary peritoneal cancer with a germline and/or somatic BRCA mutation who are in response following a second or subsequent line platinum-based chemotherapy for relapse. Olaparib needs to be started within 8 weeks of the last infusion of the last cycle of chemotherapy and patients need to have a WHO performance score 0/1.

Rucaparib as a maintenance treatment in patients with high grade epithelial ovarian, fallopian tube or primary peritoneal cancer with and without a germline and/or somatic BRCA mutation who have had a recent first or subsequent relapse and are in response following a second or subsequent line platinum-based chemotherapy. Rucaparib needs to be started within 8 weeks of the last infusion of the last cycle of chemotherapy and patients need to have a WHO performance score 0/1.

PARP inhibitors have shown activity as a treatment option in relapsed disease in BRCA positive patients but are currently not available for this indication in UK.

6.9. Hormone Therapy in Relapsed Disease

The value of endocrine therapy with tamoxifen or aromatase inhibitors is not fully defined, but it represents a low-toxicity option in patients with asymptomatic relapsed disease as alternative to watchful waiting as demonstrated in the Paragon trial. [125-127]

6.10. Low-Grade Serous Ovarian Cancer

Low-grade serous cancers make up approximately 10% of serous ovarian cancers and have a distinct pathology, clinical pattern and prognosis compared to high-grade serous cancers. A diagnosis of low grade serous cancers may be de novo or progress from a precursor serous borderline tumour. The preoperative management is the same as for high-grade serous tumours and neo-adjuvant chemotherapy can be considered if deemed unresectable for primary debulking. The adjuvant treatment options for patients with low-grade cancers follow the same guidance as high-grade tumours however this histological sub-type does appear to have relative chemoresistance compared to high-grade. Therefore, further effective therapy is required.

A small retrospective study looked at maintenance endocrine therapy in patients with stage II-IV low-grade serous ovarian cancer who had completed primary chemotherapy. [128] Those receiving maintenance endocrine therapy had an improved progression-free survival of 65 versus 26 months with a trend to improved overall survival that did not reach significance. This option can be discussed with patients and more evidence will become available with current trial NRG-GY019 which is comparing platinum/taxane chemotherapy followed by letrozole maintenance therapy to letrozole monotherapy.

In recurrent low-grade serous cancer there are several treatment options that can be considered including chemotherapy and hormone therapy. Secondary debulking can be appropriate in selected patients. In view of relative chemoresistance to chemotherapy there have been 2 clinical trials assessing MEK-inhibitors for relapsed disease and while the MILO/ENGOT-ov11 (Binimetinib) trial was stopped early as it did not show benefit over physician's choice chemotherapy there was evidence of activity and KRAS mutation might predict response to Binimetinib. [129] The NRG-GOG 0281 treatment with Trametinib resulted in a 52% reduction in risk of disease progression or death with improved progression-free survival compared to physician choice of chemotherapy or letrozole. [130] Trametinib was made available through the Cancer Drug Fund during COVID-19 pandemic for treatment in England and Wales.

6.11 Response Evaluation

This is usually achieved with a combination of CA 125 and CT scans. Women with an elevated CA125 pre-treatment should have their CA125 levels checked at regular intervals during chemotherapy as levels correlate with tumour response and overall survival. [131] CT scans are useful as a baseline and usually do not need to be repeated until completion of six cycles of chemotherapy, or if there is suspicion of progression on treatment. Patients with normal baseline CA 125 should have a CT scan after 3 cycles to assess response, as should patients who are being considered for interval debulking.

6.12. Follow Up

Absence of symptoms does not indicate absence of disease as approximately 40% of asymptomatic women with no clinical evidence of recurrence can have disease at the time of second-look laparotomy. [132] Elevated CA 125 can accurately predict tumour recurrence and often does so prior to symptoms developing. A randomised study however showed no difference in survival in patients treated with second-line chemotherapy at biochemical relapse compared to patients who delayed treatment until they became symptomatic. [133] The authors suggested that on the basis of no increased survival benefit, that there was no value of performing routine CA 125 levels. This may be an oversimplification as there clearly must be some value in having a marker that predates symptomatic relapse, for example patients with a long natural history that might be candidates for secondary cytoreduction. It is recommended that until further data emerge patients are counselled at the time of follow up regarding the relative limitations and advantages of routine CA 125 measurement and a decision be made regarding its use on an individual basis.

Clinical follow up should take place on a three monthly basis for the first year, followed by six monthly intervals for two years, followed by annual review for a further 2 years. Consideration should be given to the establishment of nurse-led follow up clinics, with the combined oncology clinics reserved for patients at high risk or with suspected relapse.

7. Germ Cell and Other Non-Epithelial Cancers

These are a heterogeneous group of cancers which are rare but often curable. The management of these cancers should always be discussed in a multidisciplinary setting to ensure appropriate diagnosis, choice of surgical treatment and adjuvant treatment.

The following non-epithelial ovarian cancers will be discussed [61, 134]:

- Carcinosarcoma of the ovary
- Sex-cord and stromal tumours
- Germ cell tumours
- Small cell and NET tumours of the ovary
- Squamous carcinoma arising within a dermoid cyst
- Struma ovarii malignum

7.1. Carcinosarcoma of the ovary

These are rare tumours accounting for approximately 2-4% of all ovarian cancer tumours.

Surgically these should be treated as EOCs and undergo complete surgical staging.

7.1.1 Treatment

This should be considered in all patients with carcinosarcoma as all should be considered as high grade even stage 1. There is still no consensus on the optimal chemotherapeutic regimen for these patients; carboplatin and paclitaxel or regimens including ananthracycline and ifosfamide can be considered. Small series have reported similar response rates between these regimens: the local preference is for carboplatin and paclitaxel as per EOC as first line treatment. Patients with poor performance status can be offered single agent carboplatin in this setting. In patients with advanced disease or recurrence ifosfamide has shown activity but these patients are often treated using recommendations for EOC.

Follow-up should follow protocol as for EOCs.

7.2. Sex-cord and ovarian stromal tumours

These tumours account for approximately 7% of malignant ovarian cancers and derive from the sex cords and ovarian stroma or mesenchyme. [135] These

tumours can present with a combination of various elements including the female cells (granulosa cells, theca cells and their luteinized derivatives), male cells (Sertoli and Leydig cells) and fibroblasts of gonadal stromal origin as well as morphologically indifferent cells. This classification includes:

- Granulosa cell tumours, adult and juvenile forms

Granulosa cell tumours (GCT) are the commonest tumour in this group accounting for 70% of all malignant sex-cord stromal tumours and 3-5% of all ovarian cancers. The adult type account for 95% GCT's and usually occurs in perimenopausal women. It often presents with symptoms of excess oestrogen with endometrial hyperplasia, postmenopausal bleeding and pain and rarely a virilisation syndrome. Serum marker CA 125 is often not helpful and other markers can be helpful in diagnosis and monitoring disease e.g. oestradiol and inhibins. More than 95% of these tumours are unilateral and 78-91% are diagnosed at stage 1. This tumour has good long-term prognosis but can relapse very late and long-term follow-up is necessary.

Juvenile GCT tends to occur in prepubertal girls and often presents with unilateral, early stage disease. The majority present with isosexual precocious pseudo puberty, although rarely a virilisation syndrome can occur due to an androgen-secreting tumour.

- Fibromas, thecomas and fibrothecomas
- Sertoli cell, Leydig cell and Sertoli-Leydig cell tumours

These tumours most commonly occur in women <75 years and are rare accounting for <0.2% of ovarian cancer. These tumours are often stage 1 at presentation and low-grade with <20% becoming clinically malignant. Overall 5-year survival is 70-90% with recurrences usually occurring early. Again CA 125 is not helpful but testosterone can be a helpful marker

- Gynandroblastomas
- Sterol cell tumours
- Sex –cord tumour with annular tubules
- Associated with Peutz-Jegher syndrome
- Unclassified

7.2.1 Treatment

Cytoreductive surgery is the mainstay of treatment and is necessary to establish a diagnosis. The surgical principles are the same as in EOC although in apparent localized disease fertility-sparing surgery can be considered.

The only prognostic factor consistently significant in these cancers is the stage of disease. For Sertoli-Leydig cell tumours stage, histological differentiation, presence of heterologous elements and tumour rupture appear to have prognostic significance. Treatment guidance below as per ESMO Clinical Practice guidelines for non-epithelial ovarian cancer. [136]

7.3. Granulosa cell tumours

Stage 1A and 1C1	Adjuvant treatment not indicated
Stage 1C 2-3, Stage IIA-IV	Adjuvant platinum-based therapy (BEP or platinum-taxane)
Recurrent disease pelvic/intra-abdominal	Consider secondary debulking Consider platinum-based therapy as guided by previous treatments Consider RT for localised disease
Recurrent disease distant	Consider platinum-based therapy as guided by previous treatments Hormonal treatment in selected patients

7.4. Sertoli-Leydig tumours

Stage 1A with no high risk features	Adjuvant treatment not indicated
Stage 1A poorly differentiated or heterologous elements	Adjuvant platinum-based therapy (BEP or platinum-taxane)
Stage ≥1	Adjuvant platinum-based therapy (BEP or platinum-taxane)

Recurrent disease	Consider salvage surgery or Platinum-based chemotherapy (BEP platinum-taxane)

Long-term follow-up is recommended as recurrences can occur very late.

7.5. Germ-cell tumours

These tumours account for approximately 5% of ovarian tumours but with a high incidence in young women or adolescent girls.

This classification includes:

- Dysgerminoma
- Endodermal sinus tumour
- Embryonal carcinoma
- Polyembryoma
- Choriocarcinoma
- Teratoma: immature
- Teratoma: mature
- Solid cystic: dermoid cyst (mature cystic teratoma) or dermoid cyst with malignant transformation
- Monodermal and highly specialized: struma ovarii carcinoid, struma ovarii and carcinoid
- Mixed forms

These tumours often present with abdominal pain with rapid progression. Ascites or peritonitis secondary to torsion, infection or rupture of the tumour is also possible. Other less s common symptoms are abdominal distension and vaginal bleeding. Approximately 60-70% of women present with FIGO stage 1 or 2 disease, 20-30% stage 3 and stage 4 is infrequent. These tumours are often unilateral except for dysgerminomas which can present with bilateral disease in 10-15% cases. Tumour markers (AFP, β-hCG and LDH) can be helpful in diagnosis and should be considered in any young women presenting with a pelvic mass.

7.5.1 Treatment

Initial management should be cytoreductive surgery. As a high number of cases are stage 1 fertility-sparing surgery can be considered.

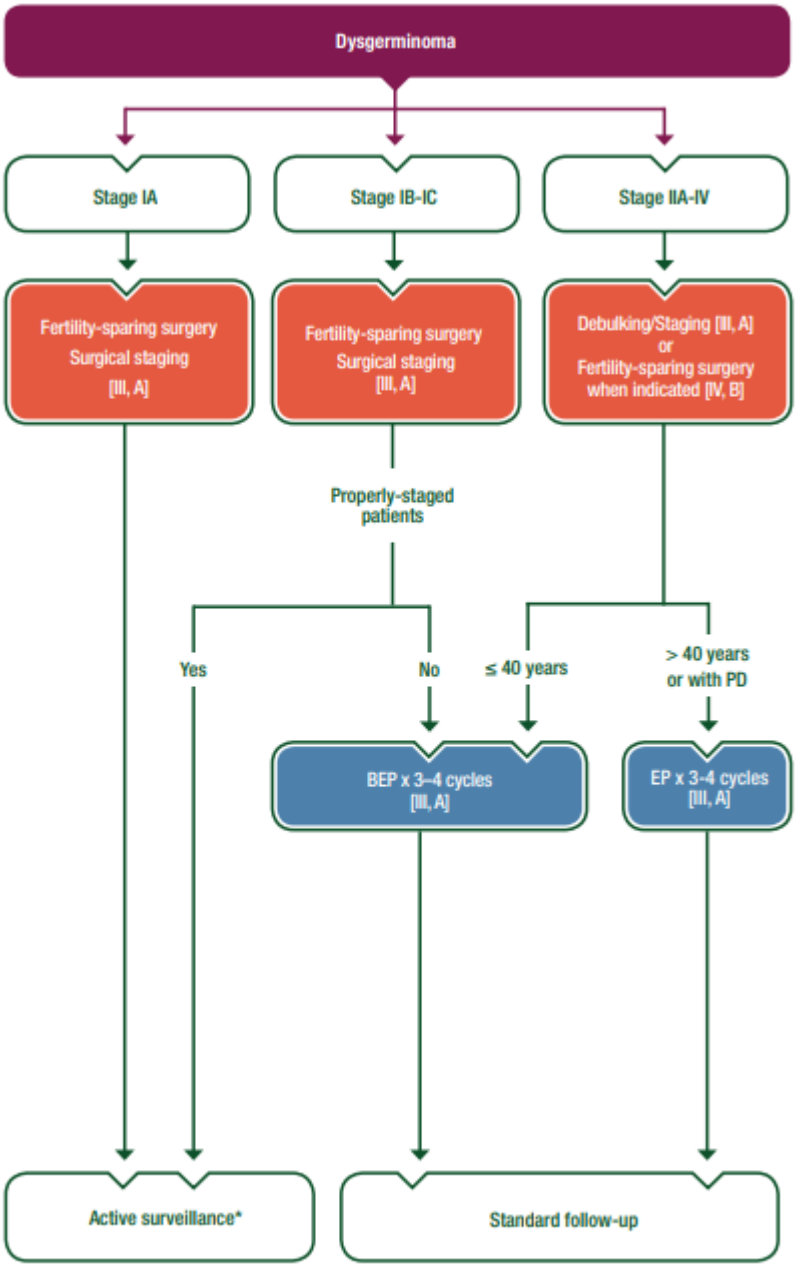


Figure 1. Management of GCTs of the ovary—dysgerminoma.
*See Table 5.
BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; GCT, germ cell tumour; PD, pulmonary disease.

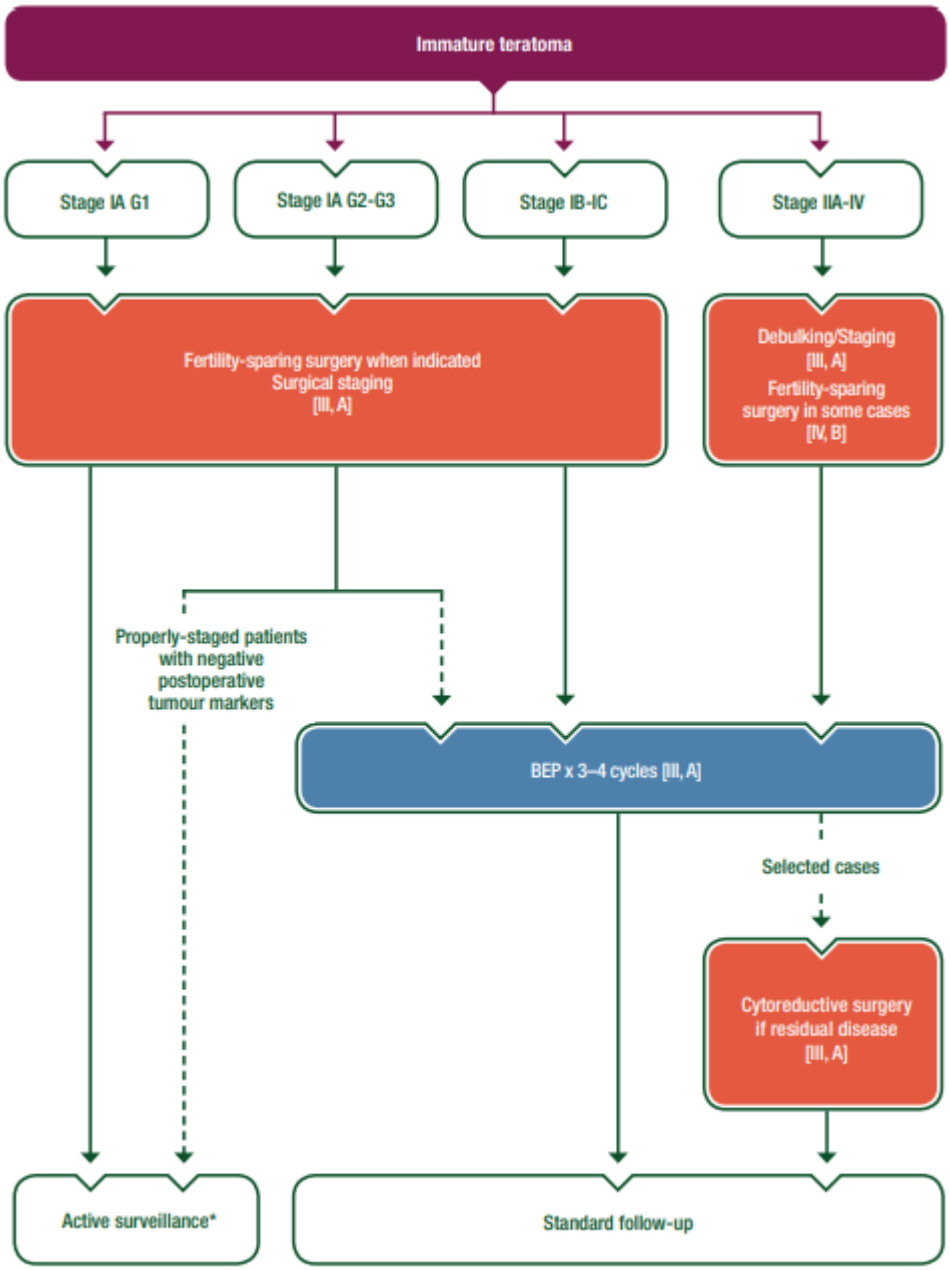


Figure 2. Management of GCTs of the ovary—immature teratoma.
*See Table 5.
⇢ Optional
BEP, bleomycin/etoposide/cisplatin; GCT, germ cell tumour.

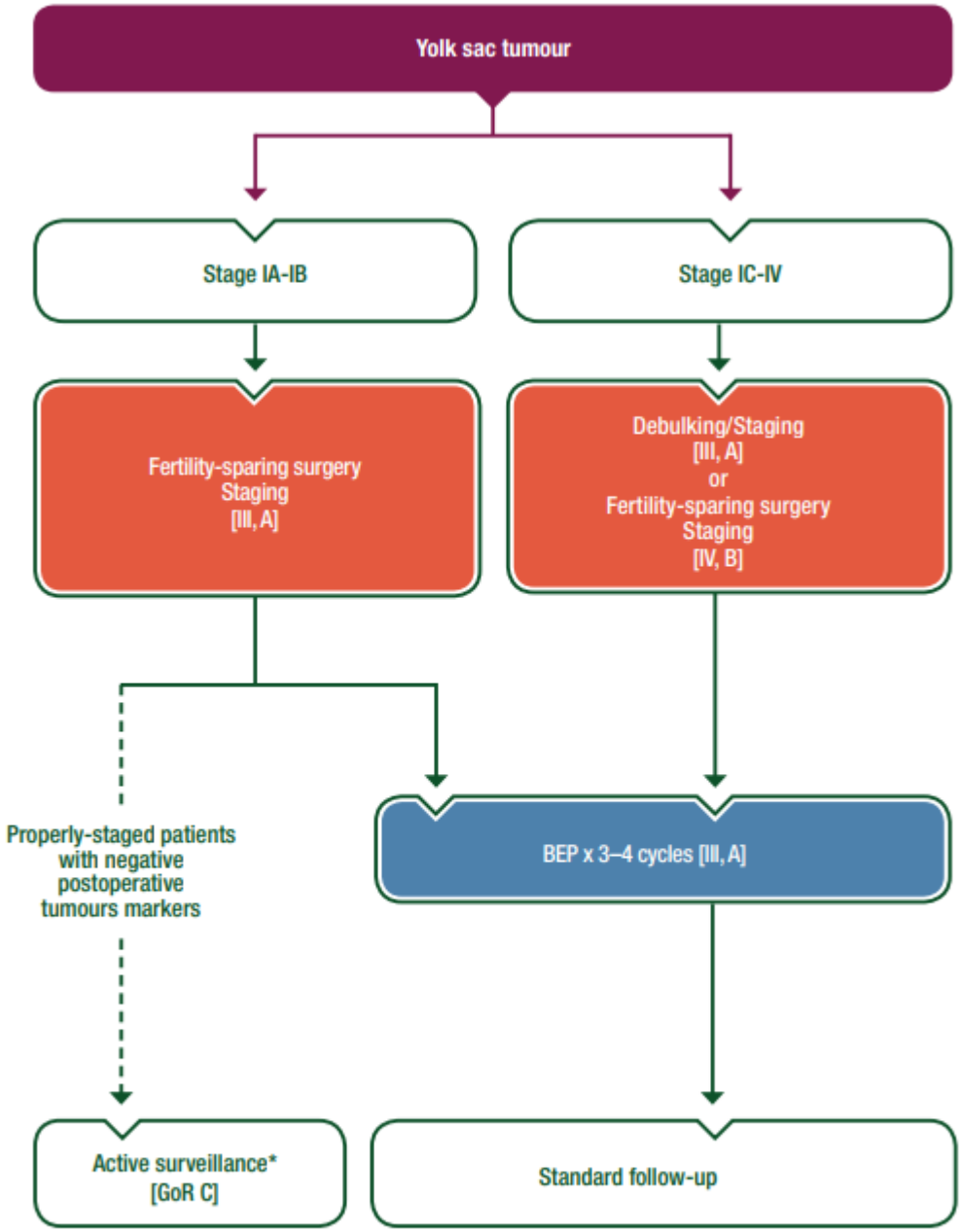


Figure 3. Management of GCTs of the ovary—yolk sac tumour.
*See Table 5.
--→ Optional
BEP, bleomycin/etoposide/cisplatin; GCT, germ cell tumour; GoR, grade of recommendation.

Patients who achieve complete clinical response after chemotherapy require clinical follow-up with tumour markers every 3 months. Regular CT scanning has been recommended but MRI may provide a safer option in these patients by reducing radiation exposure. Treatment options for recurrent disease include surgical resection, chemotherapy e.g. TIP (paclitaxel, ifosfamide and cisplatin) or radiotherapy.

7.6. Struma ovarii malignum

These strumal carcinoids or malignant struma ovarii are very uncommon and are of endodermal origin with evidence of thyroid or C-cell differentiation arising from within a teratoma. Struma ovarii are a variant with >50% thyroid tissue within a teratoma.

Current treatment options include cytoreductive surgery and then discussion for total thyroidectomy and management as for differentiated thyroid carcinoma with radio-iodine imaging and ablation.

7.7. Squamous cell carcinoma arising within dermoid cyst/teratoma

Malignant transformation within a dermoid cyst occurs in approximately 1-2% of cases and in over 80% cases is a squamous cell carcinoma. Theses tend to occur in older women with late symptoms due to pressure or torsion.

The initial treatment option is for surgical cytoreduction. If the disease is confined to the ovary without rupture, then adjuvant treatment is not necessary but in more advanced cases chemotherapy is advised. There is still considerable debate about which chemotherapy regimen to use. The options include BEP, cisplatin and 5-fluorouracil regimens or carboplatin and paclitaxel. RT can be considered as local treatment for palliation.

7.8. Small cell and neuro-endocrine cancers

These are rare and account for approximately 1% of ovarian cancers. This classification includes:

- Small cell carcinoma of ovary of pulmonary type
- Small cell carcinoma of ovary of hypercalcaemic type (SCCOHT)
- Non-small cell neuro-endocrine carcinoma (large cell variant)
- Classical primary carcinoid (well differentiated neuroendocrine cancer)
- Classical carcinoid metastatic from primary gastrointestinal type

These tumours, except for carcinoids, are often very aggressive with high mortality beyond stage 1.

7.8.1 Treatment

Standard surgical cytoreduction should be considered. Evidence is limited but suggests that adjuvant chemotherapy should be considered with platinum and etoposide similar to regimens for small cell lung cancer. Pelvic radiation may also improve survival and should be discussed. Algorithm for treatment as per ESMO guidance for SCCOHT) below. [136]

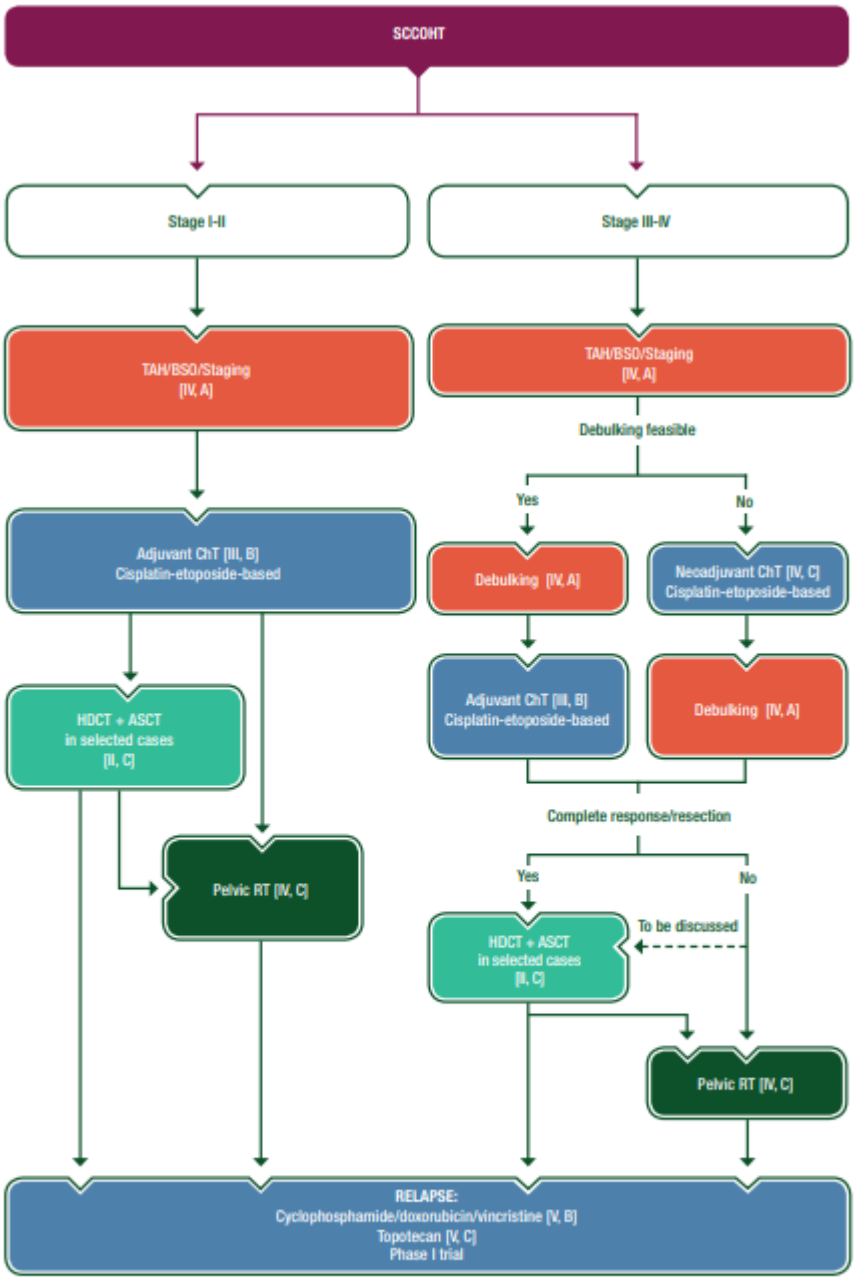


Figure 6. Management of SCCOHT.
--→ Optional
ASCT, autologous stem cell transplantation; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; HDCT, high-dose chemotherapy; RT, radiotherapy; SCCOHT, small cell carcinomas of the ovary hypercalcaemic type; TAH, total abdominal hysterectomy.

8. Metastatic Tumours

It must be remembered that 5-6% of ovarian tumours represent metastases from other organs, which include the female genital tract, breast or gastrointestinal tract (GIT). Krukenberg tumours can account for 30-40% of metastatic tumours to the ovaries, arises in the ovarian stroma and are most frequently associated with the stomach or colon and usually not until the primary disease is advanced. [137] Metastatic colon cancer can mimic a mucinous cystadenocarcinoma of the ovary. Metastatic lesions from the appendix are particularly difficult to differentiate, especially when associated with pseudomyxoma peritonei. [138] It is important to remember the possibility of metastatic lesions to the ovary and appendicectomy should be considered if a mucinous tumour of the ovary is suspected. In addition, the presence of GI symptoms pre-operatively, should prompt consideration of further investigation of the GI tract before subjecting the patient to laparotomy.

9. Borderline Ovarian Tumours

Tumours of low malignant potential (borderline tumours) are a heterogeneous group of lesions that are defined histologically by atypical epithelial proliferation without stromal invasion. They account for 10-15% of all ovarian tumours and occur predominantly in premenopausal women, whereas invasive carcinomas are more commonly found in an older age group. Prognosis is generally good however there is a mortality risk in a small group of patients who develop invasive, proliferative peritoneal disease.

9.1. Background

The majority of tumours are serous, with up to 25-50% being bilateral. [139] Most patients present as stage 1 disease, but 25-30% of women with serous tumours will have extraovarian disease at the time of presentation. [140] Micropapillary features increases the risk of both invasive peritoneal implants and recurrence. [141] Mucinous tumours make up the other common histological type. Pseudomyxoma peritonei is associated in 10% of ovarian mucinous tumours. In

these cases, the tumour is potentially of appendiceal origin and therefore is not classified as a borderline ovarian tumour. [142]

9.2. Diagnosis

Most patients usually present with an asymptomatic pelvic mass, however symptoms can present in keeping with any adnexal mass e.g. due to torsion/infarction, pressure symptoms etc. CA 125 is not a good discriminator. [143] Sonographic appearances vary widely. Use of CT, MRI and TVS doppler have been shown to predict likelihood but are not specific enough. [144] Diagnosis is made at histology.

9.3. Surgery

Borderline ovarian tumours are staged surgically using the same FIGO criteria as for other ovarian tumours. The main advantages of complete surgical staging are that prognostic information is improved, in addition to discovering areas of occult invasive disease. Frozen section can be performed at the time of operation, which can help determine the extent of the staging procedure. The diagnostic accuracy of frozen section results of ovarian pathology has been reported to have a sensitivity of 65-100% and specificity of >99% when compared with the final pathological diagnosis. [52] There are factors that lower sensitivity however, particularly size (>10cm). [54]

Furthermore, it has been estimated that 6-27% of patients with a frozen section diagnosis of borderline tumour will be upgraded to invasive cancer on final histological examination. [139]

CLINICAL PRACTICE POINT 18:
It is recommended that all cases of borderline ovarian tumours (diagnosed postoperatively) are referred to the cancer centre for pathological review.

Staging laparotomy may be radical or conservative, depending on whether or not fertility sparing is a consideration. Laparotomy is preferred to laparoscopy, due to concerns regarding cyst rupture and recurrence, especially if the cyst is > 5cm

diameter. [145] A French multicentre study showed that following surgical restaging; only 50% of patients were properly staged originally. Peritoneal deposits were present in 58% (pelvic) and 48% (abdominal), with the omentum being involved in 39%, of which 9% had invasive implants. [146] On the other hand, systemic lymphadenectomy can be omitted as it appears to offer low prognostic value. [147, 148] In the presence of mucinous tumours, appendicectomy and close inspection of the gastro-intestinal tract should be considered. [149]

Recommended staging procedure (radical):

- Midline laparotomy
- TAH+BSO
- Omentectomy
- Peritoneal biopsies and resection of macroscopic deposits
- Consider appendicectomy if mucinous tumour suspected

9.4. Fertility Sparing Surgery

Conservative surgery should be considered given the fact that many of these patients fall into the reproductive age-group and the overall prognosis is good. Unilateral salpingo-oophorectomy is preferred to cystectomy due to the higher rate of recurrence with cystectomy alone [150], especially in advanced stage disease. [151] The risk of recurrence overall ranges from 7 to 30% and can occur very late [152], however recurrences are typically non-invasive. [153] There appears overall to be no effect on survival [154] and although recurrence rates are higher in advanced disease, it would seem appropriate to consider fertility sparing surgery in all cases. [155] Pregnancy rates have been reported in excess of 30% [156] and there is no evidence that these patients are at increased risk of mortality, nor does there appear to be a detrimental effect as a result of ovulation induction. [157, 158]

It is recommended that the contralateral ovary is removed upon completion of family due to the higher rate of recurrence (15.2% vs. 2.5% for radical surgery). [139]

9.5. Restaging

Upstaging of borderline malignancy can occur in 12-47 % of presumed stage 1 serous tumours following a comprehensive surgical staging procedure. [146] Reasons for upstaging include positive peritoneal cytology, non-invasive implants and microscopic invasive implants. Studies however have shown that restaging has no impact on survival in that it remains high regardless of stage. [140, 147] It is recommended that surgical restaging be considered when there is no description of the abdominal cavity and peritoneal surface, or where there is a suspicion of extraovarian disease. [159]

9.6. Chemotherapy

There appears to be no benefit to the use of adjuvant chemotherapy in women with early stage disease, although it may be considered in the presence of invasive implants. [160]

9.7. Follow Up

The role and method of follow up is not clear. It has been suggested that true recurrence and survival rates can only be achieved with 10 year and 20 year follow-up respectively. [161] Recurrence appears to be related to the use of chemotherapy, time from treatment [162] as well as a micropapillary/cribriform histological pattern. [161]

The patients at most risk are those who develop invasive serous carcinoma, but there is no evidence that follow up effectively detects recurrence nor made any difference to survival. [144, 155] Several centres use a combination of clinical follow up, CA 125 and ultrasound. Radiological examination appears not to be important unless conservative surgery is adopted.

A suggested protocol is as follows: CA 125 (if initially elevated) and clinical examination every 6 months for up to 5 years, then consider annual review for 10 years If conservative surgery performed then add USS. Consider CT if recurrence suspected.

9.8. Management of Recurrence

Surgical cytoreduction appears to be the best option, with some evidence of improved survival. [163] The presence of invasive disease may represent

malignant transformation or de novo development of ovarian or primary peritoneal cancer, for which chemotherapy may be considered.

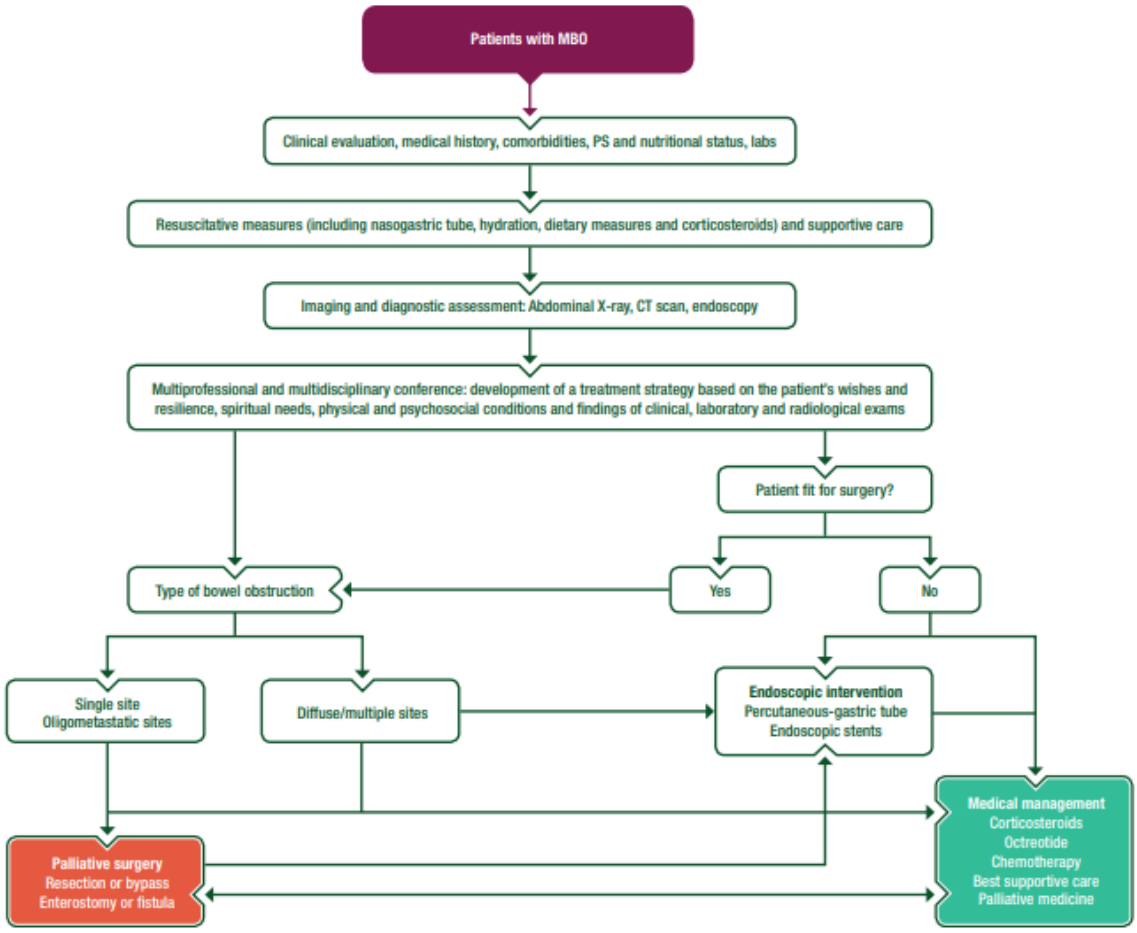


Figure 5. Algorithm for the management of MBO.
CT, computed tomography; MBO, malignant bowel obstruction; PS, performance status.

10. Malignant Bowel Obstruction

Malignant bowel obstruction is a frequent complication of ovarian cancer and it needs to be managed on an individual basis as there is a lack of evidence on optimal management. These clinical situations are complex and discussion at MDT should always be considered. The ESMO-ESGO consensus summarises options for malignant bowel obstruction as below. [103]

11. Appendix 1 Risk of Malignancy Index

The Risk of Malignancy Index (RMI) gives an estimate of the risk of ovarian cancer for women with adnexal masses. The RMI is calculated using ultrasound findings (U), menopausal status (M) and CA125 value (serum levels >35U/ml abnormal).

RMI = U x M x CA 125

Ultrasound findings are scored with one point for each of the following:

- Multi-locular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 0 (ultrasound score of 0)

U = 1 (ultrasound score of 1)

U = 3 (ultrasound score of 2 – 5)

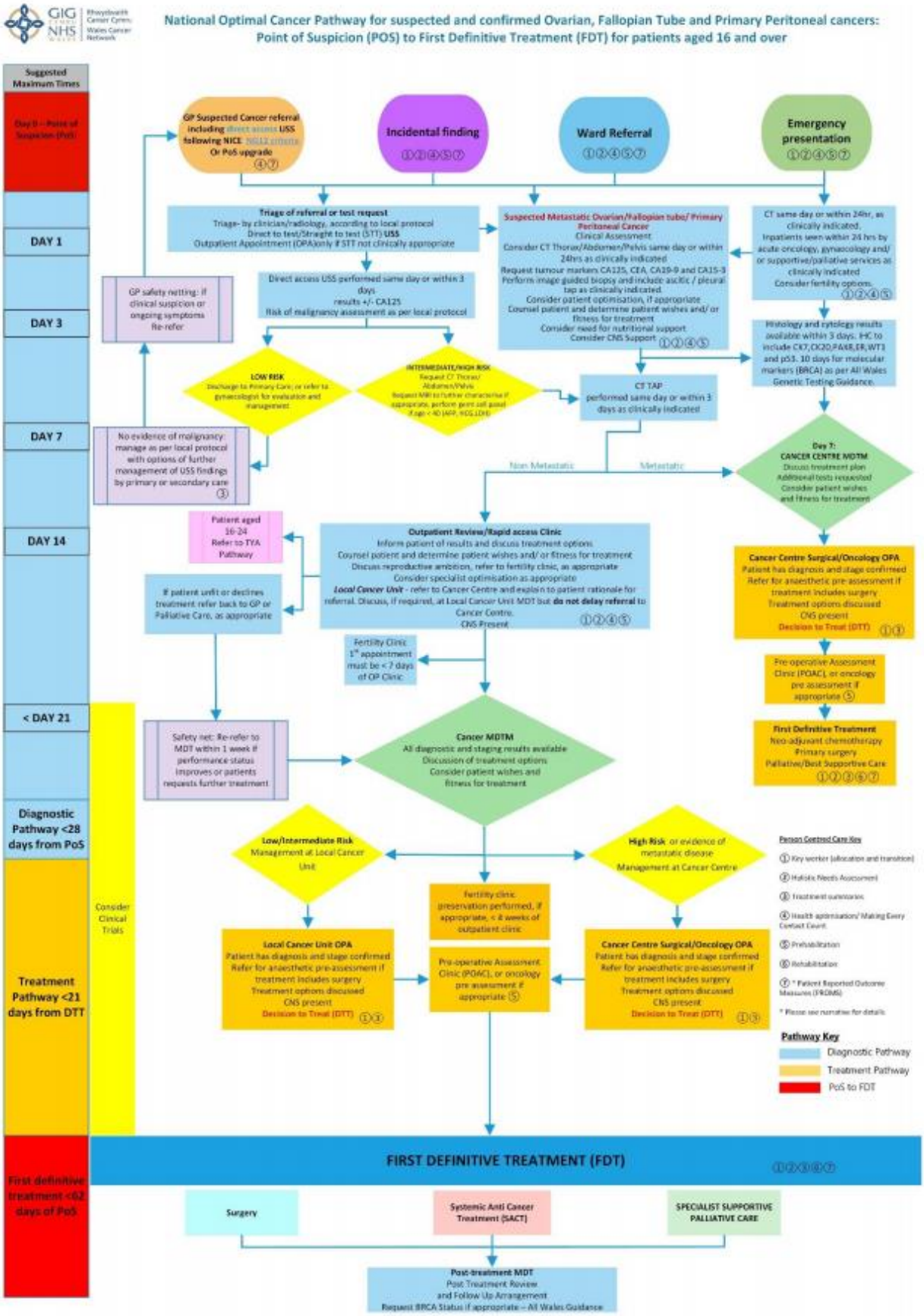
Menopausal status is defined as women who have had no period for more than one year or women over age 50 who have had a hysterectomy and is scored as follows:

- Postmenopausal status is graded M = 3
- Pre-menopausal status is graded M = 1

MANAGEMENT GUIDE:

RMI SCORE	RISK	PLAN
< 25	LOW	Manage locally
25-250	INTERMEDIATE	Discuss at MDT and manage locally if appropriate
>250	HIGH	Arrange further investigations and refer immediately to cancer centre

12. Appendix 2 - Single Cancer Pathway



13. Appendix 3 - Palliative Care

Palliative Treatment

Many patients who are treated for potentially life-limiting illness will be cured or may achieve useful and prolonged control or remission. However, many will die of that life limiting illness. For patients who present with advanced disease palliative treatment may be the only option. Disease progression also necessitates a change in management, palliation becoming the main objective.

Palliative Care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. These involve the use of palliative interventions, a palliative approach and where appropriate the involvement of Specialist Palliative Care services.

The Palliative Care Approach

The Palliative Care Approach aims to provide both physical and psychosocial well-being. It is a vital and integral part of all clinical practice, whatever the illness or its stage, informed by a knowledge and practice of palliative care principles and supported by specialist palliative care. The goal of palliative care is the best possible quality of life for patients and their families. Palliative care embraces palliative interventions and includes rehabilitation, continuity of care and also terminal care of patients dying in any setting. Advance Care Planning should also be considered early when a palliative approach is being taken.

The key principles underpinning palliative care which should be practiced by all health professionals in primary care, hospital and other settings are:

- focus on quality of life, which includes good symptom control
- whole-person approach, taking into account the person's past life experiences and current situation
- care which encompasses both the person with life-threatening disease and those who matter to that person

- respect for patient autonomy and choice (*e.g.* over place of care, treatment options, access to specialist palliative care)
- emphasis on open and sensitive communication, which extends to patient, informal carers and professional colleagues.

Many aspects of palliative care are applicable from diagnosis onwards, in conjunction with specific treatments. The spectrum of services that may be needed will overlap with support services to other patients not in a palliative phase.

Palliative interventions

Palliative interventions are non-curative treatments given by specialists in disciplines other than specialist palliative care, aimed at controlling symptoms and improving a patient's quality of life, *e.g.* the use of disease-specific treatments such palliative radiotherapy, chemotherapy, surgical procedures and anaesthetic techniques for pain relief.

Symptom control

Guidance on this is widely available, for instance from local specialist palliative care teams or from the text of the Palliative Medicine Handbook at http://book.pallcare.info/.

14. Appendix 4 - Pathology Reporting

The information presented below represents a digest of the most up to date tissue pathway and minimum dataset guidance on reporting of ovarian, fallopian tube and peritoneal carcinomas by Dr Wilkinson, Dr Vroobel and Prof McCluggage published July 2019 [164] available at Microsoft Word - G079 Dataset for histopathological reporting of carcinomas of the ovaries, fallopian tubes and peritoneum For Publication.docx (rcpath.org)

Core items to be included on the request form:

Information regarding

- Patient demographics
- Time and date of operation
- Prior chemotherapy
- Specimen type
- Previous biopsy and or cytology results
- Capsule status
- Tumour marker results where available.

Inclusion of information regarding genetic status is a non-core item recommended for inclusion on the request form where known.

Core items to be described in the macroscopic description of the pathology report include:

- Specimen type
- Capsule status
- Tumour site
- Dimensions of omentum
- Omental involvement
- Size of maximum omental deposit.

Tumour dimensions in three dimensions and a block key are also desirable.

Notes on Tissue Handling

Fallopian tubes should be dissected according to the SEE-FIM (sectioning and extensive examination of the fimbria) protocol to maximise to chance of identifying a pre-malignant lesion in fallopian tube epithelium. This involves longitudinal sections of the distal third of the fallopian tube in addition to cross sections of the remaining fallopian tube for submission of all fallopian tube tissue.

The entire appendix should be embedded when resected in cases of mucinous carcinoma.

Lymph nodes submitted for examination can be submitted whole or bisected when <5mm but are recommended sliced perpendicular to the long axis at 2-3mm intervals if larger than 5mm.

The sites of any additional peritoneal specimens should be recorded.

Core items to be described in the microscopic description of the pathology report include:

- Tumour type
- Grade
- Sites of involvement
- Peritoneal cytology
- Lymph node status
- Provisional stage (FIGO)

And for borderline serous tumours additional core data items should include micropapillary architecture and the presence or absence of omental implants. In addition, the RCPath dataset recommends inclusion of information regarding pattern of invasion for mucinous tumours, a chemotherapy response score, details of any coexistent pathology and presence or absence of intraepithelial carcinoma in cases of borderline mucinous tumours.

Tumour type is defined by the most recent WHO classification. [165]

Tumour grade description depends upon the histological type of tumour. Serous carcinomas are graded high or low grade depending upon assessment of, primarily, morphology but also with information from p53 immunohistochemical staining. Clear cell carcinomas are by definition high-grade. Endometrioid

carcinomas are graded in a similar fashion to those arising from the endometrial cavity: G1 <5% solid component, G2 5-50% solid component and G3 >50% solid component. The tumour mage be increased one grade should cytological atypia be marked. There is no evidence based grading system for mucinous carcinomas but sarcomatoid areas qualify for description as grade 3 or high-grade.

The distinction between benign and borderline epithelial tumours of the ovarian rests on an arbitrary cut-off of more than 10% epithelial proliferation.

Considerations for Borderline tumours

Implants

Invasive implants in serous borderline as classified as low grade serous carcinoma. Non-invasive implants may be described as desmoplastic where they retain a "stuck on appearance. This is a difficult area of diagnostic pathology but 'indeterminate type' should only be used as a descriptor for those implants difficult to assign invasive or non-invasive status in very rare instances. [166, 167] Implants only occur in serous-type borderline tumours of the ovary.

Microinvasion

The upper limit for diagnosis of microinvasion in serous and mucinous borderline tumours is 5mm. Microinvasion may be multifocal, destructive stromal or expansile in nature. The pattern of invasion should be recorded in mucinous tumours where present. Consideration of metastatic disease should be made in a context of extensive destructive stromal invasion in mucinous carcinomas.

Micropapillary architecture

Micropapillary architecture should be reported in serous carcinomas when there is confluence over at least 5mm.

Allocation of Primary Site in High-Grade Serous Carcinoma

Serous Tubal Intraepithelial Carcinoma (STIC) +/- early invasive mucosal carcinoma identified within fallopian tube sections dissected according to the SEE-FIM protocol indicates origin from the fallopian tube cases of high-grade serous

carcinoma. p53 and ki67 immunohistochemistry may be a useful diagnostic aid in morphologically inconclusive lesions. Primary site is also best indicated as fallopian tube in situations where the fallopian tube appears to be entirely incorporated into a tubo-ovarian mass. Assigning ovary as the primary site relies on excluding disease in either fallopian tube. Assigning primary site to the peritoneum relies upon exclusion of significant disease in the ovaries and fallopian tubes. Consideration of mesothelioma and metastatic carcinoma may also be appropriate in these cases. Cases where endometrial involvement by serous carcinoma is also identified need careful consideration for site of origin and may require immunohistochemistry to assist diagnosis.

Resections from women having received neoadjuvant chemotherapy may be difficult to interpret and determination of primary site can only be reliably made on primary debulking specimens, particularly in primary peritoneal disease. Information regarding prior treatment must, therefore, be provided on the histopathology request form.

Response to Neoadjuvant Chemotherapy

In in situation of radiologically documented, pre-chemotherapy omental disease with high-grade serous carcinoma a Chemotherapy Response Score (CRS) should be provided by the pathologist as this has been shown to correlate with progression free survival and influence subsequent management. [168] Scoring should be based upon one H&E-stained section of omentum showing the least degree of response across all those sampled. CRS 1 indicates no or minimal tumour regression, CRS2 partial tumour response and CRS 3 near-complete or complete response.

Peritoneal Washings Cytology

This is required for full and accurate staging of FIGO stage 1 ovarian carcinomas.

Lymph Node Status

Reporting extra-peritoneal lymph node involvement upstages ovarian carcinomas to stage IV. Measurement of size of deposits is important for accurate sub staging.

Staging

Final FIGO should be agreed and recorded at MDT in a context of full clinical. radiological and pathological patient data. All reports will be coded using SNOMED T and M codes in the Laboratory Information Management System.

Immunohistochemistry

Inclusion of data regarding immunohistochemistry (IHC) is listed as a non-core item in the RCPath dataset. IHC should be used as an adjunct to morphological diagnosis and as part of a panel of markers acknowledging that information from one stain alone is rarely safe or useful in diagnostic pathology. Control material should be included on the test slides as standard particularly for those IHC markers that consider loss of expression e.g. MMR and p53.

Molecular data

Inclusion of data regarding molecular information, i.e. results from DNA, RNA, protein, lipid or other molecular testing by whatever method, is listed as a non-core item in the RCPath dataset for inclusion in the microscopic part of the pathology report. It is recommended that all molecular data relating to a surgical specimen should be added to the original histopathology report to comply with best practice guidelines. [169]

Intra-operative Frozen Section Diagnosis

Frozen section is not recommended for diagnosis of ovarian tumours as there is a possibility of erroneous diagnosis of clear cell carcinoma due to cytoplasmic clearing artefact as a consequence of rapid tissue freezing. For borderline tumours, in addition, assessment of invasion requires extensive sampling and therefore precludes the frozen section technique. (162)

Criteria for Audit

Based on RPCath guidance for key performance indicators, the following 3 items are suggested as criteria for audit (162).

1. Reports should contain core data items as described above in 95% of cases.
2. Turnaround time: 80% of cases must be reported within 7 calendar days.

3. 90% of histopathology reports should be authorised within 10 calendar days.

EXAMPLE REPORTING PROFORMA FOR OVARIAN CANCER FOR PRIMARY OVARIAN CARCINOMA and BORDERLINE TUMOURS

OVARIAN MASS	LEFT / RIGHT
WEIGHT OF OVARIAN MASS	gm
SIZE OF MASS	x x mm
CAPSULE	INTACT/ DISRUPTED / INVOLVED by TUMOUR/ NOT ASSESSABLE
MACROSCOPIC SURFACE TUMOUR	YES / NO
FALLOPIAN TUBE (FT) ATTACHED	YES / NO
TUMOUR TYPE PLEASE STATE HISTOLOGICAL TYPE	
GRADE OF TUMOUR (SEE RCPATH DATASET NOV 2010 FOR GUIDANCE)	
MICROINVASION (FOR BORDERLINE TUMOURS ONLY)	PRESENT / ABSENT
LYMPH NODES	SUBMITTED / NOT SUBMITTED
NUMBER OF NODES EXAMINED FROM EACH SITE	N/A NO. SITE NO. SITE NO. SITE
NUMBER OF NODES INVOLVED FROM EACH SITE	N/A NO. SITE NO. SITE NO. SITE
NODAL EXTRACAPSULAR SPREAD	PRESENT / ABSENT N / A
PERITONEAL BIOPSIES	SUBMITTED / NOT SUBMITTED
PERITONEAL BIOPSIES INVOLVED	YES /NO SITE INVOLVED N / A

OMENTUM	SUBMITTED / NOT SUBMITTED
OMENTUM INVOLVED	YES / NO IF Y SIZE OF LARGEST DEPOSIT
PERITONEAL WASHING SUBMITTED	YES / NO
PERITONEAL WASHING CONTAINS TUMOUR CELLS	YES /NO N / A
FALLOPIAN TUBE INVOLVED	YES / NO
OVARIAN SURFACE INVOLVED	YES / NO
LYMPHOVASCULAR SPACE INVASION	PRESENT / ABSENT
CONTRALATERAL OVARY -TUMOUR	PRESENT / ABSENT IF PRESENT SIZE SURFACE INVOLVED YES /NO
CONTRALATERAL FALLOPIAN TUBE	PRESENT / ABSENT IF PRESENT SIZE SURFACE INVOLVED YES /NO
ADDITIONAL COMMENTS	
FIGO STAGE	

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