OVARIAN CARCINOMA

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**Introduction**

Ovarian cancer is common. In the UK, 7,116 cases of ovarian cancer were diagnosed in 2011, giving an incidence of 17.1 per 100,000 population (CRUK, 2015). Although the overall incidence of ovarian cancer has increased from 1971 to date, between 1997 and 2011 the European age standardised (AS) incidence rate has decreased by 11% (CRUK, 2015). Within the UK, Wales has the highest AS incidence rate (20.2 versus 17.1), the reasons for which are unclear (CRUK, 2015).

Ovarian cancer is the fifth most common cancer for women in the UK and the second most common gynaecological malignancy after endometrial cancer. Since the 1970s, survival rates in the UK have increased steadily. In England and Wales 5yr and 10yr survival rates currently stand at 46.2% and 34.5% respectively (CRUK, 2015).

Around 2% of women in the UK will develop ovarian cancer; an individual’s risk increasing with age. Whilst there are a great number of factors which are postulated to alter a person’s risk of ovarian cancer; there are few which have been proven, see table 1.

<table>
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<tr>
<th>Table 1.</th>
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<tr>
<td>Proven Risk Factors</td>
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1. **Clinical symptoms and signs**
Ovarian cancer often presents late due to vague nonspecific symptoms. Abdominal distension, bloating, early satiety, tiredness and urinary/gastrointestinal symptoms are common presenting complaints. Clinical findings of a mass, ascites or pleural effusion may or may not be present.

1.2 **Familial disease**
Hereditary ovarian cancer accounts for 5-15% of ovarian cancer cases. The majority of which (up to 90%) are associated with a BRCA mutation. Presence of a BRCA 1 mutation is thought to carry a 40-60% risk of developing ovarian cancer, BRCA 2 carries up to a 20% risk and Lynch syndrome (HNPCC) carries 3-14% risk (Mavaddat et al, 2013; Barrow et al, 2009). Figures quoted vary widely due to ascertainment bias but studies have suggested that these figures are appropriate for use in genetic clinics although the risks may be lower for those presenting without a significant family history and for those of Ashkenazi descent.

Age at diagnosis is all important. An individual’s risk if no family member is affected is 1 in 70. If 1 first degree family member is affected at less than 50 years of age then the risk increases to 1 in 40. Generally studies looking at empiric risks for more than one affected relative have wide CI for their risk figures and give variable results but genetic textbooks quote 2 relatives <60 having a 20% risk and if >60 a 10% risk (Schildkraut and Thompson, 1988). The UKCCCR study (Sutcliffe et al, 2000) suggested an 11% lifetime risk and Stratton et al (1998) in their meta-analysis again suggested around a 14% risk for 2 relatives - either first or second degree.

The North Wales Cancer Genetics Service is based in Glan Clwyd Hospital and accepts referrals when any of the following criteria are met:

- 2 or more relatives with ovarian cancer (one of whom is first degree relative)
- 1 first degree relative who has had both an ovarian and breast cancer (or the individual herself)
- At least 1 breast and 1 ovarian cancer amongst first and second degree relatives (if only one of each, breast cancer diagnosis <50 years)
- Any history of a first degree relative diagnosed with breast cancer 40 years or younger
- Any history of a first degree relative diagnosed with a male breast cancer
- Any history of a first degree relative diagnosed with a bilateral breast cancer
- Any history of a first degree relative diagnosed with a colorectal cancer 45 years or younger.

Further guidance on other acceptable referral criteria and the process undertaken are available at:
Presently families with 2 affected close relatives may be offered BRCA testing if an affected individual could provide a blood sample or, failing this, the unaffected relative could be tested if she had >10% chance of having a mutation. Those patients identified as carrying one of the BRCA mutations may be offered breast screening and breast awareness advice or risk reducing surgery for their breast cancer risk. Appropriate management of their ovarian cancer risk is less clear and is the subject of ongoing clinical trials, Options may include serial trans-vaginal ultrasound scans or risk reducing surgery. Whilst it is acknowledged that patients presenting with high grade serous ovarian carcinoma have a higher chance of harbouring a germline mutation of BRCA, in North Wales women with high grade serous carcinoma diagnosed at under 60 years of age should be offered testing from the oncology department without referral to the cancer Genetics Department.

2. Screening
This is hampered by the low incidence of the disease. There is currently no place for population screening (grade B recommendation; NHS Executive, 1999). Vaginal examination is ineffective. Use of tumour markers such as CA125 is being explored. UKCTOCS is a large RCT which is due to report shortly on the utility of screening.

3. Referral pathway (see 16. Contact names/ numbers)

3.1 For GP
If ovarian cancer is suspected then referral should be to a general gynaecologist, the lead in the cancer unit or gynaecological oncologist in the cancer centre. Current NICE guidance states that in the face of a raised Ca125 and ultrasound findings suggestive of ovarian cancer, a USC referral to the gynaecology cancer service should be instigated with the expectations of patient review within 2 weeks (NICE, 2011). Patients with a raised CA125 in the absence of an abnormal scan do not need referral to secondary care and must not be part of the USC pathway.

**Standards**
Rapid access to the specialist should be available with the patient seen within 10 days of date of receipt of the referral letter/ fax.

Definitive treatment should be commenced no later than 62 days after receipt of the referral letter/ fax.

Definitive treatment should be commenced no later than 31 days after diagnosis for non urgent suspect cancer referrals.
3.2 **For non-oncological consultants/ firms**
If the diagnosis is suspected or confirmed referral to the local unit lead or gynaecological cancer centre should be made.

3.3 **For referral from unit to centre**
This is appropriate for all cancer cases or cases suspected as cancer (RMI >250). This will be decided on a case by case basis by the MDT.

4. **Diagnosis**
The pre-operative assessment of a pelvic mass is based on menopausal status, ultrasound and CA125.

The possibility that an ovarian cyst or mass is malignant is increased if the cyst is thick walled (>3mm) has septae, solid areas (including papillary projections) or is entirely solid. Crescentic cyst wall thickening, indicating compressed but not invaded remaining ovarian parenchyma is a reliable sign of benign disease. Metastatic deposits to the ovaries are often bilateral but cannot be accurately differentiated from primary ovarian neoplasms on imaging alone. Ultrasound evidence of extra-ovarian pathology can be determined with the presence of ascites, bilateral masses or abnormalities in the omentum, spleen or liver.

The ability to accurately discriminate between a malignant and benign pelvic mass prior to surgery would allow the clinician the opportunity to consider referral to a colleague as the lead gynaecologist for gynaecological cancer management within the unit or indeed referral to the gynaecological oncology centre.

4.1 **Risk of malignancy index (RMI)**
About a ¼ to a 1/3 of women investigated by gynaecologists for adnexal masses are likely to have ovarian cancer. Note that the risk of malignancy index (RMI) can be calculated from the menopausal status of the patient, the scan appearance of the ovarian mass and the CA125 level (Davies et al, 1993; Tingulstad et al, 1996). RMI appears to be more sensitive and specific than CA125 alone.

\[
\text{RMI} = U \times M \times \text{CA125}
\]

Using a cut-off of 250 a sensitivity for ovarian cancer of 70% and a specificity of 90% is expected (Davies et al, 1993). With an RMI of <25 a risk of malignancy would be <3% and so a non-operative or laparoscopic approach could be considered. For an intermediate score of 25-250 a risk of malignancy would be 20% and management would normally be surgical within a cancer unit. Patients with a RMI >250 require discussion at the specialist gynaecology cancer MDT and are preferably managed in the gynaecology cancer centre (NICE, 2011).
Despite limited value in borderline, stage I invasive and non-epithelial ovarian cancers, the RMI is a simple, easily applicable method in the primary evaluation of patients with adnexal masses which identifies ovarian cancers more accurately than any other criterion used in diagnosis of this disease (Anderson et al, 2003).

**Risk of Malignancy Index (RMI)**

“U” is the ultrasound score
A score of 1 point is given to each of the following:
- multilocular lesion
- solid areas
- bilateral lesions
- ascites
- intra-abdominal metastases

“U” = 0 if ultrasound score 0
“U” = 1 if ultrasound score 1
“U” = 3 if the ultrasound score is 2 to 5

“M” refers to menopausal status
“M” = 1 for premenopausal patients
“M” = 3 for postmenopausal patients (including patients with >12 months amenorrhoea and for women >50 years of age after a hysterectomy).

Evidence level 2; grade B recommendation

5. **Investigations**

General Assessment: FBC, U+E and liver function tests

Other blood tests: CA125, consider CEA if any atypical findings
In women 40 years and under LDH, HCG and AFP
Radiological assessment: Ultrasound scan of abdomen and TV ultrasound of the pelvis
Characteristic findings at ultrasound include a solid or semisolid cyst, ascites, intra-abdominal masses, hydronephrosis or bowel obstruction
Chest X-ray looking for the presence of pleural effusion or pulmonary metastases
CT scan of abdomen and pelvis if ovarian cancer is suspected.

Histological assessment: Primary surgery will often proceed without histological confirmation following MDT consensus and will therefore form part of the staging/evaluation of disease. Where macroscopic disease clearance is felt not to be possible, or where diagnostic uncertainty remains histological diagnosis should be sought prior to treatment, for example omental biopsy.

5.1 Imaging for staging of ovarian cancer
Imaging in the context of ovarian cancer has traditionally been utilised in the differentiation of benign from malignant masses, as an adjunct to surgical staging and in the assessment of response to chemotherapy. It has also been used to determine relapsed disease, particularly when there is a rise in tumour markers.

However, imaging currently has a pivotal role in deciding whether patients will benefit from primary aggressive surgical procedures or whether neoadjuvant chemotherapy and delayed primary surgery would be more appropriate. Preoperative imaging can also determine the extent of surgery and provide accurate staging.

5.1.1 Ultrasound and tumour markers for diagnosis of ovarian cancer
Transvaginal ultrasound (TVS) with high frequency (5-7 MHz) probes is recommended for initial assessment of adnexal masses. Transabdominal ultrasound (TAS) is of value in the detection of ascites and peritoneal carcinomatosis, but is of limited value in the assessment of pelvic masses. Ultrasound can accurately identify the morphology of an ovarian mass, measure tumour size (Henrich et al, 2007) and appears as accurate as CT/MR for diagnosis of ovarian cancer with a sensitivity of 86-95% and a specificity of 68-90% including data from a meta-analysis (Kurtz et al, 1999; Myers et al, 2006; Van Holsbeke et al, 2007). These features retain high sensitivity in small masses less than 5cm size (Ferazzi E 2005; Evidence level 1a; grade A recommendation).

Combining grey scale morphological features with power Doppler is recommended for accurate initial characterisation and differentiation of benign from malignant masses. Power Doppler, producing qualitative assessment, has been shown to be more sensitive (Guerriero et al, 2001),
reproducible and less operator dependent in clinical practice than quantitative colour Doppler measurements of resistance index (RI), pulsatility index (PI) and peak systolic volume (Tailor et al, 1998). Addition of Doppler RI, PI, maximum systolic velocity and presence of vessels does not improve test performance and is not recommended (Myers et al, 2006).

3D TAS and TVS does not appear to significantly change the accuracy in the diagnosis of ovarian malignancy. Ultrasound contrast media have been used to increase conspicuousness of vascular areas within a suspicious mass or cyst and to improve differentiation of benign, borderline and malignant lesions, but as with 3D ultrasound the value of this in routine clinical practice has yet to be substantiated. Ultrasound is as accurate as CT/MR in identifying extraovarian or abdominal malignancy but it is less accurate than CT/MR in staging advanced disease (Tempany et al, 2000). CT and MR are more accurate than ultrasound in identifying significant (>2cm) peritoneal and nodal metastases (Tempany et al, 2000). This is important in the correct preoperative identification of peritoneal disease that is unlikely to be resectable. CT and MR appear equivalent for staging and evaluating response to treatment but CT scanning is quicker, cheaper and more readily available (Tempany et al, 2000; Vorgias et al, 2002; Qayyum et al, 2005; Sohaib and Reznek 2007; Evidence level 2a; grade B recommendation).

5.1.2 CT
CT may indicate which women may benefit from delayed surgery following neoadjuvant chemotherapy by determining extent of disease and visceral involvement. However patient co-morbidity and clinical findings must also be taken into account.
CT features indicative of advanced disease include peritoneal thickening, peritoneal implants (>2cm diameter), bowel mesentery involvement (>2cm diameter), suprarenal para-aortic lymph node involvement (>1cm diameter), hepatic metastases, omental extension to the spleen, stomach or lesser sac and extension to the pelvic sidewall or hydroureter. These were associated with residual disease after laparotomy of >1cm diameter from retrospective and prospective studies (Bristow et al, 2000; Qayyum et al, 2005). The latter study of 137 women provided a sensitivity for operability of 76% but a specificity of 99% (Evidence level 2a; grade B recommendation).

5.1.3 MRI
MRI is useful for assessing indeterminate adnexal masses on ultrasound, investigating suspected unusual complications such as evaluating the degree of invasion to adjacent structures (Kurtz A et al, 1999) and specific characterisation of some benign complex adnexal masses (eg. mature teratomas, endometriomas, haemorrhagic cysts, and hydrosalpinges). MRI is occasionally useful for the investigation of ovarian masses of dubious malignant potential at the discretion of the MDT or upon the advice of a consultant radiologist. MRI assessment of the abdomen and pelvis also
may be utilised when an allergy to CT contrast exists, in pregnancy and younger patients due to the radiation dose associated with CT scanning.

5.1.4 PET/CT
PET/CT has been shown to have poorer accuracy in determining malignancy in adnexal masses compared with MR and has lower sensitivity than ultrasound. This poor sensitivity seems to be related to tumour size and tumours with low malignant potential in particular. Thus early tumours with better prognosis may not be detected and false positives related to luteal cysts, endometriomas and inflammatory change as well as physiological bowel uptake remain a problem (Fenichel et al, 2002). PET/CT is not useful for diagnosis or staging of ovarian cancer (Yen and Lai, 2006).

5.1.5 Summary of imaging
Transvaginal ultrasound is ideal for characterisation of an adnexal mass if used with CA125. CT is recommended to stage extra-ovarian disease identified by prior ultrasound examination or by virtue of raised CA 125 levels (SIGN 2003; Togashi 2003). The justification of this lies in the poor sensitivity of ultrasound to detect para-aortic and pelvic lymphadenopathy, bowel involvement and peritoneal and omental deposits.

The presence of disease in the abdomen not only increases the stage to stage 3 or above, but requires accurate preoperative assessment to determine whether initial cytoreductive surgery would be compromised by virtue of predictable unresectable bulk disease (in particular, subdiaphragmatic areas, subcapsular hepatic or splenic deposits, peritoneal deposits in the lesser sac and involving the supracolic omentum). Suprarenal retroperitoneal and supradiaphragmatic lymphadenopathy and malignant pleural effusions are also relative contraindications to initial cytoreductive surgery.

5.2 CA125
CA125 is a high molecular weight glycoprotein with levels >35u/ml expressed in 85% of women with epithelial ovarian cancer (Bast et al, 1983; Canney et al, 1984). It is not expressed by normal ovarian serosa but can be elevated in pregnancy, endometriosis and menstruation (Jacobs and Bast Jr, 1989) and so diagnostic accuracy tends to be better in postmenopausal women. Levels are elevated in only 50% of ovarian cancer confined to the ovaries and levels are less likely to be elevated in mucinous and clear cell carcinomas (Jacobs and Bast Jr, 1989; Tamakoshi et al, 1996; Vergote et al, 1987). CA125 levels can also be elevated in carcinomas of the breast, colon, pancreas and lung (Jacobs and Bast Jr, 1989).

CA125 can be used to differentiate benign from malignant adnexal masses with a sensitivity of 78%, a specificity of 95% and a positive predictive value of 82% using a cut-off of 35u/ml (Einhorn et al, 1986). Pre-operative CA125 can also predict outcome with higher levels associated with poorer outcome in stage 1 disease (Petri et al, 2006; Obermair, et al, 2007). CA125 levels may be related to tumour volume, tumour stage and histological grade.
Outcome can be predicted from post-operative CA125 levels taken at least a month after surgery (Yedema et al, 1993). CA125 levels can be falsely elevated in the immediate post-operative period by the surgical procedure.

5.3 CEA
Elevated levels of carcinoembryonic antigen (CEA) are associated with colon and pancreatic cancer. CEA levels are also raised in benign diseases of the liver, gastrointestinal tract and lung. It may also be elevated in smokers. CEA may also be expressed by endometrioid and Brenner tumours of the ovary and in areas of intestinal differentiation in mucinous ovarian tumours. Around 25-50% of ovarian cancer patients have elevated levels of CEA.

### Standard

On identification of an ovarian cyst (>10mm diameter in a postmenopausal women and at least 50mm in a premenopausal women) then serum CA125 should be evaluated. Patients with raised RMI should undergo CT evaluation of Abdomen and pelvis.

*Evidence level 2; grade C recommendation*

### Standard

Upon suspicion of metastatic abdominal carcinoma by clinical examination or by imaging then a CEA should also be estimated. Other tumour markers (e.g. CA19.9 and CA15.3) should not be requested unless primary gastrointestinal or breast disease is suspected. Serum AFP and HCG should be measured in women <40 year of age.

*Evidence level 4; grade C recommendation*
### 6. Gynaecological cancer multidisciplinary team

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<thead>
<tr>
<th>Core team</th>
<th>Named team member</th>
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<tr>
<td>Gynae oncologist</td>
<td>Mr Leeson / Mr Toon/ Mr Peevor</td>
</tr>
<tr>
<td>Gynae lead cancer surgeon</td>
<td>Dr Rieck/ Mr Pleming</td>
</tr>
<tr>
<td>Medical oncologist</td>
<td>Prof Stuart/ Dr Azam/ Dr Mullard</td>
</tr>
<tr>
<td>Clinical Oncologist</td>
<td>Dr Bishop / Dr Neupane</td>
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<td>Pathologist/</td>
<td>Dr Lord/ Dr Pradeep</td>
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<td>Cytopathologist</td>
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<tr>
<td>Palliative care team</td>
<td>Dr Williams/ Dr Lewis-Williams</td>
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<tr>
<td>Radiologist</td>
<td>Dr Barwick/ Dr Muthu/ Dr Walsh</td>
</tr>
<tr>
<td>MDT co-ordinator</td>
<td>Ms Rees/ Ms Evans</td>
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<tr>
<td>CNS</td>
<td>Ms Hall/ Ms Evans/Ms Manning</td>
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#### Extended team

| Ultrasoundographer         | Tba                                         |
| Junior doctors             |                                             |
| Psychologist               |                                             |
| Geneticist                 | Ms Grier                                    |
| Social worker              | Tba                                         |
| Ward Sister                | Sr Williams                                 |
| Research nurse             | Ms Fernandez/ Ms Butterworth                |
| Colorectal/ urological/ plastic as required |                     |

### 6.1 Information

#### Standards

All patients must have access to a gynaecological oncology clinical nurse specialist within 24 hours of the patient being informed of her diagnosis (this should include a daytime contact telephone number for the clinical nurse specialist). Preferably the nurse specialist should be at the consultation when the patient is given her diagnosis.

All referring practitioners and/or patients GP’s should be informed by letter or secure fax within 24 hours of the patient being informed of her diagnosis.

All patients must be given appropriate literature about the management, treatment and outcome for cervical cancer such as a Macmillan leaflet or equivalent.

All these activities must be documented in the patient’s case record.

NICE, 2011
7. Pathology (WHO classification)

7.1 Epithelial ovarian cancer
There are several putative histopathologic precursor lesions of ovarian epithelial cancer, which makes up more than 90% of cases of ovarian malignancy. These include surface epithelial dysplastic change, germinal epithelial inclusion cysts, ovarian endometriosis and pre-existing benign and borderline ovarian neoplasms. Most serous carcinomas appear to arise de novo, whereas mucinous, endometrioid and clear cell carcinomas are often seen in association with pre-existing benign or borderline tumours or endometriosis. It is possible, however, that this difference between serous and non-serous tumours may simply be a reflection of the rapidity of development of serous carcinomas, rather than a true difference. Approximately ¾ of cases of serous carcinoma are high-stage at the time of the diagnosis.

Generally, accepted prognostic factors are FIGO stage and, for advanced stage patients, the volume of residual disease. Other factors that may be important include patient age, histopathologic grade and DNA ploidy. For the major types of ovarian carcinoma, histological subtype has not been shown clearly to be an independent prognostic factor when corrected for stage, with the possible exception of clear cell carcinoma. Different tumours do, however, tend to present at varying stage, which does produce differences in overall prognosis for individual tumour types. Grading of ovarian cancer, despite the fact that it has been shown in a number of studies to have importance, has never been adequately standardised, but at present most people use a three grade system and many use a modification of the endometrioid adenocarcinoma system, whereby the tumour is graded on the architectural appearances and the grade increased by one, if high-grade nuclear features are seen in an architectural grade I or II tumour.

Kurman et al (2008) has recently described 2 types of ovarian carcinoma. Type I tumours account for about 25% of all ovarian carcinomas which are slow growing and in general are confined to the ovary at diagnosis. These include low grade micropapillary serous carcinoma, mucinous, endometrioid and clear cell carcinomas. They are genetically stable and characterised by changes in K-RAS and PTEN. Type II tumours are rapidly growing, usually widely metastasised at diagnosis and include high grade serous carcinoma and carcinosarcomas. These are genetically unstable and test +ve for p53.

Subtypes of ovarian epithelial cancer
- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional
- Undifferentiated
- Mixed
Serous carcinoma is the commonest type of epithelial ovarian cancer and accounts for approximately 50% of malignant ovarian tumours. Median age of occurrence is around 55–60 years. Approximately 10% of patients with high-stage disease show predominantly surface involvement of the ovaries and peritoneum, and when the ovarian involvement is minor the diagnosis of primary peritoneal serous carcinoma or diffuse serous surface papillary carcinoma may be made. Outcome for this tumour type appears similar to high-stage serous carcinoma NOS. In cases which are difficult to diagnose on simple histology alone, immunohistochemistry may be very useful in that these tumours classically show cytokeratin 7 positivity, cytokeratin 20 negativity, CA125 positivity and WT1 positivity. Two specific variants of serous carcinoma should be clinically and pathologically recognised. The first of these is so-called psammocarcinoma, where the tumour is of low cytological grade and shows extensive psammoma body formation, involving at least 75% of cell nests. The tumour shows destructive invasion at the margins, but no significant areas of solid epithelial proliferation. This tumour appears to be very indolent and appears to occur as frequently at extra ovarian pelvic sites as within the ovary. Despite the high-stage at presentation, they appear to have a long-term survival rate in excess of 90%. Micropapillary serous carcinomas (otherwise termed micropapillary serous borderline tumours) may occur as pure ovarian tumours or together with areas of classical borderline serous ovarian tumour. The importance of this tumour pattern within the ovary appears to be that, if disease is high-stage, then the risk of invasive peritoneal implants is greater than 50% and much higher than in classical non-micropapillary borderline serous tumours with extra ovarian disease. Outcome for those tumours which are stage I, however, is probably similar to borderline tumours NOS. Many tumours are found to arise from the fimbrial portion of the fallopian tubes after careful histological examination. It is possible that a substantial proportion of high grade serous carcinoma are not of ovarian origin but are primary peritoneal or fallopian tube carcinoma (Piek et al, 2001; Kindelberger et al, 2007).

Historical data on mucinous carcinomas of the ovary is made rather unreliable by the fact that some of these tumours were in fact metastatic. Overall, mucinous tumours appear to make up approximately 10% or less of ovarian carcinomas. The majority of tumours present in stage I and for high-stage tumours it is imperative to exclude metastatic disease, particularly with bilateral ovarian involvement. Mucinous carcinomas of the biliary tree, pancreas, colon, appendix and cervix can all mimic primary ovarian mucinous carcinoma and immunohistochemistry is of less use than in serous tumours, though mucinous carcinomas of the ovary show a higher proportion of cytokeratin 7 positivity and 20 negativity, whereas colonic tumours usually show a reverse of this pattern. For primary mucinous carcinomas in stage I, recurrence and death due to disease occurs in approximately 10% of cases i.e. a similar outcome to stage I serous carcinoma.
Endometrioid carcinomas of the ovary make up around 17% of ovarian carcinomas. Around 15% of women with endometrioid ovarian carcinoma have co-existent endometrioid carcinoma of the uterine corpus. Endometrial hyperplasia is also commonly present. Usually metastatic ovarian tumour from the endometrium can be separated on the basis of careful assessment of the clinico-pathological features, but this is not always the case and even the use of molecular genetic studies does not always differentiate independent primaries from metastases. Around 15-20% of endometrioid carcinomas are associated with endometriosis either in the ipsilateral or contralateral ovary, but figures of above 40% have been seen in some series. Such patients tend to be somewhat younger than women without associated endometriosis and the tumours associated with endometriosis tend to be better differentiated and more commonly stage I than those without it. Endometrioid tumours may be very closely mimicked by metastatic carcinomas from the colon, and immunohistochemistry in this circumstance is very useful as endometrioid carcinomas of the ovary are usually cytokeratin 7 positive and cytokeratin 20 negative with the reverse pattern in colonic carcinomas. Bowel carcinomas tend to more commonly show CEA positivity than endometrioid carcinomas of the ovary, whereas endometrioid carcinomas of the ovary tend to be more frequently CA125 positive than bowel carcinomas. Some endometrioid carcinomas may closely resemble the appearances of Sertoli-Leydig cell tumours, but α-inhibin staining will often be helpful in this circumstance as will certain other immunohistochemical stains.

Clear cell carcinoma makes up approximately 7-8% of all ovarian carcinomas and several series have shown that it has the closest association with endometriosis of all carcinomas of the ovary. Whilst early stage ovarian clear cell carcinoma retains a good prognosis, advanced stages have a worse prognosis than serous or endometrioid ovarian cancer due to lower platinum sensitivity (Chan et al, 2008). Clear cell ovarian cancer also has an increased risk of thrombosis and paraneoplastic phenomena (Tan & Kaye, 2006).

Malignant transitional cell tumours can be divided into two groups, malignant Brenner tumours, and transitional cell carcinoma. Transitional cell carcinoma tends to be over diagnosed as any poorly differentiated ovarian carcinoma can take on a rather transitional appearance, and this is particularly the case for serous carcinoma. To make a diagnosis of malignant Brenner tumour and differentiate it from pure transitional cell carcinoma requires the finding of benign persisting Brenner tumour or borderline Brenner tumour. What data exists, suggests that transitional cell carcinoma may be more aggressive than malignant Brenner tumour, or at least, present often at higher stage, but may be more chemo-sensitive with platinum containing agents in comparison to Brenner and other advanced stage carcinomas.
7.2 Non-epithelial tumours

Sex cord stromal and steroid cell tumours make up one large group and germ cell tumours a second. A third group comprises non-specific tumours for example of connective tissue, lymphoid and uncertain histiogenesis. The commonest sex cord stromal tumour is the granulosa cell tumour of adult type which makes up approximately 1-2% of all ovarian tumours. These tend to occur in postmenopausal women more often than pre-menopausal, and may be associated with carcinoma of the endometrium in up to 25% of cases due to oestrogen production by the tumour. Adult granulosa cell tumours have a 10 year survival varying widely in the literature from less than 60 to more than 90%, but stage I tumours have a 10 year survival of greater than 80%. Late recurrences are common and are often not evident until much longer than 5 years after primary diagnosis. They have been reported 2, 3 or more decades after initial therapy. As well as stage, the presence or absence of tumour rupture and the size of the tumour has been related to prognosis. In contrast juvenile granulosa cell tumours, in the overall of the majority of cases, have a benign course. These tumours are usually diagnosed before the age of puberty or in young adults. 97% of such tumours occur in the first 3 decades.

Thecomas and fibromas almost always have a benign course though cellular fibromas may recur within the pelvis on occasion. Fibrosarcomas have been over diagnosed in the past as too much importance appears to have been placed on mitotic criteria alone. Both granulosa cell tumours and thecomas are prone to produce excessive oestrogen resulting in breast engorgement and hyperplasia of the endometrium.

Sertoli-Leydig cell tumours have an outcome dependant on differentiation. They account for less than 0.5% of all ovarian tumours and tend to occur most often in young women with an average age of 25 years. Virilization is a classical feature but develops in only around a third of cases. Tumours presenting at advanced stage have a very poor prognosis with a mortality close to 100% at 5 years. Overall, well differentiated tumours appear to have an excellent outcome but around 10% of those of intermediate differentiation and 60% of poorly differentiated tumours behave in a clinically malignant fashion. In those cases which do have a malignant course, recurrence tends to be much earlier than in granulosa cell tumours.

Germ cell tumours constitute the second largest group of ovarian tumours after epithelial stromal tumours, making up approximately 20% of all ovarian tumours, but the great majority of these are benign mature cystic teratoma. These make up around 95% of all germ cell tumours with all the others being rare. Although dysgerminomas may occur at any age, most occur in adolescence or early adult life, and most yolk sac tumours under the age of 30 years. Most frequent age of occurrence of yolk sac tumours is in the second and third decades. These tumours are highly chemosensitive and treatment should be within specialised centres. The same strictures apply for the treatment of immature teratomas where
outcome depends on tumour grade and stage. Extra ovarian spread in immature teratomas does not always indicate a poor prognosis as the extra ovarian elements may be differentiated.

8. Staging

Stage I disease confined to ovaries or fallopian tube(s)

a 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

b 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

c tumour limited to 1 or both ovaries or fallopian tubes, with any of the following:

c1 surgical spill
c2 capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
c3 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

a extension and/ or implants on uterus and/ or fallopian tubes and/ or ovaries

b 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

a1 positive retroperitoneal lymph nodes only (cytologically or histologically proven):

IIIa1(i) metastasis up to 10mm in greatest diameter

IIIa1(ii) metastasis more than 10mm in greatest diameter

a2 microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

b macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

c macroscopic peritoneal metastasis beyond the pelvis more than 2cm 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
a pleural effusion with positive cytology
b parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO 2014 (Prat, 2014)

Staging also includes primary peritoneal, tubal and ovarian carcinomas. The primary site should be designated where possible but if unknown should be recorded as ‘undesignated’. It is not possible to have stage I peritoneal cancer. Stage IVb also includes transmural bowel infiltration and umbilical deposit (Prat 2014).
9. **Histopathology minimum dataset**

**Reporting proforma for non-benign epithelial ovarian tumours**

Surname ……………………  Forenames ……………..…  Date of birth ……………

Hospital………………… Hospital no ………………  NHS no …………..…

Date of receipt …………. Date of report ……………… Report no ………….

Pathologist ……………………………. Surgeon ………………………..

_________________________________________________________

**MACROSCOPIC FEATURES**

Specimen type: ……………………………………………………

**Ovaries**

Right:  Dimensions ……… x …… x …… mm
Tumour involvement:  Yes ☐  No ☐
Capsule:  Intact ☐  Disrupted ☐  Involved by tumour ☐  Not assessable ☐
Surface involvement Y/N

Left:  Dimensions ……… x …… x …… mm
Tumour involvement:  Yes ☐  No ☐
Capsule:  Intact ☐  Disrupted ☐  Involved by tumour ☐  Not assessable ☐
Surface involvement Y/N

**Fallopian tubes**

Right  Length…….mm  Normal ☐  Abnormal ☐
Comment ……………………………………….

Left  Length…….mm  Normal ☐  Abnormal ☐
Comment ……………………………………….

**Uterus**

Normal ☐  Abnormal ☐  Comment ……………………………………….

**Omentum**

Biopsy ☐  Omentectomy ☐  Dimensions ………x…… x…….mm
Not involved by tumour ☐  Involved by tumour ☐  Size of largest tumour nodule……….mm
Comment ……………………………………………………………………

**Peritoneal biopsies:**  Not received ☐  Received ☐

**Lymph nodes:**  Not received ☐  Received ☐
**MICROSCOPIC FEATURES OF OVARIES**

**Right ovary**

Borderline tumour: Absent ☐  Serous ☐  Mucinous ☐  Endometrioid ☐  

Other ☐  ..........

Microinvasion:  Not present ☐  Present ☐

Invasive carcinoma: Not present ☐  Present ☐

Tumour subtype  (tick all that apply)  

<table>
<thead>
<tr>
<th>Serous</th>
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<th>Low Grade ☐</th>
</tr>
</thead>
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<tr>
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<td>Well/Grade 1 ☐</td>
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<tr>
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</tr>
<tr>
<td>Others (specify)</td>
<td></td>
<td></td>
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</table>

**Left ovary**

Borderline tumour: Absent ☐  Serous ☐  Mucinous ☐  Endometrioid ☐

Other ☐ (specify)  ..........

Microinvasion:  Not present ☐  Present ☐

Invasive carcinoma: Not present ☐  Present ☐

Tumour subtype  (tick all that apply)  

<table>
<thead>
<tr>
<th>Serous</th>
<th>☐</th>
<th>High Grade ☐</th>
<th>Low Grade ☐</th>
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### MICROSCOPIC FEATURES OF OTHER TISSUES

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<th>Left: Involved</th>
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<td>Normal □</td>
<td>Abnormal □</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Uterine serosa</td>
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<td>Non-invasive borderline implants □</td>
<td>Invasive carcinoma / invasive implants □</td>
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<td></td>
</tr>
<tr>
<td>Omentum</td>
<td>Not involved □</td>
<td>Non-invasive borderline implants □</td>
<td>Invasive carcinoma / invasive implants □</td>
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</table>

**Peritoneal biopsies**

<table>
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<th>Non-invasive borderline implants</th>
<th>Invasive carcinoma / invasive implants</th>
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</tbody>
</table>

<table>
<thead>
<tr>
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<th>No. involved</th>
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</thead>
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</tr>
</tbody>
</table>

Peritoneal cytology sample (if received): Not involved □ Involved □ Equivocal □

**Comments/additional information:**

- **Provisional FIGO stage**: ............... (may change following MDTM discussion).
- **Provisional TNM stage**: .................................
- **SNOMED codes**: T........ M...........

Signature................................. Date...........
10. **Treatment (see 17. Algorithm and 18. Summary)**

Surgery should constitute the primary treatment in all cases of ovarian cancer with the following exceptions:

- Patient not fit for surgery (due to frailty or co-morbidities)
- The disease is fixed within the pelvis
- Disease is unlikely to be completely excised with primary surgery

The aims of surgery are to make a diagnosis, accurately stage the disease and optimally debulk the tumour. For disease apparently confined to the ovary, resection should involve removal of the tumour and biopsy of sites of possible secondary deposits. The following is recommended:

- Midline laparotomy
- TAH/BSO
- infracolic omentectomy
- peritoneal aspirates/washings
- diaphragm smears
- peritoneal biopsies – biopsies of abnormal appearing pelvic and abdominal peritoneum*  
- pelvic/ para-aortic sampling - enlarged nodes should be removed. A representative sample from the external/ internal iliac nodes may be removed. Routine sampling of normal appearing para-aortic nodes is not recommended. See frozen section below.
- appendicectomy - only if likely peritoneal appendicular deposits and with pseudomyxoma peritoneii

*NICE recommendation is to provide random biopsies. (NICE, 2011. grade C recommendation)

When primary surgery is undertaken in cases of extensive disease, in addition to the above surgical procedures, maximal debulking of visible tumour should also be undertaken (Pomel *et al.*, 2008; *Evidence level 2a, grade B recommendation*). The diameter of the largest residual tumour mass appears to be most relevant to survival, with 63% 5 year survival if no macroscopic tumour after laparotomy for stage III disease dropping to less than 40% 5 year survival for tumour deposits less than 1cm in diameter (Smith and Day, 1979). There are sufficient data, albeit retrospective, to support the view that surgical debulking (optimal cytoreduction) to a level of <1cm positively impacts patient survival (Elattar *et al.*, 2011; Evidence level 2a, *grade B recommendation*). Furthermore, complete cytoreduction (0mm rather than <1cm) has been associated with further increases in median survival and is therefore desirable. A systematic review by Chang *et al* (2013) looking at 13,257 patients found that for every 10% increase in the proportion of patients undergoing
complete cytoreduction (0mm) there was a 2.3 month increase in median survival, compared to a 1.8 month increase for optimal cytoreduction alone (<1cm).

In a meta-analysis of 81 studies each 10% increase of cytoreduction conferred a 5.5% improvement of median survival (Bristow et al, 2002). From a retrospective review of 296 patients with stage IIlc disease, those with no residual disease after surgery may have improved response to chemotherapy and less platinum resistance (Eisenhauer et al, 2008). Surgical cytoreduction should be to **no macroscopic residual disease** if feasible (grade C recommendation).

The commonest sites of metastases in advanced disease are on the small and large bowel (26 to 36%). Bowel resection may improve quality of life and reduce the risk of subsequent bowel obstruction but evidence of survival advantage is lacking (Guidozzi, 1998).

**Frozen section** may provide evidence of cancer where there may be doubtful or no evidence of extra-ovarian disease on inspection during surgery as 20% of apparent stage 1 cases have involved nodes (Pecorelli et al, 1999; Morice et al, 2003). An ipsilateral pelvic and para-aortic lymphadenectomy may then be appropriate to provide optimal debulking and staging of disease. **This should be booked with the Pathology Department before the day of surgery.**

Ultra-radical surgery/aggressive cytoreduction includes removal of all disease as described above with the addition of stripping the diaphragm, peritoneum and may include liver resections, partial gastrectomy, splenectomy etc. Thus far, trials have failed to show a survival advantage for this technique and as such it is not a recommended procedure by NICE (NICE, 2013a) although can be considered for selected fit cases for whom the MDT consider may be of potential benefit. **Referrals can be made to the Northern Gynaecological Oncology Centre and Gateshead for this purpose.**

### 10.1 Conservative surgery (including germ cell tumours)

A simple pelvic clearance may be appropriate if the patient is a poor anaesthetic risk.

Young women with lower risk early stage ovarian cancer (Ia-Ic) who wish to preserve their fertility may be considered for fertility preserving surgery (Ledermann, 2013). Patients will require adequate pre-operative counselling and should be made aware of the lack of robust survival data to support this route (Marpeau et al, 2008). The surgical procedure should include a laparotomy (through ideally a midline incision) removal of the primary tumour, washings, infracolic omentectomy and a thorough inspection of the abdominal cavity. Conservative surgery does not appear to have an adverse effect upon survival for stage I disease (Schilder et al, 2002). Consideration should be given to a pelvic lymphadenectomy
ipsilateral to the tumour. If apparent early stage ovarian cancer has positive pelvic nodes it will be upstaged to at least stage IIIc. Young women who opt for fertility sparing surgery should be considered for completion surgery once they have completed their family/>35 years old. They should also have an endometrial biopsy to exclude synchronous endometrial hyperplasia or carcinoma (evidence level IV; grade C recommendation).

Young patients with germ cell tumours should have conservative surgery despite extensive disease as these tumours tend to be extremely chemosensitive. Detailed recording of residual disease at laparotomy is important for monitoring response to subsequent treatment.

Women of reproductive age who may wish to undergo surrogacy, or to store oocytes/embryos before chemotherapy should be referred for consideration of cryopreservation (NICE, 2013b). Referrals can be made to the Hewitt Fertility Centre at Liverpool Womens Hospital for this purpose. (http://www.thehewittfertilitycentre.org.uk/).

10.2 Delayed primary surgery/ interval debulking
There is little consensus on which patients with advanced ovarian cancer (IIIc-IV) should be offered neoadjuvant chemotherapy followed by delayed primary surgery (interval debulking surgery). Disease related factors may include; radiological evidence of bowel, mesenteric or omental involvement, or a fixed tumour. Patient related factors may include a poor operative candidate due to performance status or co-morbidities.

Where possible tissue diagnosis should be sought via image guided biopsy or laparoscopic guided biopsy prior to the commencement of chemotherapy (NICE, 2011). A raised CA125 in addition to cytological confirmation of ovarian cancer or adenocarcinoma may be acceptable where the safety of proceeding with a biopsy is in question. Only in exceptional cases should chemotherapy proceed in the absence of histological proof of ovarian cancer (NICE, 2011).

The landmark trial EORTC 55971 forms the basis of recommending delayed surgery following 3 cycles of neoadjuvant chemotherapy in selected IIIc/IV ovarian cancer cases (Vergote et al, 2010). This phase III clinical trial recruited 670 patients with stage IIIc-IV ovarian cancer and randomised to primary debulking surgery followed by adjuvant chemotherapy versus neo-adjuvant chemotherapy (3 cycles of carboplatin and paclitaxel) followed by interval debulking surgery and a further 3 cycles of adjuvant chemotherapy. Whilst there was no significant difference in overall or progression free survival with the two treatment arms, there was a significantly lower rate of complication including postoperative mortality (2.5% vs 0.7%) and a higher rate of optimal cytoreduction <10mm (42% vs 81%) (Vergote et al, 2010). Subsequent clinical studies have confirmed these outcome measures and have also concluded that the rate of stoma formation is significantly reduced in those

For antithrombotic prophylaxis see ‘SOPP for Inpatient Management’.

10.3 Chemotherapy

Post-operative (adjuvant) chemotherapy is recommended in the majority of cases of ovarian cancer. High risk early ovarian cancer defined as: lc-IIa, grade 3 of any stage and clear cell of any stage have all been cited as having sufficient data to consider adjuvant platinum based chemotherapy (Winter-Roach et al, 2012; Trimbos et al, 2003). NICE guidelines recommend 6 cycles of single agent carboplatin for this patient group based on the combined phase III data from both ICON1 and ACTION clinical trials (NICE, 2011; Trimbos et al, 2003). >60% of patients within these clinical trials received single agent platinum based chemotherapy (grade A recommendation). Consensus opinion suggests consideration of combination chemotherapy (carboplatin and paclitaxel) in this patient group (Ledermann et al, 2013). Whilst there is no level 1 evidence to support its use in this setting, many clinicians feel that the separation of high risk early ovarian cancer from advanced ovarian cancer is arbitrary (grade C recommendation).

Other considerations:

- Clear Cell Cancer – Contrary to stage III clear cell ovarian cancer, early stage ovarian clear cell cancers do not have a significantly worse survival outcomes when compared to early stage serous ovarian carcinoma (Sugiyama et al, 2000). This histological subtype is also known to be less sensitive to platinum based therapy (11% vs 72/5% response rates) (Sugiyama et al, 2000). Despite this, clear cell ovarian cancer of any stage (1a onwards) were regarded as of sufficiently high risk to be included in the inclusion criteria in both ICON 1 and ACTION clinical trials and therefore should all be referred for oncological opinion/discussion of the possible merits of adjuvant chemotherapy (Ledermann et al, 2013; Trimbos et al, 2003).

- Incomplete surgical staging – When full surgical staging has not occurred, often due to an unexpected finding, follow-on completion surgery is usually recommended. If this is not possible/desired by the patient it may be reasonable to proceed with combination adjuvant chemotherapy alone (carboplatin and paclitaxel) as retrospective data suggests overall survival may not be compromised following combination chemotherapy (Dizon et al, 2008).

All medically fit patients with advanced ovarian cancer (IIb-IV) should be considered for adjuvant chemotherapy following primary surgery with combination chemotherapy (6 cycles of carboplatin and paclitaxel) (Nice, 2011; Ledermann et al, 2013) (grade A recommendation). A meta-
analysis of 38,440 patients of 198 clinical trials confirmed the findings of the landmark GOG 111 and Intergroup clinical trial by showing a significant increase in survival outcomes with the addition of a taxane to platinum based chemotherapy (Kyrgiou et al, 2006; McGuire et al, 1996; Stuart et al, 1998). Single agent carboplatin is an alternative in patients with significant co-morbidities or frailty.

**All cases must be discussed at the gynaecology cancer MDT to decide further treatment.**

**Other Considerations:**

- Intraperitoneal chemotherapy - Whilst there is a great deal of interest in the use of intraperitoneal chemotherapy for advanced ovarian cancer, its use is not recommended outside of clinical trials (NICE, 2011).

- Anti-angiogenesis therapy – Bevacizumab in addition to standard chemotherapy for first line treatment of advanced ovarian cancer has failed to show a significant improvement in overall survival and is therefore not recommended in routine clinical practice (NICE, 2013a). Bevacizumab is currently available in England under the cancer drugs fund for chemo-naive stage III patients who have >1cm residual disease following debulking and stage IV disease (Thomson, 2015). This is based on a post-hoc subgroup analysis of ICON 7 where an overall survival benefit was found for this patient group (Perren et al, 2011).

- Dose-dense regimens – Weekly regimens of carboplatin and paclitaxel as an alternative to the standard three weekly schedule are postulated to improve survival outcomes. Clinical trial outcomes so far have been mixed. Results are awaited from the ICON 8 clinical trial. Dose-dense regimens in patients fit enough for combination treatment are therefore not recommended outside of **clinical trial**.

**Chemotherapy without surgery for primary peritoneal carcinoma may be considered where there is no resectable bulk disease at CT imaging in which case MDT discussion is recommended. Although at present standard staging surgery is current practice.**

**Platinum based chemotherapy is recommended** for stage II+ granulosa cell tumours (Colombo et al, 2012).

**Repeat Imaging**

Imaging with an abdomino-pelvic CT after 3 cycles of neoadjuvant chemotherapy is recommended where there was bulk disease (>1cm maximum diameter) remaining after surgery and further surgery is being contemplated.
DVT prophylaxis
Patients who are having primary chemotherapy for ovarian cancer often have multiple risk factors for venous thromboembolism (VTE). These include having advanced cancer, reduced mobility, spending time in hospital, and having pelvic tumours causing venous compression. These need to be considered in addition to any pre-existing risk factors such as prior VTE. The greater the number of risk factors the greater the chance of VTE.

The development of VTE can cause significant morbidity as well as occasional mortality and can complicate or delay the surgery that is often planned for such patients. All patients having open surgery for gynaecological cancer should have low molecular weight heparin (eg clexane 40mg daily for patients with a normal BMI: see SOPP for inpatient management) for 28 days. Women having laparoscopic surgery should have prophylaxis until discharge from hospital.

10.4 Secondary intervention and other options
Second look laparotomy does not improve survival and has been abandoned outside research protocols. Laparoscopy and biopsy may be considered for patients who present with a suspicion of primary peritoneal cancer where primary chemotherapy is indicated. These patients present clinically in a similar way to primary ovarian cancer. CA125 levels are usually raised and the disease resides within the peritoneal surfaces. On CT scanning the ovaries are typically normal sized and in advanced disease there is frequently ascites, peritoneal disease and omental thickening. Each should be individualised, neoadjuvant chemotherapy followed debulking surgery can be considered.

Standard
Early Ovarian Cancer – Optimal surgical staging via midline laparotomy, TAH, BSO and infracolic omentectomy with biopsies of peritoneal deposits, random biopsies of pelvic and abdominal peritoneum and retroperitoneal lymph node assessment. Offer high risk stage I disease adjuvant chemotherapy (NICE, 2011).
Advanced Ovarian Cancer – Surgery should aim to result in complete resection of macroscopic disease. In the case of neo-adjuvant chemotherapy, tissue diagnosis should be sought in all but exceptional cases (NICE, 2011).

Grade A recommendation.
11. Dealing with recurrent disease
Since the publication of the MRC OVO5 clinical trial, routine testing of CA125 is no longer standard practice in asymptomatic patients following initial treatment (Rustin, 2011). Investigation and subsequent diagnosis of relapse is largely based on symptoms or clinical signs. In the face of symptoms, a raised CA125 may suggest recurrence. A rise above the upper limit of normal in patients who had normalisation of CA125 following initial treatment, or a doubling of the post-treatment nadir in those that did not normalise is sufficient to suggest recurrence and should prompt further investigations i.e. restaging CT scan. An increasing CA125 predates clinical or scan evidence of recurrence in 70% of women with ovarian cancer by 4 months (Rustin et al, 2006).

11.1 Chemotherapy
Patients with a proven symptomatic relapse of ovarian cancer may be offered palliative chemotherapy assuming adequate functional status. The appropriate agents depend on the chemotherapy free interval and the functional status of the patient (see table below):

<table>
<thead>
<tr>
<th>Treatment free interval</th>
<th>Terminology Used</th>
<th>Recommended Chemotherapy</th>
<th>Alternative Options</th>
</tr>
</thead>
<tbody>
<tr>
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*BSC – Best supportive care
**LD – liposomal doxorubicin (Caelyx)
NICE (2011)
Whilst combination chemotherapy increases the risk of toxicity over single agent, the addition of taxol to carboplatin in platinum sensitive and platinum-partially sensitive recurrent disease has shown a significant overall survival benefit (absolute increase in 2 year survival of 7%) and is therefore recommended in suitable patients (Parmar et al, 2003). In all these cases, the possibility of enrolment in internal or external clinical trials should be considered.

11.2 Surgery
A survival advantage has been claimed for the surgical management of recurrent disease. However such survival may be due to innate chemosensitivity rather than surgical intervention (Covens, 2000). In a retrospective analysis of 106 women with recurrent intra-abdominal disease, 87 had multiple recurrences and 39 were asymptomatic. 82% had total macroscopic clearance with a 28% 5 year survival from the time of repeat surgery (Eisenkop et al, 2000). A retrospective study of 267 women found that complete resection was associated with performance status, FIGO stage I/II, no residual tumour after primary surgery and the absence of ascites. Only complete macroscopic resection was associated with prolonged survival (median 45.2 vs 19.7 months; Harter et al, 2006) which was statistically significant. A further retrospective study of 153 women found improved survival for a longer disease free interval (up to 12 months disease free interval providing a median survival of 30 months compared to a disease free interval up to 30 months providing a median survival of 39 months and for a longer disease free interval a median survival of 51 months: p=.005), a single site for recurrence (median survival 60 as opposed to 42 months for multiple sites of recurrence and 28 months for patients with carcinomatosis: p<.001) and less residual disease (median survival for residual disease up to 0.5cm was 56 months compared to 27 months for those with more residual disease: p=.004; Chi et al, 2006). A further retrospective review of 85 patients found that the only significant factors were a disease free interval of at least 12 months and less than 2cm diameter of residual disease at the end of primary surgery (Tebes et al, 2007). Median survival for patients who were cytoreduced to up to 1cm residual disease was 30 months vs 17 months for those with more residual disease.

In light of this modest survival advantage, debulking surgery should preferably be considered for patients with a recurrent isolated symptomatic mass, an elevated CA125 level and platinum sensitive disease (>12 months after the last cycle of chemotherapy) rather than diffuse disease on CT scanning (Evidence level 2b; grade C recommendation). Where possible, potential candidates for surgery should be recruited into the ongoing clinical trial DESKTOP III.

11.3 Radiotherapy
Radiotherapy doesn’t constitute standard treatment in either newly diagnosed or recurrent ovarian cancer. It may be considered on a case-by-case basis for isolated recurrences not amenable to surgery or in localised symptomatic cases.
11.4 Palliative care (see Palliative care file)
The provision of palliative and supportive care for patients with
gynaecological malignancies should be an integral part of service
 provision. The NICE guidance Improving Supportive and Palliative Care for
Adults with Cancer was published in March 2004 and provides detailed
recommendations which complement and inform this guidance (NICE,
2004).

There is little robust evidence from the palliative care literature that is
specific to patients with advanced gynaecological malignancies, therefore
this guidance is based on evidence from studies looking at patients with a
broad range of advanced malignancies.
Also consider the role of Macmillan nurses, terminal care with methods of
analgesia, steroids and radiotherapy. Involvement of the GP throughout is
essential.

11.4.1 Management of bowel obstruction in patients with ovarian cancer
Faecal impaction should be considered as a differential diagnosis.
Abdominal X-rays should be undertaken only if surgery is to be
considered, in which case CT abdomen may be a more appropriate
investigation.
U+E’s/ LFT’s should be checked.
A more suitable option for most patients is medical management of bowel
obstruction. Medical management should include analgesia and
appropriate anti-emetic use. The following may also be considered:
steroids, reduce GIT secretions, laxatives, re-hydration, NG tube
insertion/aspiration and drainage of ascites.
Chemotherapy is not an effective treatment in restoring bowel function and
should not be used in fully developed bowel obstruction.

<table>
<thead>
<tr>
<th>Medical management of bowel obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
</tr>
<tr>
<td>Morphine/ diamorphine (preferably via a syringe driver),</td>
</tr>
<tr>
<td>Fentanyl patch</td>
</tr>
<tr>
<td>Anti-emetics</td>
</tr>
<tr>
<td>Cyclizine/ haloperidol/ nozinan/ 5-HT agonists</td>
</tr>
<tr>
<td>(prokinetics should be avoided)</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Reduce GIT secretions</td>
</tr>
<tr>
<td>Octreotide/ buscopan</td>
</tr>
<tr>
<td>Laxatives/ suppositories</td>
</tr>
<tr>
<td>Consider stool softeners, avoiding osmotic laxatives</td>
</tr>
<tr>
<td>Hydration</td>
</tr>
<tr>
<td>Aim for oral/ subcutaneous</td>
</tr>
<tr>
<td>NG suction</td>
</tr>
<tr>
<td>Use sparingly</td>
</tr>
</tbody>
</table>

When in doubt use Diamorphine 30/ Buscopan 60/ Haloperidol 5 over 24hrs in a
driver
11.4.2 Recurrent ascites

Initial management of symptomatic ascites should involve elective paracentesis. Where possible this should be done as a day case procedure. In the majority of cases, chemotherapy will slow the recurrence of ascites and thus provide prolonged symptomatic improvement. Where chemotherapy is no longer effective, or the ascites is refractory to treatment, repeated paracentesis can become increasingly technically difficult and risky to the patient. In these cases insertion of an indwelling peritoneal catheter should be considered assuming the patient has sufficient prognosis to benefit from the procedure (predicted survival of >6 weeks).

**Standard**

Paclitaxel in combination with platinum chemotherapy is recommended for recurrent platinum sensitive/partly sensitive ovarian cancer.

Liposomal doxorubicin is recommended for platinum refractory disease.

NICE, 2011

*Grade A recommendation*

12. Survival

5yr relative survival former Anglia Cancer Network 2002-6

<table>
<thead>
<tr>
<th>Stage</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>43%</td>
</tr>
<tr>
<td>III</td>
<td>19%</td>
</tr>
<tr>
<td>IV</td>
<td>3% at 5 years (CRUK, 2014)</td>
</tr>
</tbody>
</table>

5 year survival overall is 39% (CRUK, 2014)

3 year survival in relation to residual tumour mass after primary surgery for stage III-IV disease

<table>
<thead>
<tr>
<th>Residual Mass</th>
<th>Range (%)</th>
<th>Approx. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No residual</td>
<td>65-73</td>
<td>70%</td>
</tr>
<tr>
<td>&lt; 2cm</td>
<td>76-35</td>
<td>55%</td>
</tr>
<tr>
<td>&gt; 2cm</td>
<td>34-13</td>
<td>25%</td>
</tr>
</tbody>
</table>


* no residual disease data only
12.1 **Inventory of active trials**

Active trials – Surgical: Wales Cancer Bank, DESKTOP
Active trials – Medical: TESARO

13. **Follow up**

Careful inspection and palpation of the vaginal vault and palpation for any pelvic masses should be performed 3 monthly for 2 years, 6 monthly for 1 year and then annually.

Hospital follow up should be for 5 years. A prospective questionnaire study of 948,576 women and subsequent meta-analysis showed that with a mean of 5.3 years follow up, current use of HRT was associated with an increased incidence and death from ovarian cancer. The effect was seen in serous histology only and included borderline tumours. A non-significant increased risk was seen with increased duration of use. Previous use of the combined pill did not attenuate this effect. Also past users of HRT were not at increased risk. This effect was such that over 5 years 1 extra ovarian cancer was seen in 2500 users and 1 extra cancer death per 3300 users. HRT should not be offered to women with serous carcinoma but women with serous borderline tumours should be forewarned of a slight increased risk of recurrence of borderline disease should they choose to use HRT ([grade B recommendation](#); Million Women Study Collaborators, 2007). Vaginal vault or cervical cytology is not required unless coincident CIN. Patients will need genetic counselling if other family members have had ovarian or other relevant cancers.

Granulosa cell tumours should have a serum inhibin test at each visit and follow-up should be for 10 years in view of known later recurrences between 4-6 years but can occasionally be much mater (Colombo *et al*, 2012).

All patients must be encouraged to report any symptoms suggestive of recurrent disease immediately by contacting their CNS rather than wait until their next outpatient appointment.

An RCT did not revealed a benefit for routine CA125 testing and treatment of relapse at asymptomatic elevation in comparison to treatment at onset of symptoms (Rustin and van der Burg, 2009). Patients with an asymptomatic elevated CA125 (2x above normal) were treated 5 months earlier and were re-treated for second relapse 5 months earlier in a randomised trial of 1442 women having had debulking surgery and first line chemotherapy with a normal CA125 at the end of treatment. Overall survival and quality of life was equivalent in both groups. CA125 measurement is not recommended for follow up in women without symptoms ([Evidence level 1b; grade A recommendation](#)). Imaging for ovarian cancers is suggested to monitor response to chemotherapy of for suspected relapse only and is not recommended routinely.
13.1 Identification and management of late effects of treatment
Psychosexual, emotional, bowel, genitourinary, neuropraxia other problems may need detailed discussion with the clinical nurse specialist and psychological, lymphoedema, pain, spiritual and other support services.

14. Borderline ovarian tumours (tumours of low malignant potential)
Borderline tumours account for 8-15% of serous tumours and nearly 20% of mucinous tumours. Endometrioid, Brenner and clear cell borderline tumours are uncommon (Fox, 1992). Up to 60% of serous borderline tumours are bilateral. Borderline tumours are occasionally metastatic at presentation or at follow up but long term survival is excellent with 5 year survival of 100% for stage I/IIa and about 80% for those 20% of cases with more advanced disease confined to the abdomen. However late recurrence can occur 10-15 years after diagnosis with advanced stage disease with a long term survival of around 70%.

14.1 Microinvasion with borderline tumours
Microinvasion may occur within an otherwise typical borderline tumour, usually of serous or mucinous type. In most studies, microinvasion has been found to have no adverse effect on prognosis.

It has been suggested that microinvasion in a mucinous borderline tumour should be classified as borderline tumour with microinvasion, but this is a controversial area and likely to be poorly reproducible from a histological viewpoint. However, this should be routinely attempted using published criteria.

In up to 9% of borderline mucinous tumours, one or multiple tiny foci of stromal invasion may be present. None of the reported borderline tumours with stromal microinvasion or microinvasive carcinoma developed metastases.

14.2 Management
Surgical treatment is as for epithelial ovarian cancer (see 10 Treatment). If suboptimal treatment or ovarian conservation has been performed then regular follow up is with CA125 estimations (bearing in mind the comments in 13 above) and additional TV USS if there has been ovarian conservation. Completion surgery can delayed until after child-bearing with oestrogen replacement therapy offered if appropriate. There is no role for adjuvant chemotherapy in non-invasive borderline ovarian tumours.

Further surgery is usual for symptomatic recurrence but occasional cases with invasive recurrence after surgery may benefit from chemotherapy. Follow up after definitive surgery for early stage disease is not required.
15. Non-epithelial Ovarian Cancers

15.1 Sex cord-stromal tumours and steroid tumours

Whilst many of the ovarian stromal tumours are regarded as benign, any tumour with sex-cord elements has malignant potential. Adult granulosa cell tumours are the most common of the sex-cord stromal tumours, constituting 2-5% of ovarian malignancies, followed by Sertoli-Leydig tumours (Young, 2005).

Whilst many of these tumours may secrete steroid hormones resulting in symptoms and signs of hyperoestrogenism or virilisation, most present as asymptomatic masses. The relative small numbers of these tumours inevitably prevents prospective randomised clinical trials. Data to guide management is therefore lacking, thus consensus opinion drives most management decisions.

Surgical staging and thus management is as for epithelial ovarian cancers. Patients who wish to undergo fertility preserving surgery may undergo unilateral salpingo-oophorectomy with the knowledge that retrospective data suggests equivalent outcomes in the presence of stage I disease (Zhang et al, 2007). The substantial risk of a synchronous endometrial cancer in granulosa cell tumours, and other oestrogen producing tumours, of around 9%, dictates the need endometrial sampling if uterine preservation is to be undertaken (Zanagnolo et al, 2004). The role of adjuvant chemotherapy in early sex cord tumours is uncertain and therefore not recommended (Colombo et al, 2012).

Recurrent disease should be resected whenever possible. For those cases with advanced/ metastatic or irresectable disease, palliative chemotherapy is a reasonable approach. Response rates of up to 80% have been reported for platinum regimens such as BEP (bleomycin, etoposide and cisplatin) (Gershenson et al, 1996).

15.2 Germ cell tumours

Malignant ovarian germ cell tumours (GCT) comprise a group of rare ovarian cancers originating from the ovarian primordial germ cells. Both dysgerminomas and non-dysgerminomas (immature teratoma, yolk sac tumour and endodermal sinus tumours) produce tumour products which can be measured to aid diagnosis, treatment assessment and follow-up. A raised AFP, HCG and LDH in a young (<40) women is highly suggestive of a GCT and can be diagnostic in many cases.

The staging and management of early GCT’s is with primary surgery in line with that of epithelial ovarian cancer. However, fertility sparing surgery is a reasonable option in all stages of GCTs; in early stage disease relapse rates are low, in advanced disease response rates and subsequent overall survival with BEP chemotherapy are high (Gershenson et al, 1990; Segelov et al, 1994). Biopsy only is not recommended as GCTs are heterogeneous tumours and a biopsy only may not be representative of the whole tumour.
Following surgery adjuvant chemotherapy is recommended in all but grade 1 stage 1a GCT and 1a/1b dysgerminomas (Colombo, 2012). This recommendation is based on retrospective and single arm clinical trial data with three cycles of BEP (grade B recommendation; Williams et al, 1994). Patients with metastatic disease at presentation, or disease recurrence (in the absence of previous chemotherapy) should be offered chemotherapy with BEP with the expectation of long term survivorship. 5-year overall survival for stage IV GCT is reported to be 71% (Murugaesu et al, 2006).

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This guideline is available at the BCUHB intranet site: http://www.wales.nhs.uk/sites3/page.cfm?orgid=456&pid=20413
17. **Algorithm**

**Algorithm for primary management of patients with ovarian cancer**

*Mass diagnosed at USS/CT*

- **RMI ≥250 refer to BCU West**
- **fixed or bowel, mesenteric, omental disease**
- **mobile/ predicted maximal cytoreduction**

**Consider neoadjuvant chemo if Bx proven**

**Primary surgery** (Conservative if fertility/anaesthetic concerns)

**Ideal cytoreduction to no macroscopic residual disease**

**Surgery after 3 cycles if response**

**Adjuvant chemotherapy**

- **>1cm dia residual disease**
  - **Consider interval debulking surgery**

**Relapse**

**Symptomatic recurrence**

- **Diffuse disease**
  - **Consider chemotherapy**
    - Disease free interval
      - <6 months – Caelyx, etoposide or clinical trial
      - >6 months – carboplatin/ taxol

- **Single mass**
  - **Consider surgery prior to chemotherapy**
    - If elevated CA125 level and platinum sensitive disease (>12 months after the last cycle of chemotherapy)
    - Consider DESKTOP (see section 11.2)

*consider completion surgery

*elevated CA125 and abnormal CT*
18. **Summary**

**Pre-op assessment**
- Hb, U+E, liver function tests, group and save
- CA125 (also β-HCG/ LDH/ AFP if <40 years old); CEA if metastatic
- Chest X-ray
- **CT scan abdomen/ pelvis** - if ovarian cancer suspected clinically or raised CA125 and the patient is well enough to await the result of the scan

**Surgery**
- **For suspected stage I disease** - TAH/BSO, infracolic omentectomy, peritoneal washings or aspirate, diaphragmatic smears, consider peritoneal biopsies, pelvic/ para-aortic node sampling and appendicectomy.
- **If fertility a consideration** then unilateral oophorectomy acceptable providing biopsy of contralateral ovary, infracolic omentectomy, peritoneal washings or aspirate and diaphragmatic smears are taken, but consider peritoneal biopsies, pelvic/ para-aortic node sampling and appendicectomy. Conservative surgery appropriate for tumours in women less than 30 years of age as germ cell tumours much more likely.
- **For advanced disease** then TAH/BSO/ omentectomy and maximal debulking (stage II-IV disease). This may involve bowel resection/ splenectomy etc. and so pre-operative consultation with general surgeon/ urologist may be indicated by scan findings.
- **Delayed primary surgery** after 3 cycles of chemotherapy may be considered.
- **Completion surgery** if initial procedure inadequate.
- **Interval debulking surgery** if initial procedure suboptimal and there is suitable tumour regression after 3 cycles of chemotherapy.

**Chemotherapy**
- **Chemotherapy** adjuvant chemotherapy should be considered for all fit IC-IV ovarian cancers, clear cell and poorly differentiated cancers of any stage.
- **Management of symptomatic relapse** check CA125 and CT scan. If single large resectable mass then surgery otherwise second line chemotherapy.
19. References


NICE. (2004) Improving Supportive and Palliative Care for Adults with Cancer.


Rustin GJ (2011). Follow-up with CA125 after primary therapy of advanced ovarian cancer has major implications for treatment outcome and trial performances and should not be routinely performed. *Ann Oncol*. 22 Suppl 8, viii45-viii48


Schilder JM, Thompson AM, DePriest PD et al. (2002) Outcome of reproductive age women with stage Ia or Ic invasive epithelial ovarian cancer treated with fertility sparing therapy. *Gynecol Oncol*, 87, 1-7.


Stuart G, Bertelson K, Mangioni C et al. (1998) Updated analysis shows a highly significant improved overall survival (OS) for cisplatin-paclitaxel as first line treatment of advanced ovarian cancer. Mature results of the EORTC-GCGG


Sutcliffe S, Pharoah PD, Easton DF, Ponder BA. (2000) Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. *Int J Cancer*, **87**:110-7


Classification of evidence levels

Ia  Evidence obtained from meta-analysis of randomised controlled trials

Ib  Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well designed controlled study without randomisation

IIb Evidence obtained from at least one other type of well designed quasi-experimental study

III Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

*Lower limit of acceptable evidence base is level IIa.*

Grades of recommendation

A  Requires at least 1 randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation

B  Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendation

C  Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality

*Lower limit of acceptable grade of recommendation is B.*
This guideline has been developed from the Guideline Group of the British Gynaecological Cancer Society

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<thead>
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<th>Role</th>
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<tbody>
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<td>Obstetrician and Gynaecologist</td>
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<td>Rachel Connor</td>
<td>Consultant Radiologist</td>
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<tr>
<td>Mark Heatley</td>
<td>Gynaecological Pathologist</td>
</tr>
<tr>
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<td>Gynaecological Oncologist</td>
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<table>
<thead>
<tr>
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<th>Role</th>
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<tbody>
<tr>
<td>Simon Leeson</td>
<td>Consultant Gynaecologist and Oncologist</td>
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<td>Richard Peevor</td>
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<tr>
<td>Anna Mullard</td>
<td>Consultant Medical Oncologist</td>
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