Final PMB definition guidelines for ovarian cancer

Published date: 15 April 2019

Review due: 15 April 2021

DISCLAIMER

The ovarian cancer benefit definition has been developed for the majority of standard patients. The benefit definition is subject to the provisions of Regulations 15H and 15I. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs and nursing care. However, these interventions form part of care and are prescribed minimum benefits.

ACKNOWLEDGEMENTS

The Council for Medical Schemes (CMS) would like to acknowledge all stakeholders who assisted in drafting this document, including gynecologists and obstetricians, oncologists, pathologists, radiologists, patient advocacy groups, funders and administrators.

The CMS would like to acknowledge the following clinical experts for their insights during the drafting of the document:

Dr Angelique Coetzee, Dr Anthony Levy, Dr H-T Wu, Dr Kamedran Govender, Dr Kasandri Govender, Dr Rene Krause, Dr Setheme Mosehle, Dr Sheynaz Bassa, Dr Shilendra Hariparsad, Professor Leon Snyman and Professor Paul Ruff.

The individuals mentioned below from patient advocacy groups, representatives from South African Medical Association (SAMA), pharmaceutical companies, different medical aid funders and administrators were also members of the clinical advisory committee set up to discuss member entitlements for cervical cancer. Their contributions were immensely valuable:
Dr Abongile Qamata (Medscheme) , Dr Jo Samsonowicz (Medscheme), Dr Sandile Mhlongo (Discovery Health), Ms Arlene Anderson (Janssen Pharmaceutical), Ms Kim Cardwell (Discovery Health), Ms Shelley-Ann McGee (SAMA) and Professor Manie de Klerk (MMI).

The CMS would also like to acknowledge the following individuals for their assistance in the write-up of the document:

Professor Nathaniel Mofolo, Professor Shinga Feresu, Dr Edith Madela-Mntla, and Dr Zinhle Makatini.

TABLE OF CONTENTS

TABLE of contents 4

1. Introduction 5

2. Scope and Purpose 5

3. Epidemiology 5

4. Pathology 6

5. Screening 7

6. Diagnosis, staging and risk assessment 8

7. Staging of Ovarian Cancer 11

8. Treatment 12

9. Follow up after surgical resection 22

10. Best supportive care 22

REFERENCES 23

1. INTRODUCTION

1.1. The legislation governing the provision of the prescribed minimum benefits (PMBs) are contained in the regulations enacted under the Medical Schemes Act 131 of 1998. In respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries find it difficult to know their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is coordinated by the Council for Medical Schemes (CMS) and aims to define the PMB package and to guide the interpretation of the PMB provisions by relevant stakeholders. The guidelines are based on the available evidence of clinical and cost-effectiveness, taking into consideration affordability constraints and financial viability of medical schemes in South Africa.

2. SCOPE AND PURPOSE

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with ovarian cancer in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2. The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into considerations evidence-based medicine, affordability and in some instances cost-effectiveness.

Table 1: Possible ICD10 codes for identifying ovarian cancer

ICD 10 code	WHO description
C56	Malignant neoplasm of ovary
C79.6	Secondary malignant neoplasm of ovary

The CMS acknowledges that some patients will not qualify for PMB entitlements under the definition of treatable cancers as outlined in explanatory note 3, annexure A of the Act. In these instances, when the treatment intent is no longer curative, DTP 260S, may be applied depending on the clinical case.

Table 2: Applicable PMB code for a non-curative setting in ovarian cancer

PMB Code	PMB Description		ICD10 Code	ICD10 Description
260S	# Imminent death regardless of diagnosis	# Comfort care; pain relief; hydration	Z51.5	Palliative care

3. EPIDEMIOLOGY

3.1. Globally, 240 000 women are diagnosed with ovarian cancer every year, making it the seventh most common cancer in women and the eighth most common cause of cancer deaths worldwide (Penelope et

al, 2017). With a five-year survival rate below 45%, it is responsible for 150 000 deaths and accounts for 5% of cancer deaths in the female population.

3.2. Ovarian cancer is primarily a disease of postmenopausal women (Sopik et al, 2015). It is rare in women under 40 years of age and most cancers in this group age are germ cell tumours. Above age 40, more than 90% are epithelial tumours (Webb & Jordan, 2017).

3.3. Incidence rates are highest in more developed regions, exceeding 7.5 per 100000 and lowest in sub-Saharan Africa with rates below 5 per 100000. The incidence rises with increasing age and peaks in the fifth decade, with the rate reaching a plateau after that (Gershenson et al, 2004). Approximatively, 70% of cases and 85% of ovarian cancer deaths occur after age 55 (Sopik et al, 2015).

3.4. In 2014, the age-standardised incidence rate per 100000 was 2.15 and the lifetime (0-74) risk of developing a cancer was 1 in 387. In Africa, ovarian cancer is one of the most common malignancies in females with an incidence rate of 3.7%. In South Africa, the number of new cases was 518 in 2014 (NCR, 2014).

3.5. The age-standardised incidence rate of ovarian cancer is 3.9 per 100 000 and the age-standardized mortality rate is 6.05 per 100 000 in the world. In Southern Africa, the age-standardized incidence rate is equal to 3.9 per 100 000 whereas the age-standardized mortality rate is 7.33 per 100 000. The prognosis is poor due to the fact that the diagnosis is made at a later stage. The mortality rate is about 70%. The five-year survival is only 15–20% for patients despite aggressive treatment (Penelope et.al. 2017; Smith & Guidozzi, 2009; Sopik et al., 2015).

3.6. Several risk factors have been associated with ovarian cancer. Reproductive, hormonal, hereditary and endocrinology are the most common factors (Sopik et al,2015; Rubin & Sutton, 2001).

3.7. Family history and hereditary factors are linked to the disease. Familial syndromes and germline mutations in the tumour suppressor genes BRCA1 and BRCA2 have been cited as hereditary factors (Rubin & Sutton, 2001).

3.8. The worldwide burden of ovarian cancer is thought likely to continue and whilst significant progress has been made, from an African and developing world perspective including South Africa, a screening test for ovarian cancer is not affordable and feasible for the general population (Smith & Guidozzi, 2009).

4. PATHOLOGY

4.1. Ovarian carcinomas are a heterogeneous group of neoplasms encompassing a number of different cellular subtypes based on the type and degree of differentiation. Approximately 90% of ovarian cancer originates from the ovarian surface epithelium and a number of distinct cell types: germ cells, sex cord stromal cells and epithelial cell (Fauci et al, 2009) subtypes are recognised (Scully, 1999). Ovarian cancer can develop from three distinctive cell types that are germ cells, stromal cells and epithelial cells (Fauci et al, 2009). Epithelial ovarian cancer is the most common of the three. The five main types of ovarian carcinomas are high-grade serous carcinomas (HGSCs), endometrioid carcinomas (EC), clear-cell carcinomas (CCC), mucinous carcinomas (MC), and low-grade serous carcinomas (LGSC) (Prat, 2012). Borderline tumours

are pre-invasive ovarian epithelial tumours. They are proliferative tumours which may recur and form peritoneal implants, which may cause patient demise from intestinal obstruction. Because borderline tumours may disseminate in the peritoneal cavity and even metastasise to regional lymph nodes, they require staging and use the same FIGO/TNM staging system as for ovarian carcinomas. Borderline tumours can progress to frankly invasive carcinomas. Malignant germ cell tumours include immature teratomas (grade II-III), yolk-sac tumours, choriocarcinomas, dysgerminomas and embryonal carcinomas. Sex cord stromal tumours that can behave in a malignant fashion include granulosa cell tumours, Sertoli-Leydig cell tumours, and steroid cell tumours. Other rare ovarian malignancies include malignant Brenner tumours, small cell carcinomas, somatic malignancies arising in teratomas, lymphomas and sarcomas.

4.2. Based on histopathological, molecular, and genetic studies, these epithelial tumours are divided into Type 1 and Type 2 ovarian carcinomas. Type 1 cancers tend to be low-grade and indolent tumours and include endometrioid, clear cell, mucinous, low grade serous, and transitional cell carcinomas. Type 1 cancers are recognised as genetically stable and are characterised by mutations of KRAS, BRAF, ERBB2, PTEN, PIK3CA and ARID1A. Type 2 tumours more aggressive and found at an advanced stage, comprise high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas and are very frequently associated with TP53 mutations. Approximately 20% of Type 2 carried a BRCA1/2 mutation due to a combination of germ line and somatic mutations (Bell, 2011).

4.3. Individuals, who carry the germline mutations in either BRCA1/2, are at a higher risk for ovarian cancer, amongst others, compared to the general population (Mateo, 2015). A 30 – 70% risk of developing mainly HGSC by the age of 70, is seen in women with germline mutations in BRCA1 or BRCA2 (Risch, 2006).

5. SCREENING

5.1. It is generally agreed that screening asymptomatic women for ovarian cancer with transvaginal ultrasound and CA125 tumour markers does not reduce ovarian cancer deaths. Pelvic examination and CA-125 can occasionally detect early disease. However, these are insensitive screening procedures. Transvaginal sonography is often used but gives false positive results. The sensitivity of the CA-125 is poor and false positive or negative cases are common.

5.2. The lack of established identifiable histologic precursor lesions or molecular events that precede malignant transformation and the fact that neither the time required for development of invasive disease nor the interval between stage I and stage III ovarian carcinomas is known, poses a challenge for ovarian cancer screening. Randomized, controlled trials data do not yet support routine screening for ovarian cancer in the general population (Partridge, 2009).

5.3. There is evidence on the benefits of BRCA testing and prophylactic risk reduction oophorectomy in very specific populations. Risk reduction surgery is indicated in patients with BRCA 1 and 2 and other genetic breast and ovarian cancer mutation carriers that result in high risk of developing the cancer. Schemes are

recommended to make provision for funding for the appropriate subset of patients when indicated at their own discretion as the Medical Schemes Act 131 of 1998 does not currently make provision for these.

6. DIAGNOSIS, STAGING AND RISK ASSESSMENT

6.1. Consultations

6.1.1. Physical findings are uncommon in patients with early disease, making clinical diagnosis of early ovarian cancer more difficult. Localized ovarian cancer is generally asymptomatic. Symptoms are most commonly seen with advanced disease (Fauci, 2009)

6.1.2. Patients with more advanced ovarian cancer may present with ascites and abdominal masses lead to increased abdominal girth, bloating, nausea, anorexia, dyspepsia and early satiety. Extension of disease across the diaphragm to the pleural cavities can produce pleural effusions and the development of respiratory symptoms (Berek et al., 2018).

Table 3: Recommended consultations for the diagnosis, staging and risk assessment of ovarian cancer

Treating provider	Number of consultations
GP or physician	1
Specialist (Gynaecologist / Gynaecology oncologist / Oncologist/ Surgeon)	4

6.2. Histopathology

For mucinous histology, a gastrointestinal tract evaluation is recommended to determine if an occult primary has metastasized to the ovaries (Ledermann, 2014). Mucin is not always obvious in mucinous carcinomas, so immunohistochemistry can be appropriate in other types of ovarian carcinomas to confirm their histologic type (and exclude a poorly differentiated mucinous carcinoma). Immunohistochemistry is recommended in mucinous borderline tumours as metastatic tumours (particularly low grade appendiceal mucinous tumours) can resemble borderline mucinous tumours.

Table 4: Recommended PMB level of care histopathology for ovarian cancer

Description	Comment
Immunohistochemistry	
Stains	For confirming germ cell carcinoma and metastatic adenocarcinoma
Frozen sections	Depends on clinical indication

6.3. Laboratory investigations

6.3.1. A patient with a suspicious or palpable pelvic mass detected on abdominal/pelvic exam, should have laboratory tests including a full blood count, a chemistry profile with liver function tests.

6.3.2. CA 125 is not specific to ovarian cancer as raised level may also be found in other malignancies such as breast, colon and pancreatic cancer. It has a high positive predictive value (PPV) of > 95% but a low negative predictive value (NPV) from 50% to 60% for the detection of ovarian cancer. PPV is defined as the probability of people having the disease when the test is positive whereas NPV is the probability of people not having the disease when the test is negative (Beaglehole, Bonita, & Kjellström, 1993). Thus, CA 125 is not a diagnosis test but a test to assess treatment response (Suppiah, 2018).

6.3.3. Individuals diagnosed by previous surgery or tissue biopsy, in addition, should have genetic risk evaluation undertaken.

6.3.4. Alpha-fetoprotein (AFP) should be considered to assess for germ cell tumours in women younger than 35 years with a pelvic mass (Gregory & Scheider, 1999). Alpha-fetoprotein (AFP) and Serum human chorionic gonadotropin (β-HCG) are the investigations of choice that should be considered in the diagnosis of germ cell. Its incidence in younger women (≤ 30 years old) is generally 75% (Fauci, 2009).

6.3.5. Women with suspected BRCA germline mutation based on family history of breast/ovarian cancer Lynch syndrome type II or young age of diagnosis or high-grade of endometrial cancer should undergo genetic counselling and testing (Berek et al, 2018).

Table 5: Recommended PMB level of care laboratory investigations for diagnostic work-up ovarian cancer

Description	Comment (when necessary)
Full Blood Count (FBC) including platelets	
Urea, electrolytes and creatinine (U&E + Cr)	
Liver function test (LFT)	
CA125	To monitor treatment response only No diagnostic value
Oestrogen FSH, LH	Done as a therapeutic biomarker when hormone therapy is considered.
AFP, βHCG	To assess for germ cell tumours in women younger than 35 years with a pelvic mass

6.4. Imaging radiology

6.4.1. Routine imaging is not required in all patients in whom ovarian cancer is highly suggested. Imaging in ovarian cancer has as a primary role in the determination of disease burden, the detection of distant metastases and

6.4.2. Ultrasound: abdominal / pelvic & or transvaginal: trans-abdominal scan (TAS) and transvaginal scan (TVS) are the first line diagnostic imaging modality for diagnosing ovarian cancer.

6.4.3. CT chest is done to evaluate the extent of disease and the feasibility of surgical resection (Wright, 2016). It is also used to exclude pleural effusions or pulmonary spread of malignant diseases of the ovary.

6.4.4. CT abdomen and pelvis is the preferred modality for the staging of ovarian cancer and the detection of recurrence (Suppiah, 2018). It also describes the extent of intra-abdominal disease (Berek et al.2018).

6.4.5. Magnetic resonance imaging (MRI) pelvis is clinically limited to evaluation of indeterminate pelvic lesions, the extent, localisation and operability of recurrent disease (Smit & Guidozzi, 2009).

6.4.6. Positron emission tomography (PET) scanning is recommended for detection of tumour recurrence in ovarian carcinoma with rising CA125 or equivocal or negative conventional imaging (Vorster et al, 2016).

Table 6: Recommended PMB level of care imaging radiology for work-up of ovarian cancer

Description	Comment
Ultrasound: abdominal / pelvic & / or transvaginal	Has high diagnostic accuracy (van Nagell, 2001) & can differentiate between benign and malignant ovarian masses or cysts. (Timmermann, 2001)
Chest x-ray	Should be part of the overall evaluation of a patient before surgical staging if clinically indicated (Smith & Guidozzi, 2009) Also, has use in excluding lung metastases and pleural effusions
CT chest with contrast	To exclude pleural effusions or pulmonary spread of malignant diseases of the ovary
CT abdomen and pelvis	Essential to stage disease
MRI pelvis	Increases specificity of imaging when ultrasound or CT findings are indeterminate. Especially for pelvic disease

Ultrasound chest	On motivation for drainage of pleural effusions
Exclusion	
Positron emission tomography (PET) scanning	Positron emission tomography (PET) scanning does not have an established role in the diagnosis of primary ovarian malignancy. May have a limited role in assessing disease recurrence. Not recommended as PMB level of care

6.5. Procedures

Table 7: Recommended PMB level of care procedures for work-up of ovarian cancer

Description	Comment
Diagnostic laparoscopy (with biopsy)	Can help to distinguish between patients who could benefit from primary cytoreductive surgery (PCS) and those who might have better outcomes with neoadjuvant chemotherapy and interval cytoreductive surgery. Role in surgical staging.
Colonoscopy	Not routine. Only on motivation in ovarian cancer; and approved under specific clinical criteria in patients with diffuse carcinomatosis and gastrointestinal (GI) symptoms.
Ultrasound guided biopsy	Used for diagnostic purposes.
Pleural biopsy	Used for diagnostic purposes.
Pleural tap	Used for diagnostic purposes in asymptomatic patients and temporary relief of dyspnoea in symptomatic patients with malignant pleural effusion.
Ascitic tap	Diagnostic and therapeutic.

7. STAGING OF OVARIAN CANCER

Ovarian cancer is staged surgically with pathological confirmation of the disease. Imaging allows diagnosis of liver parenchymal and pulmonary metastases (Smith & Guidozzi, 2009). Ovarian cancer is primarily staged as stages I to IV using the new FIGO (International Federation of Gynecology and Obstetrics) and the American Joint Committee on Cancer (AJCC) staging systems as shown below (Zeppernick & Meinhold-Heertein, 2014).

I	**Tumour confined to ovaries or fallopian tube(s)**	**T1**
IA	Tumour limited to one ovary (capsule intact) or fallopian tube. No tumour on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings.	T1a
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	T1b
IC IC1 IC2 IC3	Tumour limited to one or both ovaries or fallopian tubes, with any of the following: Surgical spill intraoperatively Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface Malignant cells present in the ascites or peritoneal washings	T1c
II	**Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)**	**T2**
IIA IIB	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries Extension to other pelvic intraperitoneal tissues	T2a T2b
III	**Tumour involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**	**T3**
IIIA IIIA1 IIIA1(i) IIIA1(ii) IIIA 2 IIIB III C	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis Positive retroperitoneal lymph nodes only (cytologically or histologically proven) Metastasis ≤ 10 mm in greatest dimension (note this is tumour dimension and not lymph node dimension) Metastasis *N* 10 mm in greatest dimension Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes Macroscopic peritoneal metastases beyond the pelvic brim *N* 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	T1, T2, T3aN1 T3a/T3aN1 T3a/T3aN1 T3b/T3bN1 T3c/T3cN1
IV	**Distant metastasis excluding peritoneal metastases**	**Any T, Any *N*, M1**
Stage IV A Stage IV B	Pleural effusion with positive cytology Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2)	Any T, Any *N*, M1

Based on 'DG Mutch and J Prat. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecologic Oncology 2014;133:401-04'

Notes:

1. Includes extension of tumour to the capsule of liver and spleen without parenchymal involvement of either organ.
2. Parenchymal metastases are Stage IV B.

8. TREATMENT

8.1. Surgical Management of Early stage disease

Surgery for ovarian cancer is for disease staging and debulking. Debulking is the removal of as much of the tumour as possible (American Cancer Society, 2016; Jelovac & Armstrong, 2011).

Surgery is the primary treatment for ovarian cancer as it is potentially curative if disease is confined to the ovaries (Green, 2017; Nice, 2011).

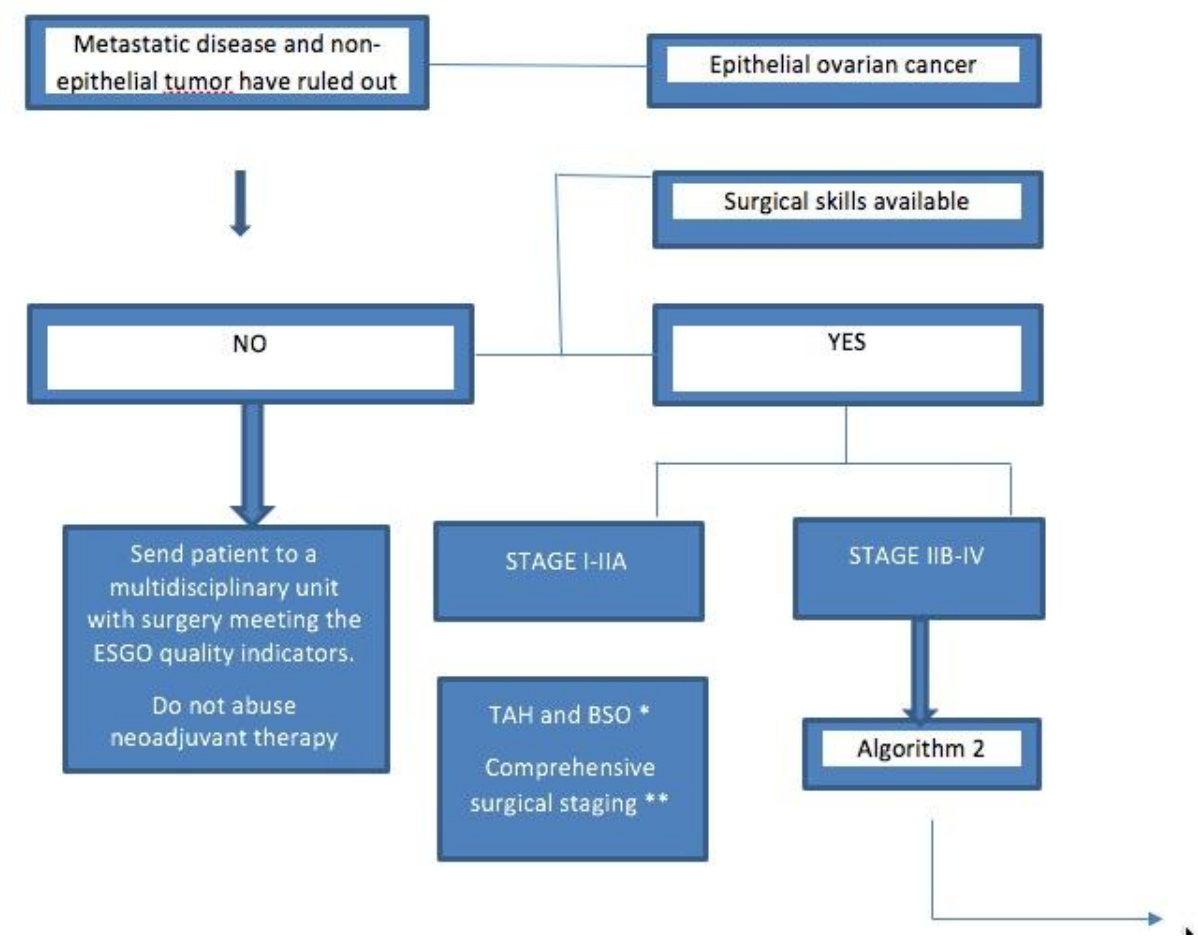
However, only a small percentage of women with epithelial ovarian cancer can be treated with surgery alone. This percentage includes patients with stage IA or IB (grade 1) serous, mucinous, endometrioid, and Brenner tumours. Treatment of grade 2 tumors remains controversial (Trimbos et al, 2003).

Fertility-sparing surgery (involving unilateral salpingo-oophorectomy, preserving the uterus and contralateral ovary), is an option for women with early-stage invasive epithelial ovarian cancers, lesions with low potential for malignancy (e.g., lesions with histologically abnormal cells that are judged to have a low likelihood of developing into cancer), germ cell tumours, or sex cord–stromal tumours (Doubeni et al, 2016; American Cancer Society, 2016). A systematic review of fertility-sparing surgery in ovarian cancer (di Bois, 2013) summed the indication as unilateral grade 1 tumours.

In apparent early stage ovarian cancer, the presence of isolated omental metastases is relatively rare. For staging purposes in such cases, random omental biopsies rather than total omentectomy may suffice (Arie et al, 2013).

Laparoscopy has dramatically altered management of many gynaecologic malignancies, but its utility in ovarian cancer has so far been limited (Abu-Rustum et al, 2005). A systematic review done by Falcetta et al, (2006) found no good-quality evidence to help quantify the risks and benefits of laparoscopy for the management of early-stage ovarian cancer as routine clinical practice.

Figure 1: Algorithm 1 for epithelial ovarian cancer surgery (Querleu et al, 2017)



* Consider fertility preservation in young patients

**When exceptions for retroperitoneal staging (See specific recommendations on surgery for early stage ovarian cancer)

8.2. Surgical Management of Late Stage Disease

8.2.1. Three-quarters of women who are newly diagnosed with invasive epithelial ovarian cancer present with stage III to IV disease (Schorge et al, 2010).

8.2.2. Debulking is very important in any patient with ovarian cancer that has already spread widely throughout the abdomen at the time of surgery. The aim of debulking surgery is to leave behind no tumours larger than 1 cm. Debulking surgery might also mean removing a piece of the bladder, and in some cases the spleen and/or the gallbladder, as well as part of the stomach, liver, and/or pancreas (American Cancer Society, 2016).

8.2.3. Secondary debulking surgery may be beneficial for the relatively few patients who have an isolated relapse after a lengthy disease-free interval (Schorge et al, 2010).

8.2.4. Diaphragmatic surgery at the time of primary cytoreductive surgery for advanced ovarian cancer may contribute to the achievement of complete cytoreduction with low perioperative complication rate (Zapardeil et al, 2011; Papadia A, 2013).

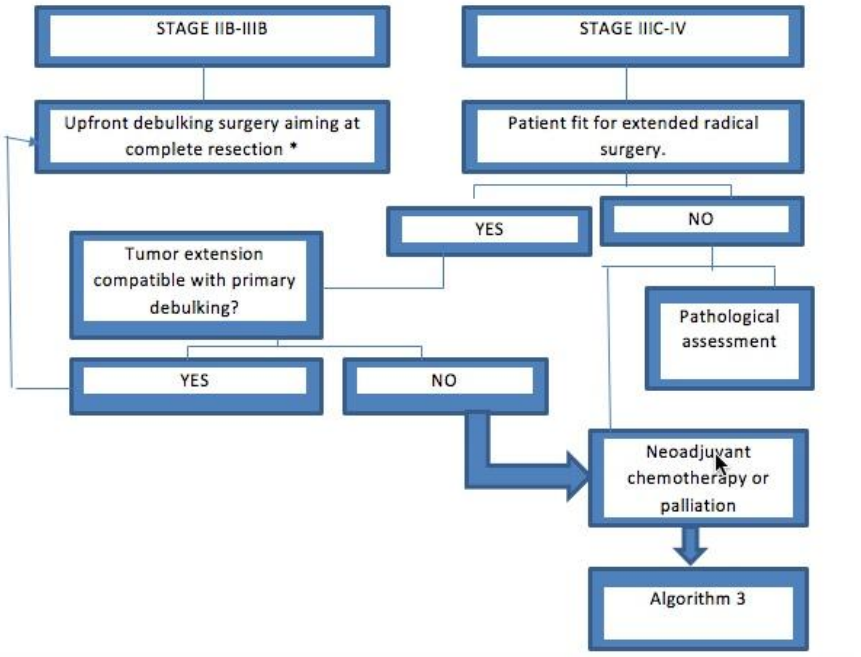
8.2.5. Bowel resection is a worthwhile endeavor in selected patients with advanced ovarian cancer to increase therapeutic efficiency (Cai et al, 2007).

8.2.6. In patients with advanced ovarian cancer, survival is improved when optimal tumour-reductive surgery is performed at the time of initial diagnosis, and to do this, it is often necessary to perform a splenectomy (Ramirez & Reis, 20017).

8.2.7. Appendectomy is not to be regarded as a routine surgical procedure in the early I-II stages of ovarian cancer, but it may help to reduce residual disease in advanced patients (Zhang, 1994; Ramirez et al, 2006).

8.2.8. Since laparoscopy may increase tumour growth rates, delays between laparoscopy and definitive surgery should be avoided (Münstedt and Franke, 2004).

Figure 2: Algorithm 2 for epithelial ovarian cancer surgery (Querleu 2017)



* With exceptions for IIIB (e.g., poor patient conditions and for very extensive disease on the bowel or peritoneum for whom neoadjuvant chemotherapy may be preferable)

Figure 3: Algorithm 3 for epithelial ovarian cancer surgery

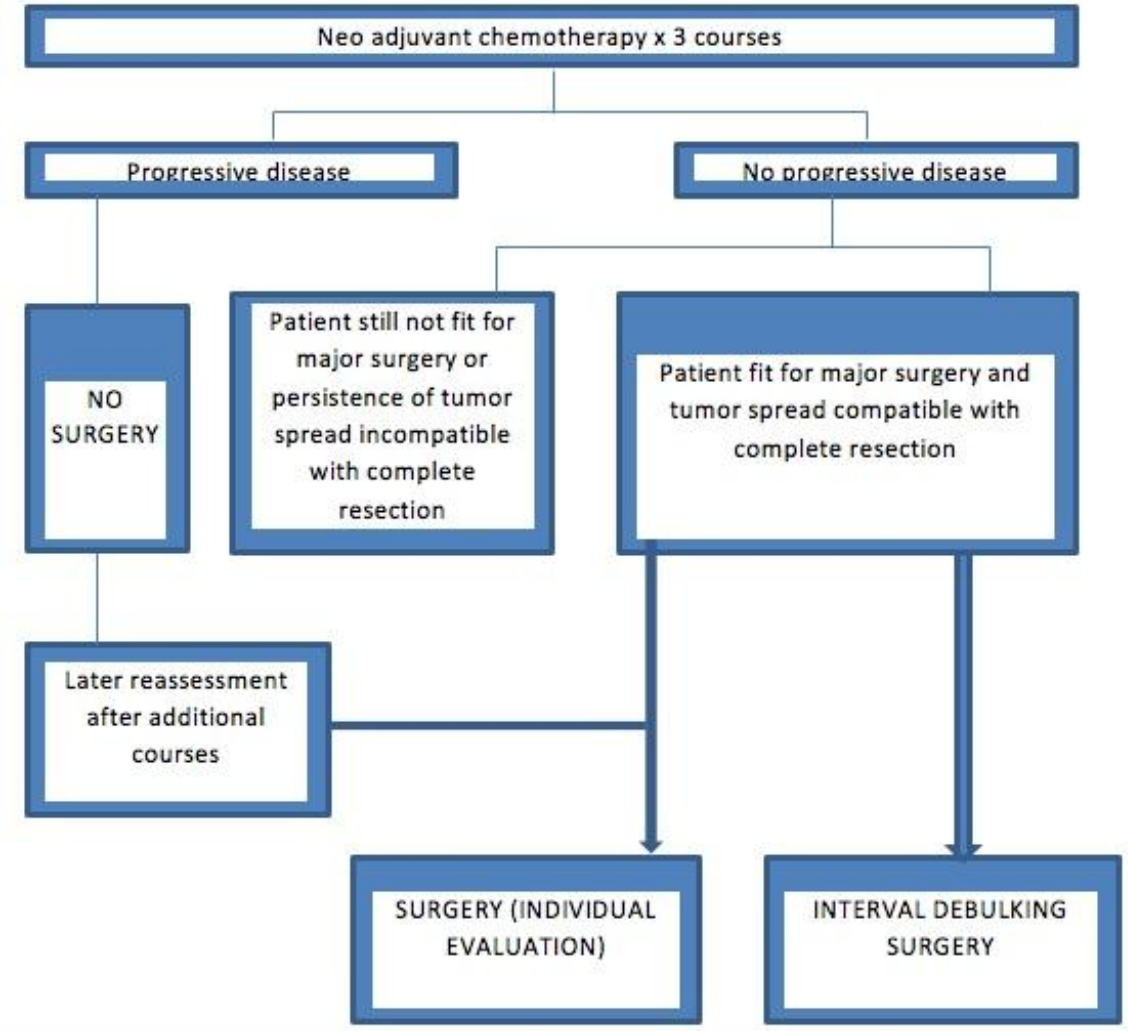


Table 8: Recommended PMB Level of care for surgical management of ovarian cancer

Description	Comment (where necessary)
Salpingo-oophorectomy (unilateral or bilateral)	Women at increased genetic risk eg. BRCA 1, 2 mutation
Total abdominal hysterectomy	
Omentectomy	In patients with epithelial ovarian cancers
Bowel resection	In late stage disease
Diaphragmatic resection	In late stage disease
Appendectomy	To reduce residual disease in advanced patients and for mucinous tumours (to exclude appendiceal mucinous tumour)
Splenectomy	In advanced ovarian cancer

Lymph node dissection	
Peritoneal washing	For staging
Debulking surgery	Where cancer has already spread widely throughout the abdomen Limited role with extensive bowel or peritoneal involvement
Excision of secondary lesion(s) advanced ovarian	
Exclusion	
Laparoscopic surgery	Not PMB level of care

8.3. Chemotherapy

Chemotherapy is the main standard adjuvant treatment for ovarian carcinoma. Until the advent of chemotherapy, postoperative irradiation was the only adjuvant treatment modality available for advanced ovarian carcinoma (Biete et al, 2010). In this section, the chemotherapy options will be differentiated between germ cell and epithelial diseases.

8.3.1. Chemotherapy for germ cell cancer

8.3.1.1. Adjuvant chemotherapy

8.3.1.1.1. Part of the argument in favour of adjuvant chemotherapy regards the potential impact on fertility in the case of recurrent disease (Lhommé, 2014).

8.3.1.1.2. Adjuvant Bleomycin/etoposide/cisplatin is the standard of care in adult females with ovarian germ cell tumours (Lhommé, 2014; Jewell, 2015).

8.3.1.1.3. Adjuvant chemotherapy with carboplatin and etoposide in patients with completely resected stage IB-III dysgerminoma is an alternative to cisplatin, etoposide, and bleomycin for selected patients for whom minimising toxicity is critical or for whom reduction in the number of treatment days is important (Williams et al, 2004). Carboplatin is recommended for stages I to IIB ovarian cancer (Grabosch , 2017)

8.3.1.2. Metastatic chemotherapy

8.3.1.2.1. Recurrent or persistent ovarian cancer after first-line chemotherapy is incurable; usually, second, third, or fourth-line chemotherapy is used in attempts to prolong life and palliate symptoms (Kataria & Kumar, 2007.

8.3.1.2.2. As single agents or in combinations of two or three drugs. Specific regimens are stage dependent. The PMB level of care consists of carboplatin, cisplatin, paclitaxel, bleomycin, etoposide, ifosfamide and vinblastine.

8.3.1.2.3. Gemcitabine and Epirubicin are not recommended as PMB level of care for germ cell ovarian tumours.

8.3.2. Epithelial Ovarian cancer

The standard therapy for patients with a primary epithelial ovarian cancer is cytoreductive surgery followed by chemotherapy.

8.3.2.1. Adjuvant / Neo-adjuvant setting

8.3.2.1.1. Chemotherapy for patients with stage IA, IB epithelial ovarian cancer (intact ovarian capsule) or borderline tumours, which are treated primarily with surgery, may be recommended if they have a high grade.

8.3.2.1.2. While neoadjuvant chemotherapy has been demonstrated as not inferior to primary cytoreductive surgery and could be considered in all patients with advanced disease, it may be of particular benefit in women who are unlikely to achieve optimal up-front surgical debulking due to extensive disease (lung or liver metastasis, disease in the portal hepatis, significant disease in the small bowel mesentery, or massive ascites) and those who are poor candidates to withstand aggressive surgery should be considered for neoadjuvant chemotherapy (Grabosch, 2017; Medscape, 2017).The biggest risk associated with the use of neoadjuvant chemotherapy is that patients with significant side effects and refractory disease will lose the opportunity for initial surgery. Therefore, establishment of an optimal regimen is necessary in order to improve the outcome of neoadjuvant chemotherapy

8.3.2.1.3. A Cochrane review of adjuvant chemotherapy for early stage epithelial ovarian cancer found that women with early-stage ovarian cancer who received adjuvant chemotherapy lived longer than women who did not, and took longer for their disease to recur after initial treatment.

8.3.2.1.3.1. The recommended PMB level of care for the neoadjuvant setting includes Carboplatin, Paclitaxel and Docetaxel. These are the same drug regimens recommended by Grabosch (2017) where Docetaxel and Paclitaxel are used substitutes in combination with Carboplatin, because they show similar outcomes, but side effect profiles are different.

8.3.2.2. Metastatic chemotherapy

i. A high proportion of patients (60–80%) with advanced ovarian epithelial cancer respond to first-line chemotherapy, but most of these patients (about 70%) will later have disease progression and thus be candidates for second-line chemotherapy (Biete et al, 2010).

ii. Systemic chemotherapy is the standard treatment for metastatic epithelial ovarian cancer (Berek, 2003).

iii. The combination of Carboplatin plus Paclitaxel is the standard of care in advanced ovarian cancer. This was supported by two non-inferiority trials in patients with optimally debulked stage III ovarian cancer (Ozols, 2003; du Bois, 2003).

iv. Other drugs which are PMB level of care include:

Gemcitabine – which has shown encouraging results as a single agent in the treatment of platinum-resistant ovarian cancer and a favourable toxicity profile (Lorusso, 2005).

Docetaxel – particularly if the patient cannot tolerate Paclitaxel (Grabosch et al, 2017).

Cyclophosphamide – metronomic oral cyclophosphamide has gained increasing interest in recent years as a promising maintenance therapy in advanced, platinum-sensitive, high-grade serous ovarian cancer. It should be considered particularly for patients who responded to platinum-based chemotherapy but cannot continue on it because of toxicity (de Boo et al, 2017).

8.3.3. Exclusions

The following medicines are not recommended as PMB level of care:

i. Bevacizumab – although the addition of Bevacizumab to standard chemotherapy, followed by maintenance therapy until progression improved the median overall survival in patients with platinum-sensitive recurrent ovarian cancer, the intention-to-treat analysis for overall survival was not significant (Poved et al, 2013; Stenger, 2017). Not recommended by NICE or TQEML

ii. Pegylated Liposomal doxorubicin – a useful drug in patients who have received multiple courses of chemotherapy and possibly even radiation, especially because of reduced bone marrow suppression and cardiotoxicity. NICE (2016), however, does not recommend PEGylated liposomal doxorubicin (PLD) monotherapy as an option for treating recurrent ovarian cancer. PLD is also not on TQEML.

iii. Topotecan – significant toxicity especially bone marrow suppression - it is indicated for platinum-resistant recurrent ovarian cancer. Often treatment is changed because of progressive disease or toxicity (Grabosch, 2017). Not on TQEML

iv. Poly ADP- ribose polymerase (PARP) inhibitors – These agents appear to have somewhat different toxicity profiles. Ongoing trials in ovarian cancer are exploring additional clinical indications and novel strategies designed to combine PARP inhibitors with other antineoplastic (Markman, 2017). Not yet registered by the South African Health Products Regulatory Authority (SAHPRA) therefore requires Section 21 approval.

v. Trabectidin – from a phase 3 trial that led to registration elsewhere but the FDA in 2010, this agent showed no improvement in progression-free survival or overall response rate seen in platinum-resistant patients. Moreover, neutropenia and liver enzyme elevations were more common with Trabectidin plus PLD than with PLD alone, although hand-foot syndrome and mucositis were less frequent. It was later registered by the FDA in October 2015 for the treatment of specific soft tissue sarcomas (STS) – that

cannot be removed by surgery (unresectable) or are advanced. This treatment is approved for patients who previously received chemotherapy that contained anthracycline (FDA, 2015). Not on TQEML

vi. Intraperitoneal chemotherapy is not standard of care

8.3.4. Hormone Therapy

The role of hormone therapy in the treatment of ovarian cancer is not clear, but if administered to patients who are positive for oestrogen receptors, it may become a viable option for the treatment of recurrent ovarian cancer (Yokoyama & Mizunuma 2013). Tamoxifen is recommended as PMB level of care only if the cancer is ER/PR positive.

Table 9: PMB level of care for chemotherapy for ovarian cancer

Indication	Medicine names	Comment
Adjuvant Germ cell	Cisplatin Etoposide IV Bleomycin	Oral etoposide is not available
Metastatic Germ cell	Cisplatin Carboplatin Etoposide Bleomycin Paclitaxel Ifosfamide Vinblastine	
Adjuvant / Neo-adjuvant : Epithelial	Carboplatin Paclitaxel Docetaxel	Docetaxel and paclitaxel show similar outcomes but side effect profiles are different
Metastatic/recurrent: Epithelial	Carboplatin Cisplatin Paclitaxel Gemcitabine Docetaxel Cyclophosphamide Doxorubicin	
Hormone therapy • Tamoxifen recommended if ER/PR positive		

Exclusions
· Bevacizumab · Pegylated Liposomal doxorubicin · Topotecan · (Poly (ADP-ribose) polymerase) PARP inhibitors (section 21) · Trabectidin · Intraperitoneal chemotherapy

8.4. Radiation

8.4.1. Palliative radiation

8.4.1.1. Radiation therapy for ovarian cancer is recommended only in the palliative setting for symptom control in metastatic disease (Fields et al, 2017).

8.4.1.2. Radiation therapy as a palliative modality in ovarian cancer may be very useful if the sole or dominant symptomatic problem for the patient is localised to a site and volume that may be safely encompassed in a radiation field; tumour regression or symptomatic relief can be obtained in these situations (Kataria & Kumar, 2007).

8.4.1.3. Palliative treatment courses of 3 to 30 Gy given in 1 to 10 fractions have been shown to be useful for a wide range of scenarios.

8.4.1.4. Intensity-Modulated Radiation Therapy (IMRT) and Stereotactic Body Radiation Therapy (SBRT) are not recommended as PMB level of care for ovarian cancer.

Table 10: Summary of radiation therapy in ovarian cancer

Palliative Radiation therapy: Conventional single volume / multiple volumes: 3Gy – 30Gy Exclusions • Intensity-Modulated Radiation Therapy (IMRT) • Stereotactic Body Radiation Therapy (SBRT)

9. FOLLOW UP AFTER SURGICAL RESECTION

There are no evidence-based guidelines regarding an appropriate follow up schedule. During the first year patients are seen every 4 months with a gradual increase in interval to every 4-6 months after 2 years and then annually after the fifth year.

At each follow up, a CA 125 should be performed. PET/CT may be more accurate in detecting recurrences in patients with elevated CA 125 levels. Contrast-enhanced CT is the modality of choice for detecting recurrence in the chest, abdomen, or pelvis. Although CT is currently the modality of choice for suspected recurrence of ovarian cancer, MRI is recommended for borderline tumors or ovarian cancers that have been previously staged with fertility preservation (to minimize ionizing radiation exposure), or when CT findings are inconclusive (Acsearch.acr.org, 2018).

10. BEST SUPPORTIVE CARE

CMS developed a PMB definition document on best supportive care for gastrointestinal oncology conditions (available at https://www.medicalschemes.com/files/PMB%20Definition%20Project/BestSupportivCare%20GIT3103docx.pdf). The document contains some guidance for the management of side effects of chemotherapy, which can be applied across all oncology conditions, i.e. management of nausea and vomiting, management of diarrhea and pain management. Other rehabilitation interventions specific to ovarian cancers should be considered for funding when referred by the primary treating provider.

REFERENCES

Abu-Rustum, N; Mourton, S, 2005. Minimally invasive surgery in ovarian cancer. OBG Manag. 2005 May;17(5):21-36

American Cancer Society. Surgery for Ovarian Cancer. Last Revised: February 4, 2016. Available at https://www.cancer.org/cancer/ovarian-cancer/treating/surgery.html. Accessed 29 October 2017

American College of Radiology. Acsearch.acr.org. (2018). [online] Available at: https://acsearch.acr.org/docs/69378/Narrative/ .Accessed on 11 April 2019.

Arie, A.B., McNally, L., Kapp, D.S. and Teng, N.N., 2013. The omentum and omentectomy in epithelial ovarian cancer: a reappraisal: part II—the role of omentectomy in the staging and treatment of apparent early stage epithelial ovarian cancer. Gynecologic oncology, 131(3), pp.784-790.

Berek, J.S., Crum, C. and Friedlander, M., 2015. Cancer of the ovary, fallopian tube, and peritoneum. International Journal of Gynecology & Obstetrics, 131(S2).

Biete, A., Valduvieco, I., Rovirosa, A., Farrús, B., Casas, F. and Conill, C. (2010). Whole abdominal radiotherapy in ovarian cancer. Reports of Practical Oncology & Radiotherapy, 15(2), pp.27-30.

Bonita, R., Beaglehole, R. and Kjellström, T., 2006. Basic epidemiology. World Health Organization.

Cai, H.B., Zhou, Y.F., Chen, H.Z. and Hou, H.Y., 2007. The role of bowel surgery with cytoreduction for epithelial ovarian cancer. Clinical Oncology, 19(10), pp.757-762.

Cancer Genome Atlas Research Network, 2011. Integrated genomic analyses of ovarian carcinoma. Nature, 474(7353), p.609.

Castellucci, P., Perrone, A.M., Picchio, M., Ghi, T., Farsad, M., Nanni, C., Messa, C., Meriggiola, M.C., Pelusi, G., Al-Nahhas, A. and Rubello, D., 2007. Diagnostic accuracy of 18F-FDG PET/CT in characterizing ovarian lesions and staging ovarian cancer: correlation with transvaginal ultrasonography, computed tomography, and histology. Nuclear medicine communications, 28(8), pp.589-595.

de Boo, L.W., Vulink, A.J.E. and Bos, M.E.M.M., 2017. Metronomic cyclophosphamide-induced long-term remission after recurrent high-grade serous ovarian cancer: A case study. Molecular and clinical oncology, 7(6), pp.1130-1134.

Du Bois, A., Lück, H.J., Meier, W., Adams, H.P., Mobus, V., Costa, S., Bauknecht, T., Richter, B., Warm, M., Schröder, W. and Olbricht, S., 2003. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. Journal of the National Cancer Institute, 95(17), pp.1320-1329.

Edwards, S.J., Barton, S., Thurgar, E. and Trevor, N., 2015. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent or refractory ovarian cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England), 19(7), p.1.

Falcetta FS, Lawrie TA, Medeiros LRF, et al, 2016. Laparoscopy versus laparotomy (open surgery) for early-stage ovarian cancer. Cochrane Database of Systematic Reviews 2016, Issue 10

Fauci, A.S., 2009. Harrison's manual of Medicine (pp. 769-72). New York: McGraw-Hill Medical.

FDA, 2015. FDA approves new therapy for certain types of advanced soft tissue sarcoma: FDA News Release. October23,2015.
Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468832.htm. Accessed on 25 January 2018.

Fields, E.C., McGuire, W.P., Lin, L. and Temkin, S.M., 2017. Radiation treatment in women with ovarian cancer: past, present, and future. Frontiers in oncology, 7, p.177.

Gershenson, D.M., McGuire, W.P., Gore, M., Quinn, M.A. and Thomas, G., 2004. Gynecologic cancer. Controversies in Management, 1.

Grabosch, S, Ovarian Cancer Treatment Protocols - Updated: Apr 03, 2017. Available: https://emedicine.medscape.com/article/2006723-overview. Accessed: 29 October 2017

Green, A.E. and Rose, P.G., 2006. Pegylated liposomal doxorubicin in ovarian cancer. International journal of nanomedicine, 1(3), p.229.

Green, A.E., 2017. Ovarian Cancer. Updated: Apr 03, 2017. Available at https://emedicine.medscape.com/article/255771-overview. Accessed: 24 October 2017.

Gregory, J.J. and Finlay, J.L., 1999. α-Fetoprotein and β-Human Chorionic Gonadotropin. Drugs, 57(4), pp.463-467.

Hunn, J. and Rodriguez, G.C., 2012. Ovarian cancer: etiology, risk factors, and epidemiology. Clinical obstetrics and gynecology, 55(1), pp.3-23.

International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION), 2003. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. Journal of the National Cancer Institute, 95(2), pp.105-112.

Jelovac, D. and Armstrong, D.K., 2011. Recent progress in the diagnosis and treatment of ovarian cancer. CA: a cancer journal for clinicians, 61(3), pp.183-203.

Kataria, S.K. and Kuman, S., 2007. The role of radiotherapy in ovarian cancer. Ind J Medical and Pediatric Oncol, 23, pp.18-23.

Ledermann, J.A., Luvero, D., Shafer, A., et al. 2014. Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma. Int J Gynecol Cancer;24: S14-19.

Lhommé, C., Leary, A., Uzan, C., Pautier, P., Gouy, S. and Morice, P., 2014. Adjuvant chemotherapy in stage I ovarian germ cell tumours: should indications and treatment modalities be different in young girls and adults?. Journal of Clinical Oncology, 32(25), pp.2815-2816.

Markman, M. 2017. The Current Status of PARP Inhibitors in Ovarian Cancer. The 2017 San Antonio Breast Cancer Symposium. December 5 to December 9, 2017. Available at http://www.targetedonc.com/conference/2017-sabcs. Accessed on 23 January 2018.

Mateo, J., Carreira, S., Sandhu, S., Miranda, S., Mossop, H., Perez-Lopez, R., Nava Rodrigues, D., Robinson, D., Omlin, A., Tunariu, N. and Boysen, G., 2015. DNA-repair defects and olaparib in metastatic prostate cancer. New England Journal of Medicine, 373(18), pp.1697-1708.

Medscape, 2017. Ovarian Cancer. Available at https://emedicine.medscape.com/article/255771-overview. Last updated on Apr 03, 2017. Accessed on 27 December 2017.

Münstedt, K. and Franke, F.E., 2004. Role of primary surgery in advanced ovarian cancer. World journal of surgical oncology,2(1), p.32.

National Cancer Registry [Internet]. Cancer in South Africa 2014. National Cancer Registry; [cited 2019 Jan 30]. Available from: https://www.nicd.ac.za/index.php/centres/national-cancer-registry/cancer-statistics/

Ozols, R.F., Bundy, B.N., Greer, B.E., Fowler, J.M., Clarke-Pearson, D., Burger, R.A., Mannel, R.S., DeGeest, K., Hartenbach, E.M. and Baergen, R., 2003. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. Journal of Clinical Oncology, 21(17), pp.3194-3200.

Papadia, A. and Morotti, M., 2013. Diaphragmatic surgery during cytoreduction for primary or recurrent epithelial ovarian cancer: a review of the literature. Archives of gynecology and obstetrics, 287(4), pp.733-741.

Partridge, E., Greenlee, R.T., Xu, J.L., Kreimer, A.R., Williams, C., Riley, T., Reding, D.J., Church, T.R., Kessel, B., Johnson, C.C. and Hill, L., 2009. Results from four rounds of ovarian cancer screening in a randomized trial. Obstetrics and gynecology, 113(4), p.775.

Poveda, A., Ray-Coquard, I., Romero, I., Lopez-Guerrero, J.A. and Colombo, N., 2014. Emerging treatment strategies in recurrent platinum-sensitive ovarian cancer: focus on trabectedin. Cancer treatment reviews, 40(3), pp.366-375.

Prat, J., 2012. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Archiv, 460(3), pp.237-249.

Ramirez, P.T. and Dos Reis, R., 2007. Splenectomy in patients with advanced or recurrent ovarian cancer: open and laparoscopic surgical techniques and clinical outcomes.Gynecologic oncology, 104(2), pp.29-32.

Ramirez, P.T., Slomovitz, B.M., McQuinn, L., Levenback, C. and Coleman, R.L., 2006. Role of appendectomy at the time of primary surgery in patients with early-stage ovarian cancer.Gynecologic oncology, 103(3), pp.888-890.

Risch, H.A., McLaughlin, J.R., Cole, D.E., Rosen, B., Bradley, L., Fan, I., Tang, J., Li, S., Zhang, S., Shaw, P.A. and Narod, S.A., 2006. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin–cohort study in Ontario, Canada. Journal of the National Cancer Institute,98(23), pp.1694-1706.

Rubin, S. C. and Sutton, G. P. 2001).Ovarian cancer. 2nd ed. Philadelphia: Lippincott Williams & Wilkins.

Sayal, K., Gounaris, I., Basu, B., Freeman, S., Moyle, P., Hosking, K., Iddawela, M., Jimenez-Linan, M., Abraham, J., Brenton, J. and Hatcher, H., 2015. Epirubicin, cisplatin, and capecitabine for primary platinum-resistant or platinum-refractory epithelial ovarian cancer: results of a retrospective, single-institution study. International Journal of Gynecological Cancer, 25(6), p.977.

Schorge, J.O., McCann, C. and Del Carmen, M.G., 2010. Surgical debulking of ovarian cancer: what difference does it make?. Reviews in obstetrics and gynecology, 3(3), p.111.

Smith, T. and Guidozzi, F., 2009. Epithelial ovarian cancer in Southern Africa. Southern African Journal of Gynaecological Oncology, 1(1), pp.23-27.

Sopik, V., Iqbal, J., Rosen, B. and Narod, S.A., 2015. Why have ovarian cancer mortality rates declined? Part II. Case-fatality. Gynecologic oncology, 138(3), pp.750-756.

Stenger, M, 2017. Adding Bevacizumab to Paclitaxel-Carboplatin in Recurrent Platinum-Sensitive Ovarian Cancer. Last updated: 5/4/2017. The ASCO Post.

Timmerman, D., Verrelst, H., Collins, W., Bourne, T. and Vergote, I., 2001. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. Letters to the Editor. Gynecologic Oncology, 80, pp.167-168.

Togashi, K., 2003. Ovarian cancer: the clinical role of US, CT, and MRI. European radiology, 13(6), pp.L87-L104.

Van Nagell JR, DePriest PD, Reedy MB, et al. 2001. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. Gynecol Oncol. 2001; 77:350-356.

Vorster, M., Doruyter, A., Brink, A., Mkhize, S., Holness, J., Malan, N., Nyakale, N., Warwick, J.M. and Sathekge, M., 2015. Appropriate indications for positron emission tomography/computed tomography, 2015. South African Medical Journal, 106(1), pp.105-122.

Webb, P.M. and Jordan, S.J., 2017. Epidemiology of epithelial ovarian cancer. Best Practice & Research Clinical Obstetrics & Gynaecology, 41, pp.3-14

Yamamoto, Y., Oguri, H., Yamada, R., Maeda, N., Kohsaki, S. and Fukaya, T., 2008. Preoperative evaluation of pelvic masses with combined 18F-fluorodeoxyglucose positron emission tomography and computed tomography. International Journal of Gynecology & Obstetrics, 102(2), pp.124-127.

Zapardiel, I., Peiretti, M., Zanagnolo, V., Biffi, R., Bocciolone, L., Landoni, F., Aletti, G., Colombo, N. and Maggioni, A., 2011. Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. International Journal of Gynecological Cancer, 21(9), pp.1698-1703.

Zeppernick, F. and Meinhold-Heerlein, I., 2014. The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Archives of gynecology and obstetrics,290(5), pp.839-842.