



Review Article

Development of Ismail's Guide wheel on the Management of Less Common Ovarian Cancers

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Abstract

We developed Ismail's Guide wheel on the Management of Less Common Ovarian Cancers as an extension to Ismail's Guide wheel on the Management of Epithelial Ovarian Cancer Including Fallopian Tube and Primary Peritoneal Cancer. The former mainly discusses the adjuvant therapy for patients with less common epithelial ovarian cancer such as clear-cell carcinoma and mucinous carcinoma along with non-epithelial OC such as malignant sex cord-stromal tumors, malignant germ cell tumors and carcinosarcomas while the latter also discusses the primary therapy for those types of tumors. This guide wheel comprises of an amalgamation of the recommendations by international health organizations including the National Comprehensive Cancer Network (NCCN), the Society of Gynecologic Oncology (SGO), the British Gynecological Cancer Society (BGCS), the National Institute of Care and Excellence (NICE), the Royal College of Obstetricians and Gynecologists (RCOG), the European Society of Gynecological Oncology (ESGO), the European Society for Medical Oncology (ESMO), the Korean Society of Gynecologic Oncology (KSGO), the Spanish Society of Medical Oncology (SEOM), the Society of Obstetricians and Gynecologists of Canada (SOGC) and the International Federation of Gynecology and Obstetrics (FIGO). Ismail's Guide wheel on the Management of Less Common Ovarian Cancers serves as a quick, feasible reference for physicians when counseling patients diagnosed with those less common ovarian cancers regarding the expected course of treatment bearing in mind the significance of individualizing treatment to each patient's unique case.

Keywords: Non-epithelial ovarian cancer; Carcinosarcoma; Malignant germ cell tumors; Sex-cord-stromal tumors; Surgical staging; Chemotherapy; Systemic therapy; FIGO classification; Guidelines, Persistent or recurrent disease; Therapy for relapse; Surveillance; Radical surgery

Abbreviations: AFP: Alpha Feto-Protein; AJCC: American Joint Committee on Cancer; BGCS: British Gynecological Cancer Society; CT: Computed Tomography; ESGO: European Society of Gynaecological Oncology; ESMO: European Society for Medical Oncology; FIGO: International Federation of Gynecology and Obstetrics; hCG: Human Chorionic Gonadotrophin; HER2: Human Epidermal Growth Factor Receptor 2; KSGO: Korean Society of Gynecologic Oncology; LDH: Lactose Dehydrogenase; LN: Lymph Node; MGCT: Malignant Germ Cell Tumors; MRI: Magnetic Resonance Imaging; NCCN: National Comprehensive Cancer Network; NICE: National Institute of Care and Excellence; OC: Ovarian Cancer; PET: Positron Emission Tomography; RCOG: Royal College of Obstetricians and Gynaecologists; SGO: Society of Gynecologic Oncology; SEOM: Spanish Society of Medical Oncology; SOGC: Society of Obstetricians and Gynaecologists of Canada; TNM: Tumors, Nodes, and Metastases

Introduction

Ovarian cancer (OC) is the most common of death due to gynecologic cancer [1-6]. OC mostly occurs in older women with a mean age at diagnosis of 62 years [1, 7]. There is no effective screening for OC [6-9]. Patients with OC are treated with both surgery and chemotherapy [7]. OC is staged using the classification by the International Federation of Gynecology and Obstetrics (FIGO) [8-12]. Women presenting with symptoms suggestive of OC, including abdominopelvic pain or urinary symptoms, can undergo cancer antigen 125 (CA-125) measurement and subsequent referral to a gynecologic oncologist in the event of abnormal findings [1,3,4,11-13]. Around 10% of OC are non-epithelial [11]. OC is relatively rare and so there is no consensus on the approach towards patients diagnosed with this disease. Several health organizations established recommendations on the management of those patients. This paper revolves around the approach towards patients with less common OC, including carcinosarcoma, clear-cell carcinoma, mucinous carcinoma, malignant germ cell tumors (MGCTs) and sex cord-stromal tumors. We compared guidelines set by the National Comprehensive Cancer Network (NCCN), the Society of Gynecologic Oncology (SGO), the British Gynecological Cancer Society (BGCS), the National Institute of Care and Excellence (NICE), the Royal College of Obstetricians and Gynecologists (RCOG), the European Society of Gynecological Oncology (ESGO), the European Society for Medical Oncology (ESMO), the Korean Society of Gynecologic Oncology (KSGO), the Spanish Society of Medical Oncology (SEOM), the Society of Obstetricians and Gynecologists of

Canada (SOGC) and the International Federation of Gynecology and Obstetrics (FIGO) [1,3-6,9-16]. The NCCN guidelines are the most frequently updated set of recommendations. We designed a management guide wheel to combine the recommendations of those guidelines to provide healthcare professionals with a simple and feasible reference to the valuable recommendations when counseling patients diagnosed with OC.

About this Wheel

Ismail's Guide wheel on the Management of Less Common Ovarian Cancers integrates the recommendations of various regarding the management of the less common types of ovarian cancer. The inner wheel (Figure 1) can be rotated along the base of the guide wheel (Figure 2) to match the treatment modalities to the type of ovarian cancer, stated on the outer rim of the guide wheel, and displays the recommended steps in chronological order (Figure 3).

The types of ovarian cancer displayed on the outer rim of the guidewheel are broadly categorized as follows:

- Carcinosarcoma
- Clear-Cell Carcinoma
- Mucinous Carcinoma
- Malignant Sex Cord-Stromal Tumors
- Primary Treatment of Malignant Germ Cell Tumors
- Adjuvant Therapy of Malignant Germ Cell Tumors

The inner wheel (Figure 1) displays the different treatment modalities as follows:

- **Primary Treatment:** a. Surgery; b. Neoadjuvant Therapy
- **Surgical Therapy:** a. Surgical Staging; b. Fertility-Sparing Surgery; c. Cytoreduction; d. Resection; e. Completion Surgery
- **Work-Up:** a. Tumor Markers; b. Imaging; c. Gastrointestinal Tract (GIT) Evaluation
- **Adjuvant Therapy:** a. Chemotherapy; b. Radiation Therapy (RT); c. Observation; d. Systemic Therapy
- **Systemic Therapy:** a. Chemotherapy; b. Immunotherapy
- **Maintenance Therapy:** a. Immunotherapy; b. Biological (targeted)
- **Therapy for Persistent/Recurrent Disease:** a. Chemotherapy (A. Additional, B. High-dose); b. Resection; c. Clinical Trial
- **Observation**
- **Monitoring / Follow-Up**
- **Surveillance**

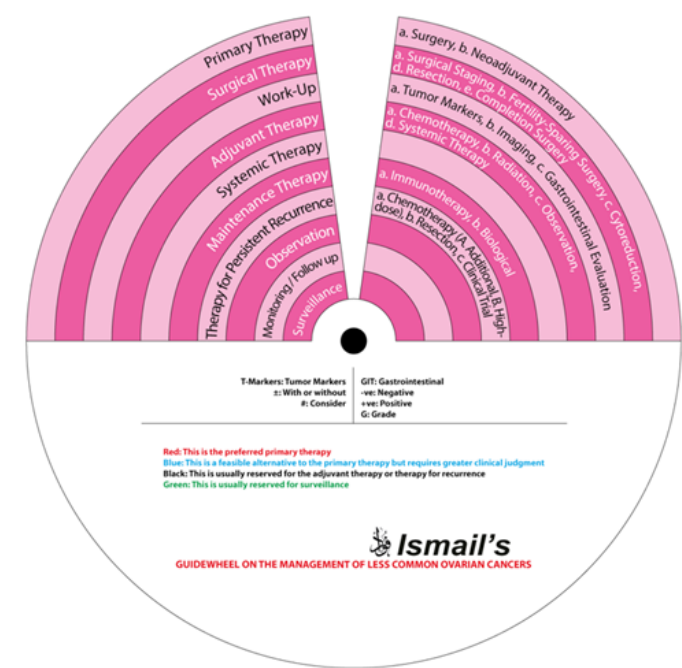


Figure 1: The inner wheel of the guidewheel displaying the various possible treatment modalities and their respective available options.

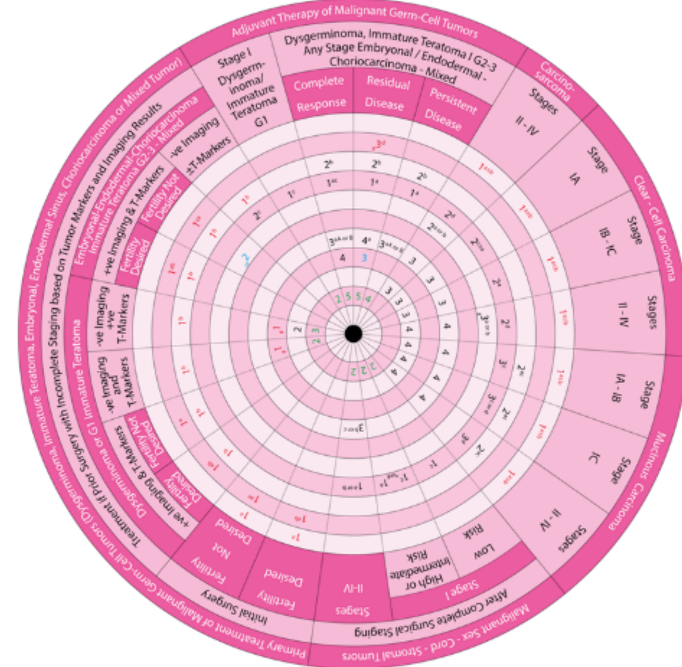


Figure 2: The base of the guidewheel demonstrating the color-coded steps of the treatment modalities that correspond to the types of ovarian cancer in chronological order.

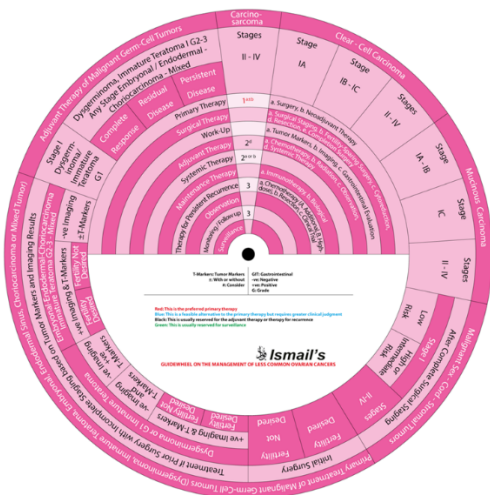


Figure 3: Ismail's Guidewheel on the Management of Less Common Ovarian Cancers fully assembled demonstrating the management of a patient with carcinosarcoma.

How to Use the Guidewheel

The back of the guidewheel displays how to use Ismail's Guidewheel on the Management of Less Common Ovarian Cancers (Figure 4). Rotating the inner wheel along the base displays the color-coded steps in the viewing slot (Figure 3). The numbers represent the steps in order as per the recommendations. The colors symbolize the following:

- Red: This is the preferred primary therapy.
- Blue: This is a feasible alternative to the primary therapy but requires greater clinical judgment.
- Black: This is usually reserved for the adjuvant therapy or therapy for recurrence.
- Green: This is usually reserved for surveillance.

Abbreviations used on the wheel include the following:

±	With or without	G	Grade
#	Consider	T-Markers	Tumor Markers
+ve	Positive	GIT	Gastrointestinal
-ve	Negative		

The FIGO 2017 classification of ovarian, fallopian tube and primary peritoneal cancer along with the corresponding Tumors, Nodes and Metastasis (TNM) staging system are displayed on the back of the wheel (Figure 4) and are listed as follows [F]:

Stages and Descriptions	
FIGO Stage I (TNM T1): The tumor is confined to the ovaries or fallopian tube(s).	
FIGO IA (TNM T1a)	Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IB (TNM T1b)	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IC (TNM T1c)	Tumor limited to 1 or both ovaries or fallopian tubes, with any of:
FIGO IC1 (TNM T1c1)	Surgical spill
FIGO IC2 (TNM T1c2)	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
FIGO IC3 (TNM T1c3)	Malignant cells in the ascites or peritoneal washings
FIGO Stage II (TNM T2): The tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer.	
FIGO IIA (TNM T2a)	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
FIGO IIB (TNM T2b)	Extension to other pelvic intraperitoneal tissues
FIGO Stage III (TNM T3): The tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.	
FIGO IIIA1 (TNM T3a1 N0/1)	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
FIGO IIIA1(i)	Metastasis up to 10mm in greatest dimension
FIGO IIIA1(ii)	Metastasis more than 10mm in greatest dimension
FIGO IIIA2 (TNM T3a2 N0/1)	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
FIGO IIIB (TNM T3b N0/1)	Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
FIGO IIIC (TNM T3c N0/1)	Macroscopic peritoneal metastasis beyond the pelvis more than 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
FIGO Stage IV (TNM M1): Distant metastasis excluding peritoneal metastases	
FIGO IVA (TNM M1a)	Pleural effusion with positive cytology
FIGO IVB (TNM M1b)	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

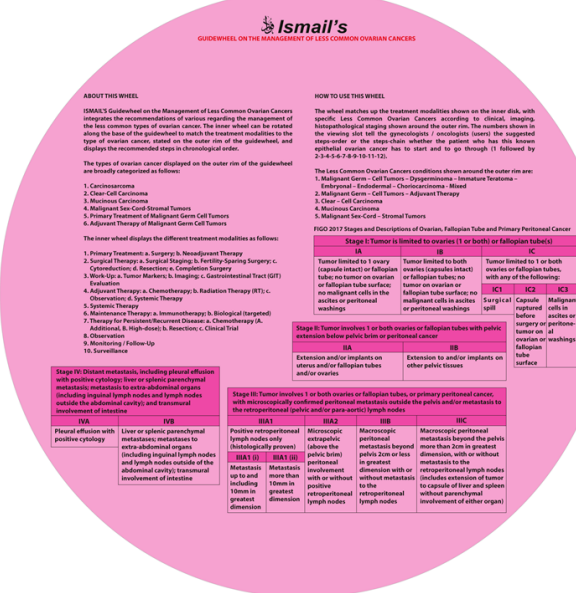


Figure 4: The back of the guidewheel displays the FIGO staging system of ovarian cancer [9] and how to use the guidewheel.

Recommendations on Managing Patients with Less Common Ovarian Cancer Using the Guidewheel

Sector 1. Carcinosarcoma (Stages I-IV) (Figure 5)

Patients diagnosed with carcinosarcoma are managed primarily (1) with surgery (a) with or without (\pm) neoadjuvant therapy (b). The second step is systemic therapy (2) with chemotherapy (a) or immunotherapy (b) with bevacizumab. Adjuvant therapy (2) involves systemic therapy (d). The next step (3) is monitoring and therapy for recurrent disease.

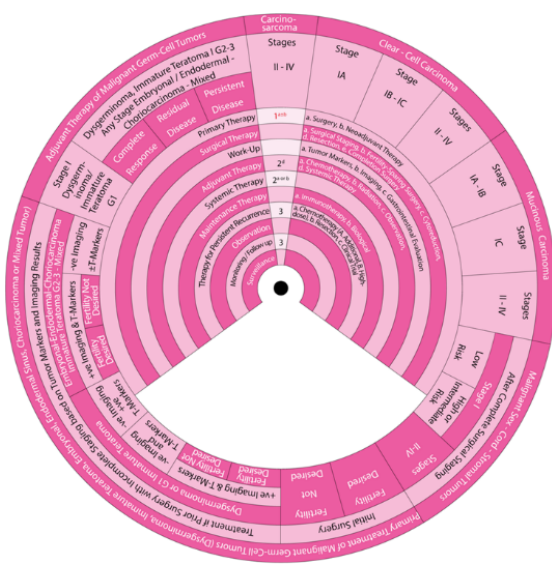


Figure 5: Carcinosarcoma (Stages I-IV).

Sector 2. Clear Cell Carcinoma (Figure 6)

Patients diagnosed with clear cell carcinoma are also managed primarily (1) with surgery (a) with or without (\pm) neoadjuvant therapy (b). For women with stage IA disease, the second step is adjuvant therapy (2) with observation (c) with or without (\pm) chemotherapy (a). Women with stages IB-IC disease are recommended to undergo adjuvant therapy (2) with chemotherapy (a). The next step (3) for women with stage I disease is monitoring and therapy for recurrent disease. Patients with stages II-IV disease are advised adjuvant therapy (2) with systemic therapy (d). Maintenance therapy (3) can be considered (#) for women with a known BRCA1/2 mutation. The next step (4) for women with stage I disease is monitoring and therapy for recurrent disease.

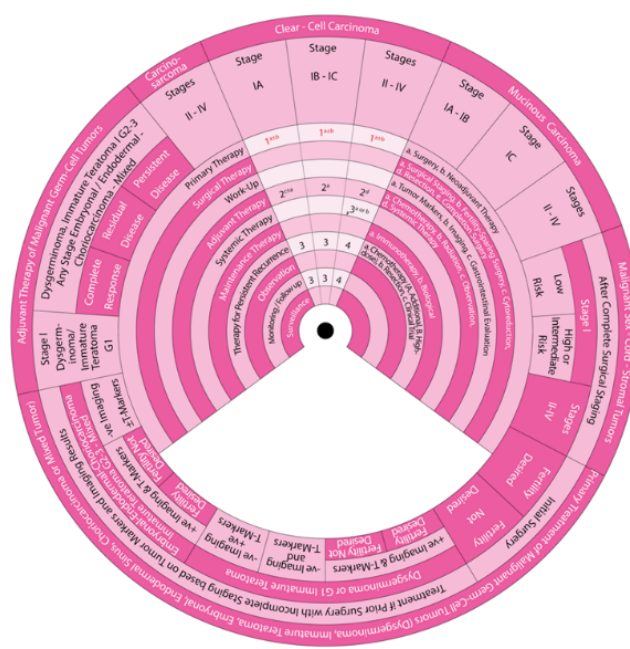


Figure 6: Clear Cell Carcinoma.

Sector 3. Mucinous Carcinoma (Figure 7)

Patients diagnosed with mucinous carcinoma are managed primarily (1) with surgery (a) with or without (\pm) neoadjuvant therapy (b). Then, further workup (2) is warranted with tumor markers (a) and GI evaluation (c). Adjuvant therapy (3) for patients with stage IA-IB disease is observation (c). Adjuvant therapy (3) for patients with stage IC disease is either observation (c) or systemic therapy (d). While patients with stages II-IV disease are advised to undergo adjuvant therapy (3) with systemic therapy (d). The next step (4) for women with mucinous carcinoma at all stages is monitoring and therapy for recurrent disease.

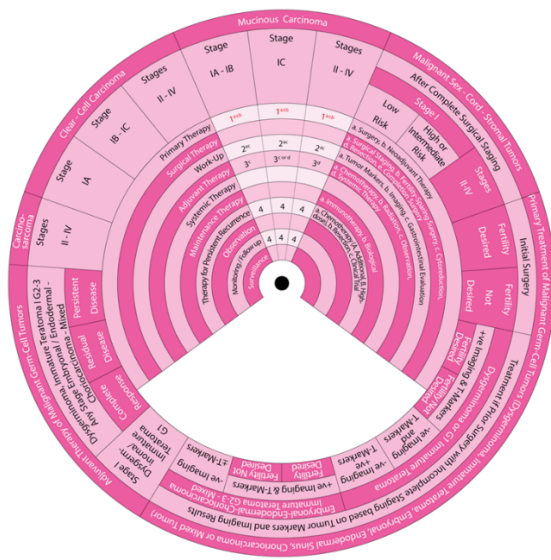


Figure 7: Mucinous Carcinoma.

Sector 4. Malignant Sex-Cord-Stromal Tumors (Figure 8)

Patients diagnosed with stage I malignant sex cord-stromal tumors are classified as having low or high risk. Those with a low risk of rupture can be observed (1c). However, those with an intermediate or high risk of rupture, adjuvant therapy is observation (1c) or patients can be considered (#) for chemotherapy (a). Patients with stages II-IV disease are advised to undergo adjuvant therapy (1) with chemotherapy (a) or RT (b). The next step for all stages is surveillance (2). For patients with stages II-IV disease, the third step (3) is therapy for recurrent disease is secondary cytoreductive surgery (b) or clinical trial (c).

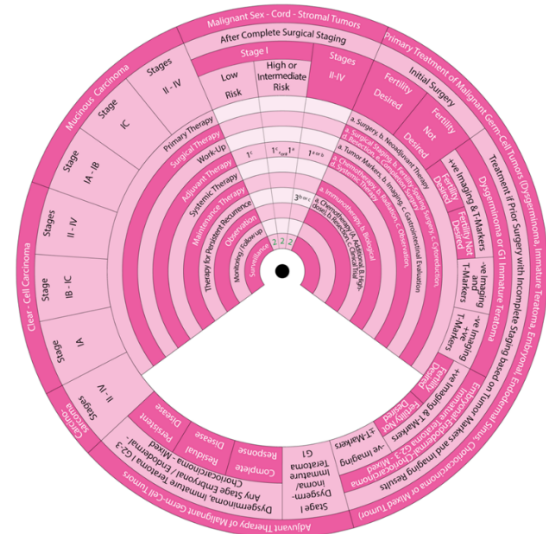


Figure 8: Malignant Sex-Cord-Stromal Tumors.

Sector 5. Primary Treatment of Malignant Germ Cell Tumors (Figure 9)

If patients diagnosed with malignant GCTs are undergoing a primary surgery, treatment depends on the desire to preserve fertility. If fertility is desired, primary treatment (1) is surgical (a) with surgical staging (1a) and fertility-sparing surgery (b). If fertility is not desired, complete staging is indicated (1a).

Patients who underwent a previous surgery and are incompletely staged are due to undergo further workup (1) with imaging (b) in the form of CT chest, abdomen and pelvis, if not done before. Those with dysgerminoma or grade 1 immature teratoma are further stratified on the results of imaging and tumor markers. Patients with both positive imaging and tumor markers are managed surgically (1) with staging (a) and/or fertility-sparing surgery (b) but if fertility is not desired, then completion surgery (b) is indicated. Patients with negative imaging but positive tumor markers can be considered (#) for observation (1). They should then be monitored (2). This is followed by surveillance (3). Patients with both negative imaging and tumor markers can be considered (#) for observation (1). The next step is surveillance (2).

Patients who are incompletely staged and diagnosed with embryonal, endodermal sinus tumor, grades 2-3 immature teratoma and non-gestational choriocarcinoma are also advised to undergo further workup (1) with imaging (b). If they have positive imaging and tumor markers and desire to preserve their fertility, then they are advised to undergo fertility-sparing surgery (1b) and staging (a). Patients who do not wish to preserve their fertility can undergo cytoreduction (c) and completion surgery (e). An alternative (or) second step is systemic therapy (2). Patients with negative imaging regardless of the presence of tumor markers, adjuvant therapy (2) with observation (c) is warranted.

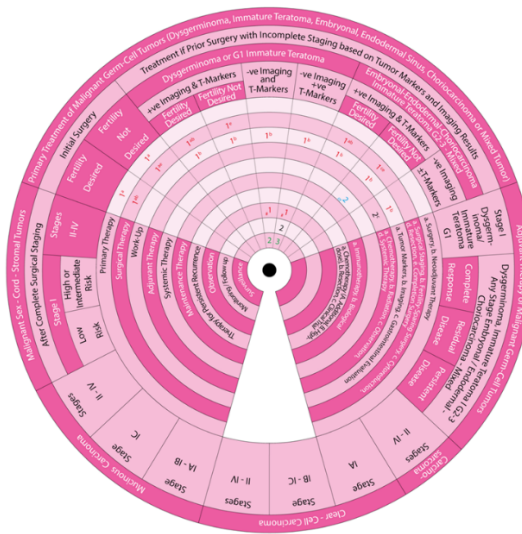


Figure 9: Primary Treatment of Malignant Germ Cell Tumors.

Sector 6. Adjuvant Therapy of Malignant Germ Cell Tumors (Figure 10)

Adjuvant therapy (1) for patients diagnosed with stage I dysgerminoma or grade 1 immature teratoma involves observation (c). If fertility is desired, primary treatment (1) is surgical (a) with surgical staging (1a) and fertility-sparing surgery (b). If fertility is not desired, complete staging is indicated (1a).

Patients diagnosed with any stage embryonal tumor, endodermal sinus tumor, nongestational choriocarcinoma or stages II-IV dysgerminoma or stage I grades 2-3 or stages II-IV immature teratoma are advised to undergo adjuvant therapy (1) with chemotherapy (a). Then, they are advised to undergo further workup (2) with imaging (b) using CT, MRI or PET/CT of the chest, abdomen and pelvis. Further management depends on patients' response to chemotherapy. Those with a complete clinical response can be observed (c) and treated for recurrent disease (3) in the case of relapse with chemotherapy (a) whether additional (A) or high-dose (B). The next step (4) is observation, followed by surveillance (5). Patients with residual disease on imaging can be considered (#) to undergo surgical resection (3d). A feasible alternative (3) is observation. The next step is treatment of recurrent disease (4) with chemotherapy (a) followed by surveillance (5). Patients with persistent disease can be treated for recurrent disease (3) with chemotherapy (a) whether additional (A) or high-dose (B). This is followed by surveillance (4).

Discussion

Cancer antigen 125 (CA-125) is high in less than 50% of early-stage EOC [7,14]. Clear-cell carcinoma is associated with endometriosis and the presence of genetic mutations including, ARID1A, PTEN and PIC3CA [1,3,8,14]. Mucinous carcinoma is associated with mutations in KRAS and human epidermal growth factor receptor 2 (HER2) amplification [8]. Clear-cell and mucinous carcinoma respond poorly to chemotherapy [3,5,14]. However, they are more likely to be detected at an early stage where they can be treated surgically [7]. The main aim of surgery is complete cytoreduction [9,10,12]. Adjuvant chemotherapy is indicated for patients with clear-cell carcinoma due to the associated high risk of recurrence [2]. Radiotherapy can be added in advanced stages of clear-cell and mucinous carcinoma [8]. Gastrointestinal evaluation with endoscopy is indicated in cases of mucinous carcinoma to rule out primary tumor arising from the gastrointestinal tract and sometimes, an appendectomy is required [3,12]. MGCTs constitute 1.5-5% of all OC [11,15-17]. MGCTs are chemosensitive; hence, advanced disease can be managed with chemotherapy without resecting the uterus and both ovaries [6,10,12,15,17]. Tumor markers that can aid in diagnosing MGCT include alpha fetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH) [6,10,15,17]. Neoadjuvant chemotherapy can reduce the extent of surgery to help preserve fertility [15]. Sex cord-stromal tumors constitute 3-7% of OC and they are associated with mutations in FOXL2 and DICER1 [11,16,17]. Tumor markers that can be measured include AFP, hCG, LDH, CA-125 and inhibin [10]. Aromatase inhibitors might be of benefit [6]. Carcinosarcoma responds to chemotherapy but has a poorer prognosis where 90% of patients present with advanced disease [3,8,12]. It is managed in the same manner as HGSC [3, 6]. Targeted treatment can also be administered depending on the molecular targets present in the tumor tissue [7]. Patients with clear-cell carcinoma might benefit from tyrosine kinase inhibitors while those with mucinous carcinoma might benefit from trastuzumab, if there is HER2 amplification [8]. In rare types of OC, participation in clinical trials is encouraged [2,6,8,10].

The most important determining factors of prognosis include the stage, tumor grade, the presence of residual disease after surgical staging [1,4,8]. Close follow-up is warranted for women diagnosed with OC with the aim of detecting recurrent disease and monitoring for side effects of treatment [15,16]. Tumor markers can be measured to detect recurrence. Women should be provided with support and education regarding their condition [15]. The presence of residual disease after surgical staging and cytoreduction is the most important determining factor of prognosis [7]. If recurrent disease is detected, imaging with CT is recommended along with CA-125 measurement since high levels are associated with recurrent OC and can be used to diagnose a relapse [1,6,14,16]. Treating recurrent disease involves chemotherapy, further cytoreduction or palliative care [1,6,9]. This guidewheel is designed to be used

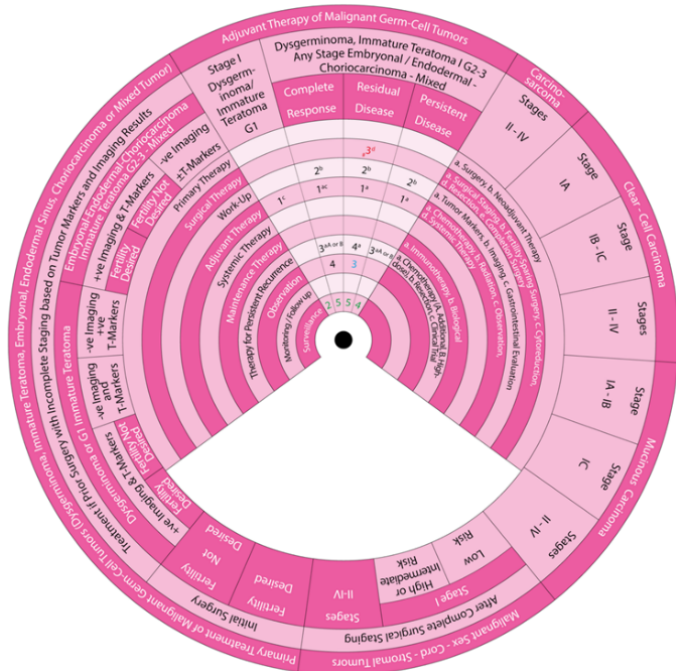


Figure 10: Adjuvant Therapy of Malignant Germ Cell Tumors.

in conjunction with Ismail's Guidewheel on the Management of Epithelial Ovarian Cancer Including Fallopian Tube and Primary Peritoneal Cancer, which covers the primary treatment of all ovarian cancers including fallopian tube and primary peritoneal cancer. This guidewheel mainly focuses on the adjuvant therapy of patients with carcinosarcoma, clear-cell carcinoma, mucinous carcinoma, MGCTs and sex-cord stromal tumors. It is not meant to replace algorithms set by international health organizations. It serves as a simplified guide to provide an overview of expected treatment of a patient given the tumor characteristics. We designed other management guidewheels for uterine, cervical and vulvar cancer in a similar manner [18-20]. We also published several chapters on the management of abnormal pap smears and cervical cancer [21-24]. Management of patients with OC requires a multi-disciplinary team. We designed this guidewheel during the COVID-19 pandemic where cancer management guidelines changed during the pandemic. However, this guidewheel does not reflect the recommendations on changes in management during these unprecedented times. Additionally, those recommendations are ideally applied in a high resource setting with highly qualified healthcare providers.

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