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SUPPLEMENT ARTICLE

Cancer of the ovary, fallopian tube, and peritoneum: 2025 update

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Abstract

In 2014, FIGO's Committee for Gynecologic Oncology revised the staging of ovarian cancer, incorporating ovarian, fallopian tube, and peritoneal cancer into the same system. Most of these malignancies are high-grade serous carcinomas (HGSCs). Stage IC is now divided into three categories: IC1 (surgical spill), IC2 (capsule ruptured before surgery or tumor on ovarian or fallopian tube surface), and IC3 (malignant cells in the ascites or peritoneal washings). The updated staging includes a revision of Stage IIIC based on spread to the retroperitoneal lymph nodes alone without intraperitoneal dissemination. This category is now subdivided into IIIA1(i) (metastasis ≤10 mm in greatest dimension) and IIIA1(ii) (metastasis >10 mm in greatest dimension). Stage IIIA2 is now "microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph node" metastasis. This review summarizes the genetics, surgical management, chemotherapy, and targeted therapies for epithelial cancers, including the treatment of ovarian germ cell and stromal malignancies.

KEYWORDS
cancer staging, chemotherapy, fallopian tube, FIGO cancer report, ovary, peritoneum

1 | INTRODUCTION

1.1 | Primary sites: Ovarian, fallopian tube, and peritoneal cancer

In 2014, the International Federation of Gynecology and Obstetrics (FIGO)'s Committee for Gynecologic Oncology revised its staging to incorporate ovarian, fallopian tube, and peritoneal cancer in the same system after extensive international consultation. Where possible, the primary site (i.e., ovary, fallopian tube, or peritoneum) is designated; however, if it is not possible to clearly identify the primary site, these should be listed as "undesignated".[1,2]

It has been presumed that fallopian tube malignancies were rare.[2] However, histologic, molecular, and genetic evidence shows that the vast majority of tumors that were previously classified as high-grade serous carcinomas (HGSCs) of the ovary or peritoneum originate in the fimbrial end of the fallopian tube.[3–8] Therefore, the incidence of fallopian tube cancers has been substantially underestimated. Contemporary data support the view that high-grade serous ovarian, fallopian tube, and peritoneal cancers should be considered collectively, and that the convention of designating these malignancies as having an ovarian origin should no longer be used, unless that is clearly the primary site. It has been suggested that extrauterine tumors of serous histology arising in the ovary, fallopian tube, or peritoneum should be described collectively as "Müllerian carcinomas"[1,2] or "pelvic serous carcinomas".[9] The latter tumor designation is controversial because some peritoneal tumors might arise in extrapelvic peritoneum. Therefore, the simple term "serous carcinoma" is preferred, with most of these being HGSCs.[10]

Although there has been no formal staging for peritoneal cancers, the FIGO staging system is used with the understanding that it is not possible to have a Stage I peritoneal cancer.

1.1.1 | Primary site

Ovarian epithelial tumors may arise within endometriosis or cortical inclusions of Müllerian epithelium, likely a form of endosalpingiosis. These include low-grade endometrioid carcinomas, clear cell carcinomas, borderline and low-grade serous carcinomas (LGSCs), and mucinous carcinomas. These tumors are thought to evolve slowly from lower-grade precursor conditions (such as endometriotic cysts and cystadenomas).[5] Fallopian tube carcinomas arise in the distal fallopian tube from premalignant serous proliferations with *TP53* mutations (p53 signature) or from serous tubal intraepithelial carcinomas (STICs). The majority of these are HGSCs[11] but can also include carcinosarcomas. All of these high-grade carcinomas are almost always associated with mutations in the *TP53* gene.[5,12]

1.1.2 | Lymphatic and lymph node drainage

The lymphatic drainage of the ovaries and fallopian tubes is via the utero-ovarian, infundibulopelvic, and round ligament pathways and an external iliac accessory route into the following regional lymph nodes: external iliac, common iliac, hypogastric, lateral sacral, paraaortic lymph nodes, and, occasionally, the inguinal nodes.[1,13–15] The peritoneal surfaces can drain through the diaphragmatic lymphatics and hence to the major venous vessels above the diaphragm.

1.1.3 | Other metastatic sites

The peritoneum, including the omentum and pelvic and abdominal viscera, is the most common site for dissemination of ovarian and fallopian tube cancers. This includes diaphragmatic and liver surfaces. Pleural involvement is also seen. Other extraperitoneal or extrapleural sites are relatively uncommon but can occur.[1,13–15] After systematic, careful pathological review has excluded a tubal or ovarian site of origin, malignancies that appear to arise primarily on the peritoneum are designated as peritoneal cancer and have a similar pattern of spread. They may also frequently involve the ovaries and fallopian tubes secondarily. These "peritoneal" tumors may arise in endosalpingiosis or possibly from migrated p53 mutated tubal epithelia cells.[11,16]

1.2 | Classification rules

Although computed tomography (CT) scans can delineate the intra-abdominal spread of disease, the specificity and sensitivity for predicting optimal surgical cytoreduction is relatively low. In addition, ovarian, fallopian tube, and peritoneal cancers should be staged surgically.[17] Fludeoxyglucose-positron emission tomography (FDG-PET)/magnetic resonance imaging (MRI) appear to have a higher diagnostic performance than CT scans but are costly and their role in routine practice is uncertain at present.[18] Operative findings determine the precise histologic diagnosis, stage, and therefore the prognosis of the patient.[1,9,13,15,19,20]

In selected patients with advanced-stage disease, it is appropriate to initiate chemotherapy before planned surgery after three cycles of treatment. In these cases, histological confirmation of the diagnosis is considered essential before starting neoadjuvant chemotherapy (NACT), not only to be certain of the diagnosis but also to ensure there is sufficient tissue for testing for homologous recombination deficiency (HRD) as well as somatic *BRCA* testing (see "Interval debulking surgery (IDS)" below).

Chest radiographs may serve as a screen for pleural effusions. As distant metastases are infrequent, there is no requirement for other radiological evaluation unless symptomatic. Serum CA125 levels are useful in determining response to chemotherapy, but they do not contribute to staging.

1.2.1 | Fallopian tube involvement

Fallopian tube involvement can be divided into three categories. In the first, an obvious intraluminal and grossly apparent fallopian tube mass is seen with tubal intraepithelial carcinoma (carcinoma in situ) that is presumed to have arisen in the fallopian tube. These cases should be staged surgically with a histological confirmation of disease. Tumor extension into the submucosa or muscularis and to and beyond the serosa can therefore be defined. These features, together with the laterality and the presence or absence of ascites, should all be taken into consideration.[1,3,6,7]

In the second scenario, a widespread serous carcinoma associated with a tubal intraepithelial carcinoma is observed. A visible mass in the endosalpinx may not be seen but the histologic findings should be noted in the pathology report since they may indicate a fallopian tube primary. Tumors obliterating both fallopian tube and ovary may belong to this group; however, whether a presumptive assignment of a tubal origin can be made in such cases is controversial given that tubal intraepithelial carcinoma may not be confirmed.

In the third scenario—risk-reducing salpingo-oophorectomy—tubal intraepithelial carcinoma may be the only finding. It should be reported as originating in the fallopian tube. The majority of early HGSCs are found in the fimbria of the fallopian tube, irrespective of genetic risk.[21,22]

1.2.2 | FIGO staging

The updated, revised FIGO staging system combines the classification for ovarian, fallopian tube, and peritoneum cancers. It is based on findings made mainly through surgical exploration (as outlined above). Table 1 presents the 2014 FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum. The equivalents within the Union for International Cancer Control (UICC) TNM classification are presented in Table 2.

TABLE 1 FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum.

Stage I: Tumor confined to ovaries or fallopian tube(s)	**T1-N0-M0**
IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	**T1a-N0-M0**
IB: 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	**T1b-N0-M0**
IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following	
IC1: Surgical spill	**T1c1-N0-M0**
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	**T1c2-N0-M0**
IC3: Malignant cells in the ascites or peritoneal washings	**T1c3-N0-M0**
Stage II: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	**T2-N0-M0**
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	**T2a-N0-M0**
IIB: Extension to other pelvic intraperitoneal tissues	**T2b-N0-M0**
Stage III: Tumor involves one 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	**T1/T2-N1-M0**
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):	
IIIA1(i) Metastasis up to 10 mm in greatest dimension	
IIIA1(ii) Metastasis more than 10 mm in greatest dimension	
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	**T3a2-N0/N1-M0**
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	**T3b-N0/N1-M0**
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	**T3c-N0/N1-M0**
Stage IV: Distant metastasis excluding peritoneal metastases	
Stage IVA: Pleural effusion with positive cytology	
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	**Any *T*, any *N*, M1**

In addition to these changes, several other modifications of the former staging system have been made to better prospectively capture the data. Stage IC is now divided into three categories: IC1 (surgical spill), IC2 (capsule ruptured before surgery or tumor on ovarian or fallopian tube surface), and IC3 (malignant cells in the ascites or peritoneal washings). Stage IIC has been eliminated. The updated staging includes a revision of Stage IIIC based on spread to the retroperitoneal lymph nodes alone without intraperitoneal dissemination, because an analysis of these patients indicates that their survival is significantly better than those who have intraperitoneal dissemination.[23] This category is now subdivided into IIIA1(i) (metastasis ≤10 mm in the greatest dimension) and IIIA1(ii) (metastasis >10 mm in the greatest dimension). Stage IIIA2 is now "microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph node" metastasis. The wording of Stage IIIB has been modified to reflect the lymph node status. Stage IVB now includes metastases to the inguinal lymph nodes.

1.2.2.1 | *Regional lymph nodes (N)*

The classifications for regional lymph nodes are as follows: NX = regional lymph nodes cannot be assessed, N0 = no regional lymph node metastasis, and N1 = regional lymph node metastasis.

1.2.2.2 | *Distant metastasis (M)*

The classifications for distant metastasis are as follows: MX = distant metastasis cannot be assessed, M0 = no distant metastasis, and M1 = distant metastasis (excluding peritoneal metastasis).

1.3 | Histopathologic classification

The majority of cases of ovarian cancer are of epithelial origin. FIGO endorses the WHO histologic typing of epithelial ovarian tumors. It is recommended that all ovarian epithelial tumors be subdivided according to the classification given below.[24]

The histologic classification of ovarian, fallopian tube, and peritoneal neoplasia is as follows: serous tumors; mucinous tumors; endometrioid tumors; clear cell tumors; Brenner tumors; undifferentiated carcinomas (this group of malignant tumors is of epithelial structure, but they are too poorly differentiated to be placed in any other group); mixed epithelial tumors (these tumors are composed of two or more of the five major cell types of common epithelial tumors. The types are usually specified); and cases with HGSC in which the ovaries and fallopian tubes appear to be incidentally involved and not

TABLE 2 Cancer of the ovary, fallopian tube and peritoneum: FIGO staging (2014) compared with TNM classification.[a]

FIGO (designate primary: Tov, Tft, Tp, or Tx)[b,c]	Union for International Cancer Control		
	T	*N*	M
Stage[d]			
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
	T3a	N1	M0
IIIB	T3b	N0	M0
	T3b	N1	M0
IIIC	T3c	N0–1	M0
	T3c	N1	M0
IV	Any *T*	Any *N*	M1
Regional nodes (*N*)[e]			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)[f]			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis (excluding peritoneal metastasis)		

[a]*Source*: Prat J.[283]

[b]The primary site—that is, ovary, fallopian tube, or peritoneum—should be designated where possible. In some cases, it may not be possible to clearly delineate the primary site, and these should be listed as "undesignated."

[c]The histological type should be recorded.

[d]The staging includes a revision of the Stage III patients and allotment to Stage IIIA1 is based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination, because an analysis of these patients indicates that their survival is significantly better than those who have intraperitoneal dissemination.

[e]Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.

[f]Extension of the tumor from the omentum to the spleen or liver (Stage IIIC) should be differentiated from isolated parenchymal splenic or liver metastases (Stage IVB).

the primary origin can be labeled as peritoneal carcinoma or serous carcinoma of undesignated site, at the discretion of the pathologist.

Epithelial tumors of the ovary and fallopian tube are further subclassified by histologic grading, which can be correlated with prognosis. This grading system does not apply to non-epithelial tumors.[25] Two grading systems are applied. For non-serous carcinomas (most endometrioid and mucinous), grading is identical to that used in the uterus, based on architecture with a one-step upgrade if there is prominent nuclear atypia, as follows: GX = grade cannot be assessed, G1 = well differentiated, G2 = moderately differentiated, and G3 = poorly differentiated.

In the 2014 WHO classification, grading for mucinous carcinomas was removed as it has no prognostic significance.[26] WHO recommended that mucinous ovarian cancers are classified as either expansile (confluent, non-destructive) or infiltrative (stromal invasion) based on the classification suggested by Lee and Scully.[27] Such classification appears to be prognostic, particularly in FIGO Stage I mucinous ovarian cancers. In contrast, the International Collaboration on Cancer Reporting suggests that if grading is undertaken, the FIGO grading for endometrioid cancers should be used.[28]

Similar to endometrial endometrioid cancers, endometrioid ovarian cancers can be associated with inactivating mutations of *PTEN* and activation of PI3 kinase signaling as well as to mutations in *CTNNB1* (beta-catenin), *PIK3CA*, and *ARID1A*. *TP53* mutated endometrioid cancers are more aggressive with a poor prognosis.[29] The Cancer Genome Atlas (TCGA) molecular classification of endometrial cancer[30] can also be used for endometrioid ovarian cancers.[31]

Serous carcinomas are the most common cell types in both the ovary and fallopian tube. More than 90% of fallopian tube carcinomas are HGSCs. Other cell types have been reported but are rare.[1,2,32] Serous carcinomas are graded in a two-grade system befitting their biology. HGSCs, including both classic appearing and those with solid, endometrioid-like, and transitional (SET) features, have a high frequency of mutations in *TP53*.[33–35] The "moderately differentiated" serous carcinoma is no longer used as the vast majority have mutations in *TP53* and are considered high-grade tumors.[25,34–36] LGSCs are often associated with borderline or atypical proliferative serous tumors and associated with mutations in the mitogen-activated protein (MAP) kinase gene pathway in approximately 50% of cases, including *BRAF* and *KRAS* mutations, and are wild-type *TP53*.

Non-epithelial cancers, although uncommon, are extremely important. These include granulosa cell tumors, germ cell tumors, sarcomas, and lymphomas. They are discussed below as separate entities. Metastatic neoplasms to the ovary, such as tumors arising in the breast, lower reproductive tract sites (cervix or uterine carcinomas), and gastrointestinal tract (signet ring cell [Krukenberg] carcinomas, low-grade appendiceal or pancreaticobiliary mucinous tumors, and other neoplasms) are graded and staged in accordance with their respective sites of origin.[1,2]

2 | EPIDEMIOLOGY

Malignant tumors of the ovaries occur at all ages, with variation in histologic subtype by age. For example, in women aged under 20 years, germ cell tumors predominate, while borderline tumors typically occur in women in their 30s and 40s—10 or more years younger than in women with invasive epithelial ovarian cancers, which mostly occur after the age of 50 years. Although incidence and mortality have been slowly and continuously decreasing since the 1990s, ovarian cancer continues to have the highest fatality-to-case

ratio of all the gynecologic malignancies. In 2023, there were nearly 19 710 new cases annually in the USA and an estimated 13 270 women lost their lives to the disease.[37] Despite declining mortality rates, ovarian cancer still accounts for approximately 5% of cancer-related deaths in women and remains the fifth leading cause of cancer mortality among women.[38] The lifetime risk of being diagnosed with ovarian cancer is 1.3%, while the risk of dying from it is almost 0.9%.[39] Although ovarian cancer accounts for approximately 23% of gynecologic cancers, it is responsible for 47% of all deaths from female genital tract malignancies.

The overall incidence of epithelial tumors is in the range of 9–17 per 100 000, with the highest rates observed in high-income countries, except for Japan.[40] This incidence increases with age, with the largest number of patients with epithelial ovarian cancer found in the 60–64-year age group. In low-income countries, the median age at diagnosis is approximately a decade earlier.[41,42]

Established risk factors for epithelial ovarian tumors include reproductive risk factors. Women who have never had children are twice as likely to develop this disease. Early menarche and late menopause increase the risk of ovarian cancer.[43] First pregnancy at an early age and the use of oral contraceptives have been associated with lower risks of ovarian cancer.[44] The relationship of these variables to fallopian tube cancer is unclear but is likely similar given that it is now recognized that the majority of HGSCs arise in the fallopian tube but have been designated ovarian in origin in the past, which would impact on findings from epidemiological studies.

2.1 | Genetics

Hereditary factors are implicated in approximately 20% of ovarian, fallopian tube, and peritoneal cancers:[45–49]

1. Most hereditary ovarian cancers are due to pathogenic mutations in either the *BRCA1* or *BRCA2* genes. At least 15% of women with high-grade non-mucinous ovarian cancers have germline pathogenic mutations in *BRCA1/2* and, importantly, 44% do not have a family history of breast/ovarian cancer. All women with high-grade non-mucinous invasive ovarian cancers should be offered genetic testing irrespective of their family history of breast/ovarian cancer or age.
2. Inherited deleterious mutations in *BRCA1* and *BRCA2* are the major genetic risk factors. Women with germline pathogenic mutations in *BRCA1* and *BRCA2* have a substantially increased risk of ovarian, tubal, and peritoneal cancer—ranging from lifetime risks of 39%–44% and 10%–20% with *BRCA1* and *BRCA2* mutations, respectively.[46–49] Typically, these cancers occur at an earlier age than sporadic cancers, particularly in *BRCA1* mutation carriers, with a median age of diagnosis in the mid-40s.[50]
3. There are several other low- to moderate-penetrance genes that can also predispose to ovarian, fallopian tube, or peritoneal cancer. A study using next-generation sequencing of constitutional DNA samples from 1915 women with ovarian cancer was carried out to identify germline mutations using a panel of 20 genes, including *BRCA1* and *BRCA2*, DNA mismatch repair genes, double-stranded DNA break repair genes, such as *CHEK2* and *ATM*, as well as the *BRCA1*-associated complex or the *BRCA2*/Fanconi Anemia pathway genes (including *BRIP1*, *BARD1*, *PALB2*, *RAD50*, *RAD51C*, and *RAD51D*, among others). Approximately 80% of mutations were in *BRCA1* or *BRCA2*, and approximately 3% of patients carried mutations in the Fanconi Anemia pathway genes, whereas only 0.4% had mutations in mismatch repair genes.[51] In an earlier similar study of 360 patients, 24% carried germline loss-of-function mutations including 18% in *BRCA1* or *BRCA2* and 6% in *BARD1*, *BRIP1*, *CHEK2*, *MRE11A*, *MSH6*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, or *TP53*.[52,53]
4. Women carrying inherited mutations in the mismatch repair genes associated with Lynch syndrome type II have an increased risk of several cancers, including colon, endometrial, and ovarian cancer. Typically, the ovarian cancers that occur are endometrioid or clear cell and are usually Stage I.[53]

The Society of Gynecologic Oncology (SGO) and National Comprehensive Cancer Network (NCCN) guidelines as well as all international guidelines recommend that all women diagnosed with ovarian, fallopian tube, or peritoneal carcinoma, regardless of age or family history, should receive genetic counseling and be offered germline genetic testing.[54] Women whose family history suggests Lynch syndrome type II should undergo appropriate genetic counseling and testing.

Women with a documented germline *BRCA* mutation, are advised to have a risk-reducing bilateral salpingo-oophorectomy (RR-BSO) after appropriate counseling and at the completion of childbearing. Guidelines suggest that women with a pathogenic *BRCA1* mutation have a RR-BSO between the ages of 35 and 40 years and women with a *BRCA2* pathogenic mutation between the ages of 40 and 45 years.[55] Surgical removal of both ovaries and fallopian tubes reduces this risk substantially and is associated with a reduction in ovarian cancer–specific mortality.[56] There is a small risk of subsequent diagnosis of peritoneal cancer after RR-BSO, which is higher if STIC lesions are present. The risk of STIC lesions is increased in women who have RR-BSO at ages older than recommended in the guidelines.[57]

2.2 | Global barriers

Global disparities in outcome have been described within any stage of ovarian cancer, suggesting that issues regarding access to care are likely critical factors.[58,59] Societal factors, economic barriers to treatment, inadequate resources at the hospital, the need for early detection programs, and lack of organization of the gynecologic oncology subspecialty[60,61] were identified as central in a recent analysis[62] of a global survey.[63] Furthermore, in low- and middle-income countries, the mean age of diagnosis has been found to be approximately 10 years earlier, the reason for which is uncertain.[64]

3 | SCREENING

To date, there are no effective screening methods that have been shown to reduce the mortality of ovarian, fallopian tube, or peritoneal cancers. Studies using CA125 and/or ultrasonography of the pelvis do not have an acceptable level of sensitivity and specificity based on trials carried out in the general population[65,66] as well as the high-risk population.[67,68] The U.S. Preventive Services Task Force (USPSTF) recommends against screening asymptomatic women for ovarian cancer with pelvic ultrasound or serum tumor marker measurements, which is in keeping with many other organizations.[69] *The USPSTF noted that there was "fair evidence that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer, but because of the low prevalence of ovarian cancer there is fair evidence that screening could likely lead to important harms which outweigh the potential benefits".*[70] A recent study on multimodal screening for high-risk women, using CA125 levels assessed with the risk of ovarian cancer algorithm (ROCA) every 4 months and annual transvaginal sonography (TVS) (or earlier if indicated by the ROCA), found that screening was associated with a higher proportion of Stage 1 or 2 diagnoses and significantly increased rates of no residual disease after surgery.[71] The authors concluded that risk-reducing salpingectomy-oophorectomy remains the treatment of choice for women at high risk of ovarian/fallopian tube cancer.[71] The recently reported UK Collaborative Trial of Ovarian Cancer Screening trial, which recruited over 200 000 women, found that those in the multimodal screening group had a lower incidence of advanced-stage disease at diagnosis (75% vs. 86%; $P=0.0003$), a higher likelihood of undergoing primary surgery (61% vs. 42%; $P<0.0001$), and a greater chance of having no residual disease after debulking surgery (46% vs. 30%; $P<0.0001$) compared to the no-screening group. There was a borderline statistically significant increase in survival in the multimodal screening group at 18 years (21% vs. 14%).[66,72] The Normal Risk Ovarian Screening Study tested a two-stage screening strategy in postmenopausal women where significantly rising CA125 levels prompted TVS and surgery if abnormal. They reported a positive predictive value of 50% and high proportion with Stage I or II cancers, but it should be noted that there were only two Stage I HGSCs. This study needs to be validated and needs to determine whether there is a survival benefit, and we recommend adhering to screening guidelines at present.[73]

Women at increased genetic risk should be encouraged to consider risk-reducing bilateral salpingo-oophorectomy as this is the most effective way to reduce mortality in this population of women.[39,40] A bulletin from the American College of Obstetricians and Gynecologists has recommended that opportunistic (at the time of a clinically indicated hysterectomy) bilateral salpingectomy be considered in women not at genetic risk who wish to retain their ovaries as a way to reduce their risk of later developing HGSCs.[74]

4 | DIAGNOSIS

Patients with epithelial ovarian cancers confined to the ovary or fallopian tube at initial diagnosis have a very good prognosis.[75–78] The symptoms are often very insidious, and their duration is not very different between patients with early-stage or advanced-stage disease.[19,20] This may reflect the different biological behaviors of the various histologic subtypes; for example, clear cell, mucinous, and endometrioid cancers are commonly early stage at presentation, whereas HGSCs are most often Stage III because of early dissemination.

Approximately two-thirds of all epithelial "ovarian" cancers are Stage III or IV at diagnosis. Presenting symptoms include vague abdominal pain or discomfort, menstrual irregularities, dyspepsia, and other mild digestive disturbances, which may have been present for only a few weeks.[19,20,79] As the disease progresses, abdominal distention and discomfort from ascites generally worsen and may be associated with respiratory symptoms from increased intra-abdominal pressure or from the transudation of fluid into the pleural cavities. Abnormal vaginal bleeding is an uncommon symptom.

Serous fallopian tube and peritoneal cancers present with the same symptoms as ovarian cancer. Past analyses have been biased because many fallopian tube cancers have been presumed to arise in the ovaries as discussed earlier.

A detailed medical history must be taken to ascertain possible risk factors, history of other cancers, and history of cancer in the family. A complete physical examination, including general, breast, pelvic, and rectal examination, must then be performed.[1]

A preoperative chest radiograph should be taken to screen for pleural effusion and a CT scan of the abdomen and pelvis should be performed to delineate the extent of intra-abdominal disease. However, in the absence of extra-abdominopelvic disease, radiological scanning does not replace surgical staging. Tumor markers, including CA125, CA 19–9, and carcinoembryonic antigen (CEA), should be considered.[1] With a high CA125 level, the most common diagnosis would be epithelial ovarian, fallopian tube, or peritoneal cancer. Tumor markers, such as human gonadotropin (hCG) and alpha-fetoprotein (AFP), are mandatory to exclude germ cell tumors in younger patients with a pelvic mass or suspicious enlargement of an ovary.

Specific biomarkers and algorithms can aid in distinguishing malignant from benign pelvic masses. Ultrasound, CA125, and menopausal status have been combined to create a Risk of Malignancy Index (RMI) that achieved a sensitivity in the range of 71%–88% and specificity of 74%–97% for predicting the presence of ovarian cancers in women with pelvic masses.[80] OVA includes CA125, apolipoprotein A1, transthyretin, transferrin, and B2-microglobulin combined with imaging and menopausal status; it demonstrates a sensitivity of 92% at a specificity of 42% in postmenopausal women, and a sensitivity of 85% at a specificity of 45% for premenopausal women.[81] A similar sensitivity and higher specificity have been attained with a Risk of Ovarian Malignancy Algorithm (ROMA) calculated from CA125 and HE4 values combined with menopausal status alone, without imaging.[82] The ROMA has been shown to be superior to the RMI.[83] A second-generation OVERA panel test includes CA125, apolipoprotein A1, transferrin, follicle-stimulating hormone, and HE4 producing a sensitivity of 91%, specificity of

69%, and negative predictive value of 97%.[84] Both the OVERA and ROMA panels have been approved for use by the U.S. Food and Drug Administration (FDA). Utilization of these panels could assure that women with suspicious adnexal masses are referred to gynecologic oncologists.

A gastric or colonic primary with metastases to the ovaries may mimic ovarian cancer, and if CEA or CA 19–9 are elevated, this should be considered. A ratio of more than 25:1 (CA125 and CEA) favors an ovarian primary, though it does not completely rule out a primary in the gastrointestinal tract.[85]

A current mammogram should be considered as patients are often in the age group where breast cancer is prevalent. A colonoscopy is indicated when symptoms suggest possible colorectal cancer.[1]

The following factors point to the presence of a malignancy and are useful in the clinical assessment of masses: age of the patient (young for germ cell, older for epithelial malignancies), bilaterality, tumor fixation clinically, ascites, ultrasonographically complex—especially if solid areas, CT finding of metastatic nodules, and elevated tumor markers.

5 | PRIMARY SURGERY

In general, the prognosis of epithelial ovarian, fallopian, and peritoneal malignancies is independently affected by the following:[1,86,87] stage of cancer at diagnosis, histologic type and grade, and maximum diameter of residual disease after cytoreductive surgery.

5.1 | Staging surgery

A thorough staging laparotomy is an important part of management. If the preoperative suspicion is malignancy, a laparotomy should be performed. Minimally invasive staging surgery, however, can be considered. Studies have shown no difference in surgical outcomes, recurrences, and survival between open and minimally invasive staging surgeries.[88–100] If there is no visible or palpable evidence of metastasis, the following should be performed for adequate staging:[1,13,14]

- Careful evaluation of all peritoneal surfaces
- Retrieval of any peritoneal fluid or ascites; if there is none, washings of the peritoneal cavity should be performed
- Infracolic omentectomy
- Selective lymphadenectomy of the pelvic and para-aortic lymph nodes, at least ipsilateral if the malignancy is unilateral
- Biopsy or resection of any suspicious lesions, masses, or adhesions
- Random peritoneal biopsies of normal surfaces, including from the undersurface of the right hemidiaphragm, bladder reflection, cul-de-sac, right and left paracolic recesses, and both pelvic sidewalls
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy in most cases; fertility-sparing surgeries are discussed below
- Appendectomy for mucinous tumors, if the appendix appears abnormal.

Upon opening the abdominopelvic cavity, the peritoneal fluid should be sent for cytology. In the absence of ascites, irrigation should be performed and washings sent for cytology.

The laparotomy should proceed with a detailed examination of the contents, including all the peritoneal surfaces. In addition to the suspicious sites, biopsies from the peritoneal reflection of the bladder, the posterior cul-de-sac, both paracolic gutters, subdiaphragmatic surfaces, and both pelvic sidewalls should be taken. The primary tumor, if limited to the ovary, should be examined to look for capsular rupture. All obvious sites of tumor must be removed wherever possible in addition to total hysterectomy and bilateral salpingo-oophorectomy. The omentum, pelvic, and para-aortic lymph nodes should be removed for histologic examination.

In younger women, fertility-preservation may be desired. In these patients, conservative surgery, with preservation of the uterus and contralateral ovary, should be considered after informed consent.[76] Recent guidelines support fertility-sparing surgery for patients with Stage I epithelial ovarian cancer, clear cell cancers, mucinous cancers, LGSCs, low-grade endometrioid cancers, borderline tumors, granulosa cell tumors, and all stages of germ cell tumors. Reproductive specialists should be involved early in the process, ideally before the beginning of any oncological treatments.[101,102] Interested readers are encouraged to read the guidelines for greater detail.[101]

Ovaries and fallopian tubes should be evaluated as thoroughly as possible to establish the site of origin. If visible, the entire tube, particularly the distal portion, should be submitted for pathology and examined using the SEE-FIM protocol.[49]

5.2 | Cytoreductive (debulking) surgery for advanced-stage disease

5.2.1 | Primary debulking surgery (PDS)

At least two-thirds of patients with ovarian cancer present with Stage III or IV disease. This may affect the performance status and fitness for surgery. However, the most important prognostic indicator in patients with advanced-stage ovarian cancer is the volume of residual disease after surgical debulking. Patients whose disease is completely resected to no macroscopic (microscopic only) residual disease have the best overall survival (OS).[87,103] Therefore, patients whose medical condition permits should generally undergo a primary laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal attempt at optimal cytoreduction.[1,86,87] This may necessitate bowel resection, and occasionally, partial or complete resection of other organs. Based on the randomized Lymphadenectomy in Ovarian Neoplasm (LION) trial, the removal of clinically negative lymph nodes during cytoreductive surgery does not increase the progression-free survival (PFS) or OS and should not be undertaken[104] (Level of Evidence: A).

5.2.2 | Interval debulking surgery (IDS)

In selected patients with apparent Stage IIIC and IV disease who are not considered to be good surgical candidates, 3–4 cycles of NACT may be given initially after histological confirmation of the diagnosis with core biopsies, followed by IDS and additional chemotherapy as demonstrated in the EORTC and Chemotherapy or Upfront Surgery (CHORUS) Trials.[105,106] These two randomized prospective trials showed that in selected patients, IDS after NACT showed equivalent survival with less morbidity compared with primary cytoreductive surgery. NACT followed by IDS may be particularly useful in patients with a poor performance status, significant medical co-morbidities, or who have disease unlikely to be optimally cytoreduced, i.e., visceral metastases large volume pleural effusions or evidence of extraperitoneal disease.[107,108] In selected patients whose primary cytoreduction is considered suboptimal, particularly if a gynecologic oncologist did not perform the initial surgery, IDS may be considered after 2–3 cycles of systemic chemotherapy.[1,105,106,109] A histopathologic scoring system for measuring the response to NACT has been developed and validated by Bohm et al.,[110] who reported criteria for defining a chemotherapy response score (CRS) based on a three-tier system. A CRS of 3 (complete or near-complete pathological response) was associated with a better prognosis. These results have been validated in an independent West Australian cohort.[111]

Based on a more recent review of the National Cancer Database of over 7800 patients between 2013 and 2018, IDS might be safely performed by minimally invasive surgery with similar OS compared to laparotomy if the patient showed a good treatment response to NACT.[112] The NCCN guidelines recommend that in select patients, minimally invasive procedures may be used for IDS provided optimal cytoreduction can be achieved.

6 | CHEMOTHERAPY

6.1 | Chemotherapy for early-stage cancer

The prognosis of patients with adequately staged tumors with Stage IA and Stage IB grade 1–2 epithelial cancers of the ovary is very good; adjuvant chemotherapy does not provide additional benefits and is not indicated. For example, a SEER study reported no apparent survival advantage of adjuvant chemotherapy in patients with Stage I grade 1–2 endometrioid ovarian cancer. For higher-grade tumors, including high-grade serous cancers, and for patients with Stage IC disease, adjuvant platinum-based chemotherapy is given to most patients, although there is uncertainty about the absolute survival benefit in women with Stage IA and IB cancers who have had thorough surgical staging.[75] Stage I clear cell cancers are considered high-grade and have typically been treated with adjuvant chemotherapy, although there is uncertainty of benefit, and a retrospective Asian study did not demonstrate benefit in patients with Stage IA–IC1 tumors. There is also uncertainty regarding adjuvant chemotherapy in Stage I mucinous cancers, with guidelines now suggesting avoiding chemotherapy in the expansile subtype. All patients with Stage II disease should receive adjuvant chemotherapy. The optimal number of cycles in patients with Stage I disease has not been definitively established, but typically 3–6 cycles are administered. The Gynecologic Oncology Group (GOG) 157 study suggested that three cycles of carboplatin and paclitaxel was equivalent to six cycles;[78] however, in a subgroup analysis, six cycles appeared superior in patients with HGSCs.[113]

There is no evidence to support adjuvant therapy for carcinoma in situ of the fallopian tube (STIC lesions), and it is not recommended.[1,2,114] However, it should be noted that patients with *BRCA* mutations with STIC lesions may be at increased risk of late onset peritoneal cancers years later[115] (Level of Evidence: A).

6.2 | Chemotherapy for advanced-stage ovarian cancer

Patients who have had primary cytoreduction should receive chemotherapy after surgery[1,116] (Table 3). The accepted standard is six cycles of platinum-based combination chemotherapy, with carboplatin and a taxane (paclitaxel or docetaxel).[117–121] Docetaxel is an option in patients who have had a significant allergic reaction to paclitaxel or who develop early sensory neuropathy as it has less neurotoxicity, but it is more myelosuppressive than paclitaxel. The Scottish Gynecological Cancer Trials Group (SCOT-ROC) study randomly assigned 1077 women with Stage IC–IV epithelial ovarian cancer to carboplatin paclitaxel or docetaxel.[122] The efficacy of docetaxel was similar to that of paclitaxel but 11% of patients experienced grade 2 or higher neuropathy compared with 30% of patients treated with paclitaxel. The median PFS was 15.1 versus 15.4 months. The MITO-2 trial randomized over 800 patients to receive either carboplatin and pegylated liposomal doxorubicin (PLD) or carboplatin and paclitaxel. The trial was powered to show a PFS advantage, but the median PFS was not statistically different at 19.0 and 16.8 months with carboplatin/PLD and carboplatin/paclitaxel, respectively.[123] The median OS times were 61.6 and 53.2 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.72–1.12; $P=0.32$). Carboplatin/PLD produced a similar response rate but different toxicity (much less neurotoxicity and alopecia but more stomatitis) and could be considered as an option in patients where paclitaxel cannot be used or based on patient preferences.

Although intraperitoneal chemotherapy has been shown to be associated with improved PFS and OS in selected patients with optimally debulked Stage III ovarian cancer, it is not widely used (outside the USA) because of concerns regarding increased toxicity and catheter-related problems, and the benefits are still debated.[124–127] The GOG 172 trial compared intravenous paclitaxel plus cisplatin with intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel in patients with Stage III ovarian or peritoneal carcinoma, with no residual disease greater than 1 cm in diameter.[126] Only 42% of patients in the intraperitoneal group completed six cycles of the assigned therapy, but the intraperitoneal group had an improvement in

TABLE 3 Chemotherapy for advanced epithelial ovarian cancer: Recommended regimens.[a]

Standard drug regimens	Dose	Administration (h)	Interval	No. of treatments
Carboplatin Paclitaxel	AUC = 5–6 175 mg/m^2	3	Every 3 weeks	6–8 cycles
Carboplatin Paclitaxel	AUC = 5–6 80 mg/m^2	3	Every 3 weeks Every week	6 cycles 18 weeks
Carboplatin Docetaxel	AUC = 5 75 mg/m^2	3	Every week Every 3 weeks	6 cycles
Cisplatin Paclitaxel	75 mg/m^2 135 mg/m^2	3	Every 3 weeks	6 cycles
Carboplatin (single agent)[b]	AUC = 5	3	Every 3 weeks	6 cycles, as tolerated

Abbreviation: AUC, area under the curve dose by the methods of Calvert et al.[284] and Nagao et al.[285]

[a]Reproduced with permission from Berek et al.[1]

[b]In patients who are elderly, frail, or poor performance status.

PFS of 5.5 months (23.8 vs. 18.3 months; $P = 0.05$) and an improvement in OS of 15.9 months (65.6 vs. 49.7 months; $P = 0.03$).

The GOG 252 trial reported a median PFS of approximately 27–29 months in over 1500 patients with optimal Stage II–III disease treated with regimens consisting of different combinations of intravenous and intraperitoneal cisplatin, carboplatin, and paclitaxel, in combination with bevacizumab, which raised questions about the role of intraperitoneal chemotherapy.[128] The treatment arms included intravenous carboplatin area under the curve (AUC) 6 plus intravenous weekly paclitaxel at 80 mg/m^2, intraperitoneal carboplatin AUC 6 plus intravenous weekly paclitaxel at 80 mg/m^2, and intravenous paclitaxel at 135 mg/m^2 on day 1 plus intraperitoneal cisplatin at 75 mg/m^2 on day 2 plus intraperitoneal paclitaxel at 60 mg/m^2 on day 8. In addition, each arm received intravenous bevacizumab at 15 mg/kg with cycles 2–6 of chemotherapy and then alone for cycles 7–22. The median PFS by intent-to-treat analysis was 24.9 months (intravenous carboplatin), 27.3 months (intraperitoneal carboplatin), and 26.0 months (intraperitoneal cisplatin). An analysis limited to patients with optimal Stage III tumors and no gross residual disease found a median PFS of 31–34 months in all three arms. The median OS for all patients enrolled was 75.5, 78.9, and 72.9 months, respectively, and the median OS for Stage II/III with no gross residual disease was 98.8 months, 104.8 months, and not reached.[128] By comparison, the GOG 172 trial comparing intraperitoneal and intravenous chemotherapy regimens in ovarian cancer had a median PFS of 23.8 months with intraperitoneal cisplatin (vs 18.3 months with intravenous) with an improvement in OS in favor of intraperitoneal injection.[126] In addition, the median PFS was 60 months in patients with no residual disease in GOG 172. Differences in the cisplatin arm from the GOG 172 study include a dose reduction from 100 to 75 mg and a shorter infusion time from 24 to 3 h.[126] If intraperitoneal treatment is used, it would be appropriate to follow the GOG 172 protocol rather than the modified protocol with a lower dose of cisplatin accepting the increased toxicity.

The role of intraperitoneal carboplatin in combination with dose-dense paclitaxel was evaluated in the JGOG phase III iPocc trial, which showed an improved PFS (23.5 vs. 20.9 months; HR 0.83, 95% CI 0.69–0.99) for intraperitoneal carboplatin every 3 weeks plus dose-dense paclitaxel versus intravenous carboplatin every 3 weeks plus dose-dense paclitaxel.[129]

Combination chemotherapy with intravenous carboplatin and paclitaxel is the standard treatment option for patients with advanced disease, with evidence to support the addition of bevacizumab. The advantages and disadvantages of the intravenous versus intraperitoneal routes of administration of these drugs should be discussed with the patient in light of the results of GOG 252 discussed above, which did not demonstrate improved outcomes with intraperitoneal chemotherapy when bevacizumab was added to intravenous chemotherapy. Intraperitoneal chemotherapy is applicable only to patients with advanced disease who have had optimal debulking and have less than 1 cm residual disease. It should be used only in centers that have experience with intraperitoneal chemotherapy.

The recommended doses and schedule for intravenous chemotherapy are: carboplatin (starting dose AUC 5–6) and paclitaxel (175 mg/m^2) every 3 weeks for six cycles.[1]

The Japanese GOG (JGOG) reported an alternative dose-dense regimen of carboplatin AUC 6 every 3 weeks for six cycles and weekly paclitaxel 80 mg/m^2 and showed improved PFS and OS.[130,131] An Italian trial (MITO-7) investigated a different schedule of weekly carboplatin (AUC 2 mg/mL/min) plus weekly paclitaxel (60 mg/m^2) compared with carboplatin (AUC 6 mg/mL/min, administered every 3 weeks) and paclitaxel (175 mg/m^2).[132] The co-primary endpoints were PFS and quality of life, which is unique for an ovarian cancer trial. The weekly regimen did not significantly improve PFS compared with the conventional regimen (18.8 vs. 16.5 months; $P = 0.18$) but was associated with better quality of life and fewer toxic effects, and could be considered a reasonable option particularly in elderly patients in whom combination chemotherapy is planned. The International Collaboration on Ovarian Neoplasms (ICON) 8 trial investigated dose-dense paclitaxel in a non-Japanese population.[133] Over 1500 predominantly Caucasian patients were randomized to receive one of three regimens: arm 1: carboplatin AUC 5/6 and paclitaxel 175 mg/m^2 every 3 weeks, arm 2: carboplatin AUC 5/6 every 3 weeks and paclitaxel 80 mg/m^2 weekly, and arm 3: carboplatin AUC 2 and paclitaxel 80 mg/m^2 weekly. All patients had received NACT

with planned interval debulking or received chemotherapy after initial primary cytoreductive surgery. There was no benefit found for the dose-dense regimens. The PFS was 24.4 months with every 3-week dosing, compared with 24.9 and 25.3 months in arms 2 and 3, respectively. The OS was reported recently and the median OS was 47.4, 54.1, and 53.4 months in arms 1, 2, and 3, respectively.[134] These results are very different from those of the JGOG trial, and it seems that the likely explanation is due to pharmacogenomic differences between these two ethnic groups.[135] However, to complicate matters, ICON8B has recently been presented but not yet published in a peer-reviewed journal.[136] This was initially planned to be a three-arm trial and recruited high-risk patients with Stage III and larger than 1 cm residual disease, Stage IV as well as all patients with Stage III disease who received NACT. They were randomized to bevacizumab 7.5 mg/kg plus q 3-weekly carboplatin and paclitaxel (BEV + q3wCT) versus BEV+ q 3-weekly carboplatin and dose-dense weekly paclitaxel with bevacizumab (q3wCddwT) versus q3wCddwT alone. The latter arm was dropped when the results of ICON8 were available. There were 292 patients in BEV + q3wCT and 287 in BEV+ q3wCddwT. The study was closed and analyzed when 465 progression events were considered sufficient for primary analysis, giving a power of 87% for the targeted effect size of 0.75. PFS was better in BEV+ q3wCddwT compared to BEV + q3wCT. The median increased from PFS 16.7 to 22.2 months (HR 0.75, 95% CI 0.62–0.90; $P = 0.002$). The median OS increased from 40.9 to 51.1 months (HR 0.77, 95% CI 0.62–0.96; $P = 0.020$). This study has not yet impacted on guideline recommendations and is likely to do so; however, we need to wait for the publication to analyze the details, including adverse effects in depth.

Two studies (GOG 218 and ICON7) reported a modest, but statistically significant increase in PFS in patients receiving maintenance bevacizumab following q 3-weekly carboplatin, paclitaxel, and concurrent bevacizumab.[137,138] The GOG 218 trial randomized patients with Stage III and macroscopic residual disease as well as Stage IV ovarian cancer to the following: (1) six cycles of carboplatin and paclitaxel plus placebo for cycles 2–22 (control group), (2) six cycles of carboplatin and paclitaxel in combination with bevacizumab (15 mg/kg) for cycles 2–6, followed by placebo (initiation group), and (3) six cycles of carboplatin and paclitaxel with bevacizumab for cycles 2–22 (throughout group). The median PFS was 10.3, 11.2, and 14.1 months in the control, initiation, and throughout groups. respectively.[138] The ICON7 trial included patients with early-stage high-risk disease (Stage I or IIA clear cell or grade 3) and advanced-stage (Stage IIB–IV) and randomized to six cycles of chemotherapy or six cycles of chemotherapy plus bevacizumab (7.5 mg/kg), followed by 12 cycles of maintenance bevacizumab.[137] Restricted mean PFS was statistically different at 22.4 versus 24.1 months (control vs. bevacizumab) although the clinical significance can be questioned. There is no evidence to demonstrate an OS benefit, but a subgroup analysis of the ICON7 trial reported an improved median survival (30.3 vs. 39.4 months) in patients with suboptimal Stage III and Stage IV disease.[137,139] The role, optimal dose (7.5 mg/kg vs. 15 mg/kg), timing (primary vs. recurrent disease), and duration of treatment of bevacizumab are still debatable. Similarly, there was no difference in OS between the three arms in GOG 218; however, in an exploratory subgroup analysis, the median OS for Stage IV disease was 32.6 versus 42.8 months (control vs. throughout).[140]

Van Driel et al.[141] reported the results of a randomized trial in which 245 patients with Stage III epithelial ovarian cancer who had received three cycles of NACT underwent IDS. These patients were then randomized to receive either three more cycles of paclitaxel plus carboplatin with or without hyperthermic intraperitoneal chemotherapy (HIPEC). The addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival (14.2 vs. 10.7 months) and OS (45.7 vs. 33.9 months) and did not result in higher rates of adverse effects. These findings are provocative and raise important questions. Unfortunately, the study did not have an arm with intraperitoneal cisplatin alone without HIPEC; therefore, it is not possible to know whether the improved survival was due to the addition of intraperitoneal cisplatin alone or HIPEC. Confirmatory trials are in progress to determine the role of HIPEC. A phase II trial by Zivanovic et al. did not show improved outcomes for HIPEC after secondary cytoreduction.[142] However, the CHIPOR trial showed improved outcomes for patients with platinum-sensitive disease who underwent secondary cytoreduction with HIPEC after six cycles of platinum-based chemotherapy.[143] Currently, NCCN guidelines state that the use of HIPEC at the time of IDS can be considered while the European Society of Gynecologic Oncology (ESGO) guidelines did not reach a consensus regarding the role of HIPEC at the time of IDS and recommend against HIPEC at the time of secondary cytoreduction indicating considerable controversy.[144]

In patients who may not tolerate combination chemotherapy because of medical co-morbidities, frailty, or advanced age, single-agent, intravenously administered carboplatin (AUC 5–6) can be given. However, this approach has been challenged by the EWOC-1 trial,[145] a randomized phase 2 trial that enrolled 120 vulnerable and elderly patients to either carboplatin (AUC 5) and paclitaxel 175 mg/m^2 every 3 weeks for six cycles (arm A), carboplatin (AUC 5–6) alone every 3 weeks for six cycles (arm B), or weekly carboplatin (AUC 2) and paclitaxel 60 mg/m^2 weekly for 18 weeks (arm C). The median PFS was 12.5 months (95% CI 10.3–15.3), 4.8 (95% CI 3.8–15.3), and 8.3 (95% CI 6.6–15.3), respectively ($P < 0.001$) and the median OS for arms A, B, and C was not reached (NR) (21–NR), 7.4 (5.3–NR), and 17.3 (10.8–NR), respectively ($P = 0.001$). The Independent Data Monitoring Committee recommended that the study be closed as survival in arm B (carboplatin alone) was significantly worse than in the combination arms. The findings of this trial raise questions about the place of single-agent carboplatin; however, it should be noted that it was a small trial, and the findings need to be confirmed.

6.3 | Neoadjuvant chemotherapy

An increasing proportion of patients with advanced-stage ovarian cancer is being treated with upfront NACT for 3–4 cycles before

interval debulking and further chemotherapy. This is based on the results of four trials that have reported equivalent outcomes regarding PFS and OS, but less morbidity and lower mortality compared to PDS.[107] Vergote et al. reported the results in 2010 of the first randomized EORTC-NCIC (National Cancer Institute of Canada) study of PDS versus three cycles of NACT followed by interval debulking.[105] All the patients had extensive Stage IIIC or IV disease. Patients were randomly assigned to either PDS followed by at least six courses of platinum-based chemotherapy or to three cycles of platinum-based NACT followed by IDS in all patients with a response or stable disease, followed by at least three further courses of platinum-based chemotherapy. The median PFS in both groups was 12 months. The median OS was also similar at 29 versus 30 months (PDS vs. NACT). There was lower postoperative morbidity and mortality in the NACT group. The median OS was considerably less than the 60+ months expected with PDS and optimal cytoreduction followed by chemotherapy, suggesting that the study included a cohort of patients with very advanced disease and a poor prognosis. The study provoked much discussion and debate regarding the role of NACT.

The CHORUS trial randomized patients to NACT followed by interval debulking and then three additional cycles or PDS followed by six cycles of platinum-based chemotherapy.[106] The optimal debulking rate was only 16% in the PDS group compared to 40% after NACT, which is lower than would be expected. The median duration of surgery was only 120 min in both groups, which was criticized as it did not seem to be long enough for aggressive debulking surgery and optimal cytoreduction. There was a postoperative mortality rate of 5.6% in the PDS group, which is high. The median PFS was 12 months in both groups, and the median OS was similar at 22.6 versus 24.1 months (PDS vs. NACT).

More recently, the Japanese Oncology Group (JGOG 0602) reported the results of a randomized trial of NACT versus PDS in selected patients with Stage III–IV ovarian cancer.[146] The primary endpoint was OS, and it was designed as a non-inferiority trial. Between 2006 and 2011, 301 patients were randomized, 149 to PDS and 152 to NACT. The median OS was 49.0 and 44.3 months in the PDS and NACT arms, respectively. The HR for NACT was 1.052 (90.8% CI 0.835–1.326), and one-sided non-inferiority *P* value was 0.24. In contrast to the previous two trials, the non-inferiority of NACT was not confirmed, with the caveat that this was a relatively small trial. The authors concluded that the non-inferiority of NACT was not confirmed and that NACT may not always be a substitute for PDS.

The SCORPION trial investigated whether NACT followed by IDS was superior to PDS in terms of perioperative complications and PFS in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with high tumor burden. Patients underwent initial laparoscopy to confirm FIGO Stage III/IV disease and to assess their suitability for inclusion in the trial.[147] They were randomized on the operating table to either immediate surgery or NACT. Of the 171 included patients, 84 were randomized to surgery and 87 to chemotherapy. They achieved a complete resection rate of 47% with PDS compared to 77% in the NACT group, and both arms achieved optimal resection of over 90%. The aim was to demonstrate the superiority of NACT over PDS, but the median PFS and OS were 14 and 43 months for PDS and 14 and 43 months NACT, respectively. Consistent with other studies, morbidity was greater in the PDS group with major complications occurring in 46% of the patients compared to 9.5% in the neoadjuvant group. Of concern, 8.3% of the PDS group died from surgical complications whereas there were no postoperative deaths in the NACT group. Hospital stays were significantly shorter for NACT.

It should be noted that both JGOG 0602 and SCORPION were carried out in expert centers selected for the skill and surgical expertise but were both underpowered to demonstrate superiority or non-inferiority of NACT versus PDS.

A recent, systematic review and meta-analysis that included four phase 3 trials with a total of 1692 patients concluded that NACT with carboplatin and paclitaxel followed by IDS does not negatively impact the survival of women with advanced ovarian cancer compared to PDS, but that perioperative complications and mortality are significantly reduced by 70%–80%.[148] Despite these four trials, there remain divergent views regarding the role of NACT. For selected patients with poor prognostic features, NACT seems advisable given the equivalent outcomes regarding PFS and OS and lower perioperative morbidity and mortality. NACT is indicated in patients who are medically unfit for upfront surgery or who have a high risk of surgical morbidity and mortality, including those with parenchymal liver and lung metastases. However, PDS should be offered to patients with a good performance status and a more favorable prognosis. There are several models from the Mayo Clinic as well as Memorial Sloan Kettering Cancer Center among others that have been advocated to improve patient selection for PDS as well as algorithms to guide management.

6.4 | Maintenance chemotherapy

Almost 80% of women with advanced-stage disease who respond to first-line chemotherapy relapse. There have been several trials conducted to determine if there is a benefit of maintenance chemotherapy in these patients immediately after their primary treatment in an effort to decrease the relapse rate.[149] These were all negative and there is no evidence to support maintenance chemotherapy after completion of first-line therapy.

6.5 | Maintenance therapy with PARP inhibitors

There is increasing evidence to support the role of maintenance therapy with PARP inhibitors after response to treatment in the first-line setting as well as in patients with platinum-sensitive recurrent ovarian cancer. In the SOLO1 trial, patients with Stage III and IV high-grade serous/high-grade endometrioid ovarian cancer, a germline or somatic *BRCA1* or *2* mutation, and at least partial response to adjuvant platinum-based chemotherapy were randomized to olaparib maintenance or placebo.[150] A 70% risk reduction for progression of disease

or death was seen for olaparib (HR 0.3) with a median PFS not reached versus 13.8 months with placebo. Twice as many patients were progression free after 3 years (60.4% vs. 26.9%), which is unprecedented. At the 5-year follow up, 48% of the patients randomized to 2 years of olaparib were progression free compared to 21% in the placebo arm. The median PFS was 56 versus 13.8 months (HR 0.33).[151] At the 7-year follow-up, 45.3% of olaparib patients versus 20.6% of the placebo patients were alive and had not received the first subsequent treatment. The hazard ratio for OS was 0.55 (95% CI 0.4–0.76; $P=0.0004$ [$P<0.0001$ was required to declare statistical significance]).[152]

The PRIMA trial enrolled a subset of patients considered to be at high risk of relapse and included patients with Stage III and IV high-grade serous and endometrioid ovarian cancer with response to chemotherapy, but regardless of *BRCA* status. It included those with suboptimal residual disease for Stage III after surgery as well as patients who received NACT and all patients with Stage IV disease.[153] Patients were randomized to niraparib or placebo for 3 years. In the overall population, the median PFS was 8.2 versus 13.8 months (control vs. niraparib). In the HRD subgroup, as determined using the Myriad myChoice test, the median PFS was 10.9 versus 22.1 months. In the homologous recombination proficient (HRP) subgroup, the difference was smaller although statistically significant (5.4 vs. 8.1 months). In the long-term follow-up, there was no OS benefit in the overall population (46.6 vs. 48.8 months; HR 1.01, 95% CI 0.84–1.23), HRD group (71.9 vs. 69.8 months; HR 0.95, 95% CI 0.70–1.29), or HRP group (36.6 vs. 32.2 months; HR 0.93, 95% CI 069–1.26).[154]

The PRIME trial, which evaluated niraparib as first-line maintenance in 384 Chinese patients with newly diagnosed advanced ovarian cancer, showed similar results. The median PFS improved in the intention-to-treat population compared to placebo (24.8 vs. 8.3 months) and in the studied subgroups. Median PFS was not reached versus 10.8 months in patients with germline *BRCA* mutation and 19.3 versus 8.3 months in patients without germline *BRCA* mutation, not reached versus 11 months in HRD patients, and 16.6 versus 5.5 in HRP patients.[155]

In both trials, niraparib dosing was reduced to 200 mg if the patient's body weight was less than 77 kg and platelet count was less than 150 10^3/μl.[156]

The ATHENA-MONO trial studied rucaparib as first-line maintenance. Median PFS was 28.7 versus 11.3 months for the HRD patients (rucaparib vs. placebo) and 12.1 versus 9.1 months in the HRP patients.[157]

The VELIA trial randomized patients with advanced-stage ovarian cancer to the following groups: (1) platinum and paclitaxel chemotherapy (control), (2) veliparib with chemotherapy, and (3) veliparib with chemotherapy followed by veliparib maintenance.[158] There was significant benefit from adding veliparib to chemotherapy and maintenance. In the *BRCA* mutation group, the median PFS was 22 versus 34.7 months, 20.5 versus 31.9 months in the HRD group, and 17.3 versus 23.5 months in the intention-to-treat population. The results of the HRP patients were not reported.

In the PAOLA trial, patients with Stage III/IV HGSCs, regardless of BRCA status and at least partial response, were randomized to bevacizumab or bevacizumab plus olaparib maintenance therapy.[159] The median PFS for the intention-to-treat population was 16.6 versus 22.1 months (without vs. with olaparib), 21.7 versus 37.2 months in the *BRCA*-mutated group, and 16.6 versus 28.1 months in the HRD group excluding *BRCA*. However, in the HRP or unknown group, there was no difference in median PFS (16 vs. 16.9 months). Long-term follow-up showed significant OS benefit for the HRD group but not for the intention-to-treat population. In the HRD group, 5-year OS was 65.5% versus 48.4% (without vs. with *olaparib*).[160] The PAOLA trial design did not include olaparib monotherapy, making it difficult to ascertain the contribution of bevacizumab. Nevertheless, the *olaparib* plus *bevacizumab* combination received FDA approval as first-line maintenance for HRD patients.

Data from another first-line combination maintenance trial, DUO-O, were recently presented.[161] The three-arm phase III trial randomized patients with advanced ovarian cancer without somatic or germline *BRCA* mutation but stratified by HRD/HRP. Patients in arm 1 received carboplatin/paclitaxel plus bevacizumab followed by bevacizumab maintenance. Patients in arm 2 received carboplatin/paclitaxel plus durvalumab plus bevacizumab followed by durvalumab plus bevacizumab maintenance. Patients in arm 3 received carboplatin/paclitaxel plus durvalumab plus bevacizumab followed by durvalumab plus bevacizumab plus olaparib maintenance. An improvement in median PFS was seen between arm 3 and arm 1: in HRD patients 45.1 versus 23.3 months (HR 0.46, 95% CI 0.33–0.65), in the intention-to-treat population 25.1 versus 19.3 months (HR 0.63, 95% CI 0.52–0.76),[162] and in the HRP patients 20.9 versus 17.4 months (HR 0.69, 95% CI 0.54–0.86). Similar to the PAOLA trial, DUO-O did not include olaparib monotherapy, making it difficult to ascertain the contributions of the maintenance therapy components.

All PARP inhibitors are associated with mainly low-grade adverse effects, such as nausea, fatigue, and myelosuppression (anemia can be caused by all, neutropenia and thrombocytopenia mainly by niraparib), which can mostly be managed with dose reductions and interruptions.

There is also good evidence to support the role of PARP inhibitors as maintenance therapy after response to chemotherapy in patients with recurrent platinum-sensitive ovarian cancer.[163–167] Patients with *BRCA* mutations (both germline and somatic) appear to have the greatest benefit.

6.6 | Immune checkpoint inhibitors (ICIs)

There may be a role for ICIs in the first-line setting in combination with chemotherapy as well as in maintenance either alone or in combination with a PARP inhibitor or angiogenesis inhibitor. Several trials have addressed or are addressing these important questions. JAVELIN100, the first trial to be reported, was a negative trial.[168] This was a randomized, open-label, phase 3 trial that evaluated avelumab in combination with and/or after chemotherapy versus chemotherapy alone in 998 patients with previously untreated epithelial ovarian cancer.

PFS was not improved versus control, prespecified futility boundaries were crossed, and the trial was stopped. The IMagyn500 trial investigated the role of atezolizumab in 1300 patients with recently diagnosed advanced-stage ovarian cancer and was also a negative trial with no difference in PFS between the two arms.

Despite the strong theoretical rationale for combining and ICIs with a PARP inhibitor, the ATHENA-COMBO trial investigating nivolumab and rucaparib versus rucaparib and placebo was a negative trial.[169] Furthermore, it is challenging to interpret the results of DUO-O as the combination of olaparib and durvalumab and bevacizumab was superior to the control of bevacizumab as well as the bevacizumab and durvalumab arm. Ideally, there should have been an arm with a PARP inhibitor with bevacizumab. Instead, the contribution of ICI to olaparib and bevacizumab cannot be determined (see above[162]). Time will tell whether there is a role for ICIs in the first-line treatment of patients with ovarian cancer or whether it is possible to identify a subset who are most likely to derive benefit. However, it seems unlikely that there will be a significant benefit with PD1/PD-L1 inhibitors based on the negative trials reported to date. It is possible that the dual immune checkpoint blockade will be more active (see the "Immunotherapy in recurrent ovarian cancer" section below).

7 | SECONDARY SURGERY

7.1 | Second-look laparotomy

A second-look laparotomy (or laparoscopy) was previously performed in patients who have no clinical evidence of disease after completion of first-line chemotherapy to determine response to treatment. Although of prognostic value, it has not been shown to influence survival and is no longer recommended as part of the standard of care[170] (Level of Evidence: C).

7.2 | Secondary cytoreduction

Secondary cytoreduction is defined as an attempt at cytoreductive surgery at some stage after completion of first-line chemotherapy. Retrospective studies suggest that patients benefit if all macroscopic disease can be removed, which usually means patients with a solitary recurrence. Patients with a disease-free interval longer than 12–24 months and those with only 1–2 sites of disease appear to derive most benefit.[171,172] The role of secondary cytoreductive surgery is being evaluated in randomized clinical trials. The role of secondary debulking surgery has been addressed in the DESKTOP III trial.[173] That study included patients with a PFS longer than 6 months after first-line chemotherapy and who were considered to be good candidates for surgery based on a positive AGO Study Group score, defined as an ECOG performance status score of zero, ascites of 500 mL or less, and complete resection at initial surgery. Harter et al.[173] reported that the median PFS in 206 women who met these criteria and who were randomized to undergo surgery followed by chemotherapy was 18.4 months, compared with 14 months in 201 women who were randomized to receive only second-line chemotherapy. Median PFS overall was 18.4 versus 14 months, and 21.1 (with complete cytoreduction) versus 13.7 months (with residual disease) versus 14 months (with chemotherapy only). Median OS showed an OS benefit of more than 12 months for patients undergoing complete secondary cytoreduction (61.9 vs. 46 months). OS for patients who underwent surgery and were only incompletely cytoreduced was only 28 months, stressing the importance of complete cytoreduction. Results of the GOG 213 trial, however, showed no statistically significant difference in PFS, with 18.9 versus 16.2 months and OS with 50.6 versus 64.7 months (with vs. without secondary cytoreduction).[174] In view of these two trials, secondary cytoreduction can be considered a safe option for carefully selected patients. In contrast, the GOG 213 trial did not demonstrate a survival advantage with secondary debulking surgery. The trial randomized 240 patients to secondary cytoreduction before chemotherapy and 245 to platinum-based chemotherapy and bevacizumab. The HR for disease progression or death (surgery vs. no surgery) was 0.82 (95% CI 0.66–1.01; median PFS 18.9 and 16.2 months, respectively). The phase III SOC-1 trial,[175] which randomized 357 patients with recurrent platinum-sensitive disease to chemotherapy versus secondary debulking followed by chemotherapy, reported an improvement in PFS (17.4 vs. 11.9 months), but no significant advantage in OS (58.1 vs. 52.1 months; HR 0.8, 95% CI 0.61–1.05).[176] There is likely a role for secondary cytoreductive surgery, although patient selection is critical as outcomes are likely to be better in patients with a long treatment-free interval, with a limited number of sites of disease and in whom complete resection is possible with macroscopic residual disease. Surgery is unlikely to be of benefit if there is evidence of ascites and carcinomatosis and in patients with poor performance status (Level of Evidence: B).

8 | FOLLOW-UP FOR MALIGNANT EPITHELIAL TUMORS

There is no evidence to show that intensive clinical monitoring during follow-up after completion of primary surgery and chemotherapy with early initiation of chemotherapy in asymptomatic women with recurrent disease improves OS or quality of life. In asymptomatic patients with CA125 progression and small volume disease or no radiological evidence of recurrence, it is appropriate to delay starting chemotherapy. However, there may be a subset of patients who are suitable for secondary debulking surgery at the time of recurrence.

The objectives of follow-up include the following: early recognition and prompt management of treatment-related complications, including provision of psychological support; early detection of symptoms or signs of recurrent disease; collection of data regarding the efficacy of any treatment and the complications associated with those treatments in patients treated in clinical trials; promotion of healthy behavior, including screening for breast cancer in patients with early-stage disease, and screening for cervical cancer in patients undergoing conservative surgery.

There are no evidence-based guidelines regarding the appropriate follow-up schedule. During the first year after treatment, patients are seen every 3 months with a gradual increase in intervals to every 4–6 months after 2 years and then annually after the fifth year. At each follow-up, the patient should have her history retaken, including any change in family history of cancer and attention to any symptoms that could suggest recurrence; a physical and pelvic examination should also be performed. This is an opportunity to refer appropriate patients for genetic testing if it was not done at diagnosis or during treatment. CA125 has traditionally been checked at regular intervals, but there has been debate regarding the clinical benefit of using CA125 progression alone as a trigger for initiating second-line chemotherapy. A large MRC OV05-EORTC 55955 study showed that treating asymptomatic patients with recurrent ovarian cancer with chemotherapy on the basis of CA125 progression alone did not improve survival. It also showed that early treatment in asymptomatic patients had a negative impact on quality of life.[177] That study has generated considerable debate regarding the use of CA125 for follow-up, but most agree that it is reasonable not to immediately initiate treatment unless there is a clear clinical indication to do so. However, it is worth reflecting on the fact that this trial was conducted in an era where there were limited treatment options for patients with recurrent ovarian cancer beyond re-introduction of platinum-based chemotherapy, which is very different today. Furthermore, this study was carried out well before PARP inhibitors were available and there are many more options available at recurrence, including multiple clinical trials. It seems timely to question the timing of treatment at recurrence. The timing of treatment should be based on symptoms, clinical and radiological findings, and the platinum-free interval and with input from patients. Guidelines suggest that imaging tests, such as ultrasonography of the pelvis, CT, MRI, and/or PET scans, should be performed only when the clinical findings or the tumor markers suggest possible recurrence. This has been challenged recently by findings in patients with platinum-sensitive recurrent ovarian cancer receiving maintenance therapy with a PARP inhibitor, where almost half of those with RECIST-defined progressive disease did not exhibit CA125 progression. This raises important questions about the adequacy of relying solely on CA125 for surveillance and suggests the imaging should be incorporated, particularly for patients on maintenance therapy.[178]

9 | CHEMOTHERAPY FOR RECURRENT EPITHELIAL CANCER OF THE OVARY, FALLOPIAN TUBE, AND PERITONEUM

The majority of patients who present with advanced epithelial cancers of the ovary, fallopian tube, and peritoneum will relapse with a median time to recurrence of 16 months. Patients with recurrent ovarian cancer constitute a heterogeneous group with a variable prognosis and a variable response to further treatment. The most widely used clinical surrogate for predicting response to subsequent chemotherapy and prognosis has been the progression-free interval or the "platinum-free interval," which is defined as the time from cessation of primary platinum-based chemotherapy to disease recurrence or progression.[179,180] This has been useful to define specific patient populations; however, it has several limitations and depends on how patients are followed. In particular, it depends on how recurrence is detected and defined. Patients with a treatment-free interval of less than 6 months are classified as platinum resistant and generally treated with non-platinum–based chemotherapy, while those with a treatment-free interval of more than 6 months are considered to be platinum sensitive and are commonly treated with platinum-based chemotherapy. Patients who progress while on treatment or within 4 weeks of stopping chemotherapy are classified as platinum refractory.[179,180]

There have been modifications to these definitions, and time to progression or recurrence rather than treatment-free interval or platinum-free interval has been used to define specific patient populations. There has been significant change in practice over the last 20 years and patients have been routinely followed with regular CA125 testing after completion of chemotherapy. For example, the "platinum-resistant" subgroup may include asymptomatic patients with CA125 progression alone at 3 months after chemotherapy or radiological evidence of recurrence as well as those who are symptomatic with clinical recurrence. The Fourth Ovarian Cancer Consensus Conference reached agreement that distinct patient populations should be based on the interval from last platinum therapy and the time to progression. The progression-free interval is defined from the last date of platinum dose until progressive disease is documented.[179,180] More recently, ESMO-ESGO guidelines have moved away from the terms "platinum resistant" or "platinum sensitive" and now categorize patients as having platinum-non-eligible ovarian cancer, which includes those who progress on or immediately after their last platinum-based chemotherapy or have contraindications to platinum. Platinum-eligible ovarian cancer includes all other cases of relapse. Despite these guidelines, most clinicians and clinical trials still use the terms "platinum sensitive" and "platinum resistant," and it will be hard to change this as it is so ingrained.[181]

For patients whose disease is considered platinum-sensitive, the ICON4 study showed an advantage in terms of OS and PFS for a combination of carboplatin and paclitaxel versus single-agent carboplatin[182] (Level of Evidence: A).

For patients with persistent neuropathy after first-line treatment with paclitaxel, gemcitabine[183] or pegylated liposomal doxorubicin[184] may be substituted for paclitaxel. A large GCIG study (CALYPSO) compared carboplatin (AUC 5) and pegylated liposomal doxorubicin (30 mg/m^2) every 4 weeks (CD) with carboplatin and paclitaxel (CP) in 976 patients.[185] The CD arm had statistically superior PFS compared with the CP arm, with a median PFS of 11.3 versus 9.4 months, respectively. There was no significant difference in the OS between the treatment groups. The median OS was 33 versus 30.7 months for the CP and CD arms, respectively. The CD arm was better tolerated, with less severe toxicities, and this combination is now widely used (Level of Evidence: A).

There is evidence that the addition of bevacizumab to the regimen of carboplatin and gemcitabine improves PFS compared with carboplatin and gemcitabine in platinum-sensitive disease. In the OCEANS study,[186] 484 patients with platinum-sensitive disease were randomly assigned to carboplatin (AUC 4 on day 1) and gemcitabine 1000 mg/m^2 on days 1 and 8 with or without bevacizumab (15 mg/kg on day 1) every 21-day cycles. Bevacizumab could be given concurrently with chemotherapy for a maximum of 10 cycles followed by bevacizumab alone until progression of the disease or toxicity. The addition of bevacizumab to carboplatin and gemcitabine resulted in an improvement in PFS (12 vs. 8 months; HR 0.48, 95% CI 0.39–0.61); however, there was no difference in OS between the two arms. Treatment with bevacizumab was associated with higher rates of serious hypertension (17% vs. <1%), proteinuria grade 3 or higher (9% vs. 1%), and non-central nervous system bleeding (6% vs. 1%).[186] The OV21 trial randomized 682 patients with platinum-sensitive recurrent ovarian cancer to six intravenous cycles of bevacizumab (15 mg/kg, day 1) plus carboplatin (AUC 4, day 1) plus gemcitabine (1000 mg/m^2, days 1 and 8) every 3 weeks (standard group) or six cycles of bevacizumab (10 mg/kg, days 1 and 15) plus carboplatin (AUC 5, day 1) plus pegylated liposomal doxorubicin (30 mg/m^2, day 1) every 4 weeks (experimental group), both followed by maintenance bevacizumab (15 mg/kg every 3 weeks in both groups) until disease progression or unacceptable toxicity. The median PFS was 13.3 months (95% CI 11.7–14.2) in the experimental group versus 11.6 months (95% CI 11.0–12.7) in the standard group (HR 0.81, 95% CI 0.68–0.96; $P = 0.012$).[187] The results of this trial support the experimental regimen in clinical practice.

Furthermore, there is evidence that the addition of bevacizumab to carboplatin and pegylated liposomal doxorubicin shows an improved PFS compared to carboplatin plus gemcitabine and bevacizumab in platinum-sensitive disease.[187] The median PFS in this phase trial of 682 patients with a first recurrence was noted to be 13.3 versus 11.6 months. The phase III trial MITO16B-MaNGO OV2B-ENGOT OV17 provided evidence in platinum-sensitive disease that the re-challenge with bevacizumab in combination with platinum-doublets is associated with a prolonged PFS (8.8 vs. 11.8 months without and with bevacizumab).[188]

There is a role for angiogenesis inhibitors in platinum-resistant ovarian cancer. In the AURELIA trial, women with recurrent platinum-resistant ovarian cancer were randomized to standard of care, i.e., weekly topotecan, weekly paclitaxel, or monthly liposomal doxorubicin versus these agents combined with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks).[189] Patients in the experimental arm had a longer PFS of 6.7 versus 3.4 months and a higher overall response rate of 30.9% versus 12.6%. An exploratory subgroup analysis noted an increase in OS for weekly paclitaxel plus bevacizumab from 13.4 to 22.4 months (with and without bevacizumab).[190] The findings in the AURELIA trial changed the standard of care, although there are now other options with antibody-drug conjugates (ADCs), which are discussed below.

9.1 | ICIs in recurrent ovarian cancer

There has been a lot of interest in exploring the role of ICIs in patients with recurrent ovarian cancer, including those with platinum resistance. However, the general results of these studies have been disappointing, with low response rates reported. For example, KEYNOTE-100 evaluated pembrolizumab, an anti-PD-1 antibody, in patients with recurrent ovarian cancer after multiple prior lines.[191] The overall response rate was 8%, with a combined positive score (quantifying the number of PD-L1 positive cells) over 10 and the objective response rate (ORR) was in the range of 11%–18%. Similarly, the response rate with avelumab, an anti-PD-L1 antibody, was 10% in recurrent ovarian cancer.[192] However, there may be a role for combination regimens, which are being explored. For example, the phase I/II TOPACIO trial using niraparib and pembrolizumab in recurrent platinum-resistant ovarian cancer showed a response rate of 18%.[193] The combination of the CTLA-4 antibody ipilimumab with nivolumab, an anti-PD-1 antibody induction followed by nivolumab maintenance had an ORR of 31.4% compared to 12.2% with nivolumab alone in a recently reported randomized phase 2 trial.[194] Although the median PFS was longer with combination, it was only 3.9 versus 2 months and the benefit questionable given the increased toxicity. In the BrUOG phase II on ovarian and extrarenal clear cell cancers, the combination of 240 mg nivolumab every 2 weeks and 1 mg/kg ipilimumab every 6 weeks, an ORR of 33%, PFS of 5.6 months, and an OS of 24.6 months for the combination treatment were reported.[195]

The multicohort Leap-005 trial recently reported preliminary data on another combination treatment using pembrolizumab and the multi-tyrosine kinase inhibitor lenvatinib. In 31 patients with recurrent ovarian cancer, the response rate was 32% and the disease control rate 74%.[196] Another phase II trial reported on the combination of pembrolizumab, bevazicumab, and oral metronomic cyclophosphamide (50 mg daily) in 30 patients with platinum-resistant and 10 patients with platinum-sensitive disease. A response rate of 47.5% and stable disease in 47.5% were noted.[197] There are still more trials in progress and these are likely to read out over the next few years. It will take time to define the role of ICIs in patients with recurrent ovarian cancer, but it seems likely that only a small subset benefits and the challenge is to identify who these patients are.

9.2 | Antibody-drug conjugates

ADCs are a class of anticancer drugs that employs the specificity of an antibody in combination with the cytotoxicity of a small molecule anticancer drug. The antibody provides selectivity. The cells take up the ADC by endocytosis. The cytotoxic drug, the payload, is released in intracellular compartments such as endosomes or lysosomes. The linker can be cleavable, e.g. by cathepsins that are located in lysosomes and activated by the low pH in lysosomes, or it can be non-cleavable. In the latter case, the antibody will be

degraded intracellularly and only the cytotoxic agents remain and thereby become active. In the former case, the cytotoxic agent may evade the cell and kill tumor cells nearby as well, the so-called "bystander killing".[198,199]

Mirvetuximab soravtansine (IMGN853) is an ADC combining a monoclonal antibody against folate receptor α (FRα) with the maytansinoid DM4.[200] Maytansine inhibits microtubule assembly, induces mitotic arrest and is thereby cytotoxic. After a promising dose-escalation study on single-agent mirvetuximab,[201] a phase Ib trial of mirvetuximab soravtansine (MIRV, 6 mg/kg adjusted ideal body weight every 3 weeks) combined with bevacizumab in platinum-resistant ovarian cancer showed that this combination was well tolerated and effective. The ORR was 39% (including 5 complete and 21 partial responses) and the median PFS was 6.9 months.[202]

In the Forward I phase III trial, 366 patients with platinum-resistant disease, 1–3 prior lines, and tumors positive for FRα were randomized 2:1 to 6 mg/kg MIRV versus standard chemotherapy. Overall, no difference in PFS was noted (4.1 vs. 4.4 months). The treatment was well tolerated with grade 3 adverse events in 25.1% versus 44%. In the high FRα subgroup, an improved ORR of 24% versus 10%, a CA125 of 53% versus 25%, and an improved PFS of 4.8 versus 3.3 months was noted.[203] In the single-arm Soraya trial, 106 patients with FRα-high platinum-resistant ovarian cancer and prior bevacizumab use received MIRV. Using the Ventana FOLR1 assay, at least 75% of viable tumor cells should exhibit at least 2+ level membrane staining by immunohistochemistry (IHC). Furthermore, an exploratory analysis of patient samples from the Forward I trial showed that using this PS2+ scoring was more reliable than the 10x scoring used in the Forward I trial. An ORR of 32.4%, including 5 complete and 29 partial responses, was seen.[204] In the phase III Mirasol trial, 453 patients with FRα-high (≥75% of cells with +2 staining) platinum-resistant ovarian cancer were randomized to MIRV or investigator's choice chemotherapy. The ORR was 42.3% versus 15.9%, the median PFS was 5.6 versus 3.98 months ($P < 0.001$), and, most notably, the OS was significantly longer with MIRV (16.46 vs. 12.75 months, HR for death 0.67, 95% CI 0.5–0.89). In addition, fewer grade 3 or higher adverse events were noted (41.7% vs. 54.1%).[205]

In April 2024, the FDA granted accelerated approval for trastuzumab deruxtecan in Her2-positive (IHC 3+) solid tumors with no treatment alternatives, which included ovarian cancer. Trastuzumab deruxtecan targets Her2 expression cells and carries the topoisomerase inhibitor I as payload. The FDA approval is based on the phase II cohort study Pan-Destiny02, which included a cohort of 40 patients with ovarian cancer. This trial showed an ORR of 45%, a median PFS of 11.1 months, and a median OS of 13.2 months in the ovarian cancer cohort.[206]

Data on another ADC, datopotamab deruxtecan, was recently presented at ESMO 2024.[207] This ADC targets the surface protein Trop2 (trophoblast cell surface antigen 2), which has been associated with accelerated tumor growth and poor prognosis in solid tumors, including breast, gastric, lung and gynecological cancers. In the 26 patients with platinum-resistant ovarian cancers, an ORR of 34.6%, a disease control rate (DCR) of 80.8%, and a median duration of response (DoR) of 5.6 months were noted.

9.3 | PARP inhibitors as monotherapy in patients with recurrent ovarian cancer

The initial approval of the PARP inhibitors for late-line treatment was based on the following studies: study 42 for olaparib,[208] the QUADRA study for niraparib,[209] and an integrated analysis of data from study 10 part 2A and Ariel 2 parts 1 and 2 for rucaparib.[210] At the final OS analysis of the Ariel 4 trial, a possible detriment in OS was seen for rucaparib (median OS 19.4 vs. 25.4 months in the intention-to-treat population, and 14.2 vs. 22.2 months in the platinum-resistant group).[211] A post-hoc analysis of SOLO3 found a potential detriment for olaparib in patients who had received three or more prior lines.[212] Neither Ariel 4 nor SOLO3 were powered to assess between-group differences in OS. These trial results lead to "Dear Health Care Provider Letters" in June 2022, and for rucaparib and olaparib in August 2022. Based on the totality of data and the single-arm nature of the QUADRA trial, which prevents assessment of OS data, a letter for niraparib followed in September 2022. Subsequently, these PARP inhibitors were voluntarily withdrawn by the pharmaceutical companies for the single-agent PARP-inhibitor late-line treatment.[213]

With few exceptions, recurrent disease is not curable and the aim of treatment is to maintain quality of life and palliate symptoms, particularly in patients with platinum-resistant ovarian cancer.[214] There are many potential treatment options, including chemotherapy, angiogenesis inhibitors, radiation therapy, or surgery in selected patients and inclusion in clinical trials. There is a subset of patients who may benefit from secondary surgical debulking.

The optimal management of a patient with platinum-resistant or refractory disease is complex and requires a careful assessment of the patient's performance status, symptoms, and extent of disease. Attention to symptom control and good palliative care are essential components of management.

10 | ONGOING TRANSLATIONAL RESEARCH

Between 2006 and 2012, TCGA collected data on 12 different types of cancers with the goal of comparing the complete cancer genomes with the normal human genome and identifying characteristic and common genetic abnormalities in human cancers.[215,216] TCGA showed that approximately half of the analyzed high-grade ovarian cancers had defects in the double-strand DNA homologous repair (HR) pathway.[217] TCGA described four subtypes, which, in contrast to the findings of the TCGA for endometrial cancer, have not been shown to be of prognostic or therapeutic value. Ongoing efforts are focused on characterizing tumor heterogeneity[218] and

tumor microenvironment.[219] The new class of ADCs (see above) directed against specific surface molecules, such as FOLR1, Her2, and Trop2, are recent examples of the successful application of precision oncology in ovarian cancer. Biobanking of ovarian cancer tissue and patient blood samples has been established in several national and international institutions.[220–222] Multiple efforts to improve the experimental in vitro model systems are on the way, including ascites-derived spheroids and 3D culturing in patient-derived organoids.[223,224]

11 | MANAGEMENT OF LOW-GRADE SEROUS CANCERS

LGSCs comprise 5%–10% of serous ovarian cancers and up to 8% of all ovarian cancers.[225] They are typically diagnosed at a younger age than in women with HGSCs, with a median age of 47–54 years at diagnosis, and are characterized by a relatively indolent behavior and resistance to cytotoxic chemotherapy.[226] In contrast to HGSCs, they do not have *TP53* mutations, but may have *KRAS* or *BRAF* mutations, as well as activation of the Ras–Raf–MEK–ERK signaling pathway.[227,228]

Most patients with LGSCs have advanced-stage disease at initial diagnosis and the surgical management is similar to that in patients with high-grade cancers, with attempts at total resection of tumor—with the exception of fertility-sparing surgery in younger women with tumors confined to the ovary. Platinum-based NACT for advanced-stage LGSC was associated with a radiological response rate of 4%, which is much lower than response rates of up to 80% in patients with HGSCs.[229] Similarly, the response rates to chemotherapy have been reported to be low in several studies and the rate was only 3.7% (4.9% in patients with "platinum-sensitive disease" and 2.1% in those with "platinum-resistant disease") in a report of patients with recurrent LGSC.[226] It is now accepted that the terms "platinum sensitive" and "platinum resistant" do not apply to LGSCs. A retrospective, exploratory, case–control analysis of over 5000 patients receiving adjuvant chemotherapy in clinical trials included 145 (2.8%) patients with LGSC, of whom 37 had suboptimal debulking and were evaluable for response evaluation.[230] The response rate was higher than in other studies, at 23.1% in this small subset of patients with LGSCs compared with 90.1% in patients with HGSCs.

The majority of LGSCs are ER-positive, and endocrine therapy has long been employed in the treatment of recurrent and metastatic LGSCs. Although clinical benefit has been reported, the supporting evidence has historically been limited to retrospective studies until more recently. For example, endocrine therapy was reported to have a response rate of 9% in a retrospective analysis of 64 patients with recurrent LGSC.[231] The PARAGON trial was the first prospective trial of endocrine therapy in LGSCs. A total of 36 patients were enrolled. Clinical benefit at 3 months (primary endpoint) was observed in 23 patients (64%, 95% CI 48–78) and was similar at 6 months (61%, 95% CI 43–75). The median duration of clinical benefit was 9.5 months (95% CI 8.3–25.8).[232] The response rate by RECIST was 14%, stable disease in 50%, and progressive disease in 36%. Median PFS was 11.1 months (95% CI 3.2–11.9). The ORR was identical to the response rate reported for letrozole in 44 patients who received endocrine therapy in the control arm with physician choice of treatment in the GOG281/LOGS trial of trametinib versus physicians' choice and which is discussed below. It should be noted that there were no responses observed with tamoxifen (0/27). There have also been reports of maintenance therapy with endocrine therapy in LGSCs after surgery alone or after adjuvant chemotherapy. For example, in 26 patients with LGSCs of the ovary or peritoneum, adjuvant hormone therapy after debulking surgery was associated with a median PFS of 22 months and a recurrence rate of 14.8%.[233] In this small study, survival of the patients treated with adjuvant hormonal therapy was not significantly different to an age- and stage-matched control group of patients with LGSC treated with surgery and adjuvant chemotherapy. A retrospective analysis was reported of 203 patients with LGSC of the ovary or peritoneum who received either maintenance/adjuvant endocrine therapy or observation, based on physician discretion, after primary cytoreductive surgery and platinum-based chemotherapy.[234] Patients who received adjuvant endocrine therapy had significantly longer median PFS (64.9 vs. 26.4 months) compared with the patients in the observation group, without significant prolongation of OS (115.7 vs. 102.7 months). The role of maintenance/adjuvant endocrine therapy in patients with LGSC is being tested in a large phase III NRG trial (NRG-GY019, NCT04095364), which is currently recruiting.

There are also studies investigating the addition of CDK4/6 inhibitors to aromatase inhibitors in LGSCs. The preliminary data of GOG 3026 were presented recently. In this single-arm trial, 51 patients with recurrent LGSCs received 600 mg of the CDK4/6 inhibitor ribociclib for 3 weeks on, 1 week off, and letrozole 1 mg/day for a 28-day cycle until disease progression. The ORR was 23% (all partial responses) and the clinical benefit rate 79%. The median duration of response was 19.1 months.[235]

Bevacizumab appears to be an active agent in LGSC, with retrospective studies suggesting a response rate of 40%. A systematic review that included 153 patients with LGSCs treated with bevacizumab reported an overall response rate of 47%, highlighting the need for further evaluation in prospective clinical trials.[236]

LGSCs commonly show mutations in the MAP kinase pathway, particularly in BRAF, KRAS, and NRAS. In view of this, there have been several studies exploring targeted therapy with MEK inhibitors (MEKi). In a GOG phase II trial (GOG 0239) of the MEKi selumetinib in 52 women with recurrent LGSC, the overall response rate was 15%, with one complete response and seven partial responses and 65% of patients having stable disease.[237] The median PFS was 11.0 months. The MILO trial was an open-label phase III trial that randomized patients with recurrent LGSCs to either chemotherapy (physician's choice of pegylated liposomal doxorubicin, paclitaxel, or topotecan) or MEK162 (binimetinib). This trial was stopped after a planned interim analysis showed that the hazard ratio for PFS crossed the predefined futility boundary.[238] The median PFS was 9.1 months (95% CI 7.3–11.3) for binimetinib and

10.6 months (95% CI 9.2–14.5) for chemotherapy (HR 1.21, 95% CI 0.79–1.86), resulting in early study closure after 341 patients had enrolled. Secondary efficacy end points were similar in the two groups: overall response rate 16% versus 13% and median OS 25.3 versus 20.8 months for binimetinib and chemotherapy, respectively. More recently, a randomized trial (NRG-GOG 0281) of the MEK inhibitor trametinib versus chemotherapy reported an improved ORR of 26.2% versus 6.2% in recurrent LGSC of trametinib compared to standard chemotherapy. In addition, the median PFS increased from 7.2 months with chemotherapy to 13 months with trametinib. OS was also increased although this was not statistically significant.[239] The observed treatment effect was seen in mutation-positive and -negative patients although the response rates were higher in patients with *KRAS*, *NRAS*, or *BRAF* mutations (50% vs. 8.3% of patients whose tumors lacked these mutations). It should be noted that that MEK inhibitors are associated with several adverse effects and that 36% of patients discontinued treatment because of toxicity. This remains an area of active investigation and there are data showing that a combination of avutometinib, a RAS/RAF inhibitor, in combination with defactinib, a FAK inhibitor, is active in LGSC with an ORR of 45% and 60% in patients with *KRAS* mutations. This combination is being compared to the physician's choice of treatment in a prospective phase 3 trial (GOG 0397/ENGOT-ov 81/RAMP301).[240] There are many outstanding questions that are under investigation, including which patients with MAP kinase mutations benefit from MEK inhibitors and whether the site of the activation mutation is important. Furthermore, there is evidence that NOTCH signaling may lead to resistance. It is possible that NOTCH inhibitors may have a role. Finally, 45% of LGSCs exhibit high expression of FRα, and ADCs targeting are currently under investigation in clinical trials.[241]

Follow-up of patients with no evidence of disease is the same as for those with malignant epithelial carcinomas. In a recent consensus, conference panelists agreed that clinicians should follow the NCCN guidelines, but CT scans of the chest, abdomen, and pelvis should be incorporated into surveillance rather than rely on CA125 alone. The majority preferred CT to PET/CT. In patients who have had fertility preservation, ultrasound of the remaining ovary is also indicated. In patients on aromatase inhibitors, bone mineral density should be monitored[242] (Level of Evidence: C).

11.1 | Management of low malignant potential (borderline) tumors

Compared with invasive epithelial cancers, borderline tumors tend to affect a younger population and constitute 15% of all epithelial tumors of the ovary.[243] Nearly 75% of these are Stage I at the time of diagnosis. The following can be said for these tumors:[244]

- The diagnosis must be based on the pathology of the primary tumor
- Extensive sectioning of the tumor is necessary to rule out invasive cancer
- The prognosis of these tumors is extremely good, with a 10-year survival of approximately 95%
- Invasive cancers that arise in borderline tumors are often indolent and have a low response to platinum-based chemotherapy
- Spontaneous regression of peritoneal implants has been observed
- Early stage, serous histology, and younger age at diagnosis are associated with a more favorable prognosis
- Although gross residual disease after primary laparotomy is associated with poorer prognosis, mortality from the disease remains low
- Those patients who have invasive implants in the omentum or other distant sites are more likely to recur earlier. Some centers consider invasive implants to be LGSC. The WHO nomenclature was changed in 2014 accordingly.[24] The classification of serous borderline tumors with invasive implants, however, remains controversial.[242] ESGO considers it premature to define serous borderline tumors with invasive implants as LGSCs.[181] Further research on the biology and clinical significance of invasive implants is needed
- Chemotherapy has not been shown to be beneficial in borderline tumors.

Causes of death include complications of disease (e.g. small bowel obstruction) or complications of therapy, and only rarely malignant transformation. The mainstay of treatment is primary surgical staging and cytoreduction. For patients with Stage I disease who want to preserve fertility, conservative surgery via unilateral salpingo-oophorectomy can be considered after intraoperative inspection of the contralateral ovary to exclude involvement.[245] For patients with only one ovary, or bilateral cystic ovaries, a partial oophorectomy or cystectomy can be considered for fertility preservation. For all other patients, total hysterectomy and bilateral salpingo-oophorectomy are recommended, with maximal cytoreduction if the disease is metastatic.

Patients with borderline tumors in all stages of disease should be treated with surgery. The response to chemotherapy is low. Uncommonly, some patients recur early and have higher-grade invasive cancers and may possibly benefit from chemotherapy.[246]

In patients with late recurrence of the disease, secondary cytoreduction should be considered. Follow-up of patients with no evidence of disease is the same as for those with malignant epithelial carcinomas, but at less frequent intervals. If the contralateral ovary has been retained, it should be followed by TVS, at least on an annual basis[1,244,247] (Level of Evidence: C).

12 | MANAGEMENT OF GRANULOSA CELL TUMORS

In general, sex-cord stromal tumors can be classified as follows: (1) pure stromal tumors that include fibromas and thecomas, (2) pure sex-cord

tumors that include adult and juvenile granulosa cell tumors, and (3) mixed sex-cord stromal tumors, including Sertoli-Leydig cell tumors. Granulosa cell tumors account for approximately 70% of sex-cord stromal tumors and 3%–5% of all ovarian neoplasms.[2] There are two types of granulosa cell tumors: juvenile and adult. Because of the high estrogen production, the juvenile type typically presents with sexual precocity, while the adult type may present with postmenopausal bleeding. The majority of patients are diagnosed with Stage I tumors. The peak incidence is in the first postmenopausal decade.[2,248]

Granulosa cell tumors are generally indolent (i.e., with a tendency to late recurrence). Stage at diagnosis is the most important prognostic factor. Other prognostic factors include age at diagnosis, tumor size, and histologic features. If metastatic, adequate cytoreduction is the mainstay of treatment. If the patient is young and the disease is confined to one ovary, conservative surgery should be performed.[249,250]

The infrequency of the disease, and its protracted course, has resulted in a lack of prospective studies. There is no evidence that adjuvant chemotherapy or radiotherapy improves the results of surgery alone for Stage I disease. The value of postoperative adjuvant chemotherapy for higher-risk Stage I disease (tumor size >10 cm, capsule rupture, high mitotic count) is uncertain and has not been tested in randomized studies. Platinum-based chemotherapy is used for patients with advanced or recurrent disease, with an overall response rate of 63%–80%.[250–252] Bleomycin/etoposide/cisplatin (BEP) has been widely used to treat patients with metastatic granulosa cell tumor (GCT); however, there is significantly increased toxicity of bleomycin in patients aged over 40 years. There were several deaths associated with bleomycin in early GOG trials, which led to them to reduce the bleomycin dose to 20 units/m^2 IV every 3 weeks (×4) to reduce toxicity.[253] Carboplatin and paclitaxel appear to have a similar response rate and less toxicity than BEP.[252] The non-inferiority phase II trial GOG-0264 (NCT01042522) randomized patients with recurrent/metastatic GCTs to paclitaxel 175 mg/m^2 plus carboplatin AUC 6 for six cycles every 3 weeks (PC) versus BEP for four cycles (bleomycin 20 units/m^2 IV push on day 1, etoposide 75 mg/m^2 on days 1–5, and cisplatin 20 mg/m^2 on days 1–5 every 3 weeks). The trial was stopped early since the PC arm met futility criteria. The futility analysis was supported by an estimated HR of 1.11 (95% CI 0.57–2.13), which exceeded the predetermined threshold for non-inferiority (1.10). The median PFS was 27.7 versus 19.7 months (PC vs. BEP). PC patients had fewer grade 3 or higher adverse events (PC 77% vs. BEP 90%). Only 23 patients had measurable disease, with an ORR of 50% (5/12) with BEP and 18% (2/11) with PC. The confidence intervals are wide and there was no statistical difference between the two regimens. The authors concluded that both regimens can be considered recurrent/metastatic GCTs.[254]

Bevacizumab has also been reported to have single-agent activity, with a response rate of 16% in 36 patients with GCTs and measurable disease.[255] ALIENOR/ENGOT-ov7 is a randomized phase 2 trial that compared weekly paclitaxel with weekly paclitaxel in combination with bevacizumab in 60 patients with relapsed GCTs. The overall response rate increased with the addition of bevacizumab (25% with weekly paclitaxel vs. 44% with the combination), but there was no statistical difference in the primary endpoint: PFS at 6 months was 71% (95% CI 55–84) and 72% (95% CI 55–87) in the weekly paclitaxel and weekly paclitaxel with bevacizumab arms, respectively.[256]

Hormonal therapies have also been widely used to treat patients with recurring GCTs. A systematic review of retrospective studies involving 31 patients reported an overall response rate of 71%.[257] In a single-center retrospective series of 15 patients treated with letrozole, the partial response rate was 41%, with a median PFS of over 20 months. In contrast, another retrospective study of 22 patients with evaluable disease reported a lower response rate of 18%, although 64% achieved stable disease with aromatase inhibitor therapy.[258] The PARAGON trial remains the only prospective study, reporting a 10.5% partial response rate with anastrozole and a high proportion of patients achieving stable disease.[259] It remains unclear whether the stable disease is attributable to therapy or the indolent nature of GCTs.

There are significant variations in follow-up recommendations for surveillance. GCIG Guidelines advise regular review including clinical history for symptoms, physical examination with pelvic examination, and tumor markers (inhibin) every 4 months for the first 2 years, every 6 months during years 3–5, or until progression. They also make the point that some advise prolonged follow-up for 10 or 15 years. They recommend pelvic ultrasound every 6 months for patients who have undergone fertility-sparing surgery with CT scans of the abdomen and pelvis every year. For patients with elevated levels of inhibin B and/or anti-Müllerian hormone (AMH) at the initial diagnosis of granulosa cell tumors, inhibin B and/or AMH appear to be reliable markers during follow-up for early detection of residual or recurrent disease.[260] There is an increased risk of breast cancer in patients with adult granulosa cell tumors and breast cancer screening should not be forgotten.

There is no evidence-based preference for inhibin B or AMH as a tumor marker.[261] Inhibin B and serum AMH have been reported to have a similar sensitivity (94% and 92%, respectively) and specificity (83% and 82%, respectively) for recurrence. Serum inhibin is a useful tumor marker in postmenopausal women. AMH is preferable to inhibin B for surveillance of premenopausal patients as levels can fluctuate during the menstrual cycle[262] (Level of Evidence: C).

13 | MANAGEMENT OF GERM CELL MALIGNANCIES

This group of ovarian tumors consists of a variety of histologically different subtypes that are all derived from the primitive germ cells of the embryonic gonad. Malignant ovarian germ cell tumors (MOGCTs) represent a relatively small proportion of all ovarian tumors. Before advances in chemotherapy, the prognosis for these aggressive tumors was poor. The use of platinum-based chemotherapeutic regimes has made germ cell malignancies among the most highly curable cancers.[248]

13.1 | Presentation

These are the most common ovarian tumors in the second and third decades of life. They are frequently diagnosed by finding a palpable abdominal mass in a young woman who complains of abdominal pain. The following are the symptoms of germ cell tumors in order of frequency:[248] acute abdominal pain, chronic abdominal pain, asymptomatic abdominal mass, abnormal vaginal bleeding, and abdominal distention.

13.2 | Histological classification

The classification of ovarian germ cell tumors is important to determine prognosis and for treatment with chemotherapy. Germ cell tumors are classified below.[2,248] Histological diagnosis may be difficult and immunohistochemical markers can be valuable and have been added here in parenthesis: dysgerminoma (OCT3/4, PLAP, D2-40, NANOG, CD117), embryonal carcinoma (OCT3/4, CD30, NANOG, SOX10), teratoma (immature, mature, mature with carcinoma [squamous cell, carcinoid, neuroectodermal, malignant struma, etc.]) (SALL4 commonly positive in all MOGCTs including immature teratomas). Extra-embryonal differentiation is as follows: non-gestational choriocarcinoma (b-hCG, inhibin), and endodermal sinus tumor (or yolk sac tumor) (AFP, glypican-2 typically; PLAP can be positive).

13.3 | Diagnosis, staging, and surgical management

Ovarian germ cell tumors are staged similarly to epithelial carcinomas, although the staging system used for male germ cell tumors is probably more useful. The approach to treatment is based on the principles of management of metastatic germ cell tumors of the testis (i.e., low, intermediate, and poor risk). Dysgerminoma is the equivalent of seminoma in testicular cancer.[263] It is exquisitely sensitive to platinum-based chemotherapy and is radiosensitive. The cure rate is high, irrespective of the stage. The other histological subtypes are equivalent to non-seminomatous testicular cancers. The aggressiveness of the disease is dependent on the type, with the most aggressive being endodermal sinus and choriocarcinoma; however, with combination chemotherapy, they are highly curable.[264–268]

As chemotherapy can cure the majority of patients, even with advanced disease, conservative surgery is standard in all stages of all germ cell tumors. Conservative surgery means laparotomy with careful examination and biopsy of all suspicious areas, with limited cytoreduction, thereby avoiding major morbidity. Fertility-sparing surgery is considered the standard of care for young patients with early-stage disease and should also be considered in advanced disease given the high chemosensitivity of the MOGCTs.[269,270] The choice of approach should be tailored to avoid rupture. Cystectomies should be avoided. The uterus and the contralateral ovary should be left intact. Wedge biopsy of a normal ovary is not recommended as it defeats the purpose of conservative therapy by potentially causing infertility. Even if both ovaries are involved, a partial oophorectomy on one side should be considered. Patients with advanced disease may benefit from 3 to 4 cycles of NACT using the BEP (platinum) regimen with preservation of fertility.[271] Patients who receive conservative surgery with the preservation of one ovary retain acceptable fertility rates despite adjuvant treatment with chemotherapy. There has been no report of higher adverse obstetric outcome or long-term unfavorable sequelae in the offspring.

Secondary surgery is of no proven benefit except in patients whose primary tumor contained teratomatous elements. Surgical resection of residual masses may be beneficial in such cases, although complete resection is not necessary if the procedure would be too invasive. Mature teratomatous nodules can continue to grow (growing teratoma syndrome) and, more rarely, may undergo malignant transformation over time into an incurable malignancy, such as squamous cell carcinoma.[272]

13.4 | Postoperative management and follow-up of dysgerminoma

Patients with Stage IA disease may be observed postoperatively. A small proportion may recur, but can be treated successfully at the time of recurrence, with a high cure rate. Patients with disease beyond the ovary should receive adjuvant chemotherapy. Although radiation therapy is effective, it is no longer used because of late effects, and chemotherapy is highly effective.

A follow-up surveillance regime for patients with Stage 1A dysgerminoma is outlined in Table 4. This schedule is based on the experience of managing seminomas in men and the reports by Dark et al.[273] and Patterson et al.[274] This pragmatic follow-up schedule has not been tested in randomized trials.

13.4.1 | Chemotherapy for dysgerminoma

Dysgerminoma is extremely sensitive to chemotherapy, and treatment with chemotherapy cures the majority of patients, even with advanced disease.[248,275] The recommended chemotherapy regimen is as follows: etoposide (E) 100 mg/m^2 IV per day for 5 days every 3 weeks for three cycles, cisplatin (P) 20 mg/m^2 IV per day for 5 days every 3 weeks for three cycles, and bleomycin (B) 30 IU IV/IM on days 1, 8, and 15 for 12 weeks (optional) (note that bleomycin is dosed in International Units). If bleomycin is omitted, then four cycles of EP are commonly used (note that various schedules of bleomycin have been used and the role of bleomycin in dysgerminomas is controversial).

In adolescent patients, other options include cisplatin, etoposide, and ifosfamide (PEI or VIP), as used in pediatric protocols. There is increased interest in the de-escalation of chemotherapy in dysgerminomas as they are so chemosensitive and it may be possible to omit bleomycin and substitute carboplatin for cisplatin due to the acute

TABLE 4 Follow-up regime for Stage I germ cell malignancies.[a]

Regimen	Description
Surveillance	Baseline CT of the chest, abdomen, and pelvis, if not performed preoperatively
	Repeat CT or MRI of the abdomen and pelvis at 3 months postoperatively
	Repeat CT or MRI of the abdomen plus pelvis at 12 months
	Pelvic ultrasound at alternate visits (when not having a CT scan) for 2 years if non-dysgerminoma and for 3 years if dysgerminoma
	Chest radiograph at alternate visits
Clinical examination	
1st year	Monthly
2nd year	2 monthly
3rd year	3 monthly
4th year	4 monthly
Years 5–10	6 monthly
Tumor marker follow-up	Samples: serum AFP and hCG, LDH and CA 125 (regardless of initial value)
0–6 months	2 weekly
7–12 months	4 weekly
12–24 months	8 weekly
24–36 months	12 weekly
36–48 months	16 weekly
48+ months	6 monthly until year 10

Abbreviations: AFP, alpha-fetoprotein; CT, computed tomography; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.

[a]Adapted from Patterson et al.[274]

adverse effects and potential long-term adverse effects associated with BEP, including secondary malignancies, cardiovascular disease, hypertension, Raynaud's phenomenon, pulmonary toxicity, nephrotoxicity, neurotoxicity, deafness, decreased fertility, and psychosocial problems among others. GOG-116 is an old trial that investigated carboplatin 400 mg/m^2 and etoposide 120 mg/m^2 on days 1–3 every 4 weeks in 39 patients with Stage IB–III dysgerminoma.[276] No patients relapsed despite the very modest dose of carboplatin and 3 days of etoposide every 4 weeks for three cycles only; however, the trial closed early after the results of two trials in male patients with non-seminomatous testicular cancer reported inferior outcomes with carboplatin compared to cisplatin. Shah et al.[277] reported the results of pooled data from six trials (three pediatric and three adult) on behalf of the Malignant Germ Cell Tumor International Consortium (MaGIC), which included 126 patients with advanced-stage (Stage IC–IV) dysgerminomas who were treated with either carboplatin- or cisplatin-based chemotherapy. Survival outcomes were equivalent, with a 5-year survival of 96% in both groups, with no differences seen according to age (<25 or >25 years). Seven patients relapsed, including two who had received carboplatin-based chemotherapy and five treated with BEP; all were salvaged.[277]

When bulky residual disease is present, 3–4 courses of BEP or EP chemotherapy are commonly administered[278] (Level of Evidence: B).

The optimal follow-up schedule has not been clinically investigated in ovarian germ cancers, and the frequency of visits and investigations is controversial. Patients who have Stage I tumors and are offered surveillance need to be seen regularly. One option is to utilize the follow-up regimen presented above.[273] Patients who have had chemotherapy have a lower risk of recurrence and the frequency of CT scans can be reduced, which is similar to the approach for testicular germ cell tumors.[274] Each follow-up visit should involve taking a medical history, physical examination, and tumor marker determination. Although tumor markers are important, radiological imaging is also pertinent, especially for patients whose tumor markers were not raised at diagnosis. CT or MRI scans should be performed as clinically indicated.[273]

Patients who have not received chemotherapy should be followed closely, as 90% of relapses occur within the first 2 years. In most cases, relapse can be successfully treated (see below)[273] (Level of Evidence: D).

13.5 | Postoperative management and follow-up of non-dysgerminoma germ cell malignancies

Non-dysgerminoma germ cell malignancies are highly curable with chemotherapy, even with advanced disease. Patients with Stage IA grade 1–2 immature teratoma have a very good prognosis and should be only observed after primary conservative surgery. Adjuvant chemotherapy does not appear to add any survival benefit to this subgroup of patients. Although adjuvant chemotherapy has been routinely recommended to all other patients with Stage I non-dysgerminomatous ovarian germ cell tumors, this approach has been challenged and there may be a role for close surveillance and chemotherapy reserved for the subset (such as Stage IA yolk-sac tumors) as this is the standard of care in male patients with apparent Stage I testicular cancers. All other patients with non-dysgerminomas, and higher-stage and higher-grade immature teratomas, should receive postoperative adjuvant chemotherapy.[248]

The recommended chemotherapy regimen is etoposide 100 mg/m^2 per day for 5 days, combined with cisplatin 20 mg/m^2 per day for 5 days and bleomycin 30 IU IM/IV on days 1, 8, and 15, administered over a total of 12 weeks. For patients with good prognosis disease, three cycles of BEP are advised, while those with intermediate or poor risk disease should receive four cycles.[248]

After chemotherapy, patients with metastatic immature teratomas may have residual masses composed entirely of mature elements. These masses can increase in size (growing teratoma syndrome) and should be surgically resected after the completion of chemotherapy[279] (Level of Evidence: B).

All patients should have AFP and beta hCG to monitor their response to treatment. All patients treated with chemotherapy should be followed up with a medical history, physical examination, and

appropriate tumor markers in the same way as dysgerminomas. CT or MRI scans should be performed as clinically indicated.[246]

Relapses in patients usually occur within the first 2 years after diagnosis.[248,266] Patients who relapse after BEP may still attain a durable remission and cure with second-line chemotherapy regimens such as paclitaxel–ifosfamide–cisplatin (TIP).[266] High-dose chemotherapy and autologous marrow rescue may be considered in selected patients who should be managed in specialized units. There is no standard treatment for relapsed disease (Level of Evidence: D).

14 | SARCOMA OF THE OVARY

Ovarian sarcomas are rare and occur primarily in postmenopausal patients.[248,280] Nevertheless, accurate diagnosis and differentiation from other types of primary ovarian cancer are important, as the prognosis is generally poor.

There are two types of sarcomas. Ovarian carcinosarcomas or the older term "malignant mixed Müllerian tumors" (MMMTs), the more common of the two, are biphasic tumors composed of both carcinomatous and sarcomatous elements.[280,281] Most authors agree that most MMMTs are monoclonal in origin and should be thought of and managed as a high-grade epithelial cancer. The sarcomatous component is derived from carcinoma or from a stem cell that undergoes divergent differentiation. Thus, ovarian carcinosarcomas are best regarded as metaplastic carcinomas.

Pure sarcomas are very rare and should be treated according to the specific histologic subtype. These rare sarcomas include fibrosarcomas, leiomyosarcomas, neurofibrosarcomas, rhabdomyosarcomas, chondrosarcomas, angiosarcomas, and liposarcomas. Their management is not discussed here.

Patients with early-stage ovarian carcinosarcomas have a better outcome than those with advanced-stage disease; however, the overall prognosis is poor. They should be managed similarly to high-grade pelvic serous cancers. Their rarity prohibits any prospective randomized trials.

The principles of surgical management for ovarian carcinosarcomas are similar to those for high-grade pelvic serous cancers. After surgery, patients should receive platinum-based chemotherapy.[248] The follow-up schedule aligns with that recommended for epithelial malignancies (Level of Evidence: C).

AUTHOR CONTRIBUTIONS

MR, MF, and JB reviewed and updated the chapter on cancer of the ovary, fallopian tube, and peritoneum published in the 2021 Cancer Report.

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MR has nothing to disclose. MF receives honoraria for advisory boards from Astra Zeneca, GSK, MSD, Lilly, Novartis, and Takeda; speakers fees from Astra Zeneca; and institutional research funding from Astra Zeneca, Novartis, and Beigene. JB receives institutional research funding from Eisai, Immunogen, Tesaro; honoraria for DSMB from Merck.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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