


Epithelial Ovarian Cancer: Evolution of Management in the Era of Precision Medicine

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DISCLOSURES: Marsela Braunstein has two patents pending for diagnostic gene signatures predictive of anthracycline benefit in breast cancer patients. Stephanie Lheureux reports that she is a principal investigator or coinvestigator on clinical trials in ovarian cancer involving drugs from Roche, AstraZeneca, Merck, Tesaro, and Clovis. Amit M. Oza serves on the steering committee for the following (all of which are noncompensated): AstraZeneca, Clovis Oncology, Merck & Company, and Tesaro Inc.

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Abstract: Ovarian cancer is the second most common cause of gynecologic cancer death in women around the world. The outcomes are complicated, because the disease is often diagnosed late and composed of several subtypes with distinct biological and molecular properties (even within the same histological subtype), and there is inconsistency in availability of and access to treatment. Upfront treatment largely relies on debulking surgery to no residual disease and platinum-based chemotherapy, with the addition of antiangiogenic agents in patients who have suboptimally debulked and stage IV disease. Major improvement in maintenance therapy has been seen by incorporating inhibitors against poly (ADP-ribose) polymerase (PARP) molecules involved in the DNA damage-repair process, which have been approved in a recurrent setting and recently in a first-line setting among women with *BRCA1/BRCA2* mutations. In recognizing the challenges facing the treatment of ovarian cancer, current investigations are enlaced with deep molecular and cellular profiling. To improve survival in this aggressive disease, access to appropriate evidence-based care is requisite. In concert, realizing individualized precision medicine will require prioritizing clinical trials of innovative treatments and refining predictive biomarkers that will enable selection of patients who would benefit from chemotherapy, targeted agents, or immunotherapy. Together, a coordinated and structured approach will accelerate significant clinical and academic advancements in ovarian cancer and meaningfully change the paradigm of care. *CA Cancer J Clin* 2019;69:280–304. © 2019 The Authors. *CA A Cancer Journal for Clinicians* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Keywords: clinical trials, gynecologic oncology, medical oncology, molecularly targeted therapies, ovarian neoplasms

Introduction

Outcomes in ovarian cancer depend on timely diagnosis and access to appropriate surgery and systemic therapy, which can be considered indicators of the effectiveness of a country's health care system. Over the past 30 years, all cancers collectively have shown an increase in the 5-year relative survival rate of 20%.¹ For many cancers, the increase in survival has largely been attributed to cutting-edge research and advances in screening, surgery, and treatment methods. Despite these advances, survival rates for ovarian cancer have changed modestly for decades, even in high-resource countries such as the United States and Canada, and remain at only 47% 5 years after diagnosis; by comparison, breast cancer has a 5-year survival rate of 85%.^{2,3} Globally, there are 239,000 new cases (3.6% of all cancer cases) and 152,000 deaths annually (4.3% of all cancer deaths), making ovarian cancer the seventh most common cancer, the eighth most common cause of cancer death in women, and the second most common cause of gynecologic cancer death (after cancer of the cervix uteri) (Fig. 1).⁴

The mortality-to-incidence ratio in ovarian cancer is >0.6, and studies from US and UK registries estimate that 1 in 6 women die within the first 90 days of

Estimated age-standardized incidence rates (World) in 2018, ovary, all ages

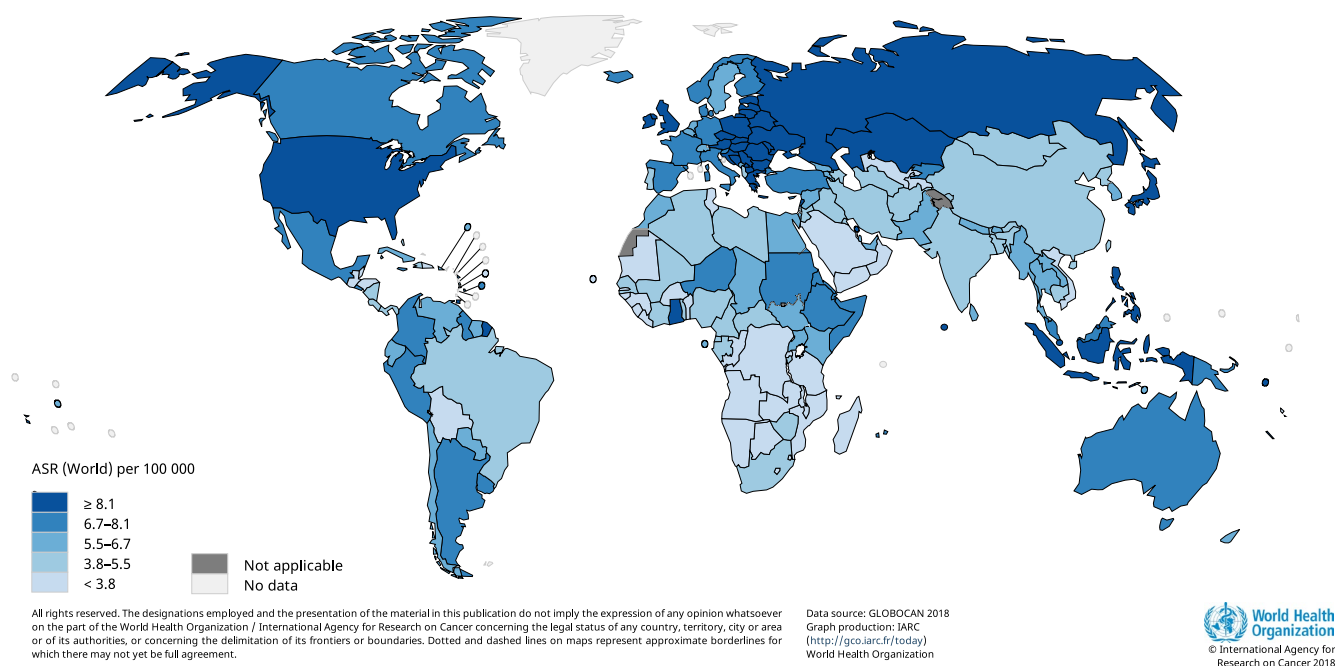


FIGURE 1. Global Incidence of Ovarian Cancer in 2018. ASR indicates age-standardized rate.

diagnosis, reflecting the potential high morbidity and mortality caused by presentation with advanced-stage disease and challenges to effective therapy, which, with appropriate therapy, should be largely avoidable.⁵ These somber numbers are due in part to the lack of effective screening options to detect ovarian cancer at an early stage and a lack of early, specific warning signs or symptoms that lead to a diagnostic delay. Although early-stage disease is highly curable (Fig. 2),^{6,7} the majority of women present with stage III/IV disease, and over 75% of patients with late-stage ovarian cancer die of their disease.⁸ Cytoreductive surgery and combination platinum-taxane chemotherapy have remained the mainstay of therapy for decades.⁹ During this time, well-conducted clinical trials have established important principles that guide therapy internationally, shape the direction of clinical research, and benchmark international consensus recommendations, which have been published by the Gynecologic Cancer Inter Group (GCIg).^{10–12} These fundamental principles emphasize the importance of surgery by a gynecologic oncologist with reduction of tumor bulk to no residual disease (R0) whenever possible, a pathologic diagnosis defining the subtype of ovarian cancer, and the appropriate systemic treatment based on tumor and patient characteristics with potential access to maintenance therapy. Each of these topics is discussed below, but it is important to ensure that these fundamental principles of good treatment are followed for all women with ovarian cancer.

Improving the survival of patients with ovarian cancer also relies on prevention. Risk factors for ovarian cancer are inherited risk (germline mutations in breast cancer susceptibility

genes [*BRCA1/BRCA2*] and Lynch syndrome), nulliparity, infertility, endometriosis, obesity, age, and recent evidence implicates an association with perineal talc application.¹³ Gravity and oral contraceptive use are associated with reducing risk, as well as epidemiologic evidence of protection conferred by the regular use of aspirin or nonsteroidal anti-inflammatory agents.^{14,15} *BRCA* mutations confer a lifetime risk of 40% to 60% with *BRCA1* and 11% to 27% with *BRCA2* of developing ovarian cancer, and conversely germline *BRCA* mutations can be detected in approximately 14% to 18% of women with ovarian cancer, particularly the high-grade serous ovarian cancer (HGSOC) subtypes, compared with approximately 1% in the general population.^{16,17} Therefore, it is important to offer genetic testing to first-degree relatives of women with known *BRCA1/BRCA2* mutations. To date, population screening in ovarian cancer has not been effective or validated. However, women at increased risk because of family history and/or *BRCA1/BRCA2* mutations are offered risk-reducing surgery, which is usually performed after child-bearing years. Efforts are ongoing to evaluate chemoprevention that leverages epidemiologic and biologic evidence supporting the use of aspirin in women at high risk by virtue of a *BRCA1/BRCA2* mutation (the STICs and STONeS trial investigating aspirin in the prevention of HGSOC; clinicaltrials.gov identifier NCT03480776).

Biology

Molecular Features of Ovarian Cancer

Epithelial ovarian cancer (EOC) accounts for over 95% of ovarian malignancies.^{16,18} Nonepithelial cancers represent

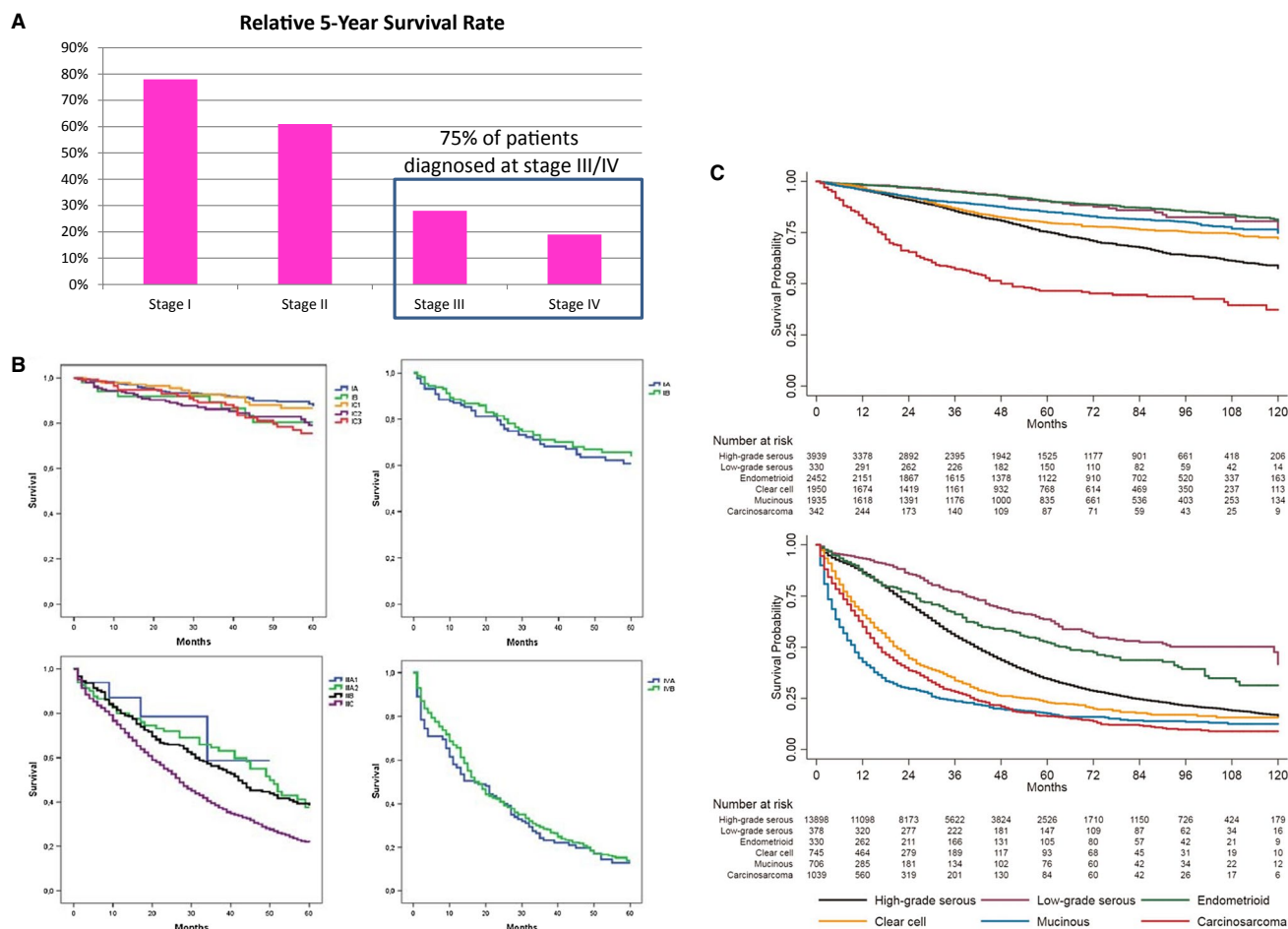


FIGURE 2. Invasive Epithelial Ovarian Cancer 5-Year Survival Rate. (A) The 5-year survival rate in women with invasive epithelial ovarian cancer is illustrated. Data were obtained from American Cancer Society. (B) Kaplan-Meier curves for 2013 Federation of Gynecology and Obstetrics stages are illustrated. Adapted from Rosendhal M, Hogdall CK, Mosgaard BJ. Restaging and survival analysis of 4036 ovarian cancer patients according to the 2013 FIGO classification for ovarian, fallopian tube and primary peritoneal cancer. *Int J Gynecol Cancer*. 2016;26:680-687 with permission from BMJ Publishing Group Ltd.⁶ (C) Kaplan-Meier survival curves of invasive epithelial ovarian cancer are illustrated by stage and histotype (2004-2014, Surveillance, Epidemiology, and End Results data), including (Top) localized and regional stage disease and (Bottom) distant-stage disease. Adapted from Peres LC, Cushing-Haugen KL, Kobel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst*. 2019;111:60-68 with permission from Oxford University Press.⁷

up to 5% of ovarian cancers and include predominantly germ cell and sex-cord stromal cancers, as well as rare, small cell carcinoma and ovarian sarcoma.¹⁶ Given the high incidence and mortality of EOC relative to other ovarian cancer histologies, this review will focus on the current management of EOC.

EOC is a heterogeneous disease consisting of tumors with different types of histologies, grades, and molecular and microenvironmental features, all of which contribute to treatment response and outcome. Histologically, EOC is classified into 5 major subtypes: high-grade serous, low-grade serous, clear cell, endometrioid, and mucinous ovarian cancer. All of these subtypes have distinct patterns of presentation and clinical outcomes, as well as responses to therapies. The distinct behaviors are based on intrinsic tumor biology, which affects prognosis and outcome. We are at

the cusp of stratified trials with predictive biomarkers—starting with histology as a biomarker and gradually embedding molecular genomics.

High-Grade Serous Ovarian Cancer

HGSOC is the most common histologic subtype, accounting for over 70% of EOCs.¹⁸ Microscopically, HGSOCs show papillary and solid growth, with large mononuclear cells that exhibit pleomorphic nuclei with prominent nucleoli and mitotic activity.¹⁹ The majority of HGSOCs are sporadic, but approximately 15% to 20% of women diagnosed with EOC have a hereditary predisposition to the disease, with mutations in *BRCA1* and *BRCA2*¹⁷ or less common alterations in other homologous recombination genes²⁰ included in the BROCA-Cancer Risk Panel.²¹ *BRCA1/BRCA2* proteins are tumor suppressors involved

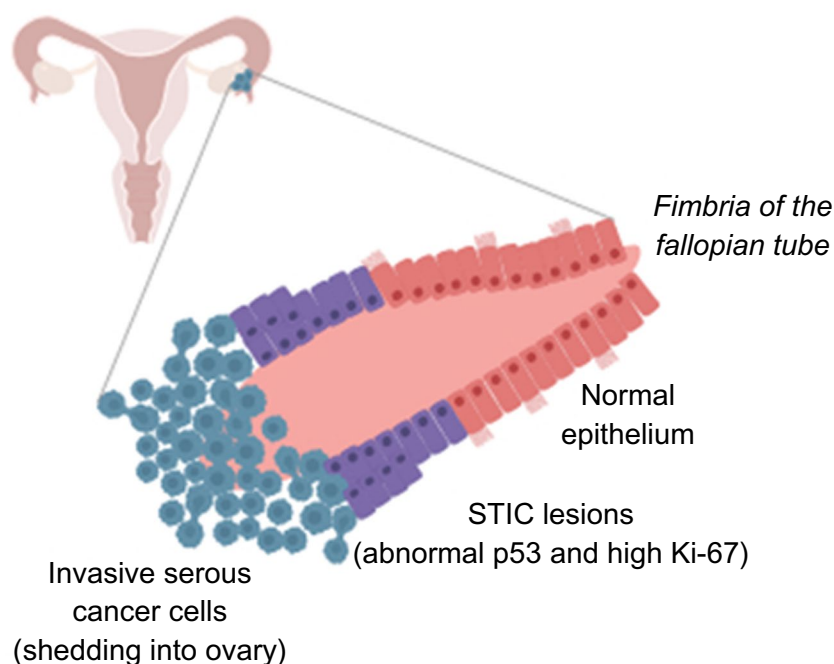


FIGURE 3. High-Grade Serous Ovarian Cancer (HGSOC) Development: From Serous Tubal Intraepithelial Carcinoma (STIC) to High-Grade Serous Cancer.

in maintenance of genomic stability and the DNA damage repair process through homologous recombination. Hallmarks of ovarian cancer in women with genetic susceptibility are: 1) younger age of presentation, often ≥ 10 years younger than the median age; 2) patient's history of other cancers, such as a breast malignancy; and 3) family history of malignancy, particularly breast and ovarian cancers in female relatives and prostate cancer in male relatives. Importantly, triaging for genetic testing based on family cancer history alone can no longer be recommended,²² because a significant percentage of women screened positive for *BRCA1/BRCA2* mutation, although they did not report any family history of cancer.¹⁷

Although its name suggests an ovarian tissue of origin, for the most common type of ovarian cancer that is high-grade serous cancer, examination of tissues removed during prophylactic, risk-reducing salpingo-oophorectomy in *BRCA1/BRCA2* mutation gene carriers identified the presence of cancer precursor lesions called serous tubal intraepithelial carcinoma (STIC) in the distal end of the fallopian tube, and not in the ovary.²³ Because lesions were commonly observed in fimbria of the fallopian tube, it has been postulated that fallopian tube epithelium is the probable site of tumor initiation (Fig. 3). Precursor STIC lesions have the exact type of tumor protein p53 (*TP53*) mutations as those observed in HGSOC in the fimbrial ends of the fallopian tubes, demonstrating a clonal relationship and a direct evolutionary descent from these cells for most, if not all, HGSOCs (Fig. 3).²⁴

HGSOC is characterized by the presence of acquired or inherited mutations in different DNA repair pathways. Mutations in *TP53* are a nearly universal characteristic of HGSOC (97%); this gene encodes a transcription factor that activates genes involved in DNA repair, the cell cycle, and apoptosis upon irreparable DNA damage. DNA double-strand breaks are repaired by the homologous recombination repair pathway, which is an error-free process requiring a homologous DNA template to function. *BRCA1*, *BRCA2*, and various other homologous recombination proteins are responsible for the repair of DNA damage that maintains genomic stability and promotes cell survival and replication. Ovarian cancers with *BRCA1* alterations (germline and somatic mutations in 12% of cases, DNA hypermethylation in 11% of cases) and *BRCA2* alterations (germline and somatic mutations in 11% of cases),²⁰ or other defects in homologous recombination repair genes, such as *EMSY*, *RAD51*, *ATM*, *ATR*, Fanconi anemia, *BARD1*, *BRIP1*, *PALB2*, *RB1*, *NF1*, *CDKN2A*, and the suppression of *BRCA1* transcriptional activation through gene methylation (11%),^{25,26} are associated with homologous recombination deficiency (HRD). The finding that HRD contributes to approximately 50% of HGSOCs²⁰ provided a rationale for using cytotoxic platinum-based chemotherapy and exploring the activity of poly (ADP-ribose) polymerase (PARP) inhibitors in HGSOC, as discussed below (see Targeted Therapies). Indeed, it has been demonstrated that PARP inhibitors are active in HGSOC beyond those with *BRCA* mutations.²⁷

TP53 mutations, when combined with *BRCA1/BRCA2* inactivation, also has an enormous impact on chromosomal instability that results in the widespread accumulation of copy number alterations (CNAs), a typical molecular feature of HGSOC. A known CNA involving the amplification and overexpression of the 19q12 genomic region containing *CCNE1*, a gene encoding cell-cycle protein cyclin E1,²⁸ leads to unscheduled DNA replication, centrosome amplification, and overall chromosomal instability.²⁶ Other pathways involved in HGSOC include FXM1, which is altered in nearly 84% of HGSOCs, followed by the Rb1 (67%), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) (45%), and Notch 1 (22%) pathways, all of which could lead to novel therapeutic opportunities for patients with HGSOC.²⁰

Gene expression studies have stratified HGSOC into 4 prognostic subtypes: differentiated, immunoreactive, mesenchymal, and proliferative. The immunoreactive subtype is associated with superior overall survival (OS), and the mesenchymal subtype is associated with the worst OS.^{20,29} Although these signatures were refined and validated independently,^{30,31} their clinical implementation is challenging, and their potential predictive role is untested. Recently, a genome-sequencing study has revealed 7 CNA signatures in HGSOC that predict OS and the probability of relapse after platinum-based chemotherapy.³² This clarifies some of the mutational mechanisms that preclude the structural alterations that dominate in HGSOC, and should contribute toward improved clinical-translational study designs.

In addition, ovarian cancer cells overexpress specific proteins at the surface, such as folate receptor and mesothelin (Fig. 4), which have been used as targets for antibody-drug conjugates (ADCs)³³ for cancer cell-specific-directed therapy. This new class of biopharmaceutical drugs has been used for treatment with a high therapeutic index. ADCs are complex molecules composed of a dedicated antibody (targeting the folate receptor³⁴ or mesothelin³⁵) linked to a biologically active cytotoxic drug used for treatment.

Low-Grade Serous Ovarian Cancer

Low-grade serous ovarian cancer (LGSOC) represents about 10% of EOCs.³⁶ Microscopically, LGSOCs display small papillae with cells of uniform nuclei and various amounts of hyalinized stroma; psammoma bodies may be present.¹⁹ On the basis of the molecular features that are quite distinct from HGSOC, a dualistic model of pathogenesis has been proposed for HGSOCs and LGSOCs. It is hypothesized that LGSOC develops from an atypical, proliferative (borderline) tumor by following a pathway that is independent and molecularly quite distinct from that of HGSOC.³⁶ Mutations in B-Raf proto-oncogene,

serine/threonine kinase (*BRAF*) (38%) or Kirsten rat sarcoma viral oncogene homolog (*KRAS*) (19%), which are mutually exclusive, are the most common aberrations detected in LGSOC.³⁷ Although they are associated with a constitutively active mitogen-activated protein kinase (MAPK) pathway, mutations in *BRAF* or *KRAS* represent a favorable prognostic factor.³⁶ An activated MAPK pathway is detected in up to 80% of LGSOCs and in 78% of their putative precursors—serous borderline tumors—suggesting a causative effect³⁸; it also provides a rationale for exploring MAPK kinase (MEK) inhibitors in the treatment LGSOC. There is also a relatively high proportion of estrogen receptor-positive/progesterone receptor-positive cancers (Fig. 4),³⁹ leading to the use of hormonal therapy in this specific ovarian cancer subgroup. In contrast to HGSOC, high CNAs and mutations in *TP53* are rare; LGSOC does not seem to be related to *BRCA1/BRCA2* gene mutations.

Ovarian Clear Cell Carcinoma

Ovarian clear cell carcinoma (OCCC) represents approximately 5% of ovarian cancers in North America and Europe; it is more prevalent in Japan, where it tends to occur in almost 25% of all patients with EOC.⁴⁰ Microscopically, OCCCs show combinations of tubules, solid areas, and complex papillae, and cells with prominent nucleoli and clear cytoplasm filled with glycogen. The pathogenesis of OCCC is not well understood; it is thought to be associated with endometriosis, a benign disorder characterized by the ectopic presence of endometrial tissue. Japanese investigators have proposed a mechanism that initiates in endometriotic cysts with the increased iron content that, through iron-induced oxidative stress, causes DNA damage, mutations, and carcinogenesis.⁴¹ Mutations in the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin-remodeling complex genes, the PI3K/Akt signaling pathway, and the receptor tyrosine kinase (RTK)/Ras signaling pathway are the major molecular aberrations observed in nearly 50%, 40%, and 29% of OCCCs, respectively. Among the SWI/SNF subunits, AT-rich interaction domain 1A (*ARID1A*) is the most frequently mutated gene, detected in 40% to 67% of OCCCs.^{42,43} In the PI3K signaling pathway, activating mutations in PIK3 catalytic subunit α (*PIK3CA*) (33%) and loss of phosphatase and tensin homolog (*PTEN*) (37%) are the most common aberrations.^{42,44} Activating *PIK3CA* mutations result in abnormal cellular growth, proliferation, survival, and angiogenesis. Interestingly, activation of either the PI3K pathway or the RTK pathway was associated with better OS,⁴² although this finding needs to be validated independently. Emerging evidence from an evaluation of 25 OCCC samples for gene expression changes and chromosomal instability suggests that OCCCs may cluster into


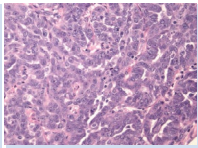
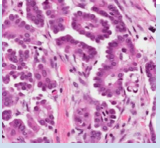

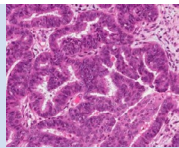
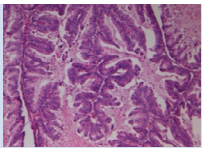






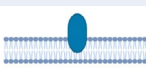


	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
 Pathology					
 Molecular features	CNA high <i>TP53</i> <i>BRCA1/2</i> HRD	CNA low MAPK act. <i>KRAS</i> <i>BRAF</i>	<i>ARID1A</i> PI3K/AKT act. RTK/Ras act. MMR	<i>PI3KCA</i> <i>ARID1A</i> <i>KRAS</i> Wnt/ β -catenin act. <i>PTEN</i>	<i>KRAS</i> <i>HER2</i> amplif.
 Platinum Chemotherapy	Sensitive	Relatively Resistant	Relatively Resistant	Sensitive	Relatively Resistant
 PARP inhibitor	Yes	-	-	Yes for high grade	-
 Folate receptor	Yes	-	-	Yes	-
 Hormone receptor	30% PR 80% ER	57% PR 87% ER	8% PR 19% ER	67% PR 76% ER	16% PR 20% ER
 Hormonal therapy use	-	Yes	-	Yes	-
 Mesothelin	50-80%		38%	?	10-30%
 MMR deficiency	-	-	Yes	Yes	-
 Anti-PD1	?	?	Yes	Yes	?

FIGURE 4. Multidisciplinary Diagnostics of Ovarian Cancer: Broad Molecular Classifiers, Gene Mutations/Pathways, and Histopathological Classification. AKT indicates AKT serine/threonine kinase 1; anti-PD-1, programmed death 1 antibody; ARID1A, AT-rich interaction domain 1A; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CNA, copy number alterations; ER, estrogen receptor; GI, gastrointestinal; *HER2* amplif., human epidermal growth factor 2 amplification; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; *PI3KCA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α ; *TP53*, tumor protein p53; *BRCA1/2*, breast cancer type 1 susceptibility protein 1/2; *PTEN*, phosphatase and tensin homolog. We thank Marjan Rouzbahman, MD, and Patricia Shaw, MD, for providing the H & E images of ovarian cancer.

3 prognostic groups.⁴⁵ Compared with HGSOEs, most OCCCs are characterized by considerably fewer CNAs, and mutations in *TP53* and *BRCA1/BRCA2* genes are uncommon.⁴⁰ Recently, a pilot study highlighted a unique subset of OCCCs that have microsatellite instability associated with enhanced immunogenicity, which may be susceptible to immunotherapy. This subgroup of OCCCs exhibited a significantly higher number of tumor-infiltrating lymphocytes (TILs), particularly programmed cell death protein 1 (PD-1)-positive TILs, compared with microsatellite-stable OCCCs as well as HGSOEs, and uniformly expressed programmed death-ligand 1 (PD-L1) in tumor cells and/or intraepithelial or peritumoral immune cells.⁴⁶

Endometrioid Ovarian Cancer

Endometrioid cancer of the ovary represents approximately 10% of EOCs. Microscopically, endometrioid ovarian cancers may be cystic or predominantly solid.¹⁹ It is thought that endometrioid and clear cell ovarian cancers arise from similar precursor cells of transformed endometrial origin. In addition, women with Lynch syndrome (hereditary nonpolyposis colorectal cancer) are also at an increased risk of developing endometrioid and clear cell ovarian cancer. Loss of expression of mismatch-repair genes (mutS homolog 6 [*MSH6*], *MSH2*, *MLH1*, and *PMS1* homolog 2, mismatch repair system component [*PMS2*]) is a characteristic of Lynch syndrome and is found in nearly 8% of Lynch syndrome-associated endometrioid and clear cell ovarian cancers.⁴⁷ An animal model has shown that deregulated WNT/ β -catenin and PI3K/PTEN signaling pathways are pivotal in the development of murine cancers that resemble human endometrioid ovarian cancer⁴⁸ and has implicated the distal oviduct as the site of origin because of notable precursor lesions that lead to endometrioid ovarian cancer.⁴⁹ Molecular profiling of human endometrioid ovarian cancers revealed that the most prevalent mutations are similar to those observed in OCCC and include *PIK3CA* (40%), *ARID1A* (30%), *KRAS* (30%), *PTEN* (16%), and *PPP2R1A* (16%).⁵⁰ Interestingly, mutations in *CTNNB1*, a gene encoding β -catenin, are particularly common, occurring in approximately 50% of low-grade endometrioid ovarian cancers.⁵⁰ High-grade endometrioid is a different entity than low-grade endometrioid and shares similarities with HGSOE.

Mucinous Ovarian Cancer

Mucinous ovarian cancer is a rare subtype representing 2.4% of EOCs.⁵¹ Some may arise from borderline tumors.⁵² Microscopically, mucinous ovarian cancer is heterogeneous and often is composed of benign, borderline, noninvasive, and invasive components that coexist within the tumor

microenvironment.¹⁹ Mucinous ovarian cancer is characterized by the presence of multilocular cysts filled with an opaque, mucoid substance and larger solid regions and papillae that project into the cysts. Evidence suggests that, based on the degree of stromal invasion, mucinous ovarian cancer may be classified into expansile (no invasion) and infiltrative types.¹⁹ In terms of the molecular features, *KRAS* mutations are the most common and are found in 50% of mucinous ovarian cancers. Mutations in the *KRAS* gene usually stimulate cellular growth. Interestingly, amplifications of *HER2* are detected in approximately 18% of mucinous cancers.⁵³ *TP53* and *BRCA* do not seem to play a prominent role in the carcinogenesis of mucinous ovarian cancers.

Treatment of Ovarian Cancer—Surgery, Systemic Therapy, and Radiation

Treatment of ovarian cancer in the early days was largely based on observations and opportunities and was less structured in an objective, evidence-based manner. To date, there has not been a randomized assessment of the role of debulking surgery versus no surgery in advanced ovarian cancer. Likewise, platinum-based chemotherapy was introduced widely through a phase 2 trial with no randomized control.⁵⁴ Similarly, whole-abdominal radiation was explored extensively in many cancers, but without key randomization against a control.⁵⁵ However, the treatment of ovarian cancer has matured over the last 50 years to an evidence-based approach that integrates optimal surgery and systemic therapy with ovarian cancer subtype specificity; it has also matured to offer a well-developed algorithm of integrated, multidisciplinary care, albeit with some important unanswered questions. Treatment decisions are based on disease stage and biology, prior therapy, and comorbidities. At present, the only opportunity for cure is at primary treatment, and the efficacy depends on stage and histology. Early-stage disease is curable in 90% of women, even in those with more aggressive histologic subtypes (Fig. 2),^{6,7} emphasizing the importance of early detection and timely specialist treatment. Unfortunately, the majority of women are still diagnosed late, challenging the efficacy of surgery, chemotherapy, and targeted agents.

Surgery

Surgery allows for accurate surgical staging, which is documented using the International Federation of Gynecology and Obstetrics (FIGO) (Table 1) and TNM staging classifications,⁵⁶⁻⁵⁸ and is also therapeutic by debulking disease.

Primary debulking surgery

Surgery has been an important bedrock of therapy for ovarian cancer, although it is important to point out that what have not been definitively demonstrated for advanced ovarian cancer are the exact role and level of benefit of

TABLE 1. 2014 International Federation of Obstetrics and Gynecology Ovarian, Fallopian Tube, and Peritoneal Cancer Staging System and Corresponding TNM

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 primary 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 primary 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	

Adapted from Prat J; FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. *J Gynecol Oncol*. 2015;26:87–89. doi:10.3802/jgo.2015.26.2.87⁵⁸

debulking per se. Sequential clinical trials have established the significant impact of surgery undertaken by a qualified gynecologic oncologist with the goal of achieving optimal debulking with no residual disease (R0).⁵⁹ Surgical staging by a qualified gynecologic oncologist is essential and involves laparotomy through a midline

incision, with full exploration of the abdomen and pelvis, followed by at least total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. The recent LION study (Lymphadenectomy In Ovarian Neoplasms) showed that systematic pelvic and paraaortic lymphadenectomy of clinical negative lymph nodes in

patients with advanced EOC and complete resection may be omitted to reduce postoperative morbidity and mortality.⁶⁰ All areas of disease should be resected, ideally with no macroscopic residual disease. Du Bois et al clearly demonstrated the impact of residual disease on outcome and showed that macroscopic residual disease after debulking is associated with inferior OS.⁵⁹ Riester et al have investigated biologic and genomic characteristics and developed predictive signatures to establish whether such features could be predictive of making disease more or less debulkable as of inferior outcome.⁶¹ Pathways significantly associated with suboptimal debulking included migration/invasion, angiogenesis, metastasis, and activation of tumor-associated fibroblasts. A recent study investigated the molecular subtypes of HGSOC and identified 5 subtypes associated with surgical outcome; in particular, a mesenchymal tumor molecular subtype was correlated with suboptimal debulking surgery.⁶²

It is imperative to consider disease biology when evaluating choice of therapy as well as the sequence of surgery/systemic therapy. Surgery clearly has a major impact on reducing tumor burden, and this is important when systemic therapy is less effective, as in low-grade serous, clear cell, and mucinous carcinoma subtypes.⁶³ Evaluating and incorporating biologic predictive biomarkers for R0 debulking remains an active area of development.

Interval debulking surgery

Surgery that is deferred until after chemotherapy is commenced because upfront surgery is not possible due to extensive disease, the clinical condition of the patient, or potential logistic reasons is termed *interval debulking surgery* (IDS). The therapeutic intent is the complete resection of residual disease and is generally considered after 3 cycles of chemotherapy. Two prospective, randomized clinical trials have evaluated primary debulking surgery (PDS) versus IDS^{64,65} and demonstrated no survival disadvantage in the patients who were randomized to IDS. Although the criticisms of these studies include potential recruitment bias, with a preponderance of patients at an advanced stage, the low frequency of R0 resections and surgical effort (time of procedure), the use of neoadjuvant chemotherapy (NACT) has increased in practice. However, the debate between PDS or IDS continues, with centers leaning one way or another; an additional randomized trial of neoadjuvant chemotherapy versus PDS in patients with advanced EOC is ongoing in select centers with R0 rates $\geq 50\%$ (Trial on Radical Upfront Surgery in Advanced Ovarian Cancer [TRUST]; NCT02828618). Optimizing assessment of the feasibility of R0 resection at presentation using imaging and, more recently, laparoscopy is becoming increasingly routine and may refine a clinical algorithm for primary management.^{66,67} The

additional benefit of accurate surgical staging and the availability of sufficient tissue for accurate pathologic assessment are important considerations.

Second-look surgery

Second-look surgery to restage EOC, including the excision of residual disease, was a common practice until a randomized clinical trial demonstrated no benefit to patients, and it has now largely been abandoned.⁶⁸

Secondary (and beyond) debulking surgery for recurrent EOC

The randomized Desktop III/ENGOT OV20 trial conducted in patients with relapsed, platinum-sensitive EOC has shown a 5-month improvement in progression-free survival (PFS) from 14 to 19.6 months for women who underwent secondary debulking compared with controls who did not undergo surgery (hazard ratio, 0.66; 95% CI, 0.52-0.83), with continuation of benefit to the time to first subsequent treatment. The magnitude of benefit was greater with R0 resection. Findings reported in the Gynecologic Oncology Group (GOG) 0213 study—a double-randomized clinical trial evaluating surgery and the addition of bevacizumab in patients with platinum-sensitive recurrence—showed that secondary cytoreduction was not associated with improved OS compared with no surgery in this population.⁶⁹ Differences in the magnitude of findings may be because of differences in patient selection between Study Comparing Tumor Debulking Surgery Versus Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer (DESKTOP III) and GOG-0213 (given use of the German Gynecological Oncology Group [AGO] score as inclusion criteria in the Desktop trial), differences in upfront debulking or abrogation of the benefit of surgery by adding bevacizumab, and the difference in the primary objective. Secondary debulking surgery should be considered for selected patients with platinum-sensitive recurrence where R0 is achievable.

Systemic Therapy

Systemic therapy has evolved from single to combination chemotherapy approaches that now incorporate the addition of targeted therapy when appropriate. As newer agents arise, they will reshape first-line therapy (see below). Standard practice now takes into account histology, stage, genomic profile, and residual disease. Contemporary stratified trials are evaluating combinations of chemotherapy, targeted agents, and immunotherapy to further refine treatment precision tailored to individual, patient-based, predictive factors. The sections below summarize key evidence for first-line therapies and touch upon recurrent-disease therapy related to these modalities, with a nuanced tree of

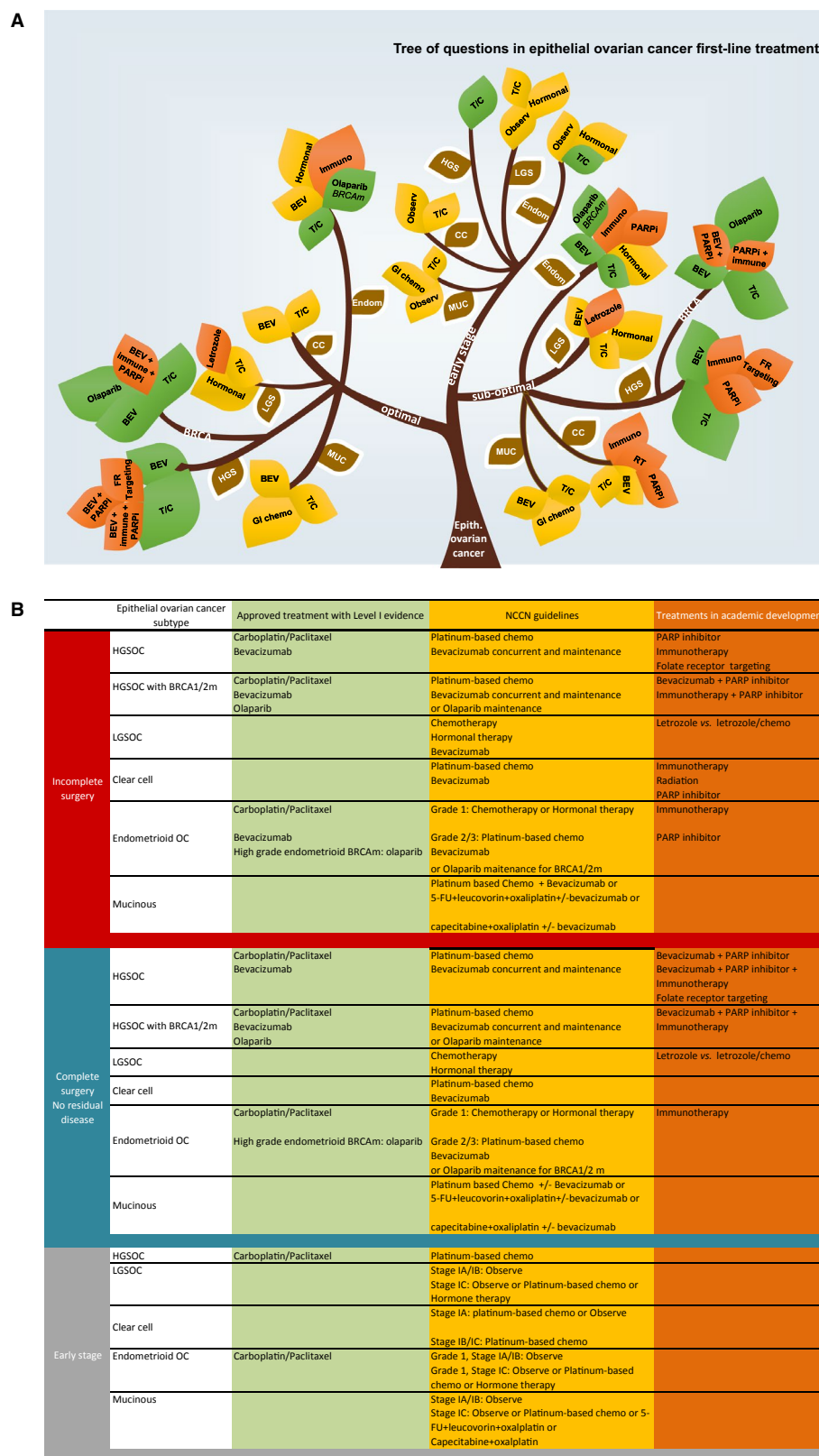


FIGURE 5. (A) Tree of Questions in Epithelial Ovarian Cancer First-Line Treatment. If NCCN guidelines match approved treatment with Level I evidence, then the treatments are shown in green color only; if the guidelines are not based on Level I evidence, the treatments are shown in yellow color. Orange indicates treatments in academic development. (B) Epithelial Ovarian Subtypes. +/- indicates with or without; BEV, bevacizumab; BRCA1/2m, mutation of the *BRCA1/BRCA2* genes; CC, clear cell; chemo, chemotherapy; Endom, endometrioid; EOC, epithelial ovarian cancer; FR, folate receptor; GI, gastrointestinal; HGS, high-grade serous; HGSOC, high-grade serous ovarian cancer; Immuno, immunotherapy; IP, intraperitoneal; IV, intravenous; LGS, low-grade serous; LGSOC, low-grade serous ovarian cancer; MUC, mucinous; NCCN, National Comprehensive Cancer Network; Observ, observation; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval; R0, reduction of tumor bulk with no residual disease; RT, radiotherapy; T/C, paclitaxel/carboplatin.

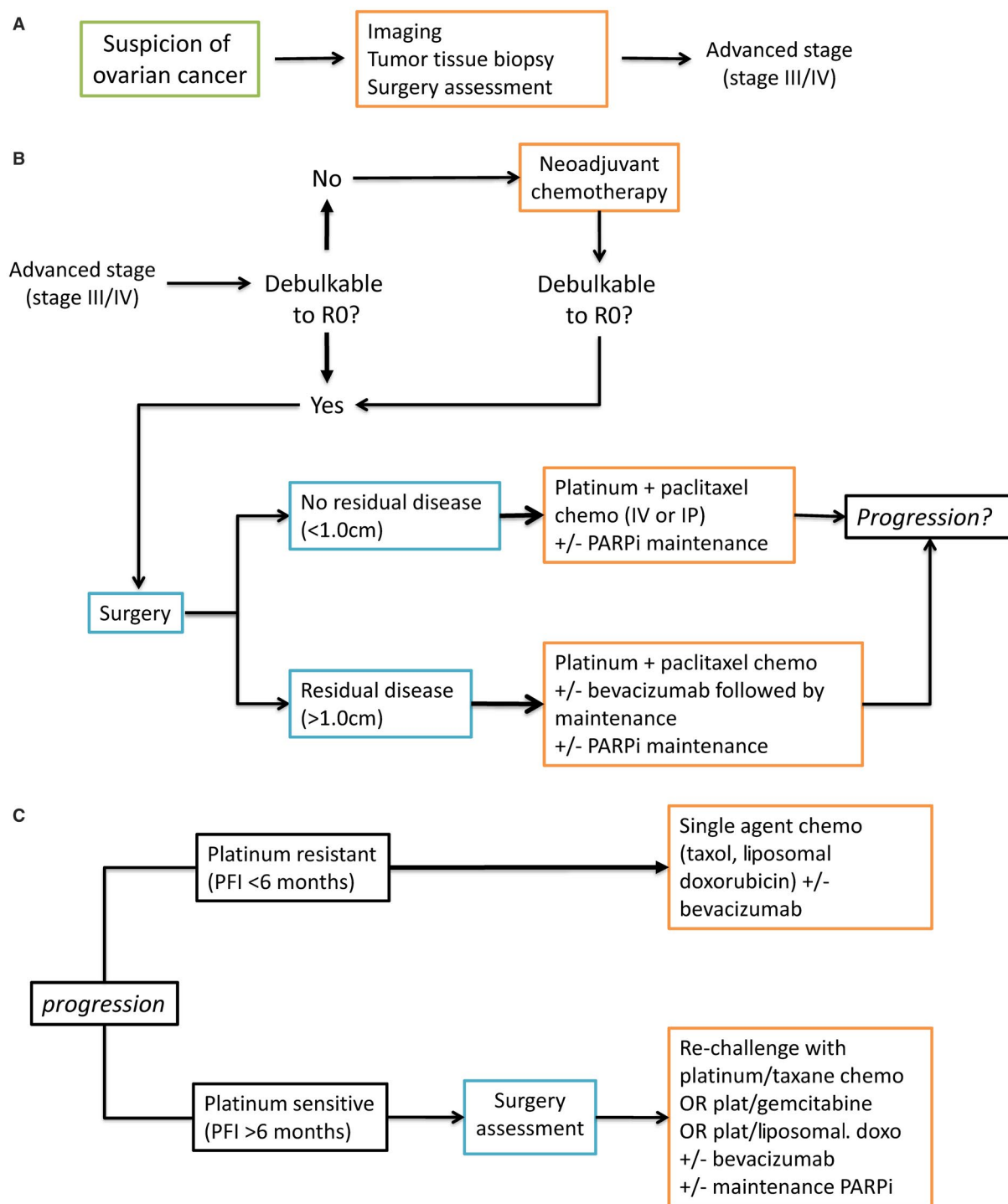


FIGURE 6. Advanced Ovarian Cancer Treatment Guidelines. (A) Diagnosis, (B) frontline management, and (C) treatment upon recurrence are illustrated. +/- indicates with or without; chemo, chemotherapy; doxo, doxorubicin; IP, intraperitoneal; IV, intravenous; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval; plat, platinum; R0, reduction of tumor bulk with no residual disease.

thought-provoking questions in the management of ovarian cancer (Fig. 5) and practical guidelines (Fig. 6) for the reader.⁷⁰

Chemotherapy

The early days of chemotherapy in ovarian cancer explored alkylating agent chemotherapy with evidence of benefit,

but important milestones were the introduction of platinum in 1976,⁵⁴ cisplatin-based combination therapy during 1984 through 1986,⁷¹⁻⁷³ and paclitaxel in 1993.⁷⁴⁻⁷⁶ These milestones dramatically improved outcome in women with advanced disease, and their combined use has been refined over the past 20 to 30 years through clinical trial participation as an international community effort. Patients with

EOC (particularly high-grade serous disease) respond very well to initial chemotherapy, with responses noted in approximately 80% of patients, but, over time, many of these patients will recur. There have been several randomized clinical trials that have addressed questions of dose, dose density, choice of platinum and/or taxane, schedule, mode of administration (intravenous [IV], intraperitoneal [IP]), role of hyperthermia, and additional chemotherapeutic agents. In brief, these studies demonstrate the following:

- Carboplatin is as effective as cisplatin and is better tolerated.⁷⁷
- Dose is important, and the target dose is an area under the concentration-time curve (AUC) of 5 (AUC 5) to AUC 6 for carboplatin or 75 mg/m² cisplatin.⁷⁸
- Higher doses of cisplatin or carboplatin above the target do not improve long-term outcome.⁷⁹
- Giving carboplatin weekly instead of every 3 weeks is well tolerated.^{80,81}
- More than 2 chemotherapy drugs in combination do not improve outcome. Several randomized trials of adding a third drug to doublet chemotherapy, either as sequential doublets or triplets, have shown there is no additional benefit to adding a third drug (International Collaborative Ovarian Neoplasm 5 [ICON5] trial)⁸²; doublet chemotherapy is optimal.
- Weekly dose-dense chemotherapy in addition to carboplatin in a Japanese study with a carboplatin dose of AUC 6 with paclitaxel 80 mg/m² on days 1, 8, and 15 improved PFS and OS.^{80,81} Other studies (the Multicenter Italian Trials in Ovarian Cancer [MITO]-7 trial; NCT00660842; weekly carboplatin at AUC 2 with weekly paclitaxel 60 mg/m², lower dose intensity)⁸³ or ICON8 (NCT01654146)⁸⁴ did not show this benefit, leading to the possibility that pharmacogenomic differences between Japanese and white patients may affect response to treatment.
- IP chemotherapy has been introduced because ovarian cancer spread is initially typically limited to the intra-abdominal cavity; thus, cellular exposure directly to IP chemotherapy has likely advantages in direct diffusion and lethality of chemotherapy in cancer cells. The biologic, molecular, physical, and mathematical basis of this would suggest that, for an IP therapy to be effective, it should be given when the residual postsurgical disease volume is small (<1 cm) and ideally microscopic at individual sites. Several randomized trials have demonstrated significant improvements in PFS and OS with the administration of IP therapy.^{85,86} These IP trial designs varied, as many allowed additional dose/intensity in the IP arm, which has impeded conclusions on IP or IV administration, dose for dose. The randomized trials that have shown benefit from IP chemotherapy used cisplatin at a dose of 100 mg/m², which improved OS but was associated with significant toxicity.⁸⁷ Substitution of carboplatin with cisplatin improves tolerability, and, in an effort to improve tolerability, the dose of IP cisplatin has been lowered to 75 mg/m²; it is unclear whether the efficacy advantage is retained with the reduced dosage.⁸⁶ However, as an aggregate, and through meta-analysis, evidence would still suggest it is reasonable to consider IP therapy in optimally debulked patients.⁸⁸ PFS outcome from the GOG 252 trial (NCT00951496), in which all patients were treated with bevacizumab 15 mg/kg IV on cycles 2 through 22 and were randomized to receive 6 cycles of 1) IV carboplatin AUC 6 and IV weekly paclitaxel 80 mg/m² (IV arm), or 2) IP carboplatin AUC 6 and IV weekly paclitaxel 80 mg/m² (IP-carboplatin arm), or 3) IV paclitaxel 135 mg/m², IP cisplatin 75 mg/m², IP paclitaxel 60 mg/m² (IP-cis arm), suggests no difference between the 3 arms and no advantage to IP therapy trial when bevacizumab is incorporated.⁸⁹ Survival outcome from the Intraperitoneal Therapy for Ovarian Cancer With Carboplatin (iPocc) study (NCT01506856), comparing IV carboplatin and IV paclitaxel administered weekly with IP carboplatin and IV paclitaxel administered weekly, may provide additional data related to IP therapies.
- The hyperthermic IP chemotherapy (HIPEC) technique introduces instillation of heated chemotherapy into the abdominal cavity at the time of surgery. Two randomized clinical trials have recently investigated the feasibility and benefit from adding a cycle of IP therapy during surgery.^{90,91} A 245-patient, multicenter, randomized, phase 3 trial demonstrated that HIPEC was feasible and tolerable.⁹⁰ Specifically, there was a significant improvement in outcome among women who underwent cytoreductive surgery with HIPEC (the surgery-plus-HIPEC group) (hazard ratio for disease recurrence or death, 0.66; 95% CI, 0.50-0.87; *P* = .003). The median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. The median OS was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group.⁹⁰ Although debate remains regarding the use of HIPEC,⁹² more research on this technology seems warranted and might be considered in the frontline setting for ovarian cancer.
- Treatment after recurrence follows a complex algorithm based on initial benefit, judged by the platinum-free interval from the last dose of platinum-based chemotherapy, which has used a period of 6 months as a guide. Recurrence after an interval of over 6 months

suggests platinum sensitivity and, as such, rechallenge with doublet platinum-based chemotherapy is proposed. Shorter intervals create the opportunity to incorporate other nonplatinum agents, such as liposomal doxorubicin, weekly paclitaxel, and gemcitabine; however, as single agents, these have only modest activity that diminishes with repeated lines of therapy. This has fueled the search for novel targeted and experimental agents, with several promising agents in early-phase and late-phase trials.

Our understanding continues to evolve to this day. The GCIG has hosted consensus meetings, most recently in Tokyo 2016, to set benchmark standards that can be adopted for clinical trial design.¹⁰ The current consensus standard for chemotherapy is a combination of carboplatin and paclitaxel, both administered every 3 weeks, or carboplatin every 3 weeks and paclitaxel weekly, in a dose-dense manner. Women who are optimally debulked can also be treated with IP chemotherapy. Major advances in efficacy are now being seen with the addition of targeted therapy to chemotherapy. There remains an active debate about IP and dose-dense chemotherapy, with European recommendations leaning away from these.^{93,94} However, in appropriate settings, both can be considered with a balanced evaluation of the risks and benefits. The community standard is to offer a total of 6 cycles of IV paclitaxel and carboplatin, on a 3-week cycle. The regimen is generally well tolerated but is associated with side effects, including nausea, vomiting, muscle pains, myelosuppression, peripheral neuropathy, and alopecia. Some of these can be effectively mitigated by appropriate supportive measures, including antiemetics, but careful attention has to be taken in managing patients on therapy.

Recurrent disease is common in ovarian cancer, and the timing from prior therapy or platinum therapy is a key concept that has shaped decision making on the choice of subsequent therapy. The GCIG definition of platinum-free interval is simple and practical but not without limitations, because it does not take into account how progression is defined (cancer antigen 125 [CA 125], radiological and/or symptomatic recurrence) or the impact of maintenance therapy on the subsequent platinum-free interval and disease biology.⁹⁵ Nonetheless, the categorization is a useful guideline, which is likely to evolve over time as our thinking evolves to view ovarian cancer as a chronic disease in which each relapse might be defined and managed differently with available options.

Targeted Therapy

Targeted agents have been gradually introduced into clinical trials for the treatment of recurrent disease to gauge activity as single agents, followed by combination treatments,

before being introduced into front-line therapy. Over the past decade, there has been significant progress with improved activity and nonoverlapping toxicity from the introduction of concurrent bevacizumab and sequential bevacizumab and PARP inhibitors. Both of these agents have demonstrated significant improvements in some women undergoing first-line therapy and can be selected on the basis of either risk or genomics.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Early studies demonstrated improved PFS and OS in many cancers, particularly colorectal, lung, and renal cancers. Ovarian cancer is a disease that has many of the hallmark features of excessive VEGF—inferior outcome associated with angiogenesis/microvessel density, ascites (capillary leakiness because of VEGF overproduction), and immediate benefit from the reduction of ascites with bevacizumab, both as a single agent as well as in combinations. Pivotal studies that assessed the role of concurrent and maintenance bevacizumab were GOG-0218 (primary endpoint, PFS) and ICON7 (primary endpoints, PFS and OS).^{96,97} Both trials demonstrated significant improvements in PFS overall in the intent-to-treat populations with concurrent and maintenance bevacizumab. In the ICON 7 trial, the prespecified high-risk group (inoperable stage III, unable to be debulked to <1 cm maximum disease, and stage IV disease) showed the greatest benefit from bevacizumab. This patient group had a significant improvement in median OS of 9 months with the addition of bevacizumab.⁹⁸ Similarly, the GOG-0218 study suggested that patients with FIGO stage IV disease may derive a survival advantage from bevacizumab when administered with and after front-line chemotherapy.⁹⁹ The 2 studies examined different doses and durations of bevacizumab; the results suggest that the effect is somewhat independent of dose, with 7.5 mg/kg demonstrating similar benefit to 15 mg/kg. However, continued therapy with bevacizumab may have additional benefit, because findings from the ROSiA trial suggest that longer therapy is better.¹⁰⁰ We are awaiting data from the confirmatory AGO trial (BOOST study; NCT01462890). Recently, the randomized, phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17 also suggested that receiving bevacizumab at recurrence after receiving it as first-line therapy still offers an additional improvement in PFS.¹⁰¹

Other antiangiogenics have been assessed in ovarian cancer, all with modest-to-moderate demonstrations of activity in PFS in recurrent and first-line settings. These include pazopanib, sorafenib, sunitinib, cediranib, VEGF trap (aflibercept), and AMG386. However, none have been

adopted in routine clinical practice because of issues of toxicity and/or the cost of licensing. Currently, bevacizumab is the only antiangiogenic in routine clinical practice.

Bevacizumab has also become a key agent in the management of patients with recurrent disease. Studies have demonstrated a significant improvement in PFS among women with platinum-sensitive, recurrent disease when added to combination chemotherapy with either carboplatin and gemcitabine (a study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma [OCEANS])¹⁰² or carboplatin and paclitaxel (GOG-0213 trial).¹⁰³ In addition, Pujade-Lauraine et al demonstrated a significant PFS improvement for women with platinum-resistant recurrence when bevacizumab was added to physician's-choice chemotherapy of weekly paclitaxel, liposomal doxorubicin, or topotecan.¹⁰⁴ These trials and others have made bevacizumab an important therapeutic agent in conjunction with chemotherapy and as a single agent for maintenance therapy in women with primary or recurrent disease. The additional toxicities related to bevacizumab need to be factored into the decision making, particularly those relating to delayed wound healing, hypertension, and propensity for bowel perforation or fistulization in the setting of bulky disease in close proximity to bowel. However, the close attention to patient selection and treatment has allowed this agent to become a major part of the standard of care in women with ovarian cancer.

The recurrent ovarian cancer treatment paradigm continues to push boundaries, as antiangiogenic agents currently are being investigated in combination with PARP inhibitors. Several ongoing trials are assessing this combination 1) as first-line maintenance therapy in the Platine, Avastin, and Olaparib in First-Line (PAOLA-1) trial (NCT02477644); 2) at the time of platinum-sensitive recurrence as treatment in the NRG-GY004 trial (NCT02446600; completed to accrual) or as maintenance in the ICON-9 trial (NCT03278717); and 3) at the time of platinum-resistant recurrence in the NRG-GY005 trial (NCT02502266). Efforts are ongoing to identify biomarkers of response or toxicities.¹⁰⁵

Poly (ADP-ribose) polymerase inhibitors

PARP enzymes, particularly PARP-1 and PARP-2, play a critical role in the repair of DNA single-strand breaks. Inhibition of PARP leads to an accumulation of single-strand breaks, causing the collapse of replication forks and the accumulation of double-strand breaks, which are commonly repaired by homologous recombination enzymes.¹⁰⁶ Ovarian cancers with *BRCA1/BRCA2* mutations or other HRDs are particularly sensitive to PARP inhibitors because

of the accumulation of unrepaired DNA breaks that lead to cellular death.¹⁰⁷ This has been referred to as “synthetic lethality” to describe the phenomenon of cell death caused by mutation or lack of function of 2 or more genes. PARP inhibitors also interfere with the NHEJ (nonhomologous end-joining) DNA-repair pathway, which is upregulated when homologous recombination pathways are deficient,¹⁰⁶ or cause trapping of PARP-1 and PARP-2 at the level of DNA breaks, resulting in the obstruction of DNA replication forks.¹⁰⁸

Germline or somatic mutations in homologous recombination genes are usually associated with an increased response to platinum-based chemotherapy, a longer disease-free interval, and a better prognosis.¹⁰⁹ However, some HGSOEs show similar clinical behavior without identifiable mutations in *BRCA1/BRCA2* or other homologous recombination genes.¹¹⁰⁻¹¹² Several PARP inhibitors (olaparib, niraparib, and rucaparib) have been investigated and are now available as treatment or maintenance therapy for patients with HGSOE.¹¹³⁻¹¹⁹ PARP inhibitors have also shown promising results in other solid tumors harboring *BRCA1/BRCA2* mutations, such as HER-2-negative breast cancer, metastatic pancreatic cancer, and castration-resistant prostate cancer.^{113,120,121} Three PARP inhibitors currently have regulatory approval in the United States from the US Food and Drug Administration for use in ovarian cancer as maintenance therapy after response to platinum-based therapy at the time of recurrence; olaparib and rucaparib are also being approved for the treatment of *BRCA1/BRCA2* mutation-related disease. The trials,^{115,116,119,122} which are summarized in Table 2, demonstrate a quite striking and consistent improvement in PFS using maintenance therapy with the addition of PARP inhibitors as switch maintenance after a response to platinum-based chemotherapy for platinum-sensitive recurrence, with a range of efficacy on a continuum from patients with mutated *BRCA1/BRCA2*, to those with HRD (defined by a Myriad or Foundation Medicine loss-of-heterozygosity assay), to those with no HRD. Importantly, because all patients benefited, the current functional biomarker of choice for the introduction of switch maintenance is the demonstration of a response to platinum-based chemotherapy. The concurrent use of chemotherapy and olaparib is limited by overlapping hematologic toxicities, which necessitate a dose reduction for both platinum and olaparib. The randomized trial for platinum-sensitive ovarian cancer revealed that the key benefit in PFS was driven by maintenance therapy.¹²³ Efforts are underway to investigate whether patients who do not achieve a response also benefit, because subgroup analyses do demonstrate a benefit in patients who have stable disease¹²⁴ and also show

TABLE 2. Landmark Trials Supporting the Use of PARP Inhibitors in the Treatment of Ovarian Cancer

THERAPY	CLINICAL PHASE	PATIENT POPULATION	BENEFIT	CONCLUSION
Olaparib maintenance	Phase 3	In first line for newly diagnosed, advanced ovarian cancer with <i>BRCA1</i> , <i>BRCA2</i> (or both) mutation after complete or partial clinical response to platinum-based chemotherapy	The risk of disease progression or death was 70% lower with olaparib than with placebo at median follow up of 41 months 60% vs. 27% (hazard ratio for disease progression or death, 0.30; 95 % confidence interval, 0.23 to 0.41; $P < .001$)	The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a <i>BRCA1/2</i> mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo Moore et al. 2018 ¹²⁸
Olaparib maintenance	Phase 2	Platinum-sensitive, relapsed ovarian cancer	PFS was significantly longer with olaparib than with placebo: 8.4 vs 4.8 mo from randomization to completion of chemotherapy	Olaparib as maintenance significantly improved PFS among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer Interim analysis showed no overall survival benefit Ledermann 2012 ¹¹⁶
Olaparib (tablets) maintenance	Phase 3	Platinum-sensitive, relapsed, high-grade serous ovarian cancer with a <i>BRCA1</i> or <i>BRCA2</i> mutation	Median PFS was significantly longer with olaparib than with placebo: 19.1 vs 5.5 mo	Olaparib tablet maintenance significantly improved PFS with no detrimental effect on quality of life in patients with platinum-sensitive, relapsed ovarian cancer and a <i>BRCA1/BRCA2</i> mutation Pujade-Lauraine 2017 ¹¹⁵
Niraparib maintenance	Phase 3	Platinum-sensitive, recurrent ovarian cancer (categorized by the presence or absence of germline <i>BRCA</i> [<i>gBRCA</i>] mutation)	Median duration of PFS was significantly longer with niraparib than placebo: 21.0 vs 5.5 mo in patients with <i>gBRCA</i> 12.9 vs 3.8 mo in patients with non- <i>gBRCA</i>	Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of PFS was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of <i>gBRCA</i> mutations Mirza 2016 ¹¹⁹
Rucaparib maintenance	Phase 3	Platinum-sensitive, recurrent, high-grade ovarian cancer	Median PFS was significantly longer with rucaparib than with placebo in: Patients with <i>BRCA</i> -mutant carcinoma: 16.6 vs 5.4 mo Patients with HRD carcinoma: 13.6 vs 5.4 mo The intention-to-treat population: 10.8 vs 5.4 mo	Across all primary analysis groups, rucaparib significantly improved PFS survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy Coleman 2017 ¹²²

Abbreviations: HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

evidence of additional antitumor activity in patients who have a partial response after platinum-based chemotherapy.¹²⁵ Careful evaluation of toxicity and quality of life has demonstrated good maintenance of quality of life with all 3 PARP inhibitors and delay or avoidance of symptoms related to recurrence or therapy for recurrence.^{126,127}

These investigational activities have led to 2 first-line switch-maintenance trials in women who were selected

on the basis of mutated *BRCA1/BRCA2* genes (Olaparib Maintenance Monotherapy in Patients With *BRCA* Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy [SOLO1]; NCT01844986) or were unselected (a Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy [PRIMA]; NCT02655016). SOLO1 demonstrated a

significant improvement in PFS over placebo when olaparib was used as switch maintenance after first-line chemotherapy in *BRCA1/BRCA2* carriers who were in complete or partial response. The median PFS for the olaparib group has not been reached, but, at 3 years, 60% of women were progression-free in the olaparib group compared with 27% in the placebo group, with a hazard ratio of 0.30 (95% CI, 0.23-0.41; $P < .0001$).¹²⁸ That trial led to US Food and Drug Administration approval in December 2018 for olaparib first-line maintenance in women with *BRCA*-mutated cancer after a response to platinum-based chemotherapy.

This trial now sets the scene for a stratified approach to systemic therapy, with the incorporation of bevacizumab based on residual disease after surgery and switch maintenance on the basis of mutations in *BRCA1/BRCA2*. This requires upfront testing for all HGSOCs. Knowledge of *BRCA1/BRCA2* mutational status (at least germline but preferably somatic as well) should be a part of the standard of care. National Comprehensive Cancer Network and Society of Gynecologic Oncology guidelines suggest universal genetic counseling and testing of all women with ovarian cancer, including fallopian tube and peritoneal cancer.^{129,130} Additional testing of somatic *BRCA1/BRCA2* status, as well as mutations in other homologous recombination (HR) genes, upon diagnosis would further expand our knowledge about who would benefit from PARP-inhibitor maintenance therapy.

The key questions regarding overlap or combinations of antiangiogenics and PARP inhibitors are being addressed in upfront clinical trials. Studies in long-term responders and patients who develop resistance are beginning to leverage next-generation sequencing technologies to identify key factors, which may allow for exceptional sensitivity or extreme resistance.^{131,132}

Evolving Therapies

Folate receptor targeting

Although normal ovarian tissue does not express folate receptor (FR), approximately 70% of primary EOCs and 80% of recurrent EOCs do express FR,¹³³ providing an opportunity to exploit FR as a selective biomarker for the delivery of ADCs. Recent trials used mirvetuximab soravtansine (IMGN853), which is an ADC consisting of an anti-FR α antibody linked to the tubulin-disrupting maytansinoid DM4 drug, a potent antimetabolic agent. As such, this ADC delivers a toxic drug in a highly selective manner to ovarian cancer cells expressing FR α . In addition, active DM4 metabolites diffuse into surrounding tumor cells, inducing a “bystander” killing effect.¹³⁴ Phase 1 and 2 trials have demonstrated proof-of-principle activity in women with recurrent, platinum-resistant ovarian cancer who received from 1 to 3 prior lines of therapy;

of 37 women treated as part of the 3 phase 1 expansion cohorts who met the enrollment criteria of moderate-to-high tumor FR α levels ($\geq 50\%$ of cells with $\geq 2+$ FR α expression), objective tumor responses were observed in 17 individuals (1 complete response and 16 partial responses) for an overall response rate of 46% (95% CI, 29.5%-63.1%) and a median PFS of 6.7 months (95% CI, 4.1-9.0 months).¹³⁵ These preliminary results are encouraging and have led to the design of PH3 Study of Mirvetuximab Soravtansine vs Investigator's Choice of Chemotherapy in Women With FR α + Adv. EOC, Primary Peritoneal or Fallopian Tube Cancer (FORWARD I), a randomized phase 3 clinical trial in platinum-resistant ovarian cancer as single agent (NCT02631876)¹³⁶ and further phase 1/2 trials evaluating the combination.

Immunotherapy

The presence of TILs, particularly CD3-positive T cells, in the pathology at the time of diagnosis of ovarian cancer confers an 8-fold improvement in the 5-year survival rate.¹³⁷ However, various histological and molecular subtypes of ovarian cancer differ in their immunogenicity^{29,31,138} and are likely related to a slow development of neoantigens, allowing for immune ignorance. In addition, tumors often downregulate major histocompatibility complex 1 (human leukocyte antigen A [HLA-A], HLA-B, and HLA-C) to evade recognition by natural killer cells and express PD-L1 or secrete molecules, such as VEGF and transforming growth factor β (TGF- β), that inactivate effector T cells and promote immunosuppressive T-regulatory cells and tumor-associated macrophages, thus fueling cancer's escape and impeding the ability of the immune system to respond because of functional exhaustion. At this stage, the tumor is not eliciting an immune response and is considered “cold.” The complex interplay between cancer's genomic changes and intricate microenvironment, not only involving immune cells but also developing hypoxic conditions and angiogenesis, are challenges in the development of effective immunotherapy. Therefore, the current goals of immunotherapy are to balance the recognition and elimination of ovarian cancer without excessive toxicity elicited by activation of the immune system. There has been tremendous progress recently in the development of innovative immunotherapies.

Despite the high expression of PD-L1 in ovarian cancer, immune checkpoint inhibitors as single agents targeting PD-1/PD-L1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have shown modest response rates of approximately 10% to 15%.¹³⁹ Assessments of the antitumor activity as well as the safety of pembrolizumab in patients with recurrent, advanced ovarian cancer have been performed as part of the KEYNOTE-100

study (NCT02674061), which demonstrated modest response and suggested that pembrolizumab monotherapy might have a higher overall response rate in patients with PD-L1 expression.¹⁴⁰ There are presently no approved immune therapies for ovarian cancer.¹⁴¹ Current approaches are ongoing to enhance the activity of checkpoint inhibitors, such as combination with anti-CTLA-4 and anti-PD-1,¹⁴² or a combination of checkpoint inhibitors with chemotherapy, such as pegylated liposomal doxorubicin (JAVELIN Ovarian 200; NCT02580058) or weekly paclitaxel,¹⁴³ epigenetic modifiers such as the DNA demethylating agent azacitidine (Hypomethylating Agent Oral Azacitidine and Durvalumab in Advanced Solid Tumors [METADUR]; NCT02811497), antiangiogenic agents such as bevacizumab (Platinum-Based Chemotherapy With Atezolizumab and Niraparib in Patients With Recurrent Ovarian Cancer [ANITA]; NCT03598270),

and PARP inhibitors (the TOPACIO [NCT02657889]¹⁴⁴ and MEDIOLA [NCT02734004] trials). After these early-phase trials, 5 large phase 3 trials have been leveraged in the front-line setting combining a PD-L1 inhibitor with chemotherapy and bevacizumab, potentially with the addition of a PARP inhibitor.

Another approach involves the use of autologous cell therapy in which a patient's cancer antigen-specific T cells are selected and expanded ex vivo before reinfusion. Preliminary results in ovarian cancer showed feasibility and an initial modest response.¹⁴⁵ A variation of adoptive T-cell therapy involves a gene-transfer technology to introduce a chimeric antigen receptor (CAR) that provides antigen specificity and the ability to trigger T-cell activation. Currently, clinical trials are investigating CARs that target mesothelin, a membrane glycoprotein overexpressed on ovarian cancer cells.

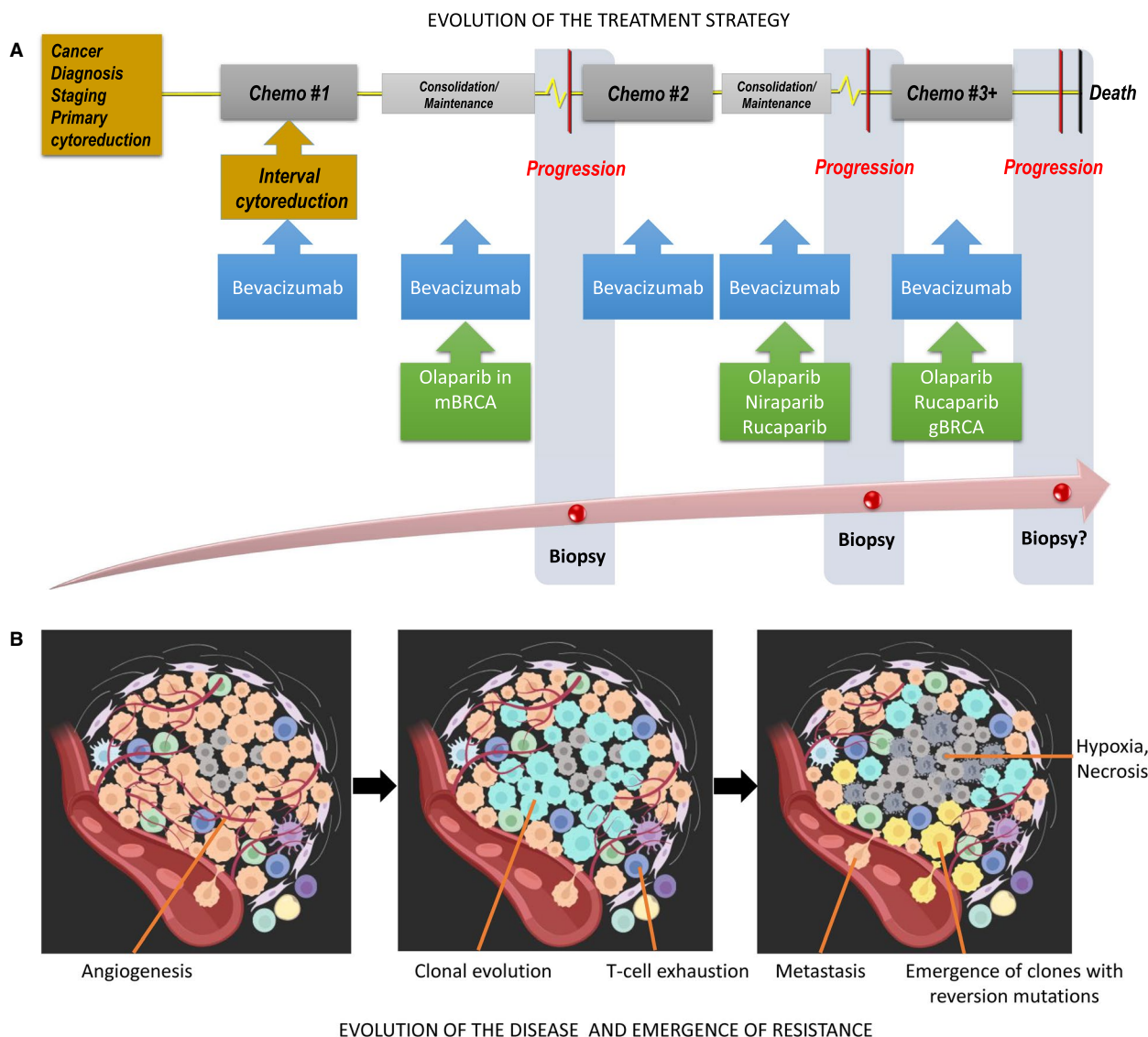


FIGURE 7. Evolution of the Disease and Its Treatment Strategy. Chemo indicates chemotherapy; gBRCA, *BRCA* germline mutation; mBRCA, *BRCA* germline or somatic mutation germline mutation.

Vaccines have not worked well against cancer cells as single agents because of a highly immunosuppressive cancer microenvironment. Current efforts are focusing on combination treatments. For instance, the DeCide trial is investigating a vaccine-based therapy against survivin, a molecule involved in the regulation of cancer cell death, replication, and progression, in combination with chemotherapy (cyclophosphamide) and epacadostat, a potent inhibitor of IDO1, which engages immune tolerance during cancer development (NCT02785250).¹⁴⁶ Similarly, the vaccine against survivin is being investigated in a triple-combination immunotherapy with chemotherapy (cyclophosphamide) and anti-PD-1 (pembrolizumab) as part of the PESCO clinical trial (NCT03029403). Finally, a patient-specific cancer “mutanome” is being explored as a customized and personalized approach to cancer vaccines.^{147,148}

Improving Outcomes

Ovarian Cancer Subtypes

To date, first-line treatment guidelines have largely been driven by HGSOC management. Recent advances in our understanding of EOC have resulted in an adjustment to treatment strategy based on the histological subtype. The management of ovarian cancer is evolving from a one-size-fits all approach to more of an approach in which we are becoming more precise about using surgery, chemotherapy, and several novel therapeutics in the management of the treatment of newly diagnosed and recurrent ovarian cancer. HGSOCs and high-grade endometrioid ovarian cancers are initially highly sensitive to platinum-based chemotherapy (Fig. 4), which remains the backbone of treatment. However, the use of chemotherapy in OCCC and LGSOC is questionable, because they are relatively chemoresistant. Different approaches are being assessed in these rare histologic subtypes exploring hormonal therapy in LGSOC and immunotherapy in OCCC. On the basis of their disease biology, MEK-inhibitor treatment has been evaluated in recurrent LGSOC. Selumetinib has been investigated in a phase 2 trial and produced an overall response rate of 15% and stable disease in 60% of patients with relapsed LGSOC, without a correlation between mutational status and response.¹⁴⁹ These preliminary results were not confirmed in a randomized study (MEK Inhibitor in Low-Grade Ovarian Cancer [MILO]; NCT01849874), which failed to demonstrate an improvement in PFS with the MEK1/MEK2 inhibitor binimetinib (MEK162, ARRY-162) compared with physician-choice chemotherapy after platinum-based chemotherapy.¹⁵⁰

Further investigations are warranted in this area, and collaboration with the GCIG and the rare tumors network is key to developing innovative trials in this population.

Sensitivity and Resistance to Therapy

In addition to distinct subtypes of ovarian cancer demonstrating different sensitivity and resistance to systemic therapy, recent studies have established considerable molecular heterogeneity based on anatomic location of disease in the same individual. This has been demonstrated at both genomic and immunologic levels. The potential causes of this heterogeneity relate to the differential evolution of cancer clones, either as a consequence of the disease or as adaptive responses to therapy, as well as the local tumor microenvironment.¹⁵¹ The consequences of this heterogeneity create a more complex landscape of ovarian cancer, which is dynamic and changing over time in response to clonal evolutionary and therapeutic pressures (Fig. 7). The genomic instability of all HGSOCs and the deficiency in DNA repair in almost 50% of HGSOCs are vulnerabilities that have allowed susceptibility to platinum chemotherapy and PARP inhibitors. Tumor and circulating cell-free DNA (cfDNA) analyses now demonstrate evolutionary adaptation in response to platinum chemotherapy and PARP inhibitors and, in some patients, result in the emergence of bridging reversion mutations, whereas in other patients they lead to multiple parallel mutations, which overcome the prior therapeutic vulnerability and confer resistance.^{117,152}

Treatment at Recurrence

A tremendous amount of research has been conducted and is ongoing to understand sensitivity to therapy as well as intrinsic or acquired resistance and to evaluate strategies to overcome treatment failure. Clinically, HGSOCs and high-grade endometrioid ovarian cancers seem to be sensitive to chemotherapy at presentation, and approximately 80% of patients respond. The median survival for all patients with advanced ovarian cancer is approximately 5 years, but only about 20% will remain disease free after initial therapy. Unfortunately, most patients will recur and follow a chronically relapsing course, requiring repeated systemic therapies. Recurrent disease is not curable, and treatment goals are to control disease, prolong the treatment-free period, control symptoms, and maintain quality of life. A balanced approach to therapy, clinical trials, symptom control, and palliative management is needed. Intrinsic resistance is seen in 10% to 15% of patients defined as *platinum refractory* and is associated with a poor median survival of <9 months. Approximately 20% to 30% of patients will recur or progress within 6 months of completing chemotherapy (termed *platinum resistant*) and have a median OS of approximately 12-18 months. Patients who remain disease free for at least 6 months after completing primary chemotherapy are *platinum sensitive* and will respond better to re-challenge with platinum or platinum doublets

than to alternative chemotherapeutic agents. Patients with platinum-resistant or platinum-refractory disease have poor responses to alternative single-agent chemotherapy, with response rates <15%. The addition of antiangiogenic agents has improved response rates and PFS significantly in platinum-sensitive and platinum-resistant disease and should be considered in these settings. Clinical trials are of paramount importance to define mechanisms of resistance and alternative methods of controlling disease. Currently, frontline clinical trials in ovarian cancer are assessing the combination of chemotherapy, an antiangiogenic agent, a PARP inhibitor, and immune therapy, which will also affect the approach to the disease at recurrence. Strong translational studies are built into these trials to guide patient selection and further therapy development.

Because disease progression is frequently symptomatic, the management of symptoms and attention to patient quality of life have to be considered. Particularly troubling in ovarian cancer are symptoms of bowel obstruction related to peritoneal disease infiltrating into the bowel or causing extrinsic compression. This requires careful conservative management, with attention to diet, fluid intake, bowel rest, and avoidance of a high-fiber diet. Occasionally, if obstruction is caused by single-level obstruction, palliative or defunctioning surgery may provide relief.¹⁵³

The management of recurrent, clear cell, low-grade serous and mucinous carcinomas present more of a therapeutic dilemma because of a lack of responsiveness to conventional chemotherapy. In this setting, the options considered are the potential for surgery or radiation and the availability of clinical trials. Precision medicine approaches to define predictive biomarkers, such as mismatch repair (as in a subset of clear-cell cancers) or mutations in targetable genes are increasingly options for consideration but are still within the realms of experimental therapies and clinical trials.

On the basis of evidence, changing the standard of care requires an objective evaluation of a new treatment through the conduct of different phases of clinical trials. If clinical meaningful benefit has been observed for a patient, this new treatment can be approved by the regulatory agency and be made available for practice. Clinical trials provide access to innovation and may be a new option for patient care. Clinical trials have evolved now in their design to integrate biomarker analyses and to identify potential predictive markers to understand biologically why patients may or may not respond to a given therapy.

Delivery of Care

The variability in providing treatment to all women with ovarian cancer may explain the diversity of outcomes nationally as well as internationally.¹⁵⁴ Making known treatments available should reduce avoidable ovarian cancer

deaths that arise from inequity related to access to cancer care within countries. Although *equality* in cancer care refers to the same treatment being available to all, *equity* means that all patients should have fair and equal access to available treatment opportunities. In well-resourced countries, inequities can stem from several factors, creating great disparity in access to cancer care: demographics, socioeconomic status, and rural/remote residence.^{154,155} Socioeconomic status, which is a measurement based on a person's education, occupation, income, and overall wealth, is closely associated with person's sex, belonging to a minority group, and exposures to cancer risk factors. Rural patients with cancer experience an additional burden of access to treatment that affects their decisions regarding treatment and, ultimately, their quality and longevity of life. To put this in perspective, the 2010 census indicated that 1 in 5 individuals in the total US population (or 19.3%) lives in a rural/remote area.¹⁵⁶ For ovarian cancer, African American women or women of lower socioeconomic status were less likely to access standard treatment and more likely to delay treatment and to receive non-standard treatment or no treatment at all.^{157,158}

Population-based studies have revealed substantial disparities in cancer survival between countries with similar wealth and health care system.¹⁵⁹ Recently, the International Cancer Benchmarking Partnership analyzed population-based cancer registry data from 1995 through 2007 in Canada, the United Kingdom, Australia, and 3 European countries (Sweden, Norway, and Denmark). Globally, the incidence of ovarian cancer in all 6 countries has been falling since 1985, and these declines are largely attributed to the protective effects of oral contraceptives, as well as increased diagnostic intensity that permits earlier diagnosis and treatment of borderline or premalignant lesions, all of which could have contributed to this trend in the long run.¹⁵⁹ However, disparities were still observed, because ovarian cancer survival was the highest in Canada, Australia, and Sweden, followed by Norway, and it was the lowest in Denmark and the United Kingdom.¹⁵⁹ International differences in the cancer registration process were not the likely factors contributing to this trend, because most countries collected high-quality data.¹⁵⁹ Geographical differences were also observed within Canada and Australia, where the ovarian cancer survival rate varied substantially between the regions examined; however, within well-resourced countries, a decrease in disparity is achievable when the resources become properly allocated to increase access to cancer care. Studies have demonstrated that combining outreach efforts with treatment programs for uninsured patients and using patient navigators for access to screening and treatment can nearly eliminate the disparity gap in underserved populations.¹⁶⁰⁻¹⁶³ It is important to ensure

that underserved populations have access to established, evidence-based care to improve ovarian cancer outcomes.

Prevention and Screening

Currently, there is no validated, population-based screening for standard practice. In an unselected population, CA 125 and ultrasound were associated with false-negative and false-positive results and hence were not recommended.¹⁶⁴ Screening high-risk populations by virtue of known inherited predisposition (*BRCA* mutations) is effective, and there are efforts to genomically identify high-risk patients in populations as genomic testing becomes easier and less expensive. In some cases, for example Ashkenazi populations, susceptibility can readily be identified using screening for 3 founder mutations. In addition, efforts are ongoing to improve genomic screening strategy.¹⁶⁵ Potential biomarkers, such as human epididymis protein 4 (HE4) (a glycoprotein secreted by Mullerian epithelia of the female reproductive tract), have been tested in combination with CA 125; a risk of ovarian cancer algorithm has been developed, and transvaginal sonography has been assessed as a biomarker test,^{166,167} but larger confirmatory studies are required. One potential approach involves analyzing DNA methylation patterns in cfDNA as a way to detect EOC early.¹⁶⁸ DNA methylation is a common epigenetic event that causes conformational changes of chromatin or interference with transcription factor binding sites, ultimately resulting in gene transcription silencing.¹⁶⁹ In contrast to the

effect observed in normal cells, DNA methylation of tumor-suppressive genes is commonly observed during cancer cell development and progression.^{169,170} Toward this end, genome-wide DNA methylation mapping is tissue-specific¹⁷¹ and may be used to distinguish between tumor-specific (circulating tumor DNA [ctDNA]) and normal cfDNA. Different studies are ongoing to assess DNA methylation as a potential screening tool.¹⁶⁸ The screening strategy is also evolving based on understanding of ovarian cancer carcinogenesis and potential risk factors.

Conclusions

The management of ovarian cancer has evolved from a “one-size-fits-all” approach to one in which we are becoming more precise about using surgery, chemotherapy, and targeted therapy. This approach will continue to evolve as we discover predictive biomarkers that will help select patients who are most likely to benefit from the therapeutic approach. The use of next-generation sequencing assays upfront will also play a key role for patients with newly diagnosed ovarian cancer, particularly as we continue to challenge treatment paradigms in the first-line management of ovarian cancer. Treatment at the time of recurrence will be guided by further understanding the disease evolution and the resistance mechanism developed by the tumor under treatment pressure. ■

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