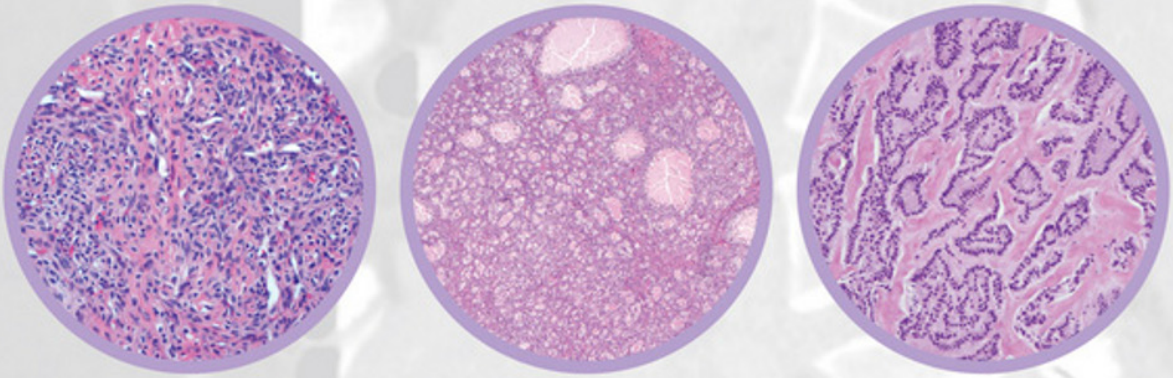
UNCOMMON GYNECOLOGIC CANCERS



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Preface

Tumors of rare histology arising in the gynecologic tract account for a disproportionate number of deaths. Some in the field have advocated that patients with rare gynecologic cancers should be managed by select experts in the field who may have more experience in diagnosing and treating these tumors. This position has resulted in a small number of experts comfortable with the management of more rare and aggressive gynecologic malignancies.

The very rarity of these histologies has made it difficult to collect information for best management strategies derived from prospective clinical trials. Often the reported experience has been limited to retrospective reports from institutions of excellence with more experience.

The primary rationale for this book is to provide a central point of access that will disseminate the most novel diagnostic and treatment strategies for rare gynecologic cancers and make the information accessible to all clinicians caring for these patients. The book aims to place equal emphasis on the clinical and pathological challenges that arise in managing and diagnosing patients with rare gynecologic tumors. To this end, I was privileged to recruit Dr. Robin Young's participation as coeditor. Each chapter contains a section describing the pathologic hallmarks characteristic of each of these rare tumors.

In the last 5 years, advances in the field and new understanding of the molecular biology driving these cancers have resulted in a shift in paradigm for their treatment. Novel management options are centered on the concept of targeted therapies for some of these tumors in place of treatment directed primarily by anatomic site of origin. Even in the modern area of electronic communication, immediate and central access to these newer principles and strategies is difficult. Textbooks contain limited information helpful to clinicians faced with a patient presenting with one of these cancers. The goal of this book is to summarize the available literature as it pertains to the biology, molecular science advances, pathologic diagnosis, imaging options, and treatment strategies for the management of more rare and aggressive gynecologic cancers.

We intend to organize the book so that each tumor is addressed systematically, proving the reader with the same information and clinical tools across each tumor type, so as to better understand the disease process, its diagnosis and appropriate work up, as well as available treatment options. Invited authors represent leaders in the field with recognized expertise in the treatment of rare gynecologic cancers. Given that these conditions often require expertise from a multidisciplinary team, contributors' expertise will be inclusive of basic science, pathology, diagnostic imaging, radiation oncology, gynecologic oncology, and medical oncology. We hope that the reader will find this book systematically organized and easy to access and that it will serve as a guide in the evaluation, diagnosis, and management of patients with more rare gynecologic malignancies. This book is dedicated to our families, our mentors, and all of our patients.

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PART 1

General Principles

1

CHAPTER 1
Molecular Targets in Gynecologic Cancers

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Introduction

The past two decades have brought an exponential increase in our understanding of the molecular drivers of cancer. These insights have led to the concept of personalized cancer care where an individual tumor can be interrogated for specific molecular alterations that may render the cancer susceptible to novel therapeutics that target that particular alteration. The advent of HER2 *(*ERBB2*)* targeted therapies for HER2 overexpressing breast cancer and EGFR inhibitors for *EGFR* (*ERBB1)* gene-mutated lung cancers are notable successes that support the concept that targeting specific molecular profiles can lead to clinical benefit.

Regarding gynecologic cancers, investigators now understand that the underlying drivers of any individual tumor may exhibit marked diversity even if both tumors have identical histology. Identifying key molecular pathways that drive subsets of tumors within ovarian, endometrial, and cervical cancer is crucial to the development of clinical trials utilizing the next generation of targeted therapeutics. This chapter seeks to explore several molecular pathways and proteins that have been shown to contribute to the pathology of significant subsets of ovarian, endometrial, cervical, and vulvar cancers. While the promise of personalized cancer medicine has yet to be fulfilled in gynecologic cancers, therapies targeting the PI3K, MAPK signaling pathways, as well as HER2 and VEGF receptors and PARP protein have been shown to have the potential to improve the therapeutic options for patients.

Phosphoinositol 3-kinase (PI3K) pathway

Oncogenic alterations in the phosphoinositol 3-kinase (PI3K) pathway (Figure 1.1) are frequent in endometrial and ovarian carcinomas [1–3]. PI3K is the upstream activator of Akt, and ultimately mTOR and it contributes to regulation of cell growth, angiogenesis, migration, and survival [2,4]. While three classes of PI3K enzymes have been described, class IA PI3Ks have been most associated with promoting carcinogenesis [5]. PI3K enzymes are activated by receptor tyrosine kinases and G-protein-coupled receptors and transfer phosphate groups to the inositol ring of phosphatidylinositol 4,5 bi-phosphate (PIP2) to produce the signaling molecule phosphatidylinositol 3,4,5 tri-phosphate (PIP3) [1]. This process is negatively regulated by the phosphatase and tensin homologue (PTEN) [5]. Direct downstream mediators AKT and mTOR become activated via phosphorylation leading to transcription events that promote growth, invasion, metastases, and cell survival.

There are many underlying mechanisms for PI3K pathway activation in cancer, including receptor tyrosine kinase activation or amplification, mutation, deletion, silencing of negative regulators of the PI3K pathway, and activation or amplification of downstream kinase mediators [4]. Correlative investigations have demonstrated a significant prevalence of gain of function mutations in the *PIK3CA* gene in breast, colon, pancreatic, brain, ovary, and, recently, high-risk endometrial cancers [2,6–12].

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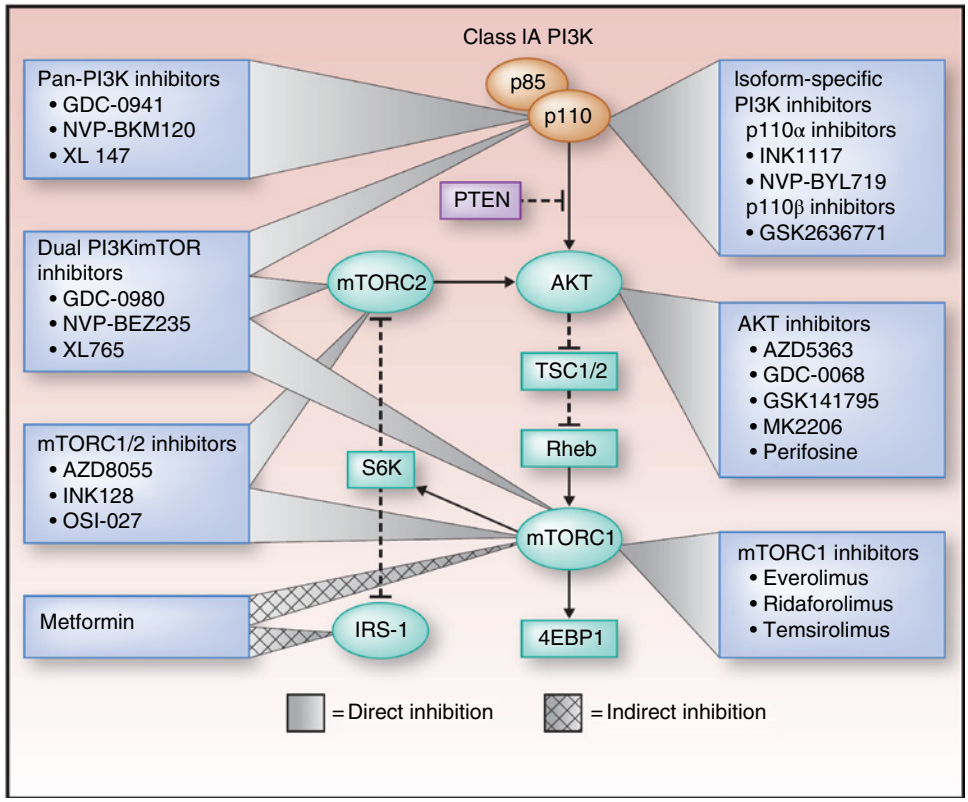

Figure 1.1 PI3K signaling cascade. Schematic showing the PI3K/AKT/mTOR and MAPK pathways and the current agents in development for targeting this cascade.

Recent reports have suggested that gene amplification affects approximately 20–40% of ovarian, endometrial, and cervical carcinomas across all subtypes, while gain of function mutations occur more commonly in endometrioid endometrial cancer and in clear-cell and endometrioid ovarian tumors at approximately a 20% rate [13–18]. Additionally, PI3K activation via these mechanisms was associated with chemoresistance and worsened survival, suggesting targeted inhibition could potentiate conventional platinum-based chemotherapy [19–24].

Given the high prevalence of PI3K pathway activation in gynecologic cancer, targeted strategies inhibiting this cascade could hold tremendous potential to benefit patients with ovarian, endometrial, and cervical cancer [11,25]. Multiple phase I and II clinical trials in endometrial and ovarian cancer have tested agents that target the PI3K pathway [26–28]. Reports from phase II trials of rapalogs inhibiting the mammalian target of rapamycin (mTOR), a downstream mediator of the PI3K pathway, have revealed both objective responses as well as clinically significant disease stabilization [27,29,30]. In addition to the rapalogs, several other classes of PI3K pathway inhibitors including direct PI3K inhibitors, PI3K/mTOR dual inhibitors, and AKT inhibitors are in development for treating ovarian and endometrial cancer [5,28,31]. Early reports from clinical trials suggest that responses to single-agent blockade have an approximately 30% prevalence, occur with or without gain of function mutations in *PIK3CA*, and manifest limited response durability resulting in treatment resistance [26, 32–35]. This observation has resulted in the hypothesis that targeted blockade of one overactive protein in a fundamental pathway, such as PI3K, AKT, or mTOR, may not result in significant clinical response. Understanding resistance mechanisms will be critical in the clinical implementation of targeted therapies.

The identification of a biomarker associated with response will be crucial to the success of targeted therapy in general. For the PI3K pathway, PIK3CA gene amplification and gain-of-function mutation in both the catalytic subunit (*PIK3CA)* and the regulatory subunit (*PIK3R1*) have been described in ovarian, endometrial, and cervical cancer. Some preclinical and clinical data have suggested that those tumors harboring a mutation have increased sensitivity to PI3K pathway inhibition [24,32,36]. Of the gynecologic malignancies, endometrial cancer has the highest prevalence of these molecular alterations. These data have clear implications for selecting candidates for clinical trials so that accrual can enrich for those patients most likely to respond; however, responses to PI3K pathway have been observed in patients that harbor no mutation or amplification, suggesting that additional criteria need to be utilized to identify those women most likely to respond [37–40]. These observations have been confirmed in phase I trials of PI3K inhibitors, although the most robust responses were witnessed in those patients that carry a tumor with specific gain-of-function mutations [41–55]. Selection of endometrial cancer patients by loss of PTEN or gain-of-function mutation in *PIK3CA* for clinical trials of agents targeting PI3K or AKT is ongoing and it has yet to be determined whether or not these signatures confer sensitivity to directed therapy.

Mitogen-activated protein kinase (MAPK) pathway

The mitogen-activated protein kinase (MAPK) signaling pathway is another growth-signaling cascade associated with multiple cancers that is an attractive target for the development of targeted therapeutics [56–58]. The receptor tyrosine kinases (RTK) family is one of the more recognized kinase families. The MAPK kinase kinase (MAPKKK) phosphorylates and activates MAPK kinase (MAPKK) that in turn can phosphorylate and activate MAPK by phosphorylation on the Thr and Tyr resides [59]. Members of the GTPase families, Ras and Rho, relay signals from the receptor complex to the MAPKKK. There are four major MAPK signaling pathways in mammals. These include extracellular signal-related kinase (ERK), ERK5, p38-MAPK 1 and 2, and c-jun N-terminal kinase (JNK)1, 2, and 3. Typically, the ERK pathways respond to growth factor stimuli and p38 MAPK and c-jun are activated in response to stress stimuli such as UV irradiation and inflammatory cytokine [60,61]. There are, however, examples of growth factors activating the p38-MAPK and c-JNK via cross talk.

Ras proteins are integral intermediate modulators connecting the membrane receptors on the cell surface with their downstream effector MAPK signaling pathways. It has been reported that between 11.6% and 83% of endometrioid endometrial cancers harbor k-ras mutations [62–67]. Investigations utilizing endometrial cancer cell line models have suggested that MAPK/ERK1-2 is involved in promoting endometrial cancer cell proliferation in a number of *in vitro* studies utilizing *KRAS* mutant cell lines and MEK inhibitor [68–73].

A recent study further highlights the complexity of the interaction among the signaling pathways. Metformin, an oral biguanide commonly used for the treatment of type II diabetes, is thought to inhibit cell proliferation locally via activation of the AMPK signaling pathway, counteracting the growth-promoting effects of the PI3K/AKT/mTOR pathway. Recently, it was shown to be effective in down-regulating of ERK and AKT signaling and increasing cell death in endometrial cancer cells that constitutively expressed k-ras in endometrial cancer. Metformin resulted in concentration-dependent activation of AMPK in endometrial cancer cell lines [74,75]. The MAPK inhibitor, Selumetinib® (AZD-6244) is being tested in the recurrent endometrial cancer (NCT01011933) [75].

MAPK appears to play a significant role in the pathophysiology of low-grade serous cancers (LGSC) of the ovary, as well as serous borderline tumors. While approximately 85% of epithelial ovarian cancers are serous, only about 10% of these are LGSC [76–78]. LGSC rarely have p53 mutations but can have mutations of *KRAS* or *BRAF*. In contrast, high-grade serous cancers typically have evidence of p53 mutations and rarely *KRAS* and *BRAF* mutations.

An estimated 80% of ovarian LGSC have an active MAP kinase pathway [79]. Likewise, 78% of its putative precursor lesion, borderline tumors, also historically termed "low malignant potential (LMP) tumors," has been shown to have an active MAP kinase pathway [79,80]. While the LGSC and high-grade serous carcinomas have different clinical outcomes and molecular profiles, they are both treated with surgery followed by platinum and taxane-based therapy. The identification of

specific pathways may result in targeted treatments leading to better outcomes.

In a phase II Gynecologic Oncology Group (GOG) trial of MEK inhibitor Selumetinib® (AZD-6244), a 15% response rate was reported. There was a stable disease rate of 65% and a medium progression-free survival (PFS) rate of 11 months in patients with recurrent LGSC [81].

Human epidermal growth factor receptor 2 (HER2)

Human epidermal growth factor receptor 2 (HER2), also called HER2/*neu* or c-erbB2 is a growth factor receptor tyrosine kinase implicated in many cancers. Amplification of the *HER2 (ERBB2)* gene and overexpression of the HER2 protein have been described in breast, colon, gastric, esophageal, ovarian, and endometrial cancers [82–88]. The *HER2*gene encodes a 185-kDa transmembrane tyrosine kinase receptor and is located on chromosome 17q21. HER2 is a well-characterized member of the human epidermal growth factor receptor superfamily that consists of three other tyrosine kinase receptors (HER1/EGFR, HER3, and HER4) that when activated by ligand, can dimerize and induce signal transduction through the MAPK and PI3K/AKT/mTOR signaling pathways [89–96]. This downstream activation leads to induction of genes that promote oncogenic transformation via cell survival, proliferation, angiogenesis, and metastasis (Figure 1.1).

High-grade endometrial cancer, including grade 3 endometrioid, uterine serous carcinoma (USC) and carcinosarcoma, has a 10–30% rate of *HER2* gene amplification, with up to 70% of tumors exhibiting HER2 protein overexpression, which has been associated with decreased overall survival [97–103]. Despite promising preclinical data, the two phase II trials of anti-HER2 therapy in recurrent endometrial cancer showed poor responses [99, 100]. These trials suggest that single-agent therapies directed against HER2 may have limited activity, possibly due to innate or drug-induced resistance [104].

In a trial of 800 ovarian carcinomas screened for membrane HER2 protein expression, 12% of tumors showed 2 or 3+ protein expression. Given the low prevalence of this event in the majority of ovarian cancers, its therapeutic value is likely limited [104–107].

Vascular endothelial growth factor (VEGF)

Angiogenesis is a key component of all tumor cell biology and has recently become a promising therapeutic target for women undergoing treatment for gynecologic cancers [108–123].

Most anti-angiogenic therapeutics target the VEGF signaling pathway. The VEGF family includes six related proteins. The most important member is VEGF-A, which was discovered first and was called simply "VEGF" before other variants (VEGF-B, C, and D) with more specialized functions involving embryonic and site-specific angiogenesis were described [124–128]. VEGF-A will be referenced as simply "VEGF" in this chapter.

Within the gynecologic malignancies, angiogenic signaling has been most studied in ovarian cancer [129]. Data suggest that angiogenesis plays a key role in metastatic spread of ovarian carcinoma, and increased angiogenic signaling has been shown to be a poor prognostic factor in ovarian cancer [122,130–137]. Analyses of ovarian cancer cell lines and human tumors have demonstrated higher levels of pro-angiogenic factors, such as hypoxia-inducible factor-1 (HIF-1), VEGF, and PDGF, as well as lower levels of anti-angiogenic factors, such as endostatins [136,137].

Retrospective studies in high- and low-grade ovarian cancer suggested benefit of utilizing bevacizumab, a humanized monoclonal antibody to circulating VEGF, in the recurrent, chemotherapy refractory setting [138–143]. Two subsequent phase II trials were published showing response rates as high as 15–21%, with a clinical benefit rate (stable disease rate + response rate) of greater than 60% [140,141]. Phase III trial data have documented the activity of bevacizumab in ovarian cancer [144–163]. In 2012, the OCEANS trial reported that combining bevacizumab with carboplatinum and gemcitabine significantly prolonged the PFS by 4 months in women with recurrent platinum-sensitive ovarian cancer compared to the combination without bevacizumab [144,145]. Notably, the experimental arm of this trial administered the bevacizumab to patients until progression of disease, raising the possibility that extended anti-angiogenic therapy also contributed to the survival benefit observed. The recent report of the AURELIA trial (NCT00976911) that randomized women with platinum-resistant ovarian cancer to liposomal doxorubicin, topotecan or weekly

paclitaxel with or without bevacizumab suggested that adding anti-angiogenic therapy improved PFS when compared to use of single-agent chemotherapy alone. The most robust synergy was noted to be paclitaxel and bevacizumab with an almost 11-month PFS prolongation [146,147]. Use of bevacizumab in first-line and maintenance ovarian cancer has been evaluated via two phase III trials, GOG 218 and ICON 7, resulting in an improved PFS but no impact on overall survival [161–163].

A growing number of other anti-angiogenic agents have entered clinical trial that target VEGF or its receptor. A phase II trial using VEGF-Trap (aflibercept) with docetaxel demonstrated a 54% response rate in recurrent ovarian cancer [148]. In addition, numerous novel receptor tyrosine kinase (RTK) inhibitors directed against VEGF receptor have been tested. Agents such as sorafinib, sunitinib, and pazopanib interact with multiple additional RTKs in addition to the VEGF receptor including the PDGF receptor, epidermal growth factor receptor (EGFR), and c-Kit. Limited clinical trials in women with recurrent ovarian cancer have been performed using these multiple RTK inhibitors and these investigations have not revealed responses as robust as those observed with bevacizumab [149–153]. None of the trials testing angiogenic agents in gynecologic cancers have tested for heightened activation of the VEGF pathway and this type of approach may be required to enrich for relevant clinical responses for some of the multikinase inhibitors [151,154–163].

The role of angiogenesis in endometrial cancer is less well-understood. Immunohistochemical staining for mean vessel density (MVD) counts has been employed in the preclinical setting to investigate angiogenesis in endometrial hyperplasia and carcinoma. Abulafia *et al.* compared MVD counts in endometrial hyperplasia compared to Stage I endometrial carcinoma finding that as the histology progressed from simple hyperplasia to invasive carcinoma, so too did the MVD counts [164]. The authors concluded that higher tumor grade and depth of invasion were directly correlated with increasing angiogenic activation [164]. Kaku *et al.* confirmed these findings with their investigation of 85 specimens from patients with Stage I and II endometrial carcinoma, where MVD was strongly correlated with tumor grade, depth of myometrial invasion, as well as lymphovascular space invasion [165]. An additional preclinical study supported the finding that higher MVD counts are associated with worse PFS and overall survival (OS), confirming that angiogenesis appears to be a clinically relevant signature in endometrial cancer [166].

One phase II trial tested single-agent sorafenib, a multitarget tyrosine kinase inhibitor (TKI), finding a modest 5% response rate [167]. Another phase II trial investigated sunitinib in this same population and reported a 15% response rate with major toxicities limited to fatigue and hypertension [168]. Bevacizumab has been studied in a phase II trial (GOG 229E) demonstrating a 13.5% response rate which compared favorably with other single agents tested in the same setting. Tumor and serum VEGF levels were quantified by immunohistochemistry and ELISA and correlated with response and survival. High tumor VEGF staining correlated with improved survival, while elevated circulating serum VEGF levels correlated with decreased survival and treatment failure [169]. This study suggests that VEGF levels could serve as biomarkers to predict which patients are most likely to respond to VEGF directed therapies.

The development of abnormal vascularity has been described in cervical cancer [170]. Investigations examining the histology of early and late cervical cancers have demonstrated that almost 3% of patients with carcinoma in situ (CIS) produced abnormal vessels noted at the time of colposcopy compared to 50% of patients with microinvasive disease and 100% of patients with frankly invasive cancer [171]. Studies examining MVD and VEGF expression have inconsistently found that MVD counts in conjunction with depth of invasion, regional lymph node involvement, and lymphovascular invasion can offer independent prognostic information for women with cervical cancer [172–177]. Higher levels of VEGF protein expression have been correlated with tumor size, lymphovascular space invasion, and lymph node metastases, as well as a shorter disease-free interval [178–180].

Bevacizumab was tested in a phase II clinical trial for women with recurrent or persistent cervical cancer. In this trial (GOG227C), Monk and colleagues observed a 10.9% response rate, with a 24% stable disease rate at 6 months in a heavily pretreated and radiated population. The median PFS was 3.4 months, with responders manifesting a 6.2-month duration of response [181,182]. While additional trials have tested agents such as pazopanib and sunitinib (both targeting VEGFR, PGFR, c-Kit), response rates were limited with modest improvements in survival measured in weeks [181,183]. In the phase III trial,

GOG240 (NCT00803062) of advanced-stage, recurrent/persistent cervical cancer, bevacizumab was evaluated in a four-by-four design with cisplatinum/paclitaxel, and topotecan/paclitaxel. Preliminary data confirmed a 3.7-month OS advantage with use of bevacizumab in combination with either cytotoxic doublet.

Perhaps one of the most promising targets in gynecologic cancers, VEGF has been the focus of many basic, translational, and clinical trial investigations, suggesting it to be a key promoter in the development and progression of epithelial ovarian, endometrial, and cervical cancer. Markers of altered angiogenesis, such as MVD or VEGF expression harbor prognostic value in these gynecologic malignancies, and clinical trials targeting mediators of neovascularization have been shown to have clear benefits in significant subsets of patients. Future challenges include the development of biomarkers that associate with response, managing the costs of expensive therapies, and vigilance in assessing whether or not anti-angiogenic therapies have unintended consequences, such as a rebound effect, which could render tumors more resistant to conventional chemotherapies.

Poly (adenosine) diphosphate [ADP]-ribose polymerase (PARP)

Perhaps one of the most notable successes of translational therapeutics has been the advent of poly (adenosine) diphosphate [ADP]-ribose polymerase (PARP) inhibition in women with a germ-line mutation in the *BRCA1* and *BRCA2* genes. PARP inhibition in patients with *BRCA* mutation has produced encouraging responses suggesting that selective targeting of a molecular fingerprint can produce responses in the select population manifesting the signature.

A subset of 5–10% of patients with epithelial ovarian cancer has germ-line inactivating mutations in the *BRCA1* and *BRCA2* genes [184–187]. Approximately, 90% of hereditary ovarian cancer is *BRCA*-associated [188]. Both *BRCA1* and *BRCA2* are tumor suppressor proteins involved with homologous recombination (HR) required for repair of double-stranded DNA breaks [189,190]. A germ-line *BRCA* mutation constitutes the first "hit" that leads to a marked predisposition for patients to develop breast and ovarian cancer, in addition to other cancers such as prostate and pancreatic [191]. These cancers are thought to arise as a result of inactivation of the other functioning *BRCA* allele. When both alleles are mutated, somatic cells utilize less meticulous repair DNA mechanisms intended for single-strand breaks, specifically base excision repair (BER), to compensate for accumulated DNA damage leading to oncogenic transformation [192]. The BER process is mediated by the PARP enzyme [193,194]. In cells lacking *BRCA*-induced HR, the inhibition of PARP would lead to apoptosis as a result of failed DNA repair. Researchers have coined the term "synthetic lethality" [195,196] to describe this *BRCA*-mutation-dependent cytotoxic effect because PARP inhibition in the setting of wild-type *BRCA* leads to minimal cellular toxicity. These characteristics make PARP inhibition an attractive therapeutic strategy.

Numerous inhibitors of PARP have been developed and a recent phase I trial evaluated olaparib (AZD 2281), an oral PARP, in 60 diverse cancer patients, finding that of the 15 women in this heavily pretreated cohort with ovarian cancer and a *BRCA* mutation, 8 patients responded, and 1 patient had stable disease [197,198]. Another phase I trial showed similar efficacy in platinum-resistant and sensitive ovarian cancer [199]. In a follow-up phase II study of women with ovarian cancer, Audeh and colleagues tested olaparib in recurrent, *BRCA*-mutated ovarian cancer and confirmed an overall response rate of 25% in 57 patients that had received a median 3–4 prior lines of therapy. At the higher dose 400 mg BID, the response rate was 33% with minimal toxicity [200].

Emerging data suggest that PARP inhibition not only offers clinical benefit to patients with *BRCA* gene mutation, but also appears to have activity in those who lack an identified mutation. In a trial of olaparib therapy in 91 women with recurrent ovarian cancer, a response rate of 41% was observed if a *BRCA* mutation, but interestingly a 24% response rate was manifest in the patients with sporadic ovarian cancer [201]. Researchers are optimistic that like in triple-negative breast cancer [202–204], responses to PARP inhibition will be observed in patients with ovarian cancer that lack *BRCA* mutation, likely secondary to epigenetic *BRCA* inactivation or "BRCAness" that has been observed in up to 31% of sporadic ovarian tumors [205–208].

PARP inhibition has also been evaluated in the maintenance setting. In randomized trial of patients with recurrent ovarian cancer to either olaparib or placebo, a significant PFS benefit (8.4 vs. 4.8 months, respectively, HR 0.35; 95% CI 0.25–0.49, $P < 0.001$) was noted. No significant difference in overall survival has been reported.

Utilizing PARP inhibition in concert with cytotoxic chemotherapy has also been a rationale approach supported by preclinical data suggesting a synergy [209,210]. Simultaneous use of platinum agents with PARP inhibitors potentiates toxicity. Despite the potential for this toxicity, trials examining PARP inhibitors such as olaparib, veliparib (ABT-888), and iniparib (BSI-201) in combination with carboplatin-containing regimens for women with platinum-sensitive and resistant ovarian cancer are expected to reveal strong responses that justify the development of upfront trials examining the use of combined therapy (NCT01033123, NCT01033292, NCT01650376, NCT01081951, NCT01459380). Synergistic effects are anticipated, particularly in those patients with *BRCA* gene mutations, though this has yet to be reported.

PARP inhibition stands as a proof of concept that molecular signatures can perform as potent biomarkers to predict response to therapies that target that specific molecular alteration. While the most robust responses in ovarian cancer have been reported in those women with a germ-line *BRCA* gene mutation, emerging genomic and clinical data suggest that a significant proportion of women with ovarian cancer who lack mutation may benefit from PARP inhibition. It is currently unclear if PARP inhibition will offer the greatest benefit in the upfront, maintenance, or recurrent setting, but the next generation of trials is expected to provide more guidance on how best to incorporate PARP inhibition into the clinical care of women with ovarian cancer.

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2

CHAPTER 2
Imaging of Rare Gynecologic Tumors

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Imaging guidelines

Imaging plays a central role in the evaluation of patients with symptoms and clinical presentations suggesting underlying pelvic pathology. As many patients present with nonspecific symptoms (i.e., pain, bloating, bleeding), any patient with concerning or unclear physical evaluation findings will typically undergo radiologic evaluation. In general, depending on the patient's symptoms, this initial radiologic evaluation will be performed with ultrasound. Occasionally, computed tomography (CT) may be a good initial choice in some patients, particularly if a large mass or large volume ascites is present on physical examination, for which evaluation by ultrasound can be limited. Magnetic resonance imaging (MRI) is typically utilized as a follow-up to ultrasound [1]. 18 F-fluorodeoxyglucose positron emission tomography—CT (PET/CT) is typically reserved for patients with known malignancy—for initial staging, evaluation of treatment response, and evaluation for recurrent or metastatic disease [2–4].

Ultrasound is an optimal first step in the evaluation of patients with suspected pelvic pathology. It is quick to perform, and is without ionizing radiation; however, it is operator-dependent [5]. Ultrasound is particularly useful in evaluation of cystic and solid lesions of the pelvis, as it is able to demonstrate any complexity or nodularity of cystic lesions, as well as evaluate for vascular flow within any solid components. Ultrasound of the pelvis should optimally be performed with transabdominal and transvaginal technique, unless the patient is unable to tolerate the endovaginal probe [6]. Potential drawbacks of ultrasound include suboptimal evaluation of the collapsed vagina and vulva, though these can sometimes be evaluated using translabial ultrasound [7]. Additionally, in patients with large adnexal or pelvic masses, ultrasound may be limited in determining the organ of origin, given the limited scope of imaging field. Once the patient has a known malignancy, ultrasound is insensitive in staging, and CT or MRI should be utilized [3].

CT is an excellent initial imaging modality in any patient who presents with physical examination findings suggesting large abdominopelvic mass, large volume ascites, or signs of pathology not confined to the pelvis. It is easily available and scanning is quick (usually <1 min) [5]. In these patients, CT should be performed with both intravenous and oral contrast if the patient's renal function allows. In particular, the use of intravenous contrast allows for evaluation of abdominal/pelvic parenchymal organ enhancement, as well as the assessment of enhancing masses. Oral contrast agents allow for delineation of the bowel; this is particularly useful in allowing for any potential cystic lesions to be differentiated from bowel, as particularly small bowel can lie within the pelvis and occasionally demonstrate fluid distention, making such distinction difficult. CT utilizes ionizing radiation, which can be a concern particularly in younger patients [1].

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