

# Chapter 18

## Ovarian Cancer

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### 18.1 Overview

The World Health Organization (WHO) classifies ovarian neoplasms according to their histological differentiation, namely epithelial tumors, germ cell tumors, and sex cord-stromal cell tumors [1]. Epithelial ovarian tumor represents the largest group, accounting for 91 % of malignant cases. Serous carcinoma is the most common epithelial subtype [2]. Epithelial ovarian cancer (EOC) is now recognized as a heterogeneous disease and is divided according to histologic subtypes: high-grade serous, low-grade serous, endometrioid, clear cell, mucinous, and Brenner carcinoma. Each histologic subtype is associated with distinct histologic features, molecular genetics, and clinical behavior. The etiology of EOC remains unclear [3]. Several factors, including genetic, reproductive, hormonal, and behavioral factors have been suggested to increase the risk for ovarian cancer. Genetic factors have the strongest and most consistent association with increased risk of EOC. At least 10 % of all EOC are reported to be hereditary, with the majority (about 80 %) of these

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related to mutations in BRCA genes and 10 % related to mutations associated with the Lynch syndrome [4]. Currently, the standard treatment of ovarian cancer includes cytoreductive surgery and combination chemotherapy with a platinum-doublet. This approach yields a 5-year overall survival, all stages combined, of 44 % [2]. The main reason for poor outcome is the advanced stage at diagnosis. Patients diagnosed at early stages have a 75 % chance of cure. This article will not focus on the screening for ovarian cancer. For a discussion of ovarian cancer screening see [5].

For the last 10–15 years, the molecular study of the biology of cancers has led to new targeted agents with tremendous success in some cancers such as chronic myeloid leukemia [6, 7]. Within each histology subtypes, a molecular sub-classification is being discovered, but it has not been used widely for clinical care yet [8]. Over the last two decades, many clinical trials have studied new combinations and strategies to improve outcome and decrease toxicity, with more successes for the latter than the former. This article will provide an overview of EOC and discuss recent advances in the management of the disease.

## 18.2 Epidemiology

EOC is the eighth most commonly diagnosed cancer and is the seventh leading cause of cancer death in females worldwide, accounting for 3.7 % (about 225,000) of the total new cancer cases and 4.2 % (about 140,000) of the total cancer deaths among females [9]. The world incidence and mortality rates of EOC are estimated to be 6.3 cases per 100,000 and 3.8 cases per 100,000, respectively [9]. The incidence rate varies widely among different ethnic groups and is higher in more developed regions. The highest incidence and mortality rates are in Europe, especially the Northern and Eastern European countries, and in North America. The lowest incidences are observed in Asia and Africa, as shown in Table 18.1 [10]. These regional patterns might help assessing environmental or genetic risks, and cultural factors that may influence EOC incidence [11].

In the United State, ovarian cancer is the eight most common cancer diagnosed, and the fifth most common cause of cancer death. In 2013, there were about 22,240 new cases of and 14,030 deaths from ovarian cancer. Ovarian cancer accounts for about 3 % of all cancers among women. The lifetime risk for women is 1 in 73, and 1 in 95 will die from this cancer. The median age at diagnosis is 63 years of age. Recently, the incidence rate has trended down by 0.9 % per year and the death rate has also been significantly decreasing, by 2.0 % per year, from 2005 to 2009 [2], trending with the reduction in hormone replacement usage after menopause. The incidence of EOC appears to vary by race, although the effects of race are difficult to separate from other factors such as environmental associations related to culture, geography, and socioeconomic status. The incidence is higher among white women, followed by American Indian/Alaska Native women, American African, and Asian/Pacific Islander, as shown in Table 18.2 [2]. African American women have the highest mortality/incidence (M/I) ratios, because they present at higher stages com-

**Table 18.1** Estimated incidence and mortality rate of ovarian cancer in 2013

Population	Incidence		Mortality	
	Numbers	ASR <sup>a</sup>	Numbers	ASR <sup>a</sup>
World	224,747	6.3	140,163	3.8
More developed regions	99,521	9.3	64,439	5.1
Less developed regions	125,226	4.9	75,724	3.1
Europe	65,697	10.1	41,448	5.4
Northern America	23,895	8.7	17,197	5.4
Australia/New Zealand	1,601	7.8	1,079	4.6
South America	12,405	6.2	6,831	3.4
Asia	102,485	5.1	60,142	3.0
Africa	13,976	4.2	10,443	3.4

<sup>a</sup>ASR Age-specific rate (per 100,000 person)

**Table 18.2** Age-adjusted epidemiology by race (2006–2010 SEER data)

Race	Incidence rate (per 100,000 person)	Mortality rate (per 100,000 person)	Mortality/Incidence (M/I) ratios
All	12.5	8.1	0.65
White	13.3	8.4	0.63
White Hispanic	11.3	6.1	0.54
White Non-Hispanic	<b>13.5</b>	<b>8.6</b>	0.63
American African	9.7	6.7	<b>0.69</b>
Asian/Pacific Islander	9.4	4.8	0.51
American Indian/ Alaska Nat	10.7	5.5	0.51
Hispanic	11.3	5.8	0.51

Bolded numbers show the highest incidence for the category

pared to women of other racial or ethnic groups [2, 12]. High-grade serous carcinoma (HGSC) is the most common and lethal subtype, accounting for 68 % of all ovarian carcinomas [13]. Most patients with HGSC usually present at an advanced stage at the time of diagnosis. Low-grade serous carcinomas (LGSC) are less common and account for approximately 2 % of all cases of EOC [13]. Patients with LGSC present at a younger of age compared to women with HGSC. LGSC behaves in an indolent fashion and is usually confined to the ovary upon presentation. Clear cell carcinoma (CCC) is the second most common EOC after serous EOC, accounting for 5–25 % of all EOCs. The prevalence varies considerably with geography [2, 14, 15]. In North America and Europe, the prevalence of CCC is about 5–13 %. In Asian countries, especially Japan, the prevalence of CCC is much higher, from 19 % to 24.5 % [15–17]. In Asian women living in the United States, CCC remains more prevalent than in Caucasians [2]. CCC usually presents at an early stage, but is associated with a poor prognosis across all stages due to the fact that it is relatively resistant to standard platinum-based chemotherapy [18–20]. Endometrioid carcinoma (EC) accounts for approximately 11 % of cases of

EOC. Patients with EC are usually at both low-stage and low-grade on presentation [13]. The least common EOC is the mucinous carcinoma (MC) with a prevalence of 2–4 % of EOC cases [21, 22].

Primary peritoneal cancer and primary fallopian tube cancer are rare malignancies, but share many similarities to ovarian cancer. These three cancers are clinically treated with the same modalities [11]. The incidence of both primary peritoneal cancers and primary fallopian tube cancers is increasing. This may reflect a recent increase in the awareness of the new EOC origin theory (see below), and a reduction in the misclassification of peritoneal and particularly tubal carcinomas among pathologists [23, 24]. In the United States, the incidence rate of primary peritoneal cancer is about 0.678 cases per 100,000. The mean age at diagnosis of primary peritoneal cancer is 67 years of age and compared to ovarian cancer, the disease presents at advanced stages [24]. Primary fallopian tube carcinomas are rare, accounting for 0.41 cases per 100,000 [23]. Adenocarcinoma is the most frequent histology seen in the fallopian tube [1]. The vast majority of primary fallopian tube carcinomas are unilateral at diagnosis [23].

### 18.3 Heterogeneity of Epithelial Ovarian Carcinomas

Traditionally, EOC has been considered a single disease. Today, EOC is recognized as a group of highly heterogeneous diseases. Based on distinctive clinical, pathologic, and molecular genetics features, Kurman et al. proposed a dualistic model that divides EOC into two groups: type I and type II, which correspond to two main pathways of tumorigenesis [25]. Type I tumors include low-grade serous, low-grade endometrioid, clear cell, mucinous carcinomas, and Brenner tumors.

These slow growing tumors are genetically stable and characterized by somatic mutations in a number of different genes including the AT-rich interactive domain 1A gene (*ARID1A*), mutations in the beta-catenin gene (*named CTNNB1*), *KRAS*, *BRAF*, *PIK3CA*, *PPP2R1A*, and *PTEN*, while *BRCA1*, *BRCA2*, or *TP53* are rarely inactivated [26–29]. Type II tumors comprise HGSOC, high-grade endometrioid carcinoma, malignant mixed mesodermal tumors (carcinosarcomas) and undifferentiated carcinomas. They are biologically aggressive tumors that are usually diagnosed at advanced stages. Type II tumors, in contrast to type I, have high level of genetic instability with frequent mutations or epigenetic modifications in *TP53* and *BRCA1*, *BRCA2*, or *BRCA* promoters [8, 25]. Mutations typically found in the type I group are not seen in type II. This molecular categorization provides an initial step in understanding the heterogeneity of ovarian cancers and their pathogenesis, and might be of clinical utility [8].

## 18.4 Cellular Origin of Epithelial Ovarian Cancer and Pathogenesis

The ovary is covered by a single layer of epithelium, which is named ovarian surface epithelium (OSE). OSE expresses mesenchymal markers such as vimentin and N-cadherin. Structurally it closely resembles the mesothelial lining of the peritoneal cavity [30]. The results from several epidemiologic studies show a significant risk reduction of ovarian cancer related to parity and oral contraceptive use, both of which are associated with a decrease in ovulation [31]. Consequently, in 1971, the so called “incessant ovulation” hypothesis postulated that repeated ovulation and ruptures in the mesothelial lining of the ovaries activate repair mechanism, which can cause metaplasia or neoplastic transformation of the OSE [32]. This hypothesis asserts that the cellular origin of EOC is the OSE, which includes the lining of cortical inclusion cysts [32, 33]. New molecular and clinicopathologic studies fail to support this hypothesis. An alternative hypothesis is that EOC originates from the Müllerian system. During the embryonic development of the female reproductive system, HOX genes are expressed uniformly along the Müllerian duct axis and are involved in Müllerian duct differentiation during embryogenesis. In adult, their expression is spatially specific: HOXA9 is only expressed in the fallopian tubes, HOXA10 in the developing uterus, HOXA11 in the lower uterine segment and cervix, and HOXA13 in the upper vagina [34]. HOXA7 has been suggested to promote differentiation of ovarian epithelial cell and, in combination with HOXA9, HOXA10 or HOXA11, to result in the histological identity of EOC with serous papillary, endometrioid and mucinous (endocervical-type) tumors, respectively [35]. None of the HOX genes is expressed in normal OSE. Several studies reported a gain of expression of HOX in EOC, thus indicating that EOC may originate from Müllerian epithelium. Consistent with this hypothesis, immunohistochemical studies demonstrate that most ovarian cancers express PAX8, a crucial transcription factor for organogenesis of the Müllerian system, but not calretinin, a marker shown on mesothelium or OSE [36]. However, some type II EOC might be of non-Müllerian origin. Most mucinous EOCs display intestinal rather than endocervical-type mucinous differentiation and therefore do not qualify as müllerian-type tumors. Brenner EOC, also called transitional cell EOC, resembles urothelium which is not Müllerian either.

Current histologic evidence favors the fallopian tube as the site of the neoplastic transformation, with cells shedding from the tubes to the surface of the ovaries and more rarely into the peritoneal cavity, explaining the similarity in behaviors among these cancers. The neoplastic stem cell originates from the fallopian tube, but grows on the surface of various organs in the geographic area “brushed” by the fallopian tubal fimbriae [22]. Histologic in depth examination of the fallopian tubes commonly identifies occult invasive cancer with histologic and molecular features resembling the ovarian HGSOC seen in women with BRCA1/2 germline mutation [37] or with sporadic HGSOC [38–40]. The preinvasive tubal lesion related to HGSOC is called serous tubal intra-epithelial carcinoma (STIC) and is characterized

by stratified, disorganized, enlarged columnar epithelial cells with highly atypical nuclei [41, 42]. STIC was first described in the fimbriae of fallopian tubes of women with BRCA1/2 germline mutations who are undergoing prophylactic salpingo-oophorectomy [42]. These lesions were not found in the ovaries of these women. Multiple studies have shown that, when carefully sectioning and extensively examining the fimbriated end by using a protocol called “Sectioning and Extensively Examining the Fimbriae (SEE-FIM)”, occult intraepithelial and invasive tubal malignancies were sevenfold higher in BRCA mutation carriers [43]. STIC is unilateral in 88 % of cases and located in the fimbriae in over 90 % of cases [38, 39, 44]. STIC occurs not only in women with a genetic predisposition to ovarian cancer but also in 48–59 % of sporadic cases of HGSOC [37, 38, 41, 44, 45]. STIC is the earliest histologically recognizable pre-neoplastic lesion in the pathogenesis of HGSOC, and has identical *P53* mutation, indicating a clonal relationship [38, 39]. Besides mutated TP53, both STIC and HGSOC express several tumorigenesis-associated oncoproteins, such as p16, fatty acid synthase (FAS), Rsf-1, and cyclin E1, whereas these proteins are rarely detected in the adjacent normal tubal epithelium [46]. Therefore, the tubal epithelium is likely the cell of origin of HGSOC, and STIC is its precursor lesion. This theory is still debated, as the evidence is not always conclusive. However, there is increasing acceptance that the fallopian tube is likely the origin for HGSOC.

Extensive epidemiological, histopathological, and molecular evidence suggests that LGSC also develops in a stepwise pattern, from tubal epithelium to borderline tumor, then sometimes to cancer [47, 48]. One new hypothesis is that mucinous and transitional cell carcinomas may arise from transitional-type epithelial nests at the tubal-mesothelial junction by a stepwise progression of tumorigenesis starting in borderline tumors [49]. Endometrioid and clear cell ovarian carcinomas arise from foci of endometriosis [28, 50–52].

## 18.5 Histopathology and Molecular Signaling Pathways

### 18.5.1 High-Grade Serous Carcinoma

Histopathological features of HGSOC consist of marked nuclear atypia with a mitotic index usually of 12 mitoses per 10 high-power fields or higher [53, 54]. Molecular testing, including immunostaining, has indicated that the morphological spectrum of HGSOC is broader than the classical solid, glandular, transitional-like, or papillary architectural patterns. The Cancer Genome Atlas (TCGA) in-depth molecular survey of more than 400 cases of HGSOC showed that single gene mutations are uncommon in HGSOC (less than 10 % of cases), with the exception of *P53* [55]. Only nine additional genes have recurrent mutations at a statistically significant level including *BRCA1*, *BRCA2*, *RBI*, *NF1*, *FAT3*, *CSMD3*, *GABRA6*, and *CDK12* genes. The hallmark of HGSOC is not the presence of single gene mutations, but the numerous somatic copy number alterations (SCNA), with more than 100 recurrent amplifications and deletions identified. Of these genetic changes, the

most studied ones involve DNA repair. *P53* mutations are present in more than 90–95 % of HGSOC cases. Tumor suppressor TP53 plays a key role in cell cycle regulation and DNA repair. Upon cellular stress, particularly DNA damage, TP53 arrests cellular growth and repairs DNA damage before cellular replication occurs. If the damage is beyond repair, TP53 triggers apoptosis [56]. *P53* mutations lead to inefficient DNA repair, genetic instability, and uncontrolled cell proliferation. Germline mutations of *BRCA1* or *BRCA2* are present in about 10 % of HGSOC, sporadic *BRCA1/2* mutations or hypermethylation of the *BRCA1* promoter are seen in an additional 11–22 % [55, 57, 58]. *BRCA1* and *BRCA2* proteins play a major role in the homologous recombination double-strand break DNA repair pathway [59]. Defective repair of double-strand DNA breaks from either of *BRCA* mutation results in abnormal chromosomal accumulation and instability [60]. Other gene defects interfering with homologous recombination that occur in HGSOC include *EMSY* amplification (8 % of cases), *PTEN* deletion (7 % of cases), *RAD51C* hypermethylation (2 % of cases), and other rare alterations. In total, about 50 % of HGSOC have a type of homologous recombination defect [8, 55]. Another repair defect seen in HGSOC is mismatched repair (MMR) deficiency seen in 28 %. MMR deficiency is associated with loss of *ARID1A* or *PTEN* and wild-type *P53* ( $p=0.024$ ) expression [61]. The TCGA study also identified abnormal signaling pathways commonly affecting HGSOC. These include retinoblastoma (RB) protein (67 %), phosphatidylinositol-3 kinase/RAS (45 %), NOTCH (23 %), and forkhead box protein M1 (FoxM1) pathways, thus providing opportunities for targeted therapy [8, 55].

### 18.5.2 Low-Grade Serous Carcinoma

Histologically, LGSC usually exhibits a papillary architecture and is distinguished from HGSOC by less than a threefold variation in nuclear size and a mitotic index lower than 12 mitoses per 10 high-power fields [54]. LGSC appears to grow from serous borderline tumors in 60 % of cases [54]. Estrogen receptors and/or progesterone receptors are expressed in most LGSC [3]. LGSC have a normal karyotype with few point mutations. *P53* mutations are rare. Signaling pathway activation is common. Up to 70 % of precancerous borderline lesions and LGSCs express mitogen-activated protein kinase (MAPK) [62]. MAPKs are serine–threonine kinases that respond to extracellular signals via two classes of surface receptors, receptor tyrosine kinases and G protein coupled receptors. These receptors stimulate KRAS, a monomeric GTPase. *KRAS* and *BRAF* mutations are found in 19–54 % and 2–35 % of LGSC, respectively [62] leading to constitutive activation of *KRAS* or *BRAF* which stimulates the MAPK pathway [63] and upregulates extracellular regulated kinase (ERK). ERK subsequently activates transcription factors, such as MYC or ELK-1, and influences a multitude of cellular activities, including gene expression, mitosis, cellular differentiation and survival [64–67]. *ERRB2* (encoding Her2/Neu) mutation is found in 9 % of LGSC, but usually not in combination with *KRAS* and *BRAF* mutations [68].

### 18.5.3 Clear Cell Carcinoma

Histologically, the WHO updated the definition of CCC in 2003 to describe this subtype as a neoplasm composed of clear cells, growing in a solid, tubular or papillary architectural pattern, with “hobnail” cells lining tubules and cysts [1]. Compared to HGSOE, CCC tends to show low mitotic and apoptotic activities [19].

Clinical features and genomic approaches suggest that CCC is heterogeneous [69]. CCC is commonly associated with endometriosis in up to 58 % of cases. The most remarkable genetic mutation is seen in the AT-rich interactive domain 1A gene (*ARID1A*), a tumor suppressor gene. *ARID1A* missense or truncation mutations are observed in approximately 50 % of CCC cases [27, 28]. *ARID1A* encodes BRG-associated factor 250A (BAF 250A), which is a key component of the SWI/SNF (SWItch/Sucrose NonFermentable) chromatin-remodeling complex. Through interactions with several cytokines and hypoxia related transcription factors, such as HIF1 and STAT3 [14, 70, 71], BAF 250A plays an important role in the regulation of proliferation, differentiation, and DNA repair [71, 72]. *ARID1A* mutations and/or loss of protein expression of BAF250A are also found in adjacent endometriosis, supporting an association between these pathologies. In gene expression profiling studies, Il-6/STAT-3/HIF pathways are commonly up-regulated, modifying appropriate regulation of hypoxia and oxidative stress [72]. For example, IL-6 expression is seen in 49 % of CCC [72]. The second important molecular finding in CCC is a high frequency of genetic alterations of phosphoinositide 3-kinase catalytic alpha (*PIK3CA*) [15, 73, 74]. PI3K/AKT/mTOR is one of the most important signaling pathways in cellular regulation, affecting cell proliferation, apoptosis, and transformation. The frequency of gene mutations of *PIK3CA* in CCC is estimated to be 30–40 % [27, 73, 74]. Isoform 2 of *AKT* is amplified in 14 % of CCC [69]. In addi-

**Table 18.3** Other molecular pathology of clear cell carcinoma

Type	Gene	Frequency	Aberration	Reference
Oxidative stress	HNF-1 $\beta$	100 %	Apoptosis	[76]
ZNF217	ZNF217	31 %	Amplification and overexpression	[77]
EGFR	HER2	14 %	Amplification and overexpression	[69]
MMR	MLS1, MSH2, MSH6 or PMS2	10 %	Loss of expression	[78]
PP2C	PPM1D	10 %	Amplification	[79]
PP2C	PPP2R1A	7 %	Mutation	[80]
GTPase	KRAS	5 %	Mutation	[29]
Apoptosis escape	TMS1/ASC	Rare	Methylation	[81]



tion, loss of *PTEN* expression, which is a key negative regulator of the PI3K pathway, has been reported in 40 % of early-stage CCC, suggesting that *PTEN* inactivation and subsequent *PI3K* activation may be an early event in CCC tumorigenesis [75]. Other important findings in CCC are also listed in Table 18.3, which may provide great potential for future biological therapy.

#### 18.5.4 Endometrioid Carcinoma

EC morphological features closely resemble that of endometrioid uterine carcinoma. Additional molecular genetics findings further demonstrate a frequent association of endometriosis with endometrioid adenofibromas and atypical proliferative endometrioid tumors adjacent to invasive well-differentiated endometrioid carcinoma, providing evidence of a stepwise tumor progression in the development of endometrioid carcinoma [82]. The Wnt/ $\beta$ -catenin signaling pathway, which is involved in the regulation of several important cellular processes including proliferation, motility, and survival, is dysregulated in up to 40 % of EC. Activating mutations of *CTNNB1*, the gene that encodes  $\beta$ -catenin, occur in 33–50 % of EC [83, 84]. *ARID1A* and *PPP2R1A* mutations are seen in both CCC and EC, with 30 % of EC having *ARID1A* mutations and 12 % having *PPP2R1A* mutations [28, 80]. Similar to CCC, mutations that deregulate PI3K/PTEN signaling pathway are also common in low-grade EC. *PIK3CA* mutations have been detected in 20 % of EC, but are less common than in CCC [73, 74]. *PTEN* mutations occur in 20 % of EC [85]. EC is associated with a loss of expression of mismatch repair proteins (MLS1, MSH2, MSH6 or PMS2) in approximately 10 % of cases [78]. *KRAS* and *BRAF* mutations have been reported in approximately 10 % of EC [25].

#### 18.5.5 Mucinous Carcinoma

The hallmark of this subtype is the presence of mucin within the tumor cells, which is produced by goblet cells, similar to the linings in gastrointestinal lining. Most ovarian mucinous tumors are benign (75 %), 10 % are borderline tumors, and 15 % are malignant. The benign and borderline tumors tend to be confined to the ovary [86, 87]. Histological features of MC resemble either endocervical (Mullerian) or gastrointestinal epithelium. Mucin production is prominent in benign and borderline components, but less conspicuous in malignant type and is frequently absent in recurrent MC. Because of the low incidence, the pathogenesis of MC is not well understood. *KRAS* mutations are more common in MC than other EOC subtypes, and are observed in 50–75 % of cases [87, 88]. Identical *KRAS* mutations have been found in the histologically benign and borderline components adjacent to the carcinoma, supporting a stepwise progression from a benign precursor lesion [25, 88, 89]. *HER2* gene amplification and/or overexpression are present in approximately

18 % of MC and borderline tumors [87, 88, 90], which may provide novel targeted therapy options. No other genetic alterations have been reported in the mucinous subtype.

## 18.6 Risk Factors for Ovarian Cancer

Epidemiologic studies have identified a number of factors that may increase or decrease the risk of EOC. Most of these findings are from case–control studies. Large epidemiologic studies provide statistically significant data that have been corroborated with results observed in prospective studies. Key causal relationships influencing the risk of developing EOC have thus been identified.

### 18.6.1 Hereditary and Family History

Women who are carrying *BRCA1/2* mutations are at significant lifetime risks of both breast cancer and EOC [91]. Familial history predicts the presence of a mutation. Women with first-degree relatives affected by breast or ovarian cancer have a *BRCA* mutation frequency of 19 % compare to 6.5 % in women who report no affected first-degree relatives [92]. However, 57 % of *BRCA1/2* carriers have no evidence of familial history [93]. An accurate pedigree must be taken from each woman diagnosed with ovarian cancer. *BRCA* mutation testing should only be done for those patients who have either a personal or family history that suggests a role of inherited cancer susceptibility and only after genetic counseling is performed, preferably by a certified genetic counselor [94, 95]. Tools are available to help the practitioner identify women for genetic risk assessment, as shown in Table 18.4 [96]. In the United State, about 1 in 500 women carries a *BRCA* mutation, with the highest prevalence seen in Ashkenazi Jews, (1 in 50) [96–98]. In *BRCA1* mutation carriers, the lifetime risks of developing breast cancer and ovarian cancer are 40–85 % and 25–65 %, respectively. *BRCA2* mutation carriers have the same risk of breast cancer than *BRCA1* mutation carrier, but a lower risk of ovarian cancer (12–20 %) [96, 99–101]. In non-*BRCA* carrier, the risk of breast and ovarian cancers are 12.5 % and 1.4 %, respectively [101]. The majority of hereditary ovarian cancers caused by *BRCA* mutations are usually diagnosed before the age of 50 [92].

Ovarian cancer is also strongly associated with hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, an autosomal dominant disease. Women with Lynch syndrome account for 1 % of EOC [102]. The main feature of the syndrome is a young age of cancer onset. The most common cancers associated with this syndrome are right-side colon cancer and endometrial cancer. About 10 % of women with Lynch syndrome will develop ovarian cancer [103, 104]. The lifetime risk of ovarian cancer might be associated with the type of DNA mismatched repair defect. Patients with *MLH1* mutations have a 5 % risk and patients with *MSH2* a 10 % risk of EOC.

**Table 18.4** Risk assessment for hereditary breast and ovarian cancer

<b>Women with a 20–25 % chance of having an inherited predisposition to breast or ovarian cancer</b>
Women with a personal history of both breast cancer and ovarian cancer
Women with ovarian cancer and a close relative—defined as mother, sister, daughter, grandmother, granddaughter, aunt—with ovarian cancer, premenopausal breast cancer, or both
Women of Ashkenazi Jewish descent with breast cancer who were diagnosed at age 40 or younger or who have ovarian cancer
Women with breast cancer at 50 or younger and who have a close relative with ovarian cancer or male breast cancer at any age
Women with a close relative with a known BRCA mutation
<b>Women with a 5–10 % chance of having an inherited predisposition to breast or ovarian cancer</b>
Women with breast cancer by age 40
Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer or high grade, serous histology at any age
Women with cancer in both breasts (particularly if the first cancer was diagnosed by age 50)
Women with breast cancer by age 50 and a close relative with breast cancer by age 50
Women with breast cancer at any age and two or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed by age 50)
Unaffected women with a close relative that meets one of the previous criteria

### 18.6.2 Reproductive and Hormonal Factor

A number of epidemiologic studies have concluded that ovarian cancer is linked to ovulation, based on a significant reduction in risk related to parity, breast feeding, and oral contraceptive use, all of which are associated with the inhibition of ovulation [31]. The risk of EOC is 40 % lower after the first birth, and decreases by 14 % with each additional pregnancy [105]. The prospective US nurse study also showed that increasing parity significantly reduced the risk of EOC (HR 0.84, 95 % CI 0.77–0.91) [106]. Breast feeding has a small protective effect (HR 0.81, 95 % CI 0.68–0.95) [105]. Breast feeding for a cumulative duration of more than 12 months compared to never breastfeeding was associated with a statistically significant decreased risk (OR 0.80, 95 % CI 0.71–0.89) [107]. Numerous epidemiological studies have consistently shown that oral contraceptives have the strongest protective effect against EOC. An analysis of 45 epidemiological studies including 13 prospective studies and 32 case-control studies of 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 21 countries found that ever-user of oral contraceptive compared with never-user is associated with a statistically significant reduction in risk of developing ovarian cancer (HR 0.73, 95 % CI 0.70–0.76) [108]. The longer the oral contraceptives use, the greater the risk reduction [105, 108–113]. Five years of oral contraceptive intake decreases the risk of EOC by 50 % [114] and the protective effect of oral contraceptive continues for as long as 30 years after cessation, slowly attenuating over time [108]. However, the use of

oral contraceptive appears to have no effect on mucinous cancers [108, 111, 113]. A similar protective effect was seen in 13,627 *BRCA* mutation carriers (HR 0.50, 95 % CI 0.33–0.75) [115]. Theoretically, tubal ligation, which prevents retrograde flow of menstrual endometrium to adnexal tissues, might reduce incidence of ovarian endometrioid and clear cell carcinoma [116]. In a large prospective cohort, women with a history of tubal ligation had a reduction in ovarian cancer risk (RR 0.33, 95 % CI 0.16–0.67) [117]. Hysterectomy without oophorectomy is also associated with a reduction in the risk of EOC (odds ratio [OR] 0.66, 95 % CI 0.50–0.86) [105].

Hormone replacement therapy (HRT) has been associated with an increase of breast cancer incidence. The recent declining use of HRT, especially in women older than 50 years, is linked to a decreasing incidence of breast cancer [118]. There is conflicting evidence of the role of HRT on the risk of EOC. Some studies demonstrate a reduced risk [119, 120], whereas two large studies show an increased risk. The Women's Health Initiative trial, a randomized study of 16,608 postmenopausal women on estrogen-progestin therapy versus placebo did not show a difference in EOC incidence (42 vs. 27 per 100,000 person-years; OR 1.58, 95 % CI 0.77–3.24) [121]. This study might have been too small. A prospective cohort study of 211,581 postmenopausal women found a risk of 1.51 (95 % CI 1.16–1.96) with HRT [122]. The association of HRT and the risk of EOC was also demonstrated in a meta-analysis [123]. The risk of EOC with HRT seems small, but is consistent with the declining incidence of ovarian cancer paralleling the decrease use of HRT in the last 10 years. Patients with endometriosis have an increased risk (about two to four times) of developing ovarian endometrioid or clear cell carcinoma [124]. Other hormonal factors possibly associated with an increased risk of EOC, include infertility [109], early menarche, and late menopause [106, 110, 125], pelvic inflammatory disease [126], polycystic ovaries [127], higher BMI [128], and animal fat consumption [129]. There is no convincing evidence that infertility treatment [130] or length of reproductive life [106] increase the risk.

### **18.6.3 Environmental Factors**

Cigarette smoking might be a risk factor for ovarian cancer. Some studies reported that smoking increase the risk of mucinous tumors [131] but others fail to show a correlation [132]. In two meta-analyses, smoking significantly increased the risk of mucinous EOC, but did not increase the risk of serous EOC [133, 134]. The association between EOC and the use of talcum powder (talc) in infancy remains controversial. Some studies report up to a 33 % increase in the risk of EOC, especially for the serous subtype, after regular genital talc exposure [135–137]. However, the Nurses' Health Study found no increase in EOC with increasing frequency of talc use [106, 107].

## 18.7 Diagnosis

### 18.7.1 Symptoms and Signs

Ovarian cancer has been called the silent killer disease because patients typically present with nonspecific symptoms, such as abdominal bloating, pelvic pressure, which are late-appearing symptoms. A large pelvic mass may cause pressure with urinary frequency or constipation. A proposed method for detection of ovarian cancer includes length of symptoms (more than 12 days per month for less than 1 year) which has a sensitivity of 56 % for early-stage and 79 % for advanced-stage disease and a specificity of 90 % for women age older than 50 years and around 85 % for women younger than 50 years [138–140]. Only 20 % of women with ovarian cancer acknowledged having such symptoms [141]. On pelvic examination, the most common clinical sign is a fixed irregular pelvic mass. Other findings include ascites, pleural effusions, and a nodule bulging into the umbilicus referred to as a Sister Mary Joseph's nodule that can also be associated with gastric, pancreatic, colon, and appendiceal cancers. Paraneoplastic events are uncommon [142] except for thromboembolic events such as a deep vein thrombosis. Patients with CCC are at highest risk (40 %) [20, 143].

### 18.7.2 Work-Up of a Suspicious Pelvic Mass

CA-125 is the most practical tumor marker in ovarian cancer, but it is not specific to diagnose ovarian cancer especially in premenopausal women. Levels might be elevated above the normal range for physiological and benign conditions such as menstruation, pregnancy, endometriosis, adenomyosis, pelvic inflammation and uterine fibroids [144, 145]. Another tumor marker is the human epididymis protein 4 (HE4), which is more specific and frequently overexpressed in ovarian cancers, especially in serous and endometrioid histologies [146]. It is approved for surveillance but not for screening of EOC. Transvaginal ultrasound (TVS) is the most useful noninvasive diagnostic test that differentiates a benign and a malignant adnexal mass [147]. Improved specificity is achieved by combining these markers and TVS. The risk of malignancy index (RMI) is a combination of CA-125 levels and pelvic ultrasound findings for a given menopausal status [148]. A RMI cut-off level of 200 yields a sensitivity of 85 % and a specificity of 97 %. Patients with a RMI greater than 200 should be referred to a gynecology oncology specialist. The risk of malignancy algorithm (ROMA) is a scoring system using CA-125 and HE4 concentrations with menopausal status to calculate the risk of ovarian cancer in women presenting with a pelvic mass [149]. ROMA is FDA approved with a cutoff of 12.5 % for premenopausal patients (67.5 % sensitivity and 87.9 % specificity) and a cutoff of 14.4 % for postmenopausal patients (90.8 % sensitivity and 66.3 % specificity). Neither HE4 alone nor ROMA scoring increases the detection of malignant disease [149].

The diagnostic and staging ability of other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and 2-(fluorine-18) fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) of ovarian cancer have been evaluated in prospective studies [150, 151]. Contrast-enhanced CT imaging is a current standard nonsurgical method for detection, staging, predicting successful surgical cytoreduction, and assessing response after treatment; however, it is difficult to detect small peritoneal deposits. For example when peritoneal disease is <1 cm, the sensitivity of CT is only 7–28 %, and this is further dependent upon anatomical location [152]. MRI is recommended for patients with a contraindication to the use of iodinated contrast agents, patients who are pregnant, patients of childbearing age with borderline tumors (to minimize ionizing radiation exposure), and those for whom an ultrasound or CT findings are inconclusive [153, 154]. Although evaluation of pelvic soft tissue infiltration was better with MRI than CT, CT has a reported similar accuracy for ovarian cancer staging (77 % versus 78 %) [151]. FDG-PET has improved sensitivity and specificity for the evaluation of adnexal masses. Increased FDG uptake in an adnexal mass has a higher specificity for ovarian cancer in postmenopausal women than in premenopausal women [154]. Currently, a good triple contrast CT or an abdominal/pelvic ultrasound is the standard of care prior to treatment.

## 18.8 Management

The treatment of EOC is multidisciplinary. Patients suspected of having EOC should be referred to a team of specialists of ovarian cancer and surgery performed by a gynecologic oncologist [155, 156]. Treatment consists in a combination of surgery and chemotherapy, except for very limited stage 1A or 1B. The NCCN guidelines rely on the experience of the last 20 years to define the sequence of treatment. However, new randomized studies suggest that alternative sequences of therapeutic modalities are equivalent and might potentially improve quality of life. The current NCCN guidelines propose a surgical staging with maximal cytoreductive surgery, followed by three to eight courses of chemotherapy with a doublet of platinum and taxane, depending on the stage of the cancer. Intraperitoneal chemotherapy is recommended after optimal debulking surgery. Neoadjuvant chemotherapy is only recommended for bulky disease or patients with poor performance status. In this chapter, we will propose a more modern therapeutic approach that considers the evidence from the most recent randomized studies. The proposed algorithm for high grade EOC is described in Table 18.5. Various considerations on each therapeutic modality are described below.

**Table 18.5** Modern algorithm for high grade epithelial ovarian cancer

	First step	Second step	Third step	Fourth step	Fifth step	Sixth step	Outcome
Isolated unilateral or bilateral adnexal mass (Clinical stage I or II)	Surgical intervention for staging and maximal cytoreductive surgery	Pathological examination confirms ovarian cancer	Observation or 3 to 6 cycles of carboplatin and paclitaxel chemotherapy depending on stage and prognostic factors	N/A	N/A	Observation with pelvic examinations. There is no evidence that serial follow-up with CA-125 increases survival, and this test is not indicated	90–75 % cure rate depending on risk factors
Adnexal mass with abdominal carcinomatosis suspicious of ovarian cancer (Clinical stage III and IV)	Diagnostic laparoscopy or biopsy (either cytology from ascites of FNA, or core biopsy)	Pathological examination confirms ovarian cancer	<ul style="list-style-type: none"> <li>The first choice is participation in a clinical trial, independently of the sequence of surgery/ chemotherapy</li> </ul>	Clinical trial	Clinical trial	Clinical trial	N/A
			<ul style="list-style-type: none"> <li>Standard option of choice is neoadjuvant chemotherapy for 3 cycles with the combination of carboplatin and liposomal doxorubicin. This combination, although more myelosuppressive, has less long term side effects than a taxane platinum doublet, is as efficacious, and should be the treatment of choice</li> </ul>	Initial maximal cytoreductive surgery or Interval debulking with maximal cytoreduction after 3 cycles of neoadjuvant chemotherapy	Administer a total of 6 cycles of platinum-based doublet or Complete 3 more cycles of same chemotherapy as neoadjuvant treatment	Observation with pelvic examinations. There is no evidence that serial follow-up with CA-125 increases survival, and this test is not indicated	20–25 % cure rate

(continued)

**Table 18.5** (continued)

First step	Second step	Third step	Fourth step	Fifth step	Sixth step	Outcome
			<i>Placement of a port if optimally debulked</i>	Administer 3 cycles of platinum/paclitaxel chemotherapy intraperitoneally as long as feasible		
			If suboptimal interval debulking	Consider changing to a different platinum doublet (taxane), administer 3 to 6 additional cycles, or refer to a clinical trial, or consider hyperthermic perfusion chemotherapy on study		Cure is unlikely
			If progression	Refer to a clinical trial or treat as a recurrent platinum resistant EOC		Not curable



## 18.9 Frontline Therapy

### 18.9.1 *Surgical Considerations*

Early clinical disease needs to be surgically staged to determine the exact extent, because upstaging EOC might change the therapeutic approach. Approximately 25–30 % of women with apparent early stage disease will be upstaged upon thorough surgical staging [157]. A significant predictor of occult metastases is histologic grading. Only 16 % of patients with grade 1 tumors were upstaged compared to 46 % with grade 3 disease [158]. Patients who have not been properly cytoreduced stand a significant risk of recurrent disease despite more frequent use of chemotherapy [159]. A fertility-sparing surgery could be considered for women who desire to preserve fertility in low-risk situations such as an apparent stage I ovarian cancer, a low-grade tumor, or a non-clear cell histology [160, 161]. Counseling is paramount as about 10 % of patients undergoing this limited procedure experience a recurrence, and about 4 % will die of EOC. Most patients will carry successful pregnancies even after adjuvant chemotherapy, with term delivery over 30 % of cases [162].

The standard surgical technique has historically been performed through a vertical abdominal incision that allows exposure of the entire abdomen. On entry into the peritoneal cavity, ascites is aspirated and submitted to cytology examination. If no ascites is present, peritoneal washings of the pelvis and paracolic gutters are obtained. All areas suspicious of being involved with EOC are removed in addition to a total abdominal hysterectomy and bilateral salpingo-oophorectomy and an infracolic omentectomy. A total paraaortic and pelvic lymphadenectomy is recommended to exclude microscopic disease. A systematic inspection of all peritoneal surfaces with random biopsies of the right hemidiaphragm, right and left paracolic gutters, pelvic sidewalls, ovarian fossa, bladder peritoneum, and cul-de-sac are performed. Optimal surgical cytoreduction is defined as residual tumors less than 1 cm. Overall survival is directly related to the size of the residual tumors [163–165]. To achieve an optimal surgery, a variety of aggressive procedures may need to be performed, such as splenectomy, diaphragm stripping, partial hepatic resection, partial bladder or ureteral resection, or bowel resection. A meta-analysis demonstrated that for each 10 % increase in maximal cytoreduction, overall survival improves by 5–6 % [155]. The role of routine retroperitoneal lymphadenectomy at the time of primary cytoreduction in patients with advanced disease is debated. A systematic lymphadenectomy, compared to the resection of bulky lymph nodes only, improves progression-free survival (PFS) in women with advanced ovarian cancer who are optimally debulked, but might not improve overall survival [166].

The role of minimally invasive surgery has been continuously expanding. Laparoscopic surgery is associated with several perioperative benefits such as decrease blood loss, shorter hospital stay, and fewer postoperative complications, improved quality of life, faster return of bowel function and shorter interval to adjuvant chemotherapy administration [167–169]. Limited data suggest equal efficacy

of laparoscopy compared to laparotomy in both early and advanced-stage ovarian cancer [168, 170]. Robotic assistance facilitates comprehensive staging [171]. Laparoscopic surgery is a good tool for evaluating operability and avoids unsuccessful laparotomy outcomes [172]. Laparoscopic or robotic surgery might cause port-site metastasis, tumor dissemination due to intraoperative cyst rupture, and incomplete staging. Most adnexal masses can be safely detached, placed intact within a specimen retrieval bag and removed from a trocar site without spillage. Intraoperative cyst rupture is usually a witness of more biologically aggressive disease that will require adjuvant chemotherapy.

Interval debulking surgery refers to surgery that is performed on patients who have previously received induction chemotherapy (or neoadjuvant chemotherapy). Even if chemotherapy helps debulking EOC chemically, the extent of the interval debulking surgery remains a prognostic factor for survival. There has been much controversy about neoadjuvant chemotherapy, which was usually tested on patients with advanced disease who were not good candidates for surgery upfront [173]. The definitive randomized study evaluated the use of neoadjuvant chemotherapy in 718 patients with stages IIIC–IV ovarian cancer. There was no difference in median overall survival and PSF between a primary-debulking arm and an interval-debulking arm. Postoperative rates of adverse events and mortality tend to be higher after primary debulking arm and quality of life better after interval debulking [174]. These results are consistent with a systematic review that includes 3 randomized controlled trials of 853 women, which demonstrates no statistically significant difference between interval debulking surgery and surgery upfront in terms of PFS (HR 0.88; 95 % CI 0.57–1.33) and overall survival (HR 0.80; 95 % CI 0.61–1.06). However, in patients whose primary surgery was incomplete or less extensive, an overall survival benefit was seen after neoadjuvant chemotherapy followed by interval debulking surgery (HR 0.68; 95 % CI 0.53–0.87) [175].

## 18.9.2 Systemic Treatment

### 18.9.2.1 Early Stage EOC

Approximately 25 % of ovarian cancers are diagnosed at stage I or II. Surgery is curative in most cases, with a 5-year survival rate of 75–90 % [142, 176]. About 20–30 % will relapse and die from their disease [177–180]. A large retrospective multivariate analysis of 1,545 patients with stage I disease demonstrated that the degree of tumor differentiation is the most powerful prognostic indicator of PFS [181]. Prognostic factors for recurrence and death in patients with early-stage EOC include age ( $\geq 60$ ), stage II, grade II or III, and positive cytology. A prognostic index made of low-risk (no or one factor), intermediate-risk (two factors), and high-risk (three to four risk factors) yields survivals of 88 %, 82 %, and 75 %, respectively ( $P < 0.001$ ) [176]. Adjuvant chemotherapy for early stage ovarian cancer is recommended under specific conditions. Adjuvant therapy has no benefit for patients with

low-risk EOC [178, 182]. In high-risk early stage EOC, two randomized clinical trials, the International Collaborative Ovarian Neoplasm 1 [ICON1] and the Adjuvant Chemotherapy In Ovarian Neoplasm [ACTION], demonstrated that chemotherapy reduces the risk of recurrence and prolongs overall survival [183]. These results are consistent with a recent meta-analysis of five randomized trials [184]. The optimal duration of adjuvant chemotherapy in early stage EOC was studied by randomizing 427 patients with comprehensive staging to three or six cycles of paclitaxel and carboplatin. The overall survival was similar for both regimens and the decrease in recurrence risk did not reach statistical significance. More grade 3 and 4 hematologic side effects were associated with more cycles of chemotherapy [185]. A subsequent analysis showed that only patients with HGSOE histology had a lower risk of recurrence with six cycles compared to three [186]. Maintenance with low-dose paclitaxel did not show a reduction of recurrence in early-stage EOC [187]. Patients diagnosed with high-risk early stage EOC, should be offered adjuvant platinum-based chemotherapy with a minimum of three cycles and perhaps six cycles for those with HGSOE.

### 18.9.2.2 Advanced Stage EOC

Most patients with ovarian cancer are diagnosed with advanced-stage cancer and evidence-based medicine shows that chemotherapy prolongs survival in women with stage III disease, whether optimally or suboptimally debulked, and possibly in patients with stage IV disease. However, overall survival rates are low at 30 % and 20 % for women diagnosed with EOC stage III and IV, respectively [188]. As previously mentioned, the most important prognostic factors include differentiation, clinical stage, and extent of residual disease after debulking surgery. Unfortunately, in the general population, optimal debulking rates are usually low, around 20 % [189, 190].

In the 1990s, randomized trials (GOG 111, OV-10, GOG 158) established that the combination of a platinum analog and paclitaxel is the standard of care in the first-line setting. To date, the combination of carboplatin and paclitaxel is the most used treatment in the management of ovarian cancer, with a response rate of about 65 %, a PFS of 16–21 months and an overall survival of 32–57 months [191–193]. Randomized trials have failed to provide evidence of benefit for dose intensification of cisplatin [194, 195], high-dose chemotherapy [196, 197], duration of paclitaxel infusion (to 96 h from 24 h) [198], or delivery of more than six cycles of a platinum-based primary chemotherapy [199, 200]. In the early 2000s many other platinum doublets and triplets failed to show a superiority over carboplatin and paclitaxel [201]. The efficacy of intravenous chemotherapy has reached a therapeutic plateau. However, the toxicity profile of other drugs might be preferable to paclitaxel which causes alopecia and permanent neurotoxicity. The Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study substituting paclitaxel for docetaxel, in combination with carboplatin, resulted in equivalent survival but had an improved toxic profile with less neuropathy and hypersensitivity, with increased dose-limiting

hematologic toxicity [202]. The MITO-2 study substituted paclitaxel for pegylated liposomal doxorubicin (PLD), in combination with carboplatin. PFS (19 versus 16.8 months) and overall survival (61.6 versus 53.2 months) were similar. There was less neurotoxicity and no alopecia, but more hematologic reversible adverse effects [203]. A meta-analysis of 820 women with stage IC-IV EOC confirmed these observations [204]. Carboplatin plus PLD should be considered the treatment of choice for first-line treatment of advanced EOC, particularly in patients at high risk of neurotoxicity or those wishing to avoid alopecia.

Potentially more interesting is the dose dense weekly administration of paclitaxel (NOVEL trial or Japanese Gynecologic Oncology Group, JGOG 3016), which has been shown to improve overall survival. The randomized compared dose dense weekly paclitaxel (80 mg/m<sup>2</sup> on days 1, 8, and 15) with every 3-week paclitaxel (180 mg/m<sup>2</sup> on day 1), in combination with carboplatin on day 1, in 631 patients with stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. This study found a significant improvement in both PFS (28.2 versus 17.5 months) and overall survival (100.5 versus 62.2 months) favoring the dose dense regimen. In subgroup analyses, improvement in survival was seen among patients who had residual disease measuring more than 1 cm (HR=0.75) or serous histology (HR=0.76) [205]. Toxicity was similar in both groups with the exception of anemia which required more transfusions in the dose dense arm. Patients delayed and discontinued dose-dense paclitaxel therapy more often than those receiving standard therapy. Given the long-term outcome, dose-dense therapy should be considered for patients with advanced stage who had a suboptimal debulking and whose tumors are HGSOC. Two on-going trials are also confirming the potential benefit of dose-dense weekly paclitaxel (MITO-7 [206] and GOG 262 [207]).

### 18.9.2.3 Intraperitoneal Chemotherapy

The rationale for intraperitoneal (IP) chemotherapy is to expose residual peritoneal tumor to high concentrations of cytotoxic agent for a prolonged period of time, and to spare normal tissues. The results of two systematic reviews and three randomized phase III trials support the use of IP platinum-based chemotherapy in patients with stage III optimally cytoreduced patients (largest diameter of residual tumor less than 1 cm) [208–212]. The PFS (23.8 months versus 18.3 months; HR 0.77,  $P=0.05$ ) and overall survival (65.6 months versus 49.7 months; HR 0.73,  $P=0.03$ ) are significantly improved [210]. The advantages of IP over intravenous therapy extends beyond 10 years [213]. Patients with microscopic residual disease, non-clear cell/mucinous carcinoma subtypes, younger age and good performance status at the time of treatment, and who received five or six cycles of therapy experienced the greatest relative benefit of IP platinum delivery [213, 214]. The longest survival to date (110 months median overall survival) was observed in patients with no residual disease receiving IP chemotherapy [214]. The high intraperitoneal concentration of cytotoxic agent is associated with increased toxicity (including grade 3 or 4 hematologic toxicity, neurologic toxicity, renal toxicity, fatigue, abdominal discomfort

and catheter-related complication) and few patients are able to receive six cycles of IP therapy [210]. If IP administration is no longer feasible, treatment should be completed intravenously for a total of six cycles. In a separate quality-of-life analysis, patients who received IP therapy had a significantly worse physical and functional well-being score, abdominal discomfort, and neurotoxicity during treatment, but recovered within 1 year after treatment completion with no persistent effects [215]. IP therapy should be reserved for women with optimal debulking. Because of the limited penetration of chemotherapy into large tumors, suboptimally debulked patients need to receive intravenous treatment.

#### **18.9.2.4 Maintenance Chemotherapy**

Only a minority of patients with advanced-stage EOC will have a long PFS. In an attempt to prolong the time to symptomatic disease progression and potentially improve overall survival, a maintenance strategy of 12 monthly cycles of single-agent paclitaxel was tested in women who attained a complete response to primary platinum-paclitaxel chemotherapy. The trial was unable to demonstrate an overall survival advantage because it was stopped early for modest improvement in PFS. Treatment-related grade 2 and 3 neuropathy is concerning (23 versus 15 %) [216]. Another randomized trial utilizing 6 monthly cycles of paclitaxel versus observation showed no improvement in overall survival or PFS [217]. The last ongoing paclitaxel maintenance study (GOG 212) is ongoing and evaluates the use of monthly paclitaxel, paclitaxel poliglumex, or observation for 12 months. Overall survival is the primary study endpoint [207]. Maintenance therapy is not a standard of care.

#### **18.9.2.5 Targeted Therapy in First Line**

Bevacizumab, a humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody, is authorized in the European Union for the treatment of various malignancies including first-line treatment of advanced-stage epithelial ovarian cancer, in combination with paclitaxel and carboplatin chemotherapy. The use of bevacizumab in first-line and maintenance was tested in two randomized phase III trials (GOG 218 and ICON7). The median overall survival is not improved, but the median PFS is prolonged by 3.8 months with 15 mg/kg and 2.4 months with 7.5 mg/kg of bevacizumab added during and after chemotherapy [218, 219]. Adverse effects of bevacizumab include hemorrhage, arterial hypertension, thromboembolism, wound healing delays, and gastrointestinal perforation. There is currently no evidence that angiogenesis inhibitors improve overall survival, nor is there enough evidence to justify the routine use of angiogenesis inhibitors in treating women with newly diagnosed ovarian cancer [220]. Additional cost of treatment is a real concern.

## 18.10 Surveillance

Following frontline chemotherapy, 75 % of patients with EOC will achieve complete clinical, radiological and biochemical remission. However, most of patients will develop a recurrent disease within 16 to 20 months after initial treatment completion [221–223]. In women with recurrent ovarian cancer, ability to achieve optimal secondary cytoreduction (no macroscopic disease) has been associated with a two to fourfold benefit in median survival [224–227]. The MRC ov05/EORTC 55955 trial indicates that there is no survival benefit from early treatment based on a raising CA-125 alone [228]. The overall survival of 265 women who recurred after an initial remission and started second-line chemotherapy after experiencing a rise in CA-125, was identical to the survival of 264 women with rising CA-125 levels whose treatment was delayed until symptoms of relapse appeared clinically. Second-line chemotherapy was started, in the early-treatment group, a median of 4.8 months before it was started in the delayed-treatment group. With CA-125 surveillance, numbers of chemotherapy treatments were higher and quality of life worse. Serial CA-125 serum levels are not indicated for the routine follow-up of ovarian cancer patients in remission after initial multidisciplinary therapy [229].

## 18.11 Management of Recurrent EOC

### 18.11.1 Surgery

Chemotherapy is the standard treatment for women with recurrent EOC. Secondary cytoreductive surgery is a subsequent surgical debulking at the first recurrence, which aims to prolong survival, to improve quality of life and to alleviate cancer-related symptoms. Secondary cytoreduction is generally considered most effective when used in selected patients with good performance status and a long disease free interval (typically greater than 12 months), who have no ascites and a limited number of metastatic sites, and for whom the recurrent cancer can be excised to microscopic or no residual disease [226, 230–232]. In a large multi-institutional review (the Descriptive Evaluation of Preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer [DESKTOP OVAR] trial) and in recent meta-analysis studies, the only statistically significant clinical variable independently associated with survival was the cytoreduction to no macroscopic residual disease [226, 230, 233]. This issue is being currently studied in the GOG 213 study, which compares secondary cytoreductive surgery with chemotherapy versus chemotherapy alone.

## 18.11.2 Systemic Treatment

In patients with disease recurrence, the choice of salvage therapy is generally based on the time of recurrence. Patients with a platinum-free interval greater than 6 months are called “platinum-sensitive” because they usually respond to reinduction with this class of agent. The probability of response is closely related to the duration of platinum-free interval; response rate to retreatment with platinum generally ranges from 20 % to 30 % for platinum-free interval of 6–12 months to more than 60 % for platinum-free intervals greater than 12 months [234]. Patients with a platinum-free interval less than 6 months are called “platinum-resistant” and should not be treated with platinum [235]. Patients progressing while receiving platinum are called “platinum-refractory” and have the worse prognosis.

### 18.11.2.1 Platinum Sensitivity

The preferred chemotherapy regimen in this situation is a doublet either with platinum or a non-platinum doublet. The largest trial (ICON4/ AGO-OVAR-2.2) compared the combination of platinum plus paclitaxel with conventional platinum-based chemotherapy in 802 patients with platinum sensitive disease. Improvements in both progression-free and overall survival were seen in the paclitaxel arm and, importantly, there was no difference in quality-of-life indices [236]. The AGO-OVAR 2.5 trial randomized platinum-sensitive patients to the combination of carboplatin and gemcitabine or to carboplatin alone. The combination arm had an improved PFS (5.8 versus 8.6 months;  $P=0.0031$ ), but, there was no significant difference in overall survival (17.3 versus 18 months;  $P=0.7349$ ). Palliation of abdominal symptoms and improvements in global quality of life was faster in patients treated with the combination [237]. Trabectedin, a marine-derived antineoplastic agent initially isolated from the tunicate *Ecteinascidia turbinata*, currently produced synthetically, binds the DNA minor-groove. In a phase III trial comparing trabectedin and PLD with PLD alone, there was an improvement in PFS for women who had recurred 6–12 months after the end of first line chemotherapy but not in women with platinum resistant disease [238]. The combination increases hematologic toxicity [239].

What the most effective doublet is has been studied in one randomized trial, the Caelyx in Platinum Sensitive Ovarian patients (CALYPSO) trial, which tested the combination of carboplatin and PLD against carboplatin and paclitaxel in platinum-sensitive patients. The PLD combination yielded a median PFS of 11.3 months versus 9.4 months for the paclitaxel and carboplatin arm (HR 0.82;  $P<0.001$ ) and was better tolerated [240]. The benefits of the carboplatin and PLD doublet include a lack of neuropathy, less drug infusion reaction, and no alopecia, making it an attractive alternative for this patient population.

### 18.11.2.2 Platinum Resistance

In contrast to platinum-sensitive disease, there is no evidence in platinum-resistance that combination chemotherapy is superior to sequential single-agent therapy, but toxicity is worse with combination regimens. Four drugs are frequently used in patients within platinum resistant or refractory disease. Paclitaxel, topotecan, PLD and gemcitabine all have shown moderate activity as single agent in this situation. Many older drugs might have some efficacy as well. There is currently no evidence from phase III studies that any one of these drugs is superior to another except for one randomized trial which showed the superiority of PLD over topotecan [241]. The choice of drug depends on the side effect profile and the schedule, and should be discussed with the patient.

## 18.11.3 Targeted Agents in Recurrent Treatment

### 18.11.3.1 Targeting Angiogenesis

The OCEANS study, which enrolled 484 patients, assessed the use of bevacizumab with gemcitabine and carboplatin in patients with platinum-sensitive disease. In the experimental arm, bevacizumab was administered until progression or toxicity. Efficacy outcomes favored the bevacizumab arm over chemotherapy alone, with response rates of 79 % versus 57 % ( $P < 0.0001$ ) and PFS (12.4 versus 8.4 months) (HR=0.484; 95 % CI, 0.388–0.605;  $P < 0.0001$ ). However, there was no difference in overall survival (35.5 versus 29.9 months,  $P = 0.094$ ). Two patients experienced gastrointestinal perforation in the bevacizumab arm [242]. This combination has received a category 2B recommendation as a possible regimen in the NCCN Guidelines.

The AURELIA study tested paclitaxel, PLD, or topotecan with or without bevacizumab in 361 platinum-resistant patients. Response rate and PFS (HR=0.48; 95 % CI, 0.38–0.61;  $P < 0.001$ ) were significantly improved in patients who received bevacizumab. In a subset analysis, the best PFS was seen with the combination of weekly paclitaxel and bevacizumab. This risk of grade 2 gastrointestinal perforation, fistula, or abscess was less than 3 %. In patient with platinum resistant EOC, the impact of bevacizumab on disease-free survival is favorable and there is a trend for better overall survival. On these bases, the FDA approved bevacizumab for patients with platinum resistant disease in 2014 [243]. Our own meta-analysis confirms the survival benefit [244].

### 18.11.3.2 Targeting DNA Repair

Olaparib, is a poly (ADP-ribose) polymerase (PARPs) inhibitor, with activity in BRCA driven ovarian cancers. The inhibition of PARPs leads to the accumulation of DNA breaks, which are usually repaired in normal cells by homologous



recombination, the pathway controlled by *BRCA1* and *BRCA2*. When *BRCA1* or *BRCA2* is mutated, repair is not possible and the cells arrest and die [245]. Up to 50 % of patients are likely to be deficient in homologous recombination repair, because of somatically acquired mutations, epigenetic inactivation, or *BRCA1/2* germline mutation. A randomized placebo-controlled trial compared maintenance treatment with olaparib in patients with platinum-sensitive disease. Patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, or placebo. Progression-free survival was significantly longer in the olaparib arm (8.4 versus 4.8 months,  $P < 0.00001$ ), with no survival benefit. Treatment is well tolerated [246]. Interestingly, progression was associated with a return to platinum sensitivity in some patients. The FDA approved olaparib in 2014 for treatment of patient with ovarian cancer and *BRCA* mutations.

### 18.11.3.3 Targeting the Folate Receptor

The folate receptor-alpha is expressed in 90 % of ovarian cancers but usually absent in normal tissue. Farletuzumab, a humanized monoclonal antibody to folate receptor-alpha, was tested in combination with carboplatin and paclitaxel in platinum-sensitive patients. Normalization of CA-125 levels was observed in 80.9 % of patients and 75 % responded to treatment by RECIST criteria [247]. EC145, a conjugate of folate and the vinca alkaloid desacetylvinblastine monohydrochloride (DAVLBH) was tested in the PRECEDENT study. Patients with platinum-resistant ovarian cancer were randomized to EC145 and PLD or single agent PLD. The combination had a better overall response (29.6 % versus 18.5 %) and PFS (11.7–21.7 weeks) compared to PLD [248]. Other drugs in clinical trials are listed in Table 18.6.

In conclusion, the biology of ovarian cancer indicates that single gene mutations are uncommon in ovarian cancer and observed in about ten different genes. The most common alteration is in *P53* then in *BRCA1* and *BRCA2*. Most common are the numerous somatic copy number alterations that have been identified. These various alterations are not easily suitable to targeted therapies and ovarian cancer should be considered a panel of different ovarian neoplastic diseases. EOC is sensitive to platinum-based chemotherapy which in combination with optimal surgery leads to a 20 % cure rate for advanced disease. The best approach to treatment is to offer patients participation in a clinical study to help making new discoveries for improving the treatment of EOC.

**Table 18.6** New drugs for ovarian cancer

Drug	Target	Trial	Trial number
Phase 3 studies			
Niraparib	PARP	A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer	NCT01847274
Pertuzumab	HER2	A study of pertuzumab in combination with standard chemotherapy in women with recurrent platinum-resistant epithelial ovarian cancer and low HER3 mRNA expression	NCT01684878
MEK inhibitor, MEK162	MEK	A study of MEK162 vs. physician's choice chemotherapy in patients with low-grade serous ovarian, fallopian tube or peritoneal cancer	NCT01849874
Rucaparib	PARP	A study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3)	NCT01968213
AMG 386	Angiopoietin	Trinova-3: a study of AMG 386 or AMG 386 placebo in combination with paclitaxel and carboplatin to treat ovarian cancer	NCT01493505
Phase 2 studies			
Oregovomab	CA-125	A controlled study of the effectiveness of oregovomab (antibody) plus chemotherapy in advanced ovarian cancer	NCT01616303
Hapten-Modified Vaccine, OVAX	Immunotherapy	Trial of autologous, hapten-modified vaccine, OVAX, in patients with relapsed stage III or IV ovarian cancer	NCT00660101

(continued)

**Table 18.6** (continued)

Drug	Target	Trial	Trial number
PankoMab	Tumor-specific epitope of mucin-1	A double-blind, placebo-controlled, randomized, phase 2 study to evaluate the efficacy and safety of maintenance therapy with pankomab-GEX™ after chemotherapy in patients with recurrent epithelial ovarian cancer	NCT01899599
Cvac	Dendritic cell vaccine	A randomized, double-blinded, placebo-controlled trial of cvac as maintenance treatment in patients with epithelial ovarian cancer in complete remission following first-line chemotherapy (australia and united states)/a randomized trial of cvac as maintenance treatment in patients with epithelial ovarian cancer in complete remission following first-line chemotherapy or following second-line treatment	NCT01521143
IDO Inhibitor INCB024360	Indoleamine 2,3-dioxygenase	A phase 2 study of the IDO inhibitor INCB024360 versus tamoxifen for subjects with biochemical-recurrent-only EOC, PPC or FTC following complete remission with first-line chemotherapy	NCT01685255
Ganetespi	Chaperones	A two-part, multicentre, international phase I and II trial assessing the safety and efficacy of the HSP90 inhibitor ganetespi in combination with paclitaxel weekly in women with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer with mutant p5	NCT02012192

(continued)

**Table 18.6** (continued)

Drug	Target	Trial	Trial number
Pazopanib	Multi-target kinase inhibitor (VEGFR1, VEGFR2, VEGFR3, PDGFR, FGFR, c-Kit and c-Fms)	Randomized study of safety and efficacy of pazopanib and gemcitabine in persistent or relapsed ovarian cancer	NCT01610206
DNIB0600A	NaPi2b, multi-transmembrane, sodium-dependent phosphate transporter	A randomized study of DNIB0600a in comparison with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer	NCT01991210
Cabozantinib	Multi-target kinase inhibitor (c-Met, VEGFR2, and RET)	Cabozantinib or paclitaxel in treating patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cavity cancer	NCT01716715

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