Advances in Diagnosis and Management of Ovarian Cancer

Samir A. Farghaly
Editor

Second Edition

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This book is dedicated to my beloved children Raied and Tamer, to the memory of my mother Amina, to my father Aly who had a great influence on me, and to my academic and professional medical career. Also, to my sisters: Soraya, Nadia and their families, to my late siblings: Nabil, Rafat, Magdy and to their present families in addition to my late nephew, Islam.

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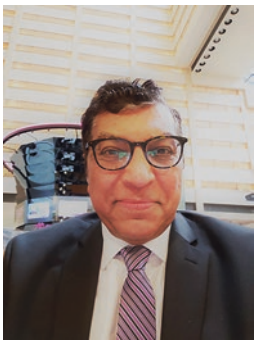
Preface



Globally, the numbers of ovarian cancer new cases were about 300,000 and 200,000 deaths in 2018. In 2021, about 21,410 new cases of ovarian cancer were diagnosed and 13,770 women died of ovarian cancer in the USA. The ovarian cancer statistics for incidence indicate that it is highest in the USA and Northern Europe and lowest in Africa and Asia. Ovarian cancer is the ninth most common cancer among women, excluding non-melanoma skin cancers. It ranks fifth in cancer deaths among women. It accounts for about 3% of all cancers in women. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 72. Her lifetime chance of dying from ovarian cancer is about 1 in 100. Incidence rates of ovarian cancer increase with aging, being more prevalent in the eighth decade of life. Patients are typically diagnosed when the disease has metastasized (stage III or IV) which has an overall survival rate between 5% and 25%. Five-year survival in ovarian cancer has doubled over the past 30 years, increasing from approximately 25% to 50%. This is a result of developments in diagnosis and more efficient management. Clearly, there is more room to increase this rate to a higher number. This could be achieved by developing novel tests for early detection and diagnosis and innovative targeted molecular therapy and surgical techniques. The ideal approach to women with ovarian cancer is a multidisciplinary one, with many professionals contributing to the excellent care and outcome that we wish to see for those individuals we are privileged to look after.

This book discusses a range of early diagnostic and therapeutic considerations, including epidemiologic, molecular genetic testing, histopathologic, and open surgical, minimally invasive surgical and targeted molecular therapy for patients with hereditary and non-hereditary ovarian cancer. The importance of updated knowledge of the epidemiology of ovarian cancer as it

affects primary prevention, early detection, and possibly therapeutic strategies are discussed in Chap. 1. The current screening and early detection are detailed in Chap. 2. The importance of ovarian cancer biomarkers and its clinical relevance are discussed in Chap. 3. The diagnosis and management of hereditary ovarian cancer are discussed in Chap. 4. The origin, histopathologic, and molecular genetic aspects of ovarian cancer are detailed in Chap. 5. The current management of patients with early-stage ovarian cancer is detailed in Chap. 6. The management of advanced stage ovarian cancer is discussed in Chap. 7. Detailed management of recurrent ovarian cancer is shown in Chap. 8. An extensive overview of chemotherapy for ovarian cancer patients is discussed in Chap. 9. Special reference to management of advanced ovarian cancer with peritoneal metastases is detailed in Chap. 10. Targeted molecular therapy for patients with ovarian cancer is thoroughly discussed in Chap. 11. The recent advances in diagnosis and management of ovarian neoplasms in the pediatric female population of less than 17 years old is discussed in Chap. 12. Finally, the importance of quality of life (QOL) as an outcome on both disease and treatment decision-making in patients affected with ovarian cancer is detailed in Chap. 13.

This book is intended for all clinicians caring for women with ovarian cancer, including attending surgeons and physicians, fellows, and residents in the disciplines of gynecologic oncology, surgical oncology, medical oncology, and primary care. Allied medical staff, palliative services, and nurse specialists will also find it a useful adjunct to getting current information on diagnosis and management of ovarian cancer.

I hope that you enjoy this book and benefit from the extensive experience of the internationally renowned contributors to this book from the USA, United Kingdom, Australia, and Turkey who have authored its contents.

I would like to thank Ms. Pinky Sathishkumar, project coordinator of this book, and Ms. Samantha Lonuzzi, clinical medicine editor at the book publishers Springer Nature for their efficiency and valuable help in the process of development, editing, and publishing of this book

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Ovarian Cancer Epidemiology

1

Fani Kokka and Adeola Olaitan

Incidence and Geographical Distribution of Ovarian Cancer

Women make up 49.5% of the world population but they form a higher proportion of those over 60 years of age in whom cancer is most likely to occur. Cancer is the leading cause of death in women worldwide, both in well-resourced and poorly resourced countries [1]. Ovarian cancer is the 8th most common cancer in women and the 18th most common overall. Worldwide there were just under 300,000 ovarian cancer cases in 2018 [2]. It accounts for 4% of global cancer incidence [3].

There are geographical variations in the frequency of ovarian cancer. Ovarian cancer incidence rates are greater in high than in middle- to low-income countries. Around the world, age-standardised incidence rates range from more than 11 per 100,000 women in Central and Eastern Europe to less than 5 per 100,000 in parts of Africa. Serbia had the highest incidence rate in 2018, while the UK ranked 19th in age-standardised rates [3].

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The number of women being diagnosed with ovarian cancer is likely to see a significant increase over the next two decades, according to a new study. The World Ovarian Cancer Coalition, a group of patient organisations, has published its 2018 Every Woman Study, which has collated data from 1000 women in 39 countries, making it the most comprehensive study ever of the global impact of ovarian cancer [4]. It predicted that ovarian cancer incidence will rise by nearly 55% in the next 20 years unless urgent action is taken, with UK incidence rates projected to increase by 15% over this period.

Types of Ovarian Cancer

Ovarian cancers are a heterogenous group (Table 1.1). The most common ovarian cancers are known as epithelial ovarian cancers of which high-grade serous cancer is the commonest. Further discussions refer to epithelial tumours except otherwise specified.

Recent data suggest that there are two types of epithelial ovarian cancer [5]: Type 1 cancers include low-grade serous, endometrioid, clear cell, and mucinous types. They tend to grow locally, metastasize late, and behave in a more indolent fashion. They are believed to arise from inclusion cysts or in implants of the ovarian surface epithelium. The endometrioid and clear cell ovarian cancer appear to arise in association with

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Table 1.1 Ovarian cancer subtypes

Type	Frequency (%)	Subtype
Epithelial	90	Serous 52%
		Endometrioid 10%
		Mucinous 6%
		Clear cell 6%
Germ cell	3	Dysgerminoma
		Embryonal carcinoma
		Endodermal sinus tumour (yolk sac)
		Choriocarcinoma
		Malignant teratoma
Sex cord/ stromal	2	Granulosa cell tumours
		Sertoli–Leydig tumours

endometriosis, suggesting that the endometrial lining, via retrograde menstruation, is the source for many type 1 cancers. They are associated with KRAS, ARID1A, PIK3CA, PTEN, and BRAF mutations. Type 2 cancers include high-grade serous, carcinosarcomas, and undifferentiated carcinomas. They are highly aggressive and they generally present at advanced stage. They are believed to arise in the fallopian tube or from the ovarian epithelium. Observational studies suggest that the majority of type 2 ovarian cancers originate as high-grade lesions in the distal end of the fallopian tube; they transform to cancerous cells that seed to the ovary and rapidly spread through the peritoneal cavity. They are associated with TP53 mutations.

Risk Factors of Ovarian Cancer

The epidemiology may, to an extent, reflect the risk factors for ovarian cancer. Because of its heterogeneity, epithelial ovarian cancer has been associated with different risk factors for the various histopathological types [6]. There is a broad spectrum of evidence suggesting sufficient or convincing data for some of the risk factors, and there are limited or probable data for others. The best quality data regarding risk factors for epithelial ovarian cancer come from two large prospective studies: (1) The United States (US) Nurses' Health Study that has followed >200,000 women, with 924 cases of epithelial ovarian cancer to date, and (2) The European Prospective Investigation into Cancer and Nutrition (EPIC) that has followed >300,000 women, with 878 cases of epithelial ovarian cancer to date [7].

Age

Older age is the main risk factor for epithelial ovarian cancer as over 50% of cases occur in postmenopausal women. In the UK in 2013–2015, on average each year more than a quarter (28%) of new cases were in females aged 75 and over [8]. Age-specific incidence rates rise steadily from around age 30–34 and more steeply from around age 45–49, with a sharp drop in the oldest age groups. The highest rates are in the 75–79 age group [6].

Family History

Family history is one of the strongest risk factors for ovarian cancer. Inherited genetics appear to be more significant than the environmental and lifestyle circumstances [9]. They cause around 5–15% of cases of ovarian cancer [6]. Personal history or family history of breast cancer and family history of a first-degree relative with ovarian cancer have been considered as risk factors for ovarian cancer; however, BRCA gene mutations appear to account for most of this increased risk [7]. General population estimated risk of carrying BRCA mutations varies between 1:300 and 1:800, and in certain groups like the Ashkenazi Jews it is estimated to be 1:40 individuals [9]. Certain populations are associated with a higher incidence of BRCA mutations. For example, Ashkenazi Jewish ancestry (those of European origin) have higher rates of carriage than in Sephardic Jews (those of African and Asian descent) and the rest of the general population [10].

The first breast cancer gene to be discovered is called BRCA1, and inherited germline mutations in BRCA1 increase the risk of breast, ovarian, uterus, cervix, pancreatic, and possibly prostate cancer [11]. Approximately 1.5% of the Ashkenazi Jewish population carries an inherited mutation in the BRCA1 gene.

The second breast cancer gene is called BRCA2. Since its discovery in December of 1995, researchers have come to a better understanding of the role of the BRCA2 gene in the development of cancer. Every cell in our body has two copies of BRCA2. One is inherited from each parent. An ancestor of Eastern European Jews, approximately 29 generations ago, developed a defect in the DNA coding for the BRCA2 gene. This DNA defect, known as the 6174delT mutation, has been passed from generation to generation. As a result, 1% of all Ashkenazi Jews living now inherit a defective copy of one of their BRCA2 genes. Carriers of the BRCA2 mutation are at increased risk of developing breast, ovarian, prostate, and pancreatic cancer [11].

Patients with BRCA1 gene mutation have a 39–46% overall risk of developing ovarian cancer by the age of 70, and patients with BRCA2 gene mutation have a 10–27% overall risk of developing ovarian cancer by the age of 70 [9]. These inherited cancers are most frequently of the high-grade serous subtype, which constitutes approximately 60% of epithelial ovarian cancers [9]. In addition, the BRCA gene mutation is the most established risk factor for fallopian tube and peritoneal cancer carcinoma [7]. BRCA mutation carriers typically present with ovarian cancer at a younger age than those with sporadic cancers. Risk-reducing surgery for known BRCA carriers with bilateral salpingo-oophorectomy has been successful in reducing epithelial ovarian cancer mortality [9].

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome, includes multiple adenocarcinomas and is associated with colon cancer, endometrial cancer, breast cancer, and other malignancies of the gastrointestinal and genitourinary systems, including the risk of ovarian cancer. Women with Lynch syndrome account for 1% of ovarian cancer. The lifetime risk of ovarian cancer in women with Lynch syndrome is 3–14% compared with 1.5% in the general population [7]. The mutations associated with this syndrome are MSH2, MLH1, PMS1, and PMS2 [12]. The most common subtypes of ovarian cancer associated with Lynch syndrome are the endometrioid and the clear cell type [9]. The typical age of diagnosis of ovarian cancer in women with Lynch syndrome is 43–50 years old [7], which is younger age than the other women, at around 60 years old.

Peutz-Jeghers syndrome, which is an autosomal dominant genetic disorder associated with benign hamartomatous polyps in the gastrointestinal tract and hyperpigmented macules on the lips and oral mucosa, has been associated with significant ovarian cancer risk from a meta-analysis that has shown that 21% of women with this syndrome develop ovarian cancer aged 15–64 [6].

All the known susceptibility genes that we currently know they are associated with ovarian cancer account for less than half of the heritable causes of this disease, suggesting there are more mutations to be discovered [9].

Reproductive Factors

Ovarian cancer risk is associated with factors affecting ovulation. Decreased risk of ovarian cancer is associated with suppression of ovulation. Early menarche and/or late menopause are associated with higher risk of ovarian cancer [13]. Multiparous women are considered to have 30–60% lower risk for ovarian cancer compared with nulliparous women [14]. Infertility, especially unexplained infertility [15], is a risk factor for epithelial ovarian cancer, but ovulation induction for treatment of infertility does not appear to increase this risk [7]. Ovarian cancer risk is 24–30% lower in women who have ever breastfed versus those who have never breastfed [6]. These risk factors may cast some light on the geographical variations as while fecundity rates have fallen in Europe and North America, there remain high rates of childbirth in Asia and Africa [16].

Exogenous Hormones

The Oral Contraceptive Pill

The oral contraceptive pill reduces the risk of ovarian cancer compared to never-users. The risk decreases further with longer use of the oral contraceptive pill [13, 17].

Hormone Replacement Therapy

Hormone replacement therapy (HRT) has been associated with ovarian cancer in a number of studies [13, 18]; however, the absolute risk appears to be small [7]. Level 2 evidence from observational and cohort studies suggests that HRT is associated with increased risk of ovarian cancer; this risk appeared to be higher to current users compared to past users; unopposed oestrogen use for more than 10 years and increasing oestrogen dose with HRT is associated with increasing risk of ovarian cancer; however, the Women's Health Initiative (WHI) randomised control trial found no statistically significant increase in the risk of ovarian cancer with combined oestrogen-progestin therapy compared with placebo (42 versus 27 per 100,000 person-years; HR 1.6, 95% CI 0.8–3.2) [7]. A meta-analysis of 52 epidemiological studies has shown an increased risk of ovarian cancer in women who use HRT [18].

Medical Conditions

Endometriosis

Based on systematic review of observational studies, endometriosis is associated with increased risk of endometrioid and clear cell carcinoma [12, 13]. Compared to non-endometriosis-associated ovarian cancer, endometriosis-associated ovarian cancer is associated with decreased overall mortality and decreased incidence of serous carcinoma [13].

High BMI

High body mass index (BMI) appears to increase the risk of ovarian cancer [7]. Body mass ≥25 kg/m^2 at age 18 years was associated with increased risk of premenopausal ovarian cancer compared to BMI <20 kg/m^2 at age 18 years. However there were no significant differences in overall risk of ovarian cancer.

Diabetes

Ovarian cancer risk is higher in diabetics compared to non-diabetics [12].

Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome appear to have an elevated risk of ovarian cancer (OR 2.52, 95% CI, 1.08–5.89) based on a meta-analysis of eight case-control studies [7].

Other Factors

Genital Powder (Talcum Powder)

Systematic review of case-control studies showed that genital powder (talcum powder) is associated with increased risk of ovarian cancer [6, 19].

Smoking

Mucinous ovarian cancer has been associated with smoking [17, 20]. The association appears to be stronger with current users and with increased duration of smoking [6, 20].

Survival

Ovarian cancer carries a poor prognosis as most women present with advanced disease. The absence of an effective screening strategy and the non-specific nature of symptoms often mimic benign disease; mean women often do not become aware that there is a problem until other organs become affected. As a consequence, the majority of woman will have disease that has spread beyond the ovaries at diagnosis, making cure less likely. FIGO staging for ovarian cancer was revised in 2014 (Table 1.2).

Table 1.2 FIGO ovarian cancer staging (2014) [21]

Stage	Substage	
I	IA	Tumour limited to one ovary, capsule intact, no tumour on surface, negative washings
	IB	Tumour involves both ovaries otherwise like IA
	IC	Tumour limited to one or both ovaries
	IC1	Surgical spill
	IC2	Capsule rupture before surgery or tumour on ovarian surface
	IC3	Malignant cells in the ascites or peritoneal washings
II		Tumour involves one or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer
	IIA	Extension and/or implant on uterus and/or fallopian tubes
	IIB	Extension to other pelvic intraperitoneal tissues
III		Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
	IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
	IIIA1	Positive retroperitoneal lymph nodes only
	IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
	IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IV		Distant metastasis excluding peritoneal metastasis
	IVA	Pleural effusion with positive cytology
	IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

It is worth noting that the lowest survival prospects of all female cancers, with 5-year survival rates ranging between 30% and 50%. By comparison, more than 80% of women with breast cancer will survive for 5 years or more in many countries. Survival depends on the stage (Fig. 1.1) of disease as well as the cancer type, with high-grade serous cancer being associated with the highest mortality rates. There is also a geographical variation in survival, which reflects awareness and access to healthcare [22].

The UK has one of the lowest survival rates when compared to other European countries (Fig. 1.2) [6].

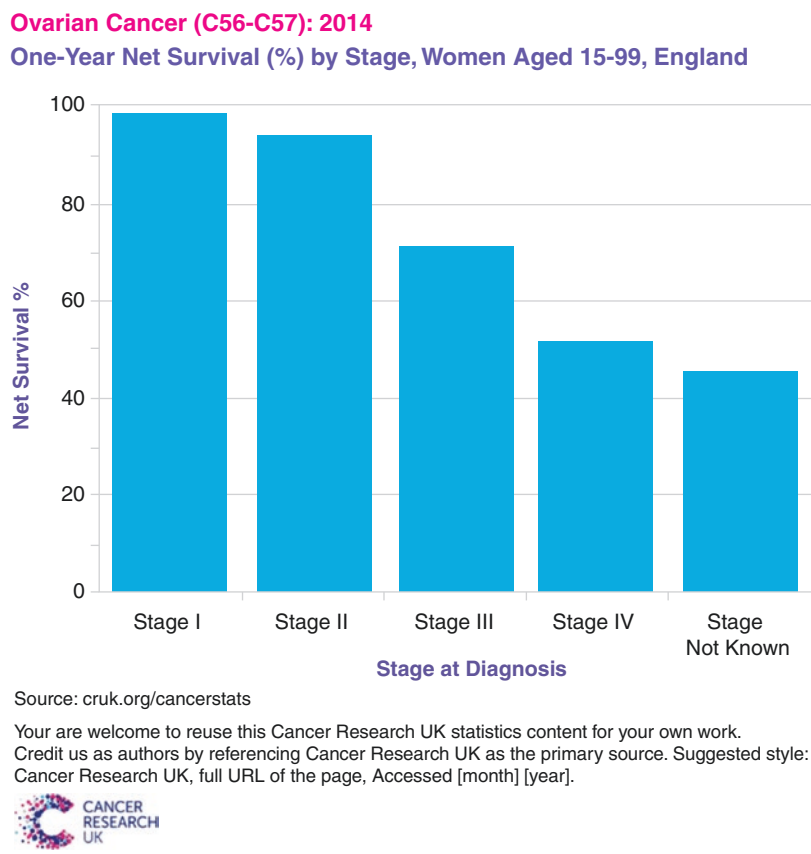

Fig. 1.1 Ovarian cancer survival by stage [6]

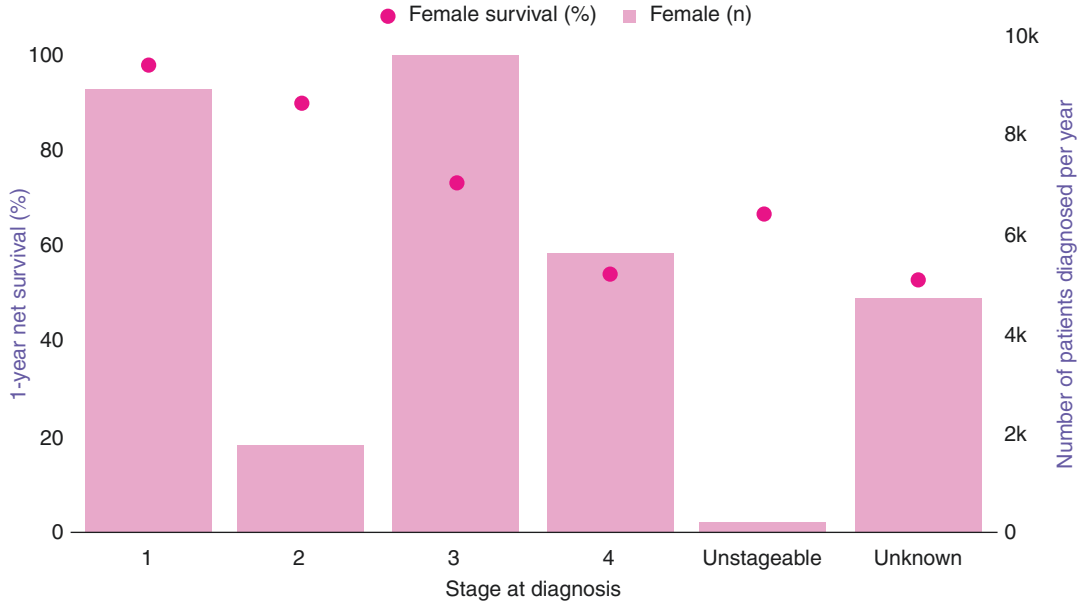

Fig. 1.2 Ovarian cancer 1-year net survival by stage, with incidence by stage (all data: adults diagnosed 2013–2017, followed up to 2018) [6]

Conclusion

Ovarian cancer is the eighth most common cancer in women and it accounts for 4% of global cancer incidence. Ovarian cancer incidence rates are greater in high than in middle- to low-income countries. The number of women being diagnosed with ovarian cancer is likely to see a significant increase over the next two decades. The most common ovarian cancers are known as epithelial ovarian cancers from which serous type is the most frequent. Epithelial ovarian cancer is a heterogeneous disease. The recognised risk factors do not account for all the types of the disease, but rather they are associated with different subtypes of ovarian cancer. Age, family history, and inherited genetics appear to be significant risk factors. In the majority of cases, ovarian cancer presents at advanced disease due to non-specific symptoms and no effective screening tests; because of this, it has poor survival range between 30% and 50%. Epidemiological evidence suggests that further studies are necessary to research the aetiology, identify screening methods, and offer treatment depending on the different subtypes of epithelial ovarian cancer.

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2 Ovarian Cancer Screening and Early Detection

Monica Levine and R. Wendel Naumann

Background

Approximately 1.3% of women born today, or 1 in 78, will be diagnosed with ovarian cancer at some point in their lifetime. This year there will be over 21,000 new cases of ovarian cancer along with nearly 14,000 deaths in the United States [1]. These cases arise from a much larger group of women presenting with pelvic masses. The overall prevalence of pelvic masses is estimated at 7% [2]. In addition, it is expected that 5–10% of American women will receive prophylactic surgery for suspected ovarian cancer at some point in their lives.

Ovarian cancer remains the leading cause of death from gynecological malignancy in the United States. A critical factor associated with the high incidence to mortality ratio is the late stage at diagnosis, largely due to the lack of early disease-specific symptoms or an effective strategy for early detection. The outcome for early-stage ovarian cancer is excellent with an 89% 5-year survival for patients with stage I cancer and 71% for stage II [3]. However, patients with ovarian cancer often do not have symptoms until the later stages of the disease and 63% of patients with epithelial ovarian cancer have already established regional or distant metastases at the time of diagnosis. Despite aggressive cytoreductive surgery and platinum-based chemotherapy, the 5-year disease-specific survival is 41% for stage III ovarian cancer and only 20% for stage IV ovarian cancer.

Carcinoma of the Müllerian epithelium includes cancer arising from the ovary, the fallopian tube, and the peritoneum. The site of origin of these tumors does not change clinical care and these cancers are often referred to collectively as "ovarian cancer." The origins of these cancers are now better understood and have implications for different screening strategies. There is a dual mechanism proposed for the origin of serous ovarian cancer with these cancers being divided into low-grade and high-grade subtypes with distinctly different developmental pathways [4]. The low-grade cancers are often confined to the ovary and develop through mutation in the PI3K growth pathway. These lesions likely start with a benign process and develop mutations that lead to borderline, micropapillary lesions, and low-grade cancers over a period of time. Low-grade cancers are much more likely to be detected early by screening and constitute a minority of deaths from ovarian cancer. It is now thought that most high-grade serous cancers start in the fallopian

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tube [5]. Serous tubal intra-epithelial carcinoma (STIC) is a putative precursor of high-grade serous carcinomas. STIC lesions are described with P53 alterations and may spread throughout the peritoneal cavity prior to any detectable abnormality on imaging or even elevation of biochemical markers. This has likely been the reason that an effective screen strategy has been elusive in ovarian cancer. Most clear cell and endometrioid ovarian cancers are thought to arise from endometriosis, which can be ovarian or extra-ovarian [6–8]. Screening by imaging would likely only be able to detect ovarian cancers that developed in the ovary, which constitute a minority of cases. Primary ovarian mucinous neoplasms are rare and probably arise within benign mucinous tumors, which are also potentially detectable by screening ultrasound [9]. These revelations concerning the origins of ovarian cancer would explain why screening has had limited success in reducing the mortality from ovarian cancer. This also highlights the need for different approaches to ovarian cancer screening that will include the detection of the STIC lesions prior to spread throughout the peritoneal cavity.

Development of a Screening Test

Considering the low prevalence of ovarian cancer, any proposed screening strategy must demonstrate a reasonable sensitivity with a very high specificity to achieve a reasonable safety margin. Even at a specificity (SP) of 99.6% and a sensitivity (SN) of >75%, the positive value (PPV) of an ovarian screening test would only be 10% in an average-risk population. This is problematic because a positive screening test often leads to surgical intervention, so a screening test that yields a positive predictive value of less than 10% is not acceptable [10, 11].

The World Health Organization (WHO) has specified prerequisite criteria that must be met for a screening test to be effective [12]. Notably, a sufficient interval must exist between onset of early-stage disease and development of advanced disease to allow for screening and intervention. Although ovarian cancer satisfies many of the WHO requirements, several particular aspects of the etiology and epidemiology of ovarian cancer complicate the question of screening:

1. There is likely not a transition from stage I through stage III as the cancer disseminates from the fallopian tube into the peritoneal cavity before imaging can determine an abnormality.
2. Clinical evidence indicates that methods in common use today are not able to identify cancers early enough to significantly alter the natural history of the disease.
3. Approximately 90% of ovarian cancers occur in a low-risk population and the relative incidence is very low.
4. Given a low prevalence of ovarian cancer (40 per 100,000 per year) among postmenopausal women, screening tests must achieve a very high specificity rate to lower the positive predictive rate to acceptable levels.

Ovarian Cancer Symptom Index

A case control study has reviewed the symptoms present prior to detecting ovarian cancer [13]. In the evaluation of 149 women with ovarian cancer compared to 255 without, the following symptoms were included in an index of six symptoms: pelvic pain, abdominal pain, increased abdominal size, bloating, difficulty eating/feeling full, that when present >12 times a month for <12 months are significantly correlated with the diagnosis of ovarian cancer. For women ≥50 years, the sensitivity was 66.7% and the specificity was 90%. Subsequent studies evaluated the performance of the Ovarian Cancer Symptom Index (OCSI) in combination with biomarkers. A prospective case-control study of 74 women with ovarian cancer and 137 healthy women found that CA-125, HE4 and OCSI were independently predicted the presence of ovarian cancer. With a tool that requires two of the three tests to be positive, sensitivity was 83.8% overall, 67.7% for early-stage and 100% for high-risk cases. However, the specificity was 98.5%, which generated a positive predictive value below the threshold of 10% [14].

In a study to evaluate the potential harms of implementing the OCSI, 5012 women were prospectively evaluated using the OCSI and were offered CA-125 and TVUS if screened positive. A total of 241 women were positive on the screen with 211 having follow-up testing (CA-125, ultrasound or both) and 20 underwent surgery. Only 6 of those 20 surgeries were performed for a pelvic mass. Two women were diagnosed with ovarian cancer within 6 months of completing the OCSI. One of those women screened positive with the OCSI and was diagnosed at an advanced stage. The other was screen negative and was diagnosed at an early stage. There were an additional six cancers diagnosed after the initial 6 months follow-up period, three of which were diagnosed at an early stage. The authors were unable to make conclusions about the efficacy of the OCSI due to the small number of ovarian cancer diagnoses. However they did suggest that the OCSI may have played a role in educating women about the symptoms related to ovarian cancer—perhaps explaining the later diagnoses [14].

Biomarkers

A number of cell-surface antigens and serum proteins are produced by ovarian tumors and can be assayed using monoclonal antibodies. Some of these assays have been applied clinically as markers of disease status and may be useful in the detection of subclinical disease. However, the current indications for the uses of biomarkers are for the pre-surgical prediction of malignancy when a pelvic mass has been found and also to determine treatment response [15–18]. CA-125 is the most robust and well-known serum biomarker for detection of ovarian cancer. The initial finding of CA-125 levels greater than 35 U/mL in approximately 83% of patients with advanced epithelial ovarian cancer and in only 1–2% of the normal population led to investigations into its use as a biomarker for ovarian cancer [19, 20]. CA-125 levels vary significantly between pre- and postmenopausal populations. In a prospective analysis of women at high risk of developing ovarian cancer, the 98th percentile was found to be 35 U/mL in postmenopausal women and 50th percentile in premenopausal women [21]. Other analyses of CA-125 have revealed a number of limitations for the test. Although CA-125 is frequently elevated in advanced-stage ovarian cancer, the protein is elevated in less than 50% of stage I disease and is often normal in early-stage cancers and mucinous carcinomas [22–28]. Moreover, a number of benign and malignant conditions may result in falsely elevated CA-125 values [29, 30]. Additional factors may influence the CA-125 level, such as race/ethnicity, age, hysterectomy, smoking history, and obesity [31]. Despite these well-recognized limitations, CA-125 remains the most widely studied serum biomarker for ovarian cancer. The best currently available protocol for early detection of ovarian cancer, a combination of screening for elevated CA-125 and transvaginal ultrasound in the presence of elevated CA-125, does not meet the stringent criteria for cost-effectiveness espoused by the US Preventive Services Task Force [32–34]. As a result, no professional group currently recommends screening for ovarian cancer in the general population [29–31].

Other potential biomarkers have been identified in patients with ovarian cancer. These include the following: CA 15-3, CA 54/61, CA 19-9, TAG-72, OVX1, M-CSF, carcinoembriogenic antigen (CEA), cancer-associated serum antigen (CASA), lipid-associated sialic acid (LASA), urinary gonadotropin fragment (UGF), HER2/neu (ErbB2), EGFR, sICAM-1, VEGF, and lysophosphatidic acid [27, 35–43]. In addition, several members of the kallikrein family of proteins have been identified as potential serum markers of ovarian cancer [44–50]. The use of gene expression array analysis has identified a number of novel markers, including Human Epididymis Protein 4 (HE4), prostasin, and osteopontin [51–53]. Different combinations of these biomarkers have been tested with respect to sensitivity and specificity of the diagnosis of ovarian cancer as noted in Table 2.1. However, the sensitivity and specificity combinations are too low to be used in screening of an average-risk population.

Table 2.1 Multi-marker panels which discriminate benign from malignant pelvic masses

Panel	Cases	Controls	SN	SP	Reference
CA-125, β2-microglobulin, transthyretin, transferrin	144	509	95	81	Hogdall et al. [54]
CA-125, midkine, anterior gradient 2 protein	46	61	95	98	Rice et al. [55]
CA-125, G-CSF, IL-6, EGF, VEGF	44	37	87	93	Gorelik et al. [56]
CA-125, IL-7	187	45	69	100	Lambeck et al. [57]
CA-125, HE4, IL-2Rα, α1-antitrypsin, CRP, YKL-40, cellular fibronectin, CA 72-4, prostasin	149	350	90	89.9	Yip et al. [58]

SN sensitivity, *SP* specificity

Table 2.2 Multi-marker panels for the preoperative prediction of malignancy in a pelvic mass

Panel	Cases	Controls	SN	SP	Reference
ROMA (CA-125, HE4, menopausal status)	89	383	94	75	Moore et al. [64]
OVA1 (CA-125, transthyretin, β2-microglobulin, ApoA1, transferrin)	151	373	93	43	Ueland et al. [65]
OVA1 (CA-125, transthyretin, β2-microglobulin, ApoA1, transferrin)	92	402	92	54	Bristow et al. [17]
OVERA (HE4, FSH, CA-125, transferring, ApoA1)	92	402	95	69	Coleman et al. [18]
CA-125, HE4, IL-2Rα, α1-antitrypsin, CRP, YKL-40, cellular fibronectin, CA 72-4, prostasin	149	350	90	90	Yip et al. [58]

SN sensitivity, *SP* specificity

HE4 is a secreted glycoprotein product of the *WFDC2* gene which has shown great promise as a diagnostic biomarker for ovarian cancer and has also recently been approved by the US Food and Drug Administration for disease monitoring [59, 60]. Studies focusing on the potential use of HE4 as a biomarker of ovarian cancer suggest that it is elevated in over 50% of ovarian cancer patients whose tumors do not express CA-125 [61]. HE4 has also demonstrated greater sensitivity than CA-125 among early-stage ovarian cancer patients and greater specificity in comparison with benign ovarian lesions [61, 62]. A diagnostic assay for HE4 has been developed and commercialized by Fujirebio Diagnostics, Inc. (Malvern, PA), and the use of HE4 for ovarian cancer monitoring has been approved by the US Food and Drug Administration (FDA) [63]. Investigations into the use of HE4 as an ovarian cancer biomarker have proceeded both in the area of population-based screening and in the differential diagnosis of a pelvic mass. Despite a number of promising reports, it has become apparent that HE4 is not sufficiently sensitive or specific to function effectively as a stand-alone test. However, the combined use of CA-125 and HE4 in the differential diagnosis of pelvic masses has received a considerable amount of attention with respect to the sensitivity and specificity of detecting a malignant mass (Table 2.2), but the specificity for this combination is too low to be an effective screening tool in a low-risk population. With the exception of HE4, the identification of additional biomarkers associated with ovarian cancer has not translated into widespread clinical implementation.

It remains unlikely that any stand-alone biomarker-based screening test will be capable of

overcoming the 10% positive predictive level required for population screening. However, work has persisted based on the notion that biomarker testing may prove effective in sufficiently defined high-risk groups or as part of a multimodal screening strategy involving transvaginal ultrasound or an equivalent imaging method as a second-line test.

Ultrasound

Ultrasound is attractive as a screening tool given the relatively low cost and lack of ionizing radiation. Imaging of the ovary has been proposed as a strategy to detect changes in size and architecture that might precede the development of symptoms and detection by pelvic examination. The American College of Obstetrics and Gynecology (ACOG) recommends transvaginal ultrasound for evaluation of a suspected or an incidentally identified pelvic mass. A cyst greater than 10 cm in size, a mass with irregularities, papillary or solid components, high color Doppler flow, or the presence of ascites should raise concern for malignancy [66]. Ultrasound alone has been explored as a screening tool. The University of Kentucky Ultrasound Study screened women for epithelial ovarian cancers, including tumors with low-grade malignant potential, in a single-arm trial with annual ultrasound. This trial enrolled 25,327 women and the results showed an improved 5-year survival when compared to historical controls at the same institution (75% vs. 54%) [67]. However, a single-arm trial is difficult to interpret as patients participating in trials may not be typical of the general population. This effect was noted in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial where the all-cause mortality was significantly reduced when compared to the general population [63].

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) enrolled 202,638 postmenopausal women between the ages of 50 and 74 years who were deemed to be at average risk for ovarian cancer. The ultrasound arm of the UKCTOCS trial screened 50,623 women with an annual ultrasound compared to 101,299 controls [68]. Ultrasound was repeated in 1 year if normal, 3 months if inconclusive, or 6 weeks if abnormal. Anyone with persistent abnormalities was evaluated by an National Health Service clinician. There was no difference in the number of early ovarian cancers or mortality between these two arms. Given the size of this trial it is unlikely that ultrasound alone will be able to significantly alter mortality in ovarian cancer.

The International Ovarian Tumour Analysis Phase 5 (IOTA-5) study prospectively followed women who were found to have adnexal masses considered to be benign by ultrasound to estimate the incidence of complications, including torsion, malignancy, or cyst rupture. An interim analysis of 3144 women 2 years after initial ultrasound found spontaneous resolution for 20.2%, and the incidence for complications low: 0.4% for invasive malignancy, 0.3% for borderline tumors, 0.4% for torsion, and 0.2% for cyst rupture. This study provides promising evidence that current algorithms to stratify risk of pelvic masses by ultrasound are a safe method of management of pelvic masses [69].

Multimodal

Biomarker testing is attractive due to the low cost and ease of testing. This type of screening can be combined with ultrasound or can be used to triage patients to ultrasound when abnormal to facilitate mass population screening. Three large, randomized trials designed to determine whether this multimodal ovarian cancer screening improves survival have reported their findings. In the PLCO Trial, 68,557 healthy postmenopausal women between the ages of 55 and 74 years were randomly assigned to undergo either annual CA-125 testing plus transvaginal ultrasound or to receive "usual care" [70]. A positive finding was defined as a CA-125 level of more than 35 U/mL or ultrasound evidence of an abnormal ovarian volume or an ovarian cyst with papillary projections or solid components. Diagnostic follow-up of positive screens was performed at the discretion of participants' physicians. The positive predictive value of a positive screening test was 1.0–1.3% during the 4 years of screening. The

overall ratio of surgeries to screen-detected cancers was 19.5:1. While screening did detect ovarian cancers, 72% of screen-detected cases were stage III or IV, suggesting that screening has not resulted in a significant stage shift [70]. The PLCO project team released its final report on survival in which they conclude that the CA-125/ultrasound screening approach does not reduce disease-specific mortality in comparison to usual care, but does result in an increase in invasive medical procedures and associated harms [71].

In Japan, the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) randomized 82,487 women to screening with ultrasound and CA-125 or to the control care with usual care (no screening) [72]. There was no significant difference in the detection of ovarian cancer. The mean follow-up in the trial was 9.2 years. A shift toward stage I cancers was seen in the study (63% versus 38%), but due to the relatively small numbers of cancers, this did not meet statistical significance.

In clinical trials, CA-125 as a single screening biomarker demonstrated limited utility when examined in a retrospective analysis of serum samples from 5550 women enrolled in a population-based registry in Sweden [73]. Later it was suggested that measurement of CA-125 values in an individual patient over time could improve the estimation of a patient's risk of ovarian cancer (Risk of Ovarian Cancer Algorithm (ROCA)) [74]. To evaluate CA-125 dynamics, the ROCA was developed based on the slope of serial CA-125 measurements drawn at regular intervals [75]. This algorithm was based on the observation that irrespective of the initial level, CA-125 measurements are stable in non-cases for periods of more than 5 years, indicating that each woman has her own baseline level of CA-125. In contrast, exponentially increasing serial values readily identify cases. When the ROCA score exceeds a 1% risk of having ovarian cancer, patients undergo TVU to determine whether additional intervention is warranted. In a retrospective examination of 33,621 serum samples from 9233 women, ROCA provided a sensitivity of 86% at a fixed specificity of 98% for the preclinical detection of ovarian cancer, compared to a sensitivity of 62% for a single CA-125 value [75]. This algorithm was confirmed to have a reasonably high positive predictive value (19%) in a subsequent prospective pilot study involving more than 13,000 postmenopausal women [76]. This ROCA algorithm was tested in a population-based screening effort in the UKCTOCS trial. This trial enrolled 202,638 postmenopausal women between the ages of 50 and 74 years who were deemed to be at average risk for ovarian cancer. Women in the UKCTOCS trial were randomly assigned to undergo annual pelvic examination (control group), annual transvaginal ultrasound (ultrasonography or USS group), or annual measurement of CA-125 evaluated over time with the use of ROCA plus transvaginal ultrasound in cases in which the ROCA was abnormal (multimodality screen or MMS group) [75, 77]. Women with persistent abnormality on repeat screens underwent evaluation by a clinical oncologist and, where appropriate, surgery. As compared with ultrasonography alone, multimodality screening had a significantly greater specificity (99.8% vs. 98.2%) and a higher positive predictive value (35.1% vs. 2.8%) ($P < 0.001$). The trial was negative with respect to the primary endpoint of reducing ovarian cancer mortality, but 25% of women in the MMS group were diagnosed at stage I as compared to 16% in the control group. While this shift toward an earlier stage is encouraging, it is predicted that this shift would likely only reduce ovarian cancer mortality by a modest 6–9% and is cost prohibitive [78]. Because of the relative lack of effectiveness and the possibility that screening could give false reassurance, the FDA ruled against using this test in the United States [79]. This strategy is currently being prospectively studied among more than 2600 high-risk women by the Gynecologic Oncology Group (protocol #199) as well as in a parallel trial being conducted by the National Cancer Institute-Cancer Genetics Network [80].

Current Screening

There have been several screening trials that have evaluated the use of ultrasound with CA-125 measurements in the general population. Combining biomarkers CA-125 or HE-4 with the Ovarian Cancer Symptom Index (OCSI) is

another screening modality reviewed [81]. Once a pelvic mass has been identified, monitoring with ultrasound or adding biochemical markers may be helpful to triage benign from malignant pelvic masses [17, 18, 69]. Currently, the United States Preventative Services Task Force (USPSTF) currently recommends against general population screening for ovarian cancer, and this recommendation has been endorsed by the Society of Gynecologic Oncology (SGO) and the American College of Obstetrics and Gynecology (ACOG) [82].

Approximately 15% of ovarian cancers are due to a mutation in the *BRCA* gene complex and this risk may be higher in certain ethnic populations [83–85]. For individuals of Ashkenazi Jewish descent, 1/40 may harbor one of the founder mutations in the *BRCA1* or *BRCA2* genes. In addition to *BRCA1* and *BRCA2*, there are several other genes in the *BRCA* pathway, as well as genes that cause Lynch syndrome that when mutated, predispose to ovarian cancer. For a woman carrying a *BRCA1* mutation, the lifetime risk of ovarian cancer may be as high as 44%, more than 30× the general population risk [86]. It is important to identify these patients not only to tailor treatment but also for the possibility of cascade testing and ovarian cancer prevention in family members. Women at increased risk of developing ovarian cancer due to hereditary predisposition (*BRCA1/2*, Lynch syndrome, *BRIP1, RAD51C, RAD51D*) are recommended to undergo risk-reducing salpingo-oophorectomy after completion of childbearing [87]. It is only in those select high-risk women who have not yet opted for surgery who may undergo annual screening with CA-125 serum measurements and transvaginal ultrasound, starting at age 30–35 years, although this is of uncertain benefit [87, 88].

Given the percentage of ovarian cancers that are attributable to inherited risk, any woman diagnosed with epithelial ovarian cancer is recommended to undergo a genetic risk evaluation and should be offered comprehensive genetic testing [87]. When a mutation is detected, cascade testing for the specific genetic mutation identified in unaffected family members is critical to identify those at the highest risk who would benefit from surgery for ovarian cancer risk reduction. If testing cannot be performed on the affected individual with cancer, family members without cancer may be offered comprehensive genetic testing if the family history indicates a hereditary cancer syndrome [87]. As the cost of genetic testing has decreased significantly, universal genetic testing for cancer predisposition has been proposed [89]. Review of family history, even when collected and complete, may miss up to 50% of patients at risk for *BRCA1/2* mutations and up to 70% of families with Lynch syndrome [90, 91]. Universal testing now appears to be cost-effective in the general population [89, 90]. Currently the USPSTF recommends against routine genetic testing, but does recommend testing in populations with higher ancestry-based risk, such as those with Ashkenazi Jewish descent [92, 93]. In the absence of a good screening test for ovarian cancer, primary prevention by way of identification of those at highest risk through genetic testing and completing risk-reducing surgery is an important way to decrease the number of ovarian cancer diagnoses each year.

Detection of STIC Lesions in the Fallopian Tube

The understanding of the natural history of ovarian cancer provides opportunities for development of new types of screening tests. The identification of serous tubal in situ carcinoma (STIC) in the fallopian tube suggests that many serous cancers actually arise in the fallopian tube instead of the ovary [5]. This hypothesis was generated from the close analysis of fallopian tubes removed as part of a risk-reducing surgery in patients with a hereditary predisposition for ovarian cancer [94, 95]. STIC lesions are present in 70% of women with ovarian cancer, supporting the theory that they are in fact precursor lesions [96]. The development of screening tests that can detect the presence of STIC precursor lesions provides promise for a novel screening approach. Sampling for precursor lesions in the fimbriae of the fallopian tube may allow for sampling

techniques to screen for precursor lesions using cytology preparations akin to the Papanicolaou smear in cervical cancer or even molecular-based screening for abnormal P53 signatures [5, 97].

It has been shown that fallopian tube cytology can be collected in fresh surgical samples to screen for neoplastic cells when gross tumor is not visible [97]. The fallopian tubes can also be cannulated and sampled at the time of hysteroscopy [98, 99]. Another technique for molecular sampling involves a technique of "liquid biopsy": utero-tubal lavage was performed in ovarian cancer patients (n = 49), analyzed for protein composition using mass spectrometry, and compared to controls (n = 127) [100]. A 9-protein classifier was developed with 70% sensitivity and 76.2% specificity [100]. In this study population, the classifier detected all stage I lesions.

Ideally screening could be performed on a blood test that would detect cancer at an early or preinvasive stage. Cell-free DNA (cfDNA) assays are now being evaluated for general cancer screening. Through analysis of noninvasive prenatal tests performed on 1.93 million pregnant women, 466 women who tested positive for multiple chromosomal aneuploidies were subjected to a multivariate cancer risk score that relied on whole genome sequencing and protein marker testing. This screening technique identified 28 of the occult 39 cancer cases in this group. The positive predictive value was 74% and specificity 98% [101]. Another prospectively run study used methylation sequencing of cfDNA from 2301 patients enrolled in the Circulating Cell-free Genome Atlas (CCGA). Within this group there were 1422 patients with cancer (>20 tumor types, all stages) and 879 controls. Patterns of methylation were used to successfully identify a certain cancer type and tissue of origin. The sensitivity of this assay ranged from 59% to 86%, but with 99% specificity [102]. It is likely that these tests will be more sensitive and potentially specific than traditional biomarker-driven screening tests. However, it is not known if this technique will be sensitive enough to detect preinvasive STIC lesions.

Triage of Pelvic Masses

Although the vast majority of women diagnosed with ovarian carcinoma will initially present with a pelvic mass, only a small proportion of all masses detected will prove to be malignant. Several strategies have been developed to improve the preoperative predication of malignancy in patients with a pelvic mass with the goal of improved outcomes by referring malignant cases to appropriate specialists [66]. An ultrasound morphology index can be used to determine the likelihood that a pelvic mass is malignant. The Kentucky index uses tumor volume, wall structure, and septal structure to calculate a score from 0 to 4 for each, with larger and more solid masses receiving the highest score. A score greater than or equal to 5 is considered indicative of malignancy, with 89% sensitivity, specificity of 73%, and PPV 46% [103]. The International Ovarian Tumor Analysis (IOTA) group through a multicenter study compiled 10 ultrasound findings, 5 that have the highest PPV for malignant masses and 5 that have the lowest PPV for malignant masses [104]. This model, known as the "Simple Rules," will classify a pelvic mass as benign or malignant with 95% sensitivity, specificity of 91%, with a positive likelihood ratio of 10.37 and negative likelihood ratio of 0.06 [104].

The addition of CA-125 or other markers can help identify masses that are malignant. CA-125 is an antigen derived from coelomic and mullerian epithelium. It is elevated in >80% non-mucinous ovarian cancer; however, it is elevated by many inflammatory intra-abdominal processes, including menses in premenopausal women, and it is not elevated in 50% of stage I disease [105].

The Risk of Malignancy Index (RMI) combines ultrasound findings with the measurement of CA-125 and menopausal status. Risk assessment using the RMI is achieved through direct multiplication of scores representing each parameter, rendering this model relatively simple to use and cost-effective. In an initial analysis, the RMI achieved a sensitivity of 85% at a specificity of 97% for the prediction of malignancy in women diagnosed with a pelvic mass. The model has

been modified in several subsequent studies, and its performance has been validated in multiple trials with sensitivity ranging between 71% and 89% and specificity from 74% to 97% [106–109]. The RMI is used routinely in the UK and several other European countries. A recent evaluation of the use of the RMI in a tertiary care setting in Denmark which included 1159 women diagnosed with a pelvic mass, reported sensitivity of 92% and specificity of 82%, respectively, with a positive predictive value of 62% and a negative predictive value of 97% [110].

The diagnostic potential of the CA-125/HE4 combination was first recognized in an investigation of circulating levels of nine biomarkers (CA-125, SMRP, HE4, CA 72-4, activin, inhibin, osteopontin, EGFR, ErbB2) in sera obtained from 233 women diagnosed with a pelvic mass [61]. HE4 was identified as the most sensitive marker in that study, and this was especially true among early-stage ovarian cancer patients. The combination of CA-125 and HE4 provided a greater overall classification accuracy than either biomarker used alone and provided a sensitivity of 76% at a specificity of 95%. This combination was then tested in a prospective multicenter study involving 531 patients [62]. Measurements of CA-125 and HE4 were used to categorize patients into high or low risk of ovarian cancer with 94% of ovarian cancer patients correctly classified into the high-risk group [62]. The Risk of Ovarian Malignancy Algorithm (ROMA), which uses CA 125, HE4, and menopausal status, accurately classifies a pelvic mass as high risk 94% of the time [62].

In a comparison of ROMA and RMI in 467 patients, the ROMA provided a higher sensitivity (94% vs. 85%) at a specificity of 75% [111]. This was particularly evident among stage I and II cancer, where ROMA detected 85% and RMI 65%. The comparative performance of ROMA versus RMI remains in question, however, as a subsequent evaluation by a separate group found that RMI outperformed ROMA among both pre- and postmenopausal women diagnosed with a pelvic mass (n = 432) [112]. In the latter study, both ROMA and RMI were outperformed by subjective assessment by ultrasound. Most recently, ROMA was evaluated in a prospective, multicenter, blinded clinical trial involving 472 patients diagnosed with a pelvic mass, 89 of which were found to have ovarian cancer [64]. In that trial, ROMA provided an overall sensitivity of 94% at a specificity of 75% with a negative predictive value of 98%. ROMA performed particularly well in the premenopausal patient subset, achieving a sensitivity of 100% at a specificity of 74%. Based upon the results of this clinical trial, ROMA was approved by the FDA for use in determining the risk of ovarian cancer in pre- and postmenopausal women with a pelvic mass.

Recent evaluations of HE4 and ROMA have produced mixed results. A number of studies have reaffirmed the complementary performance of HE4 and CA-125 and the superior diagnostic abilities of the HE4/CA-125 combination or ROMA over CA-125 alone [113–119]. Contrary to those studies, a large prospective study of women diagnosed with a pelvic mass concluded that the addition of HE4 or the use of ROMA does not offer improvement upon CA-125 [120]. These conflicting findings are likely explained by the differences in the populations, as many studies are enriched with cancer patients which may skew results [62]. These differences include an increased proportion in the number of overall cancers, mucinous tumors, borderline tumors, metastatic tumors, and postmenopausal women in the later study. Other studies suggest that ROMA was effective in ovarian cancer diagnosis in postmenopausal women but not in premenopausal women, with HE4 alone outperforming ROMA in either group [121]. Again, the incidence of ovarian cancer in the pre- and postmenopausal groups varies between these studies. A third study, which included a large proportion of borderline and extra-ovarian tumors, found that HE4 offered several advantages over CA-125 for ovarian cancer diagnosis; however, no diagnostic benefit was derived from combining them [122]. Thus, variability in the composition of the target population appears to impact the performance of the CA-125/HE4 combination. Going forward, this issue may be addressed through a re-evaluation of the specific threshold values employed in the test to better respond to

this variability, or through the incorporation of additional biomarkers to make the test more robust. In addition, any biomarker should be confirmed in population-based study.

The OVA1/OVERA Tests

A biomarker-based diagnostic test for the evaluation of patients with a pelvic mass was approved by the FDA in 2009 and is currently available under the trade name OVA1 (Vermillion, Inc.). The test utilizes a five-biomarker combination (CA-125, transthyretin, ApoA1, β2-microglobulin, transferrin) identified through serum proteomics using surface-enhanced laser desorption/ionization (SELDI) [123]. Following validation of SELDI-derived markers in retrospective samples, the final combination was assembled based on the successful development of immunoassays. The test is currently approved for use as an adjunct to physical examination and imaging and produces a risk assessment score within the range of 0–10. Separate cutoff values are employed for premenopausal (5.0) and postmenopausal women (4.4). The panel was evaluated in a clinical trial which utilized immunoassays targeting each of the five markers in a set of 524 women diagnosed with a pelvic mass and recommended for surgery [65, 124]. At the time of surgery, there were 363 benign tumors and 161 malignancies of which 151 were ovarian cancers. In a pair of reports, the developers of the kit evaluate its efficacy in several clinical settings as noted in Table 2.3. When the OVA1 panel was substituted for CA-125 within the ACOG ovarian tumor referral guidelines, it provided a sensitivity of 94% at a specificity of 35%, with a positive predictive value of 40% and a negative predictive value of 93%. This represented an increase in sensitivity and negative predictive value in comparison to CA-125, but also a decrease in specificity and positive predictive value. When the OVA1 test was added to a normal physician assessment, it provided a sensitivity of 96% at a specificity of 35% with a positive predictive value of 40% and a negative predictive value of 95%. Among patients referred to gynecological oncologists, the sensitivity and negative predictive value were higher at 99% and 98%, respectively; however, specificity was lower at 26%. In comparison to physician assessment alone, the incorporation of the OVA1 test again resulted in improvements in sensitivity and negative predictive value along with decreased specificity and positive predictive value. When the OVA1 test was directly compared to CA-125, similar trends in performance were observed. A recent evaluation of the OVA1 markers, which included all seven proteins originally identified by surface-enhanced laser desorption/ionization time of flight mass spectrometry, suggested that these markers do not improve upon the performance of CA-125 in prediagnostic samples [126]. A similar finding was noted in prediagnostic samples collected as part of the large PLCO trial indicating a potential limitation in the usefulness of the OVA1 test [127].

In an evaluation of 494 women undergoing surgery, OVA1 was found to be more sensitive than clinical observation and CA-125: OVA1 correctly identified 83% of malignancies missed by clinical impression and 71% malignancies missed by CA-125. At the time of surgery there were 92 ovarian cancers. The combination of clinical impression and OVA1 was the most sensitive (95.7%). It is important to note that OVA1 correctly identified early-stage diagnoses: 78/84 patients (93%) with stage I/II disease. However the specificity of the test was 51% as only 204/402 were accurately predicted to be benign [17]. A second-generation test, Overa, was

Table 2.3 Clinical evaluation of the OVA1 test [65, 125]

	SN	SP	PPV	NPV
ACOG + CA-125	77	68	52	87
ACOG + OVA1	94	35	40	93
PA alone	75	79	62	88
PA + OVA1	96	35	40	95
CA-125 alone	69–77	73–84	56–65	86–88
OVA1 alone	93	43	42	93

SN sensitivity, *SP* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *ACOG* American College of Obstetricians and Gynecologists' ovarian tumor referral guidelines, *PA* physician assessment

designed using HE-4 and FSH with CA-125, transferrin and apoprotein A-1. The Overa test maintained the sensitivity of OVA1 in the detection of epithelial ovarian cancer (95%) and in stage I ovarian cancer (89%), but with an improved specificity (89%) [18].

Yip et al. conducted an analysis of 175 circulating biomarkers in 499 women scheduled for surgery for pelvic abnormalities, including 149 cases of ovarian cancer [58]. A nine-biomarker combination was identified through logistic regression that provided a sensitivity of 90% at a specificity of 89% for the discrimination of benign versus malignant patients. Notably, this combination outperformed the five-biomarker panel comprising the OVA1 diagnostic test; however, the performance of this panel has not been independently validated.

Conclusion

Ovarian cancer remains the leading cause of death from gynecological malignancy in the United States. Imaging and the use of biomarkers have not been successful in identifying women with ovarian cancer at an early and curable stage in a cost-effective manner. Identifying patients at higher risk of ovarian cancer due to heritable risk through genetic counseling and germline genetic testing allows prevention in the form of risk-reducing surgery. Recent improved understanding of the pathogenesis of ovarian cancer has provided opportunity for the development of different screening modalities, such as tubal sampling, or utilizing cell-free DNA assays to screen for the presence of precursor lesions. For women presenting with a pelvic mass, the development of the ROMA, OVA1, and Overa tests represents a significant milestone in the clinical management by identifying those women who would benefit from having surgery with a specialist. Future studies that target precursor lesions, such as STIC, may be able to identify those at risk of developing ovarian cancer before a pelvic mass develops and at an earlier stage, in an effort to impact mortality from this cancer.

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Ovarian Cancer Biomarkers

3

Ece Gumusoglu-Acar and Tuba Gunel

Abbreviations

AUC	Area under the ROC Curve
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
CA-125	Cancer Antigen-125
CDKN1	Cyclin-dependent kinase inhibitor
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
ctDNAs	Cell-free tumor DNAs
CtRNAs	Circulating tumor RNAs
DNMT	DNA methyltransferase
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
FDA	Food and Drug Administration
H3K27me	Histone H3 lysine 27
H3K4me2	Histone H3 lysine 4 di-methylation
H3K4me3	Histone H3 lysine 4 tri-methylation
H3K9me	Histone H3 lysine 9
H4K20me	Histone H4 lysine 20
HATs	Histone acetyltransferases
HDACs	Histone deacetylases
HDMTs	Histone demethylases
HE4	Inter-alpha-trypsin inhibitor heavy chain H4
HER2	Human epidermal growth factor receptor 2
HMTs	Histone methyltransferases
MAGE	Melanoma-associated antigen
MiRNAs	microRNAs
MMR	Mismatch repair
MS	Mass spectroscopy
NICT	Noninvasive cancer testing
NMR	Nuclear magnetic resonance
OC	Ovarian cancer
OPLS-DA	Orthogonal partial least squares discriminant analysis
PCA	Principal component analysis
PLS-DA	Partial least squares discriminant analysis
ROMA	Risk of Ovarian Malignancy Algorithm
TKIs	Tyrosine kinase-based inhibitors
TVS	Transvaginal ultrasonography
UPLC/MS	Ultra-performance liquid chromatography-mass spectrometry

Introduction

Ovarian cancer (OC) is one of the most common gynecological malignancies among women. OC is the leading cause of gynecologi-

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cal cancer-related death [1]. Also, it takes fifth place in the most lethal cancer types list among women worldwide [2]. It has a high rate of heterogeneity because of the different types of cancer origin, so there are various subtypes of ovarian cancer which are epithelial tumors, germ cell tumors (originating from the ovary cell and follicular), and stromal tumors [3, 4]. According to Global cancer statistics done by GLOBACAN, it is estimated that there were 295,414 new ovarian cancer cases and 184,799 deaths because of ovarian cancer in 2018 [5]. It is also predicted that by 2035 there will be a worldwide increase of 55% in incidence to 371,000, and an increase in deaths of 67% to 254,000 [6].

Due to its heterogeneity, the lack of screening approaches, and asymptomatic features, OC cannot be commonly detected in the early stages, so it is called "silent killer" although it has similar symptoms with benign gastrointestinal, genitourinary, and gynecological conditions [7]. If the disease can be diagnosed at the earliest stage (stage I), recently used treatment strategies can treat approximately 90% patients. This rate is 70% when it is detected in stage-II and less than 20% at late stages (Stage II and IV) [7]. Because of the insufficient symptoms and routine pelvic examination is not adequately sensitive, only 20% of patients can be diagnosed in stage I [8]. To make an increase in survival rates, ovarian cancer must be detected at the earliest stages. Therefore, molecular and cellular studies of all ovarian cancer tumor types may lead to earlier diagnosis of ovarian cancer and it is hoped better survival rates. It is indicated by computer modelling that the detection of a greater fraction of cases in early stage could reduce mortality by 15–30% [7, 9].

In light of all this information, this chapter focused on current and future diagnostic, prognostic, and therapeutic strategies of ovarian cancer in terms of basically biomarkers. It is considered as a vital contribution to literature about a new perspective of ovarian cancer via biomarker aspect.

Current Approaches and Biomarkers in Ovarian Cancer

When tumor is small size and limited in ovaries, the most significant prognostic approach is the early diagnosis. The fact that ovarian cancer is mostly sporadic and that there are not so many specific symptoms of the disease are difficulties in determining ovarian cancer with screening tests in early stages. The most common symptoms are bloating, pelvic and abdominal pain, difficulty eating or quick saturation, and urgent or frequent urination. There are many techniques for the diagnosis of symptomatic or asymptomatic ovarian cancer. Nowadays, pelvic examination, transvaginal ultrasonography (TVS), abdominal ultrasonography, and laparoscopy (for exploration or diagnosis) approaches are the most utilized techniques for pelvic and/or abdominal pain [10, 11]. Cancer antigen-125 (CA-125) is a commonly used serum biomarker before and after an operation to surveillance of disease and metastasis [11–13]. These are the standard methods for the diagnosis of ovarian cancer.

The history of the patient in terms of personal and family information for gynecologic and other cancers is the first evaluated criteria for ovarian cancer diagnosis of an individual with ovarian cancer symptoms. After that, the suspicious patient should go to the *pelvic examination*. The sensitivity and specificity of the diagnosis of a pelvic mass by pelvic examination are shown as 40% and 90%, respectively. The cause of under that is the low accuracy of pelvic examination because a mass could easily be not detected (especially in obese patients) or, if caught, could be caused by different conditions from ovarian cancer [14]. Therefore, if ovarian cancer is suspected based on symptoms and pelvic examination, further tests are performed [15].

Transvaginal ultrasonography is the first diagnostic model of choice for ovarian screening because of detailed image acquisition. It is used for the detection of ovarian volume growth, morphological anomalies, and vascularity, for differentiating solid and cystic masses, and to detect ascites [14]. The low incidence of benign lesions

such as endometriosis and functional cysts in postmenopausal women and the presence of certain anomalies detected in serial imaging reduces the rate of false-positive results of ultrasound tests [16, 17]. However, the sensitivity and specificity of transvaginal ultrasonography are 86–94% and 94–96%, respectively, and this is not sufficient to make a definite diagnosis of ovarian cancer [14, 18].

Laparoscopy is a method that analyzes the ovaries, pelvic organs, and other tissues in this area with the help of a thin light tube. After a small incision in the abdomen, a tube is placed in the lower abdomen and images of the pelvis or abdomen are sent to the monitor. By obtaining organ images, it is possible to plan the operation or other treatment methods and also determine the stage of cancer. In addition, laparoscopic cuts can be biopsied with the aid of small devices [19]. Although the past research supports to use laparoscopy in staging of early ovarian cancer, more prospective data should be obtained to confirm equivalent survival in a patient population who can be treated [20].

Ovarian Cancer Biomarkers

Proteomics and Biomarkers

Proteomics is the most powerful techniques used to understand biological processes, and one of its main objectives is to find biomarkers of diseases in body fluids or tissues [21, 22]. There have been identified several potential protein-based biomarkers/panels for ovarian cancer; however, the validation is required. Proteome represents all different protein products of genes in a cell, and they can be found in varieties in a specific cell or condition. Therefore, the proteome is seemed to be more precise biomarkers for diseases, especially cancer, because they can differ more depending on cancer types and stages than gene-based biomarkers [22]. According to recent studies, there is still no cancer-specific gene biomarkers in clinical routine. Therefore, proteomic is a valid strategy for cancer, yet. To find a protein biomarker, different strategies can be applied. It can be detected via the comparison of the cancer patient and non-cancerous individuals in terms of protein profiles. In the final, the different weight, structure, amount, or place of protein can be identified [23]. According to the studies, this way of biomarker analysis in ovarian cancer is a unique and very sensitive method for early-stage diagnosis [24]. The other approach is the detection of a single and specific biomarker and then design new assays just like drug development [23].

Currently, CA-125 (MUC16) glycoprotein antigen, which has high-molecular weight and is located on the epithelial cell surface, is the most commonly used tumor marker for epithelial ovarian tumors [25]. CA-125 was first detected using OC125 murine monoclonal antibody [26]. CA-125 can cause the formation of high invasive characteristics in ovarian cancer cells depending on a proteolytic site on its structure [27]. The CA-125 value was found to be high in 47% of women with early-stage ovarian cancer and 80–90% of women with advanced-stage ovarian cancer [19]. It is mainly used for imaging of people diagnosed with the disease because is overexpressed in epithelial ovarian cancer (EOC) while usually low in normal ovaries. CA-125 level was found to be high in both premenopausal women with benign tumors and postmenopausal women, but this test is thought to be more effective in women with postmenopausal conditions [28]. CA-125 level is evaluated in women with ovarian cancer in order to predict the prognosis, monitoring, and prevention. Although CA-125 is the oldest and best-performing biomarker, it is not enough to use only CA-125. It may increase expression in both normal physiological conditions and cancer development. It was also found that some factors such as race, age, smoking history, obesity, and hysterectomy may change CA-125 levels. It cannot distinguish between benign and malignant tumors with high accuracy [29, 30]. Although it has disadvantages, CA-125 is still regarded as the gold standard and approved by the FDA (Food and Drug Administration) for monitoring and is commonly used as a serum biomarker for OC detection [29].

There are some proteins such as "*Inter-alpha-trypsin inhibitor heavy chain H4*" (HE4) that are normal serum proteins and show different protease pattern in specific cancer types [31]. HE4 protein-coding gene is upregulated in ovarian tumors. Although its main function is still not clear, HE4 is a secreted protein and not produced in the normal ovarian surface epithelium. However, its high expression is shown in human endometrioid epithelial ovarian cancers and serous ovarian carcinomas [11, 32]. Besides, some protein biomarkers, such as *transferrin*, are considered with systemic inflammation and are acute-phase proteins associated with other non-cancerous conditions [33]. Transferrin mainly transports plasma iron into the cell and plays an important role in cell differentiation and proliferation [34, 35]. It is shown that the transferrin reduces in ovarian cancer patient serum [33]. Transferrin has an antiapoptotic effect; thus, it promotes tumor development and survival [34]. Not all of these are cancer-specific markers and do not derive directly from ovarian cancer. Therefore, the importance of proteomic biomarkers and their specificity to ovarian cancer still need to be investigated [21]. Table 3.1 shows tumor markers used for ovarian cancer [1, 22, 36, 37].

Most of these proteins have been used with CA-125 in the diagnosis of cancer [38]. For example, the combination of CA-125, transferrin, transthyretin, and ApoA1, using proteomic analysis, yielded a sensitivity of 89% at a specificity of 92% for early detection of ovarian cancer [34, 39].

There are also biomarker-driven multivariate index assays such as Ova1, Risk of Ovarian Malignancy Algorithm (ROMA), and Overa. ROMA is one of the assays that is FDA approved and it is used for detection of ovarian cancer patients who have pelvic masses. In ROMA testing, two protein levels which are CA125 and HE4 were evaluated combining with menopausal status [25]. When compared to ROMA and CA-125 discrimination, only CA-125 is not sufficient in terms of the sensitivity and specificity which are 90.7% and 93.1% for ROMA, respectively. ROMA score of ovarian cancer are $\geq$1.31 and $\geq$2.71 in pre- and postmenopausal women, respectively [25, 26, 40].

Another FDA-approved ovarian cancer panel is OVA1 which can be used on patients with pelvic mass [29, 41]. It consists of five biomarkers (CA-125, Transthyretin, APOA-1, β2-Microglobulin, and TF) detected by SELDI-TOF-MS [42]. The patient obtains a score rang-

Table 3.1 Potential protein biomarkers of ovarian cancer [1, 22, 36, 37]

Alpha-1-antitrypsin	HE4	Mesothelin	p110 epidermal growth factor receptor
BHCG	IL-2 receptor	Mucin-like carcinoma antigen	Placental alkaline phosphatase
CA15-3	IL-6	Sialyl TN	Prostasin
CA19-9	IL-8	Soluble Fas ligand	Tumor necrosis factor receptor
CA50	IL-10	Tetranectin	Urinary gonadotropin peptide
CA54-61	Inhibin	Tumor-associated trypsin inhibitor	Galactosyltransferase
CA72-4	HER-2/neu	Osteopontin	Fibrinogen alpha fragment
CA125	Human milk fat globule protein	Matrix metalloproteinase 2	CYFRA21-1
CA195	Human milk globule 2	MCSF	"Dianon marker 70/K"
Cathepsin L	Kallekrein-6	ApoA1	Transthyretin
Carcinoembryonic antigen	Kallekrein-10	Fibrinogen beta NT fragment	Collagen alpha 1 (III) fragment
Ceruloplasmin	Kipid-associated sialic acid	Fibrinopeptide-A	Protein phosphatase-1
CRP	Lysophosphatidic acid	Ovarian serum antigen	OVX1

ing from 0 to 10. The sensitivity and sensitivity of OVA1 screening is 96% and 28% in postmenopausal women and 85% and 40% for premenopausal women, respectively [43]. Both ROMA and OVA1 are FDA-approved test for different fields of ovarian cancer detection research such as early-staging and distinguish benign and malignant masses [29]. However, the FDA approved a new version of the OVA1 test, which is OVA2 or mostly Overa [44], to test patients presenting with ovarian mass [43]. It mainly combines two multivariate index assay (CA 125-II, HE4, apolipoprotein A-1, FSH, and transferrin) and increases diagnostic sensitivity (91%) with improved specificity (69%) [43–45].

All these approaches are willed to be adapted to diagnosis and screening. However, further studies need to be investigated for increasing the number of biomarkers can be used in clinical used.

Gene-Based Biomarkers

After human genome project was completed in 2001, the gene-based causes of diseases became more clear to investigate. These data were extremely valuable to search the origin, diagnosis, and treatment of several diseases especially cancer. The developments also lead us to understand the pathogenesis of ovarian cancer via detection of alterations on genome because genetic changes may cause defects on cell division, programmed cell death, and aging, thereby inducing malignant transformation of ovarian epithelial cells [21]. After findings of the relation in between genetic mutations and ovarian cancer carcinogenesis researches driven to the find potential gene-based biomarkers specific to ovarian cancer [46]. They are mainly focused on hereditary gene mutations, epigenetic changes, and gene expression analysis [21]. In this chapter, we considered hereditary gene mutations and gene expression analysis under the same heading and epigenetic changes were detailed later because it is a wide-spreading topic for cancer research. There are several ovarian cancer-related genes which can be mutated and/or dysregulated. Approximately 23% of ovarian cancers have been associated with hereditary conditions, and among these, most of the cases (65–85%) carry germline mutations in the DNA repair genes which are breast cancer susceptibility gene 1 (*BRCA1*) and 2 (*BRCA2*) [47] and DNA hypermethylation caused inactivation of *BRCA1* in more than 11% of cases [48]. Ovarian cancer risk can be variable in individuals who are mutation carriers. For example, *BRCA1* and *BRCA2* mutation may increase the risk of breast cancer development up to 85% and ovarian cancer development risk up to 54%. In addition, mutations in the *BRCA* genes may lead to pancreatic and prostate cancer development [47].

Lynch syndrome (LS) is a hereditary nonpolyposis colon cancer (HNPCC) which predisposes to colorectal cancer, endometrial cancer, ovarian, gastric, small bowel, biliary/pancreatic, urothelial, skin, and central nervous system cancers [46]. It accounts for 10–15% of ovarian cancers associated with hereditary conditions [47]. LS is caused by germline mutations in Mismatch Repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *MLH3,* and *PMS2*). The expression of MMR proteins decreases as a result of mutation. This triggers carcinogenesis due to non-repair of DNA damage [46, 47].

Hereditary ovarian cancer is affected by many other genes (tumor-suppressor or oncogenes) such as *TP53*, *BARD1*, *CHEK2*, *RAD51*, *KRAS,* and *HER*2 [46]. The mutation in the *TP53* gene is one of the most common genetic anomalies in ovarian cancer. TP53 gene has coded a protein, p53 is involved in oncogenesis and a transcription factor, in stress conditions like DNA damage [49]. Activated p53 causes cell cycle arrest, senescence, differentiation, apoptosis, or ferroptosis [50]. In ovarian cancer cases, 2329 kinds of *TP53* mutations are identified (http://www-p53.iarc.fr/), ~70% of which are missense mutations [50]. Tumors resulting from TP53 mutations are characterized by low survival rate, high recurrence rate, increased resistance to chemotherapy, and radiation [46, 47].

K-RAS is the other important oncogene for ovarian cancer development. The *KRAS* oncogene is located on chromosome 12p12 and

encodes a 21-kDa protein (p21RAS) [51]. Coded protein takes a place in the MAP-kinase signal transduction pathway, modulating cellular proliferation and differentiation. *KRAS* oncogene mutations induced this signal transduction pathway and lead to unregulated proliferation and impaired differentiation [51]. Therefore, a mutation in this gene is directly related to carcinogenesis even in ovarian cancer. More frequent mutations of *KRAS* has been shown in mucinous than in non-mucinous neoplasms [52–54].

HER receptor family is another altered gene in carcinogenesis including ovarian cancer development. In distinct cancer types, there are many FDA-approved HER-targeted therapeutics while none for ovarian cancer so far [55]. Epidermal growth factor receptor (*EGFR*) is one of the HER family members and is overexpressed in 30–70% of high-grade serous carcinoma [56]. It drives cellular proliferation, migration, and invasion [57], and because of its high expression level in ovarian cancer, *EGFR* is a potential prognostic biomarker and also a therapeutic target in ovarian cancer. However, it is still not an effective therapy targeting *EGFR* because of poor response rate to EGFR-targeted tyrosine kinase-based inhibitors (*TKIs*) [58]. It is still not clear the relation between human epidermal growth factor receptor 2 (*HER2*) overexpression and prognosis [59]; however, a recent study indicated that *HER2* expression was associated with poor prognosis in ovarian cancer patients and may be utilized as a predicting cancer prognostic biomarker [60]. It is found that *HER2* expression level is low in the normal ovarian epithelium but is high in a variable percentage of epithelial ovarian cancer (11–66%) [60]. Therefore, it can be also a potential therapy target for ovarian cancer treatment.

Activating mutations and amplification of kinase signalling pathway genes involved in tumorigenesis [61]. PI3K/AKT pathway is very important in ovarian cancer as well because it regulates several cellular processes including cellular proliferation, survival, and migration [61–64]. *PIK3CA* gene and its downstream gene, *AKT2*, are considered to be important in ovarian cancer development. Amplification of *AKT-2* has been identified in nearly 12% of type II ovarian cancer cases [65]. Because of their roles and expression levels on ovarian cancer, especially *AKT2* has been considered as a potential prognostic marker and drug target for therapy [46].

Recently, these all mentioned genes and their mutations can be used to detect the patients carrying a high risk of ovarian cancer and may give an idea about clinical treatment strategies of ovarian cancer.

Metabolite-Based Biomarkers

Although there were many ovarian cancer biomarker studies, almost all have been used on genomics and proteomics approaches. However, most genomics and proteomics methods have certain limitations like low detection efficiency, complex sample preparation procedures, and high cost [66]. Therefore, metabolomics is considered another strategy for biomarker studies of cancer types including ovarian cancer. Metabolomics is one of the omic approaches and a global quantitative assessment of endogenous small metabolites in the biological system [21, 66]. Metabolomics searches small molecules in terms of their high-throughput identification and quantification, and interactions within biological networks [67]. Thus, it represents "upstream" changes in genes and "downstream" changes in proteins [68]. Because of vast chemical and physical types of small molecules, it is still not possible to measure the concentration of all metabolites with an only method [69]. There are two metabolite detection techniques, namely, nuclear magnetic resonance (NMR) spectroscopy and MS (mass spectroscopy), used in both individual and group samples, the cells, tissues, or biofluid materials [21, 69, 70]. There are several studies showing the relationship between dysregulation and cancer survival such as pancreatic adenocarcinoma, bladder cancer, and colorectal cancer [71–73].

The metabolome is also used in early detection and diagnosis of cancer, drug response, and toxicity [21, 68].

While performing the biomarker research of cancer-related metabolomics, complex raw data

obtained from the assessment of many endogenous metabolites should be interpreted for human measurements. Firstly, from vast number of signals of endogenous small molecules, pattern recognition is done from liquid biopsy samples and tumor tissues [69] mostly via principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), orthogonal partial least squares discriminant analysis (OPLS-DA), and regression analysis [74]. For next step, compound-identification approaches are followed to match spectral features of the unknown compound(s) to curated spectral databases of reference compounds generally by the Human Metabolome Database, MassBank, KEGG, and METLIN databases [69, 75, 76]. The last step is quantitation and accurate recognition of biomarkers based on cancer-specific features like prognosis or response to therapy [68, 69].

The relation of ovarian cancer with the synthesis pathways of aminoacyl-tRNA, phenylalanine, tyrosine and tryptophan, urea cycle and metabolism of glycine, serine, threonine, glutamate and amino groups has been shown [29]. To mention the dysregulated metabolites in ovarian cancer, there are several types of small molecules which are metabolites of cellular respiration/carbohydrate metabolism, lipid metabolites, amino acid metabolites, nucleotide metabolites, and other significant metabolites. In the diagnosis of ovarian cancer, 1H NMR spectroscopy was used in serum obtained from 38 patients with non-operative EOC, 12 benign ovarian cyst patients, and 51 healthy subjects. According to the results, 1H NMR region which is 2.77 and 2.04 ppm (parts per million) from the origin was determined with 100% sensitivity and specificity. These findings show that the distinction between normal and EOC serum can be made completely using 1H NMR metabolomics analysis. It was understood that it should be further developed as a potential method for early diagnosis of EOC [77]. In another study, it has been shown that there is a significant change in borderline tumors and carcinomas in terms of 51 metabolites. Thus, it is stated that there are consistent and important alterations in the primary metabolism of ovarian tumors, and these changes can be identified by large-scale metabolic profiling [78]. Additionally, another working group analyzed metabolites on 158 serum and 112 tissue samples for EOC patients and demonstrated that deregulation of 4-hydroxyphenyllactic acid and 3-hydroxyisovaleric acid are related with poor overall survival in serum metabolomics study, while high concentration of 3,4-dihydroxybutyric, 2,4-dihydroxybutyric, and adipic acids in tissue are associated with poor overall survival in tissue [79]. Xie et al. made a metabolite analysis on 98 plasma samples from EOC patients via the ultra-performance liquid chromatography-mass spectrometry (UPLC/MS) systems in both positive (ESI+) and negative (ESI−) modes. They selected four metabolites, namely, kynurenine, acetylcarnitine, PC (42:11), and LPE (22:0/0:0), as potential predictive biomarkers. It was found that they could be used to predict the overall survival and distinguish the short-term mortality and long-term survival for EOC patients based on their discrimination performance (AUC (Area under the ROC Curve) value of 0.82) [66].

According to the data obtained from a limited number of studies, metabolism has been shown to be potentially useful in the diagnosis of ovarian cancer; however, metabolomics is still a very new field and needs to be developed. Advancements in the field of metabolomics focus on cancer research are very important for the whole molecular analysis of malignant tumors.

Epigenetic-Based Biomarkers

Epigenetic is a mechanism involved in gene expression regulation without any genetic alteration in the DNA sequence. These changes are mainly histone methylation and acetylation, DNA methylation and miRNAs associated alterations. Recently, epigenetic changes are also associated with tumor formation besides cell differentiation, embryogenesis, inactivation of the X chromosome, genome imprinting, and many others [80–84]. Currently, epigenetically regulated cancer-related genes have been implicated in the initiation and progression of malignant ovarian tumors [85].

Histone modifications are epigenetic mechanisms that play an important role in gene regulation, tumor formation, and progression. Although the mechanism of histone modification alterations in ovarian cancer is still not fully understood, the histone modification changes are found as related to malignant ovarian cancer initiation and development. Therefore, they are potential histone modification biomarkers for diagnosis, prognosis, and therapy of malignant ovarian tumors. Histone modifications are acetylation, deacetylation, and methylation on histone proteins [86]. ***Histone acetylation*** is mainly related with chromatin relaxation and thereby gene transcription and is regulated by two main enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) [86, 87]. An imbalance between HATs and HDACs causes pathogenesis of ovarian cancer [86]. It is shown that the upregulation of HDACs 1–3 relates to high-grade tumors, resulting in the poor prognosis of ovarian cancer [88]. It is also demonstrated that histone acetylation causes the overexpression of Rb and CDKN1 (cyclin-dependent kinase inhibitor), which stimulate cell proliferation in ovarian cancer [89]. SIRT1 is a nicotinamide adenine dinucleotide (NAD+)-dependent lysine deacetylase and a class III HDAC. The upregulation of SIRT1 was shown in malignant EOC compared to benign and is more frequently expressed in serous epithelial ovarian cancer to mucinous [90]. ***Histone methylation*** is another histone modification and mostly occurs on lysine or arginine residues. It plays an important role in many different biological processes like posttranscriptional regulation to faithful chromosomal transmission during mitosis [91–93]. Histone lysine methylation regulates transcriptional activation and gene silencing according to the particular residue methylated, the degree of methylation, and the site of the methylated histone within a specific gene locus. Similar to acetylation, histone methylation is controlled by a balance between histone methyltransferases (HMTs) and histone demethylases (HDMTs) [86]. Histone H3 lysine 4 di- and tri-methylation (H3K4me2 and H3K4me3) have been linked to "open" chromatin and active transcription. On the contrary, methylation of histone H3 lysine 9 (H3K9me), histone H3 lysine 27 (H3K27me), and histone H4 lysine 20 (H4K20me) are related to "closed" chromatin and transcriptional repression [94, 95]. It is shown that the suppression of H3K27me3 in ovarian cancer cell lines overexpressing the dominant-negative mutant H3-K27R causes the upregulation of tumor suppressor gene *RASSF1* via relaxation of chromatin structure; thus, ovarian cancer cells become sensitive again to cisplatin treatment [96].

The other epigenetic controlling mechanism involving carcinogenesis and malignant transformation is ***DNA methylation*** which can be considered possibly having more importance than genetic alterations like mutations, deletion, and translocations [97]. In carcinogenesis, two main DNA methylation phenomena, namely, hypomethylation of oncogenes and hypermethylation of tumor suppressor genes, resulting in overexpression and suppression of genes, respectively, occur in the cells [98]. The main epigenetic silencing mechanism is DNA methyltransferase (DNMT) mediated methylation of deoxycytosine located within the CpG dinucleotides [84, 99–101]. According to studies, there are several hyper- and hypomethylated genes in ovarian cancer [102]. Moreover, they are considered as potential prognostic and diagnostic biomarkers in ovarian cancer to increase the survival rate. For examples of genes regulated by methylation in OC; familial *BRCA1* gene mutations detected in 5–10% of EOC cases, promoter hypermethylation of non-mutated *BRCA1* allele is the second alteration involving OC carcinogenesis [84, 103]. *ABCA1* hypermethylation is related to decreased overall survival [102]; besides, promotor hypermethylation of *OPCML* (tumor suppressor activity), *TES* (involved in regulation of cell motility), and *RASSF1A* (tumor suppressor activity as well as an inhibitor of the anaphase-promoting complex) genes are involved in OC development [84, 103]. Hypomethylation of CpG sites within the *MSX1* gene is related with resistant high-grade serous ovarian cancer [104]. These genes can be a biomarker for predicting the prognosis of patients with ovarian cancer [105, 106]. For example, tumor DNA from 50 patients with ovar-

ian or primary peritoneal tumors showed tumor-specific hypermethylation of at least one of the six tumor suppressor gene promoters (*BRCA1*, *RASSF1A*, *APC*, *p14ARF*, *p16INK4a*, *DAPKinase*) in a panel. A similar gene mutation pattern was observed in 41 of 50 patients (82% sensitivity). Contrary to these data, hypermethylation was not observed in tissues and serum of 40 control subjects that did not show tumor structure (100% specificity) [21, 107]. *HOXA10* and *HOXA11* genes take role in very early ovarian tumor initiation by promoter methylation and are discriminated normal and malignant ovaries [84, 108, 109]. *PTEN* suppression via methylation has also been mostly detected in primary epithelial ovarian carcinomas [110]. In ovarian cancer, vast majority of tumor suppressor genes have been detected to be suppressed by promoter hypermethylation and downregulated, including *DAPK*, *LOT1*, *TMS1/ASC*, and *PAR4* (pro-apoptotic function and cell cycle regulation), *p16*, *SPARC*, *ANGPTL2*, and *CTGF* (tumor suppressor activity), *ICAM-1* and *CDH1* (cell adhesion), *PEG31* (role in imprinting), and many others [84]. Gene methylation measurements in the promoter region involve early diagnosis of ovarian cancer, detection of disease progression, and prediction of response to therapy. DNA methylation biomarkers have some advantages over other molecular-based biomarkers. For example, DNA methylation is more stable both in vivo and ex vivo [111], a smaller amount of tissues requirement to obtain enough DNA for methylation analysis [112]; and relative accuracy through quantitative assay because DNA methylation measurements are comparable with absolute reference points [106, 113]. Otherwise, there are some disadvantages of genome-wide methylation analysis in clinical practice which are need for large set of DNA methylation identified and complicated statistical analyses [106]. It still has a vast amount of place in ovarian cancer detection, therapy response, and surveillance.

MicroRNAs (MiRNAs) are small (18–24 nt) regulatory non-coding RNA family detected in serum and important for the diagnosis of human diseases. In human, there have been ~2300 distinct miRNAs described [114] and mostly conserved in related species. MiRNA targets and suppresses certain mRNAs and regulates post-transcriptional gene expression. Indeed, one miRNA can regulate up to 30 mRNAs and one mRNA can be regulated by several miRNAs; then, an alteration of miRNA expression can regulate several processes and diseases [115] such as glaucoma, neurodegenerative diseases [116], cardiovascular pathologies [117], metabolic diseases [118], and cancer [119]. Therefore, altered regulation of miRNA expression is significant for cancer development. In addition, several miRNAs related to chemoresistance have similarly altered expression in OC and recurrent tumors [120]. Therefore, miRNAs can be valuable biomarkers for involving OC carcinogenesis. In 2007, altered miRNA expression levels were firstly shown in between normal tissue and ovarian cancer and found that miR-200a, miR-141, miR-200c, and miR-200b overexpressed in ovarian cancer and miR-199a, miR-140, miR-145, and miR-125b1 downregulated [121]. Then, methylation and miRNA expression relation has been investigated and found that demethylating an ovarian cancer cell line induced upregulation of miR-21, miR-203, and miR-205 [121]. Afterwards, the biomarker researches turn their focus on miRNAs for diagnosis, treatment response, and prediction of OC. To use miRNAs in diagnostic tools, they should have two main characteristics which are their possible potential to differentiate between subtypes and the possibility to detect microRNA expression patterns in body fluids [122]. Thus, they are one of the main noninvasive biomarkers used for OC. Because of this feature of miRNAs, we consider discussing this biomarker class of OC later under liquid biopsy biomarkers.

Liquid Biopsy Biomarkers

As a new approach to cancer investigations, non-invasive testing of cancer-related cells, nucleic acids or small molecules in liquid biopsy samples, became commonly accepted strategy. Against to tissue biopsy, liquid biopsy is far less invasive and it allows to identify the predictive

and prognostic cancer biomarkers through detection of circulating tumor cells (CTCs), tumor nucleic acids ("circulating tumor DNA/RNA"), and exosomes [4]. Therefore, early and multiple assessments of the disease can be performed, such as retrospective monitoring, identification of treatment effects, and investigation of clonal development. Identification, analysis, and evaluations of cancer-related markers from liquid biopsy materials will lead to developing cancer diagnosis, treatment, surveillance, imaging, and therapy response. Noninvasive cancer testing (NICT) can be analyzed "real-time" and at every stage of cancer. Besides the benefits of NICT, there are several limitations of this approach like limited accuracy rate, still not entirely performable into the clinic, and complexity of high-throughput data analysis [4, 123]. In spite of these challenges, liquid biopsy sampling and analysis has important potential for clinical cancer diagnosis in future.

Some cancer-derived cells are detected in liquid biopsy samples and appear as solid tumor cells that have broken away into the circulation or other body fluids [124]. These cells are named as "***Circulating Tumor Cells***" (CTC) and mainly originated from tumor mass via accidentally with external forces (surgery, tumor growth, etc.) or intentionally epithelial-mesenchymal transition (EMT) process for plasticity and metastatic potential [123]. CTCs can be recognized in both metastatic patients and patients with early, localized tumors. Thus, CTCs have an important potential in terms of clinical usage for cancer detection or therapy response in ovarian cancer. It has been shown that CTCs were detected in most (98.1%) of the serum of ovarian cancer patients via nanoroughened microfluidic platform [125]. CTCs are also considered as the cause of metastasis and recurrence because of their EMT potential and stem-like features. Therefore, it is aimed to identify therapy-resistant tumor cells and to overcome treatment failure by analyzing CTCs transcriptional profiles [4, 126]. Blassl et al. showed 15 single CTCs with positive for stem cell (CD44, ALDH1A1, Nanog, Oct4) and EMT markers (N-cadherin, vimentin, Snai2, CD117, CD146) from three ovarian cancer patients [126].

Cell-free tumor DNAs (ctDNAs) are other markers for NICT and can be detected in body fluids. They are originated from mainly apoptotic tumor cells and it is proven by carrying tumor-specific anomalies such as the presence of mutation in circulating tumor DNA (ctDNA), loss of heterozygosity of microsatellite, and methylation of CpG islands [127–129]. The level of ctDNA is increased directly proportional to tumor stage [130, 131]. Studies showed the presence of ctDNA in the pelvic washings, ascites, serum, and plasma for gynecologic cancers [4]. CtDNA is also demonstrated as a biomarker for imaging of gynecologic malignancies and is as sensitive and specific as FDA-approved serum biomarker CA-125. It is also a powerful technique for early detection of ovarian cancer recurrence when compared to imaging techniques [132]. Vanderstichele et al. demonstrated the difference of ctDNA copy number variation profiles in between malignant and benign tumors using whole-genome low-coverage sequencing with an area under the curve of 0.89 [133]. Methylation markers of ctDNA could also be used for distinguishing benign from malignant tumors [134]. Liggett et al. showed the analysis of the methylation profile on the promoters of two genes (*PGR-PROX* and *RASSF1A*) for distinguishing malign and benign tumors with a sensitivity of 80% and a specificity of 73% [135]. Moreover, analysis of *TP53* mutations in cfDNA was used to monitor tumor burden and to follow the response to treatment in 40 patients (mainly relapse cases) with high-grade serous ovarian cancer [134, 136]. CtDNA-based approaches are feasible into the clinic but need more investigation.

Tumor-specific gene transcripts can be found in the circulation of cancer patients [137]. In spite of the high amount of RNase amount in the blood, ***circulating tumor RNAs (ctRNAs)*** are quite stable thanks to possibly protection by ***exosomes*** (such as microparticles, microvesicles, multivesiculas) that pass through the cell membrane into the bloodstream [4, 137]. One sort of ctRNA, miRNAs (18–21 nt length and non-coding regulatory RNAs), can be detected in the circulation, and according to their expression profiles, tumor and healthy tissue can be distin-

guished [138]. Recently, there is a vast interest on miRNA expression profiling in EOC and many studies showed altered expressions of circulating miRNAs in cancer patients. For instance, 59 EOC operation samples are compared with 15 normal ovarian species using a "custom" microarray and found 29 differently expressed miRNAs [121]. A new meta-analysis found that multiple miRNAs panels are promising for screening and diagnosis with a combined diagnosis odds ratio of 30.06 (95%CI [8.58–105.37]) [139]. The expression of circulating miRNA levels can also be correlated to prognosis and survival [134].

Tumor cells secrete extracellular vesicles, mainly exosomes, into circulation. Similar to circulating microvesicles, exosomes have been indicated to have specific functions and play an important role in coagulation, intercellular signalling, and the management of debris. Exosomes include several molecules such as proteins, metabolites, RNAs (mRNA, miRNA, long non-coding RNA), DNAs (mtDNA, ssDNA, dsDNA), and lipids and are used in cell communication [140–142]. The circulating exosome levels can be higher in cancer patients than healthy individuals [143]. This situation can be explained by the relation with exosome biogenesis and hypoxia, secretory pathways upregulation, and *TP53* alterations were all enhanced in cancer cells [134, 144, 145]. There are several exosomal biomarkers such as tyrosine receptor kinase B which takes role in progression and prognosis [146]. Szajnik et al. showed that exosomes from OC plasma contain different levels of *TGF-β1* and melanoma-associated antigen (MAGE) 3/6 proteins compared with benign tumors, indicating a diagnostic value for these biomarkers [147].

Future Perspective in Ovarian Cancer Biomarkers

There is a lot of research about new molecular targeted therapeutics of ovarian cancer today. Therefore, in the near future, it will be treated as an acute disease rather than chronic disease. Early diagnosis and treatment will be possible with the development and change of strategies. The personalized drugs used in chemotherapy in accordance with their genetic characteristics will create the way for effective treatment. At the same time, immune system healing applications will be improving current long-term survival rates of ovarian cancer. Therefore, biomarker studies will improve the ovarian cancer treatment, diagnosis, and surveillance. After all these developments, the survival rate will bump up which is the main aim of all cancer researchers and survivors. It can clearly be said that nucleic acids are accelerating serum biomarkers ctDNA, mRNA, miRNAs, or other small RNAs. The combination diagnosis markers which can be nucleic acids and proteins or other biomarkers will sharply increase the OC diagnosis rate and screening accuracy. It is even not too far that replacement of conventional detection methods such as laparoscopy, pelvic examination or other imaging approaches with serum biomarkers based diagnosis or annual screening [44]. The future goal of cancer investigations is to adapt the research to the clinic via validations and reaching high accuracy rates.

Conclusion

Ovarian cancer is the fifth most important cause of cancer-related deaths among women in the world and the leading cause of death from gynecologic malignancies [2]. The early detection of ovarian cancer makes a significant increase in the 5-year survival rate of patients. There are several detection methods for ovarian cancer, but molecular diagnosis methods are more accurate, faster, and suitable for early detection. However, they need to be improved by further studies. To improve treatment and survival, biomarker studies have a crucial role to illuminate the ovarian cancer and treat it before metastasis. Biomarkers can be detected in the tumor samples via OC-specific features which are altered genes, proteins, metabolomes, and transcripts. Moreover, liquid biopsy investigations are recent techniques used in the detection and treatment of ovarian cancer. Liquid biopsy biomarkers are CTCs, exosomes, circulating

tumor DNA, RNAs, and circulating free small RNAs, mainly miRNAs. Obviously further studies are required. In addition, these biomarkers may become an important part of the clinical strategies used in cancer diagnosis, treatment, and imaging. We hope to contribute to ovarian cancer diagnosis, treatment, and surveillance by clarifying biomarker studies.

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Hereditary Ovarian Cancer

4

Angela George

Background

The existence of an underlying genetic component in the development of epithelial ovarian cancer, and a link with early onset breast cancer, had been suspected for many years prior to the discovery of the first ovarian cancer susceptibility genes, BRCA1 (breast cancer susceptibility gene 1) and BRCA2 (breast cancer susceptibility gene 2). This grew from the observation of a number of families in which multiple women were diagnosed with ovarian cancer over several generations, and often at a younger age than those without a family history of ovarian cancer. Subsequent studies of a series of five large families with numerous cases of breast and ovarian cancer showed linkage to an area on Chromosome 17 (Ch17 q12-q23), later identified as BRCA1 [1]. Mutations in this gene were later identified in families with ovarian cancer only, confirming the causative role of BRCA1 in ovarian cancer susceptibility and the genetic link between breast and ovarian cancer [2]. Further investigation of high-risk breast and ovarian cancer families without BRCA1 mutations led to the identification of BRCA2 in 1994 [3, 4]. The importance of BRCA1 and BRCA2 mutations in the clinical management of ovarian cancer has grown significantly since their first discovery, particularly in the last 10 years. As new treatments are developed to exploit the biological differences in BRCA-mutated ovarian cancers, interest has grown in identifying other ovarian cancer susceptibility genes in which mutations may also have treatment implications, particularly those with a role in homologous recombination, such as BRIP1, RAD51C and RAD51D. Interest is also beginning to rise in the identification of ovarian cancer patients with an underlying inherited mutation in one of the four Lynch syndrome genes, which appears to be a useful predictor for those who will benefit from immunotherapy, such as checkpoint inhibitors [5]. Finally, there have recently been several genes identified in those with non-epithelial ovarian cancer, such as small cell ovarian cancer, hypercalcaemic type (SCCOHT). In this chapter, the prevalence, phenotype, risks and implications associated with each of the inherited forms of inherited ovarian cancer will be discussed as the increasing role these mutations play in clinical management is discussed.

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BRCA1 and BRCA2 Mutations

BRCA1 and BRCA2 (henceforth referred to as BRCA) are both tumour suppressor genes, with mutations in the gene resulting in loss of function of tumour suppression [6]. Together they play a vital role in the homologous repair of double-strand DNA (dsDNA) breaks, together with roles in co-regulating transcription and modifying chromatin re-modelling (BRCA1) and maintaining chromosomal instability (BRCA2) [3, 7, 8]. Women who inherit mutations in either of these two genes have increased risks of breast and ovarian cancers, while BRCA2 mutations have also been associated with increased risks of pancreatic cancer, male breast cancer and prostate cancer.

Prevalence

The reported prevalence of BRCA mutations in women with ovarian cancer varies widely, with the highest rates reported in populations selected for a strong family history of breast and/or ovarian cancer, or those of Ashkenazi Jewish descent. Lower mutation rates are reported in unselected populations, but these also vary widely depending on the country of origin. The wide variation can be in part explained by the differing population rates of mutations, with recurrent (founder) mutations reported in many countries. The best known of these are the Ashkenazi Jewish mutations, in which one of three specific mutations are present in 1:40 of those of Ashkenazi Jewish descent. There are other well-recognized founder mutations in one or both genes in most countries, many of which are specific to a particular geographical location. This can lead to widely varying mutation prevalence rates, depending on the location and recruitment sites of patients for each study. Recent large, unselected studies of ovarian cancer patients reported rates of 10–12% in non-mucinous ovarian cancer and rates of 15–18% in those with high-grade serous ovarian cancer [9, 10].

Cancer Risks

The cancer risks reported in those carrying a BRCA mutation also vary significantly, depending on the population assessed. The early papers based on families with a strong family history and high penetrance reported lifetime ovarian cancer risks of up to 82% by age 70 (BRCA1) and 37% by age 80 (BRCA2) [11, 12]. The higher risks were reinforced by the restrictive criteria initially used to select individuals for BRCA testing, which required women to have a strong family and/or personal history of multiple BRCA-related cancers to qualify for testing. This was partly to reflect the high cost and lengthy time taken to undertake testing with the early methods. As the technology has advanced, and testing has become faster, cheaper and therefore more widely offered, it has become clear that many women with ovarian cancer and an underlying BRCA mutation do not have a strong—or any—family history, and that earlier figures are an overestimate of risk for many women. The more recent studies of patients unselected for family history have suggested lifetime ovarian cancer risks of 44% for BRCA1 carriers and 17% for BRCA2 carriers by age 80 [13]. These risks are significantly lower than the risks quoted from early studies and may well impact on the decision when—and if—to undergo risk-reducing interventions.

Screening and Risk-Reducing Surgery

As ovarian cancer is generally diagnosed at a late stage, when cure is unlikely, there has long been interest in screening to identify women at a much earlier stage where overall survival can be improved. The institution of a high-risk breast screening programme in BRCA carriers has been very successful in detecting pre-malignant changes in the breast, but attempts to replicate this success in ovarian screening have thus far not improved mortality [14, 15]. The largest screening study in the high-risk population thus far to

report is the UKFOCSS (UK familial ovarian cancer screening study), which assessed screening with serum CA-125 (using their custom algorithm ROCA), together with transvaginal ultrasound. All women recruited were assessed as having a lifetime risk of ovarian cancer of 10% or higher, and all were advised that risk-reducing bilateral salpingo-oophorectomy (BSO) was the standard recommended intervention.

In Phase II of their trial, 4348 women underwent 13,728 women-years of screening, with a median follow-up of 4.8 years. Surgery was performed in 3.7% of women following a positive screen (162/4348), of which 13/162 (8%) had a screen-detected cancer. Of the remainder, the majority had benign ovarian pathology (64%), while 2 (1.3%) had borderline tumours and 52 (35%) had other/no pathology identified [16]. A further 6 patients had normal screens but occult cancers detected at RRBSO, and 18 patients had cancer diagnosed >1 year after last screen. There is currently no overall survival data to support the role of screening over RRBSO, although this may change in future with further evidence. These findings are echoed by the mortality update for the ovarian screening arm of the large prostate, lung, colorectal, ovarian (PLCO) screening study. This update published after the patients had been followed for ~19 years after randomization showed a slightly higher number of deaths in those in the screening arm, compared to those in usual care [17].

The current standard of care intervention recommended to reduce future ovarian cancer risk therefore remains for women to undergo risk-reducing bilateral salpingo-oophorectomy (BSO), once they have completed their family, and are of an appropriate age. The recommended age varies from country to country, but the current recommendations are for surgery to be undertaken from age 35 to 40 for BRCA1 and 40 to 45 for BRCA2, to reflect the different age of increasing risk. Further details of international recommendations for BSO are shown in Table 4.1. This surgery has been shown to reduce the lifetime risk of ovarian cancer by up to 95%, with a residual small risk of primary peritoneal carcinoma [18, 19]. However, there are long-term risks associated with an early removal of the ovaries, and the resulting surgical menopause, which play a role in less than universal uptake of RRBSO. While many women are able to use hormone replacement therapy (HRT) to ameliorate the side effects, those with a prior diagnosis of oestrogen-receptor positive breast cancer will be unable to do so. These issues have led to growing interest in the possibility of undertaking risk-reducing salpingectomy alone, with a second procedure to remove the ovaries around or after the time of physiological menopause. This suggestion grew out of the recognition that much of the 'ovarian' cancer found in those with a BRCA1/2 mutation originates in the fimbrial end of the fallopian tube, rather than the ovary itself. This was supported by evidence from series of patients undergoing RRBSO, where pre-malignant changes have been identified in the fallopian tube, without equivalent pre-invasive stages of high-grade ovarian malignancy. The identified changes, ranging from a p-53 signature and atypical hyperplasia, leading to serous tubal intra-epithelial carcinoma (STIC) and then invasive malignancy, suggest a clear progression [20,

Table 4.1 International recommendations for screening and risk-reducing ovarian surgery

Organization (year)	Routine screening	Surgical recommendations
NICE (2016)	Not recommended	RRBSO at appropriate age
ESMO (2016)	Not recommended	RRBSO from age 35 to 40 years
SGO (2017)	Not recommended	RRBSO from age 35 to 40 years for BRCA1, 40–45 years for BRCA2
NCCN (2018)	Not recommended	RRBSO from age 35 to 40 years for BRCA1, 40–45 years for BRCA2
USPTF (2018)	Do not routinely recommend any screening	No recommendation

RRBSO risk-reducing bilateral salpingo-oophorectomy, *NICE* National Institute of Clinical Excellence, *ESMO* European Society of Medical Oncology, *SGO* Society of Gynecological Oncology, *NCCN* National Comprehensive Cancer Network, *USPTF* US Preventative Task Force

21]. Studies are currently ongoing to assess the level of risk reduction offered by salpingectomy alone with delayed oophorectomy, and the frequency of complications from two surgical procedures. The clear benefits of preventing an early menopause on organs such as the bones, brain and heart may also have to be weighed up against losing the demonstrated benefit in reducing breast cancer risk, particularly in those with a BRCA2 mutation. This benefit has previously been reported to be as high as a 50% risk reduction, together with a positive impact on breast cancer survival [18, 22–24].

Phenotype

BRCA mutations are predominantly reported in those with high-grade serous cancer, although they have also been associated at a lower frequency in those with endometrioid, clear cell cancer and carcinosarcoma. They are very rare in those with mucinous and low-grade cancers. Women with a BRCA mutation have a younger mean age of ovarian cancer diagnosis, and are more likely to develop visceral metastases, which are otherwise rare in epithelial ovarian cancer [25]. Of note, the presence of visceral metastases in BRCA carriers does not correlate with a poorer survival, unlike in those without a BRCA mutation. Numerous studies have reported a clear survival benefit in those with a BRCA mutation, particularly BRCA2, which has largely been attributed to improved platinum sensitivity and prolonged platinum-free intervals in mutation carriers [26–28].

Treatment

Perhaps the greatest driver for the routine testing of ovarian cancer patients has been the development of new treatments and recognition of the differential responses to existing chemotherapy drugs in those with underlying BRCA mutations. These have led to the increasing stratification of treatment for patients based on BRCA status and an era of more personalized treatment for these patients. The first evidence for differential responses came from in vitro studies, demonstrating the role of the BRCA1 protein in repairing damage from DNA-crosslinking agents such as platinum. This was subsequently confirmed in clinical studies that showed higher response rates and prolonged platinum sensitivity in women with a BRCA mutation than those without [27, 29–31]. Conversely, intact BRCA protein is required for the full benefit of microtubule stabilizing agents such as taxanes, suggesting that BRCA mutation carriers may have lower rates of response to these drugs, although this has not been formally tested [32]. A higher response rate in BRCA mutation carriers has also been reported with pegylated liposomal doxorubicin (Caelyx). The evidence for this first came from a study assessing olaparib versus Caelyx in ovarian cancer patients with BRCA mutations. This study had used the reported response to Caelyx in platinum-resistant patients from previous studies (~10%) to determine the power for their study. Surprisingly, this study demonstrated equivalent response rates to both drugs, despite olaparib performing at the level expected [33]. It was subsequently confirmed that this was due to a much higher response rate in BRCA mutation carriers than in those without [34, 35].

PARP Inhibitors

It has now been 12 years since the first landmark study was published, reporting the role of PARP inhibition in BRCA-mutated ovarian cancer and demonstrating the efficacy of synthetic lethality. We now have multiple studies assessing the benefit of these drugs across several different tumour types with underlying BRCA mutations. PARP is a nuclear enzyme required to repair single-strand DNA breaks, via the base excision repair (BER) pathway. If this pathway is inhibited, DNA damage is caused, either as double-strand breaks or persistent single-strand breaks leading to the collapse of the replication fork [32]. Each of these require functional BRCA proteins for repair, leading to the prediction that tumour cells in those with underlying BRCA mutations would be

Table 4.2 Phase III trials of maintenance PARP inhibitors in BRCA-mutated ovarian cancer

PARP inhibitor	Study	Population	PFS (months)	HR
Olaparib	SOLO2	295 patients, treated with 2 prior lines of platinum-based chemotherapy with complete or partial response	19.2 vs. 5.5 $p < 0.001$	0.30
Olaparib	SOLO1	391 patients treated with 1 prior line of platinum-based chemotherapy with complete or partial response	NR vs. 13.8 $p < 0.001$	0.30
Niraparib	NOVA	203 BRCA-mutated patients from 553 total patients, treated with 2 prior lines of platinum-based chemotherapy with complete/partial response	21 vs. 5.5 $p < 0.001$	0.27
Rucaparib	ARIEL3	196 BRCA-mutated patients from 564 total patients, treated with 2 or more prior lines of platinum-based chemotherapy with complete/partial response	16.6 vs. 5.4 $p < 0.0001$	0.23

highly sensitive to these drugs [36]. This was confirmed in the proof-of-concept trial with olaparib, in which responses were confirmed in 12/19 heavily pretreated, platinum-resistant ovarian cancer patients [37]. Subsequent studies have confirmed the benefit of PARP inhibitors as a maintenance treatment in multiple lines of ovarian cancer, as well as other BRCA-mutated cancers. Additional models of the anti-tumour effects have also been identified, including PARP1 trapping, activation of the NHEJ and impaired BRCA1 recruitment [38, 39].

The use of PARP inhibitors therapeutically can currently be split into two main categories—maintenance and treatment. The first evidence for benefit in the maintenance setting came with Study 19. This study randomized women who had received at least two lines of platinum-based chemotherapy, and had a partial or complete response to their most recent platinum-based chemotherapy, to receive either olaparib capsules or placebo until progression. A known BRCA mutation was not required for entry, but the population was enriched for BRCA carriers, and all patients had to provide tumour and blood for subsequent testing. The initial results demonstrated an improvement in progression-free survival (PFS) from 4.8 to 8.4 months in those treated with olaparib [40]. A pre-planned analysis by BRCA mutation status showed a median PFS increase from 4.3 to 11.2 months in BRCA mutation carriers receiving olaparib ($p < 0.00001$) [41]. Subsequent phase III studies demonstrated benefit following first platinum-sensitive relapse for BRCA carriers treated with olaparib (SOLO2), niraparib (NOVA) and rucaparib (ARIEL3) [42–44]. One study has so far reported the use of first line maintenance (SOLO1), although others have completed recruitment and results are awaited [45]. Further details of the landmark studies are shown in Table 4.2.

Resistance and Super-Responders

As use of PARP inhibitors has increased, so too has the recognition of both resistance mechanisms and a group of patients who have long-lasting responses (the 'super-responders'). In both, mutational knowledge has proven vital. It is clear that in a proportion of patients who develop resistance, this is due to the development of secondary BRCA mutations in the tumour that restore BRCA function. Such mutations have been identified in multiple resistant individuals, although they do not account for all resistance [46–48]. Conversely, a subset of germline mutation carriers with ongoing durable responses have been studied in more detail to try to identify why they have continued to respond for so long. A number of features common to the super-responders were identified, including BRCA2 (rather than BRCA1) mutations, particularly those with mutations in the RAD51 or DNA-binding domains in the BRCA2 gene. This suggested that both gene of origin and site of mutation may influence duration of response [49].

Survival

The heightened response to platinum agents and longer progression-free intervals translate into longer median survivals for stage and age matched patients with BRCA mutations, compared to those without [27, 28]. A recent meta-analysis of patients suggested this benefit may have reduced by 10 years post diagnosis, but the patients included in this analysis predated the widespread use of agents targeting PARP, which is likely to further extend survival of BRCA-mutated patients, over and above that of those without mutations [43–45, 50]. For those with a BRCA mutation, this means consideration must be given to their other cancer risk, such as breast cancer.

Lynch Syndrome

An inherited component to cancer susceptibility was first mooted in 1895, with 'Family G', a family in which multiple family members over several generations died from cancers of the colon, womb and stomach at young ages. Subsequent work by Henry Lynch on this family and others led to the recognition of 'Cancer Family Syndrome', later renamed as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), and finally as Lynch syndrome [51]. This description is now used to describe the disease phenotype caused by germline mutations in one of four mismatch repair (MMR) genes, causing an inherited predisposition to colorectal, endometrial and ovarian cancer, among others.

There are currently four mismatch repair genes in which inherited mutations result in Lynch syndrome, of which three—MLH1, MHS2 and MSH6—are associated with an increased risk of ovarian cancer. Mutations in these genes are associated with microsatellite instability, which had already been linked to hereditary colorectal cancer [52]. Microsatellites are short DNA sequences of 1–5 bp that are repeated 15–30 times, occurring throughout the genome. If the mismatch repair system is impaired, these microsatellites accumulate mutations that are not repaired and become unstable. This work led to the discovery of the four MMR genes, between 1993 and 1997, with current figures suggesting MLH1 and MSH2 account for ~80–85% of Lynch families, with MHS6 and PMS2 accounting for 10–12% and 3–5%, respectively [53–58]. Each gene has a distinct risk associated with it, including specific cancers and age of onset.

Unlike many other genes, it is possible to screen tumours to detect those who may carry an inherited Lynch mutation to target testing. This can be undertaken by one of two methods—either testing for microsatellite instability (MSI) or undertaking immunohistochemistry (IHC) for the protein products of the four genes. If an abnormality is found (either microsatellite instability high, or loss of one or more of the MMR proteins on IHC), patients can be referred to genetics for consideration of confirmatory testing. Both methods are thought to correlate well, with those with normal tumour testing unlikely to have a germline mutation. As abnormal IHC or MSI can be caused by somatic mutations, or epigenetic changes such as MLH1 promoter hypermethylation, Lynch syndrome is only confirmed in those who are found to have a germline mutation in one of the four genes.

Prior to the more widespread use of tumour testing, the selection of patients to undergo testing for Lynch syndrome was based on one of two formal scoring criteria—the Amsterdam (later Revised Amsterdam) or Bethesda Criteria. Each used a combination of qualifying tumour types and ages at diagnosis among the patient and their family members to determine if they were likely to have underlying criteria. These criteria vary in their detection, with the Revised Amsterdam generally less sensitive (but more specific) than the Revised Bethesda, as the latter considers a wider range of tumour types. However, with the increasing use of molecular changes to select patients for testing, their use now is generally in those without underlying molecular changes but a strong family history, in advising on appropriate screening for family members.

Prevalence and Phenotype

Mutations in the Lynch genes are reported in 1–2% of ovarian cancer patients, predominantly those with non-serous ovarian cancer such as clear cell and endometrioid [59, 60]. Mutations are rare in those with high-grade serous cancers, which are more commonly associated with BRCA mutations. Many studies that report significant numbers of high-grade serous ovarian cancers with Lynch gene mutations have not undertaken formal histological review and are using old reports that often predate the 2014 FIGO definition of high-grade serous cancers and so must be interpreted with caution [61]. A higher rate of mutations has been reported in those with synchronous endometrial and ovarian cancers or those with a strong family history of early onset colorectal or endometrial cancer [62, 63]. Those with a mutation tend to be diagnosed with early-stage disease and have a significantly younger age of onset, with mean ages ranging from 45 to 50 in multiple studies, compared with 50–55 in BRCA carriers and 60–65 in the sporadic population [61, 64, 65].

Risk

The lifetime risk of ovarian cancer varies by gene and study, with early studies suggesting higher lifetime risks for MLH1/MSH2 carriers than recent studies and newer studies demonstrating higher risks for MSH6 than previously reported. The updated estimates from the large prospective Lynch syndrome database suggests an ovarian cancer risk by age 75 of 10% (MLH1), 17% (MSH2) and 13% (MSH6) [58]. There is no clear evidence of an increased risk of ovarian cancer with PMS2 [66]. Of note, the previously reported risks for ovarian cancer may have been mediated by the routine removal of the ovaries as part of the treatment of endometrial cancer, thus lowering the potential future risk. Additionally, in earlier generations, many carriers died of their first cancer, leaving few alive to determine the risks of second or third cancers. As cancer survival rates have improved, together with the expansion of universal screening programmes, more patients survive their sentinel cancers.

Second Cancer Risk

Women with a Lynch mutation will often present initially with colorectal or endometrial cancer. Each of these represents an opportunity to detect an underlying Lynch mutation in those not already known to be a carrier, and prevent subsequent diagnoses. Two recent papers provided updated risk estimates for tumours by gene, as demonstrated in Table 4.3. These present a number of opportunities to intervene with screening, risk-reducing surgery or chemoprevention to reduce future cancer risk.

Ovarian Cancer Screening

A number of studies have investigated the role of various screening modalities to detect ovarian cancer at an earlier stage. Although none have looked specifically at Lynch carriers, these women were included in the UKFOCSS cohort, and also in the PLCO cohort. To date, neither of these has shown a benefit from screening [16, 17]. However, Lynch carriers have a prevalence of tumours diagnosed at an earlier stage than non-carriers, suggesting they may have different biological behaviour to non-carriers, and may be more amenable to early detection than BRCA-related tumours. Further work is required in this area.

Table 4.3 Cancer risk by Lynch cancer gene

	MLH1[a] (%)	MSH2[a] (%)	MSH6[a] (%)	PMS2[b]
Colorectal cancer	46	43	15	13%
Endometrial cancer	43	57	46	12%
Upper GI cancer	21	10	7	NSE
Urinary tract cancer	8	25	11	NSE
Brain tumours	1	5	1	NSE

NSE not significantly elevated
[a] Denotes risk by age 75
[b] Denotes risk by age 80

Currently the only proven form of risk reduction for ovarian cancer is risk-reducing surgery, but the age at which this should be undertaken is unclear. The earlier age of onset in Lynch carriers compared to BRCA carriers suggests this may need to be recommended from age 35 onwards, especially for those with MLH1/MSH2 mutations; however, many women have yet to complete their families at this stage. Women with Lynch mutations are also often recommended to undergo risk-reducing hysterectomy due to the high risks of endometrial cancer, and most choose to undertake this as a single surgical procedure rather than two operations. Those who undergo RRBSO before menopause are generally advised to begin HRT unless there are specific contraindications, to prevent a surgical menopause and the subsequent increased risks. This may be with oestrogen alone if a hysterectomy has also been performed.

Aspirin Use

The CAPP2 study assessed the use of aspirin chemoprevention (600 mg/day) versus placebo in risk of developing first cancer, either colorectal or non-colorectal in those with a germline Lynch mutation. This study showed that aspirin significantly reduced both groups of cancer, the latter including ovarian cancers, with a HR of 0.65 ($p = 0.03$) [67]. The aspirin was taken for a mean of 25 months, leading to questions about both optimal dose and duration of treatment. The CAPP3 study was subsequently designed to investigate these, with patients randomized to receive either 300 mg BD, 300 mg OD or 100 mg OD, for a total of 5 years. The first 2 years of treatment are blinded, with patients unblinded after 2 years and re-consented to continue with the same dose for a further 3 years. CAPP3 has just completed recruitment.

Implications for Treatment

The renewed interest in finding ovarian cancer patients with underlying Lynch mutations has largely been driven by the rise of immunotherapy, and the large number of trials assessing its benefit in ovarian cancer. The early trials in all ovarian cancer patients have been disappointing, suggesting response rates of <10%, but higher response rates have previously been reported in those with MMR-deficient patients [5]. Pembrolizumab is currently approved in the USA for use in any MMR-deficient tumour, irrespective of tumour type, the first drug to be approved in this way. This is particularly important given the relative chemo-resistance of recurrent clear cell/endometrioid ovarian cancer, the predominant histological subtypes in those with Lynch syndrome.

Other Homologous Recombination Genes

To date, pathogenic mutations in BRIP1, RAD51C and RAD51D have all been associated with an increased susceptibility to ovarian cancer; however, these are relatively rare, and together account for ~2% of ovarian cancer. There is now interest in detecting these mutations as part of a move towards larger panel testing, particularly given their role in homologous recombination, and the possible therapeutic implications of this for the use of PARP inhibitors. Although these mutations are too rare to have been examined separately in a specific trial, patients with mutations in these genes were included in the HR-deficient cohorts of the NOVA and ARIEL trials, in which patients had improved progression-free survival over those treated with placebo.

BRIP1

BRIP1 mutations were first associated with an increased ovarian cancer risk in the Icelandic population and have subsequently been identified in other ovarian cancer populations [68]. Unusually, these women do not appear to have a younger age of onset than the sporadic population mean of 64 years, which may account for the low rates in some early studies that looked only in young-onset patients. Women with a mutation

generally present with late-stage high-grade serous ovarian cancer and appear to behave similarly to BRCA carriers in response to chemotherapy, although this has not been specifically studied. The current evidence suggests carriers have a lifetime ovarian cancer risk of 5.8%, which falls below the threshold for undergoing RRBSO in many countries; however, the later age of cancer diagnosis suggests this could be recommended to occur at the time of physiological menopause, reducing long-term complications. BRIP1 carriers do not appear to have significantly increased risks of breast cancer [69].

RAD51C

Several studies have now demonstrated a moderate increased risk of ovarian cancer in carriers of a RAD51C mutation. Phenotypically, these patients also resemble BRCA carriers, with the majority of carriers diagnosed with high-grade serous ovarian cancer (71%) and at stage 3 or 4 [70]. The age of ovarian cancer diagnosis was generally older than BRCA carriers, with 71% aged ≥50 years and no ovarian cancer diagnoses below age 40. The RAD51C carriers had varying lifetime risks of ovarian cancer, of 5.2% by age 70 or 9% by age 80, again putting them below the threshold for RRBSO in many countries [70, 71]. The breast cancer risk for carriers remains unclear, with some studies suggesting a modest increase and others showing no significant increase over the general population [72–74].

RAD51D

RAD51D was first established as an ovarian cancer susceptibility gene in 2011, and further studies have confirmed its position as a rare but consistent moderate-risk gene. Again, carriers appear to present with predominantly high-grade serous ovarian cancer at a late stage, but the relative rarity of the gene, and small numbers of reported carriers mean there is a wide age range reported in carriers, although most are diagnosed after 50 years [70, 75]. The lifetime ovarian cancer risk by age 70 in carriers is estimated to be approximately 12%, with RRBSO generally recommended from age 50 onwards. There is no clear increased risk of ovarian cancer in RAD51D carriers, with reported risks similar to the general population. In vitro studies have suggested a marked sensitivity to PARP inhibitors, although a separate trial has not been undertaken in RAD51D carriers, although they were included in the HR-deficient cohorts of the rucaparib and niraparib studies.

Non-epithelial Ovarian Cancer

While much rarer than epithelial ovarian cancer, underlying germline mutations have now been associated with non-epithelial forms of ovarian cancer. These tumour types, which predominantly occur in young women, have implications for risk of second tumours, and may also have treatment implications.

DICER1

Germline mutations in DICER1 are most commonly associated with an increased risk of pleuropulmonary blastoma, but further assessment of families and tumour spectra identified an increased risk of Sertoli-Leydig tumours in young affected women. These women generally present in their late teens/early twenties and have an increased risk of bilateral tumours (either synchronous or metachronous). Patients with these tumours who have a family history of pleuropulmonary blastoma or other phenotypic features of DICER1 syndrome, such as cystic nephroma, should be referred for genetic testing.

Small Cell Cancer of the Ovary, Hypercalcaemic Type (SCCOHT)

Small cell ovarian cancer of hypercalcaemic type (SCCOHT) is a rare but very aggressive malignancy, characterized histologically by the presence of SMARCA4 mutations in the tumour [76,

77]. Recent studies have demonstrated germline mutations in SMARCA4 are present in a small proportion of affected women, predominantly found in those with very early onset (pre-puberty), or in those with a family history [77]. Mutations in this gene had already been associated with other rhabdoid tumours, suggesting SCCOHT was molecularly closer to these tumours than other ovarian cancer types. Further investigations have shown SCCOHT typically have a very low mutational burden, with far fewer mutations per megabase than other ovarian cancer types.

The discovery of the underlying role of somatic SMARCA4 mutations in SCCOHT has allowed more definitive diagnoses but has also led to the development of targeted agents. These are of particular interest, given the aggressive behaviour of this tumour with rapid relapses and subsequent poor responses to chemotherapy in the recurrent setting. A phase II study of EZH2 inhibitors in rhabdoid tumours including SCCOHT has suggested a benefit for these patients, as have preclinical studies of HDAC inhibitors and CDK4/6 inhibitors such as palbociclib. There has also been interest in immunotherapy with checkpoint inhibitors despite the low tumour mutational burden, as a high proportion of PD-L1 receptors and drug responses have been described in these patients. This may be an important potential treatment option in future for these patients, who otherwise have very poor outcomes.

Conclusion

The rapidly moving therapeutic landscape of ovarian cancer treatment is increasingly stratified by germline mutation status across multiple different histological subtypes. The incorporation of routine testing for these patients is now becoming an important part of management, to ensure patients are able to benefit from recommendations regarding chemotherapy choice or use of targeted agents. Finding those with mutations also allows family members to undergo testing and benefit from risk-reducing options, with the benefit of reducing cancer burden in future generations. It is likely that the role of germline mutations in ovarian cancer management will continue to grow, as the range of therapeutic options increases for such patients.

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Ovarian Cancer Pathology

5

Mona El-Bahrawy

Introduction

Ovarian tumours encompass a large variety of neoplasms derived from the different histological components of the ovary and adjacent tissue of the female gynaecological tract. The WHO classification of tumours of the ovary is presented in Table 5.1 [1], and the FIGO classification for staging is presented in Table 5.2 [2]. This chapter will address principally the malignant tumours in the classification, and their putative precursors.

Table 5.1 The WHO classification of tumours of the ovary [1]

Serous tumours
Serous cystadenoma NOS
Serous surface papilloma
Serous adenofibroma NOS
Serous cystadenofibroma NOS
Serous borderline tumour NOS
Serous borderline tumour—micropapillary variant
Serous carcinoma, non-invasive, low grade
Low-grade serous carcinoma
High-grade serous carcinoma
Mucinous tumours
Mucinous cystadenoma NOS
Mucinous adenofibroma NOS
Mucinous borderline tumour
Mucinous adenocarcinoma
Endometrioid tumours
Endometrioid cystadenoma NOS
Endometrioid adenofibroma NOS
Endometrioid tumour, borderline
Endometrioid adenocarcinoma NOS
Seromucinous carcinoma
Clear cell tumours
Clear cell cystadenoma
Clear cell cystadenofibroma
Clear cell borderline tumour
Clear cell adenocarcinoma NOS
Seromucinous tumours
Seromucinous cystadenoma
Seromucinous adenofibroma
Seromucinous borderline tumour
Brenner tumours
Brenner tumour NOS
Brenner tumour, borderline
Brenner tumour, malignant
Other carcinomas
Mesonephric-like adenocarcinoma
Carcinoma, undifferentiated, NOS
Dedifferentiated carcinoma
Carcinosarcoma, NOS
Mixed cell adenocarcinoma
Mesenchymal tumours
Endometrioid stromal sarcoma, low grade
Endometrioid stromal sarcoma, high grade
Leiomyoma NOS
Leiomyosarcoma NOS
Smooth muscle tumour of uncertain malignant potential

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Table 5.1 (continued)

Myxoma NOS
Mixed epithelial and mesenchymal tumours
Adenosarcoma
Sex cord stromal tumours
Pure stromal tumours: Fibroma NOS
Cellular fibroma
Thecoma NOS
Thecoma, luteinised
Sclerosing stromal tumour
Microcystic stromal tumour
Signet ring stromal tumour
Leydig cell tumour of the ovary NOS
Steroid cell tumour NOS
Steroid cell tumour, malignant
Fibrosarcoma NOS
Pure sex cord tumours: Adult granulosa cell tumour of the ovary
Granulosa cell tumour, juvenile
Sertoli cell tumour NOS
Sex cord stromal tumour with annular tubules
Mixed sex cord stromal tumours: Sertoli–Leydig cell tumour NOS
Well differentiated
Moderately differentiated
Poorly differentiated
Retiform
Sex cord stromal tumours, NOS
Gynandroblastoma
Germ cell tumours
Teratoma, benign
Immature teratoma NOS
Dysgerminoma
Yolk sac tumours NOS
Embryonal carcinoma NOS
Choriocarcinoma NOS
Mixed germ cell tumour
Monodermal teratoma and somatic-type tumours arising from a dermoid cyst
Struma ovarii NOS
Struma ovarii, malignant
Strumal carcinoid
Teratoma with malignant transformation
Cystic teratoma NOS
Germ cell-sex cord stromal tumours
Gonadoblastoma
Dissecting gonadoblastoma
Undifferentiated gonadal tissue
Mixed germ cell-sex-cord stromal tumour NOS
Miscellaneous tumours
Adenoma of rete ovarii
Adenocarcinoma of rete ovarii
Wolffian tumour
Solid pseudopapillary tumour of the ovary
Small cell carcinoma, hypercalcaemic type
Small cell carcinoma, large cell variant
Wilms tumour
Paraganglioma
Metastases to the ovary

Table 5.2 FIGO classification of tumours of the ovary, fallopian tube and primary peritoneum [2]

I: Tumour limited to the ovaries
IA: Tumour limited to one ovary (capsule intact) or fallopian tube surface; no malignant in ascites or peritoneal washings
IB: Tumour limited to one or both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant in ascites or peritoneal washings
IC: Tumour limited to one or both ovaries or fallopian tubes with any of the following:
IC1: Surgical spill
IC2: Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
IC3: Malignant cells in ascites or peritoneal washings
II: Tumour involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal
III: Tumour involves one or both ovaries or fallopian tubes, and/or primary peritoneal carcinoma, with cytologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1: Retroperitoneal lymph node metastasis only
IIIA1i: Lymph node metastasis up to 10 mm in greatest dimension
IIIA1ii: Lymph node metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above pelvic brim) peritoneal involvement with or without Retroperitoneal lymph node
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension with or without retroperitoneal lymph node metastasis
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without retroperitoneal lymph node metastasis (excludes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
IV: Distal metastasis excluding peritoneal metastasis
IVA: Pleural effusion with positive cytology
IVB: Parenchymal metastasis and metastasis to extra-abdominal organs (including Inguinal lymph nodes outside the abdominal cavity)

Epithelial Tumours

Malignant epithelial tumours are the commonest types of ovarian cancers, and most patients present with advanced-stage disease [1].

Serous Tumours

Ovarian serous carcinoma comprises two types: high-grade serous carcinoma and low-grade serous carcinoma. These are not considered two grades of the same tumour, but rather two distinct types of tumours, which develop through different molecular pathways and have different precursor lesions/theories for origin.

High-Grade Serous Carcinoma (HGSC)

This is the commonest type of ovarian carcinoma. There are different theories regarding the origin of ovarian HGSC. It was traditionally believed that the ovarian surface mesothelium undergoes metaplastic change to epithelium of tubal type, which then due to mutations resulting from the effects of ovulatory events undergoes neoplastic transformation [3]. Another theory suggests the fallopian tube as the primary site of origin. This is based on the finding of foci of invasive and non-invasive carcinoma more in fallopian tubes than in the ovaries in specimens of risk reducing salpingo-oopherectomy from women with confirmed *BRCA* mutations [4–6].

Further support to this theory is the fact that approximately 60% of cases of ovarian HGSC show foci of non-invasive serous carcinoma in the fallopian tube. Serous tubal intraepithelial carcinoma (STIC) is the term referring to non-invasive intraepithelial high-grade serous tubal intraepithelial neoplasia (Fig. 5.1). In these lesions the cytomorphology is similar to that of ovarian HGSC. Immunostaining reveals a P53 expression profile indicative of *TP53* mutation and a high proliferation index. In cases that show both STIC and ovarian HGSC, both lesions have been shown to harbour similar *TP53* mutations [7, 8].

Another possibility is that there is field change in tubal epithelium and ovarian metaplastic surface epithelium that results in multiple foci of tumour development. In our experience and that of others there are at least 15–30% of cases of HGSC in which the fallopian tubes show no evidence of intraepithelial or invasive carcinoma [9, 10].

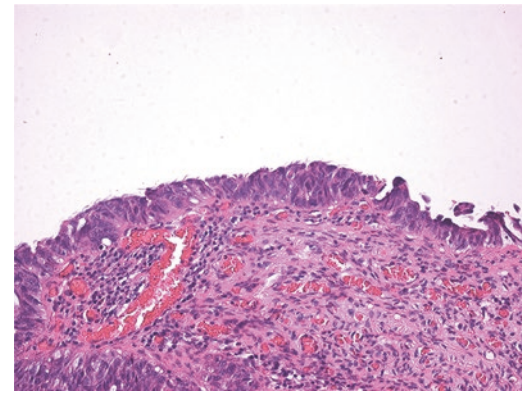

Fig. 5.1 Serous tubal intraepithelial carcinoma (STIC): The tubal epithelium shows stratification and notable cytological atypia

The mean age of patients presenting with HGSC is 63 years. The morphology of HGSC is variable with numerous architectural patterns including solid, papillary, transitional and glandular and there is notable cytological atypia and mitotic activity [1] (Fig. 5.2).

Immunophenotype and Genetic Profile

HGSC cells express PAX8, WT-1 and P16 (usually strong diffuse) [11–13]. The presence of P53 expression profile that is suggestive of the mutant type is supportive of the diagnosis in context of the morphology as *TP53* mutation occurs in virtually all cases of HGSC. Mutant P53 shows two patterns of expression. Strong diffuse nuclear staining in 60% or more of the cells occurs in the presence of missense mutation. Complete loss of expression is seen with nonsense mutation where a truncated protein not detected by the P53 antibody is expressed (Fig. 5.3). Both patterns are in contrast to the profile of the wild type P53, which shows variable intensities of nuclear expression.

Inactivation of *BRCA1* and *BRCA2* through germline or somatic mutation or promoter hypermethylation is present in about 50% of HGSC cases [14].

Ovarian carcinoma is sensitive to chemotherapy, particularly to platinum drugs with remis-

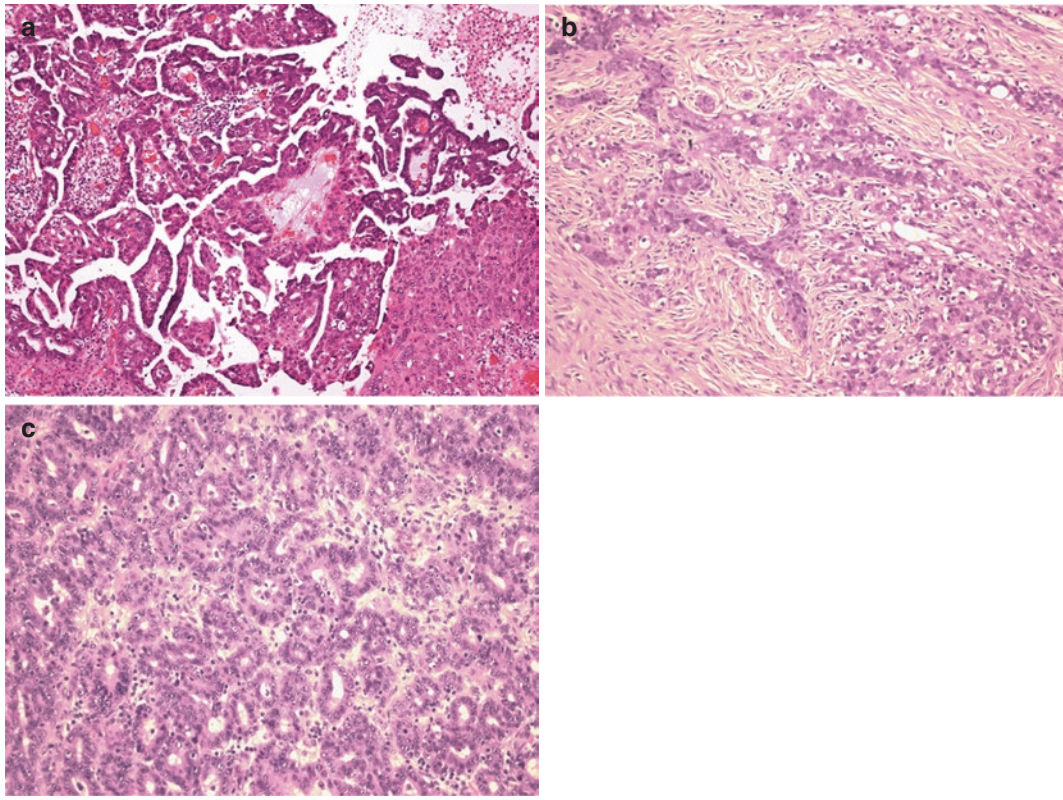

Fig. 5.2 High-grade serous carcinoma (HGSC): HGSC can show variable architectural patterns including papillary (**a**), solid and corded (**b**) and glandular (**c**)

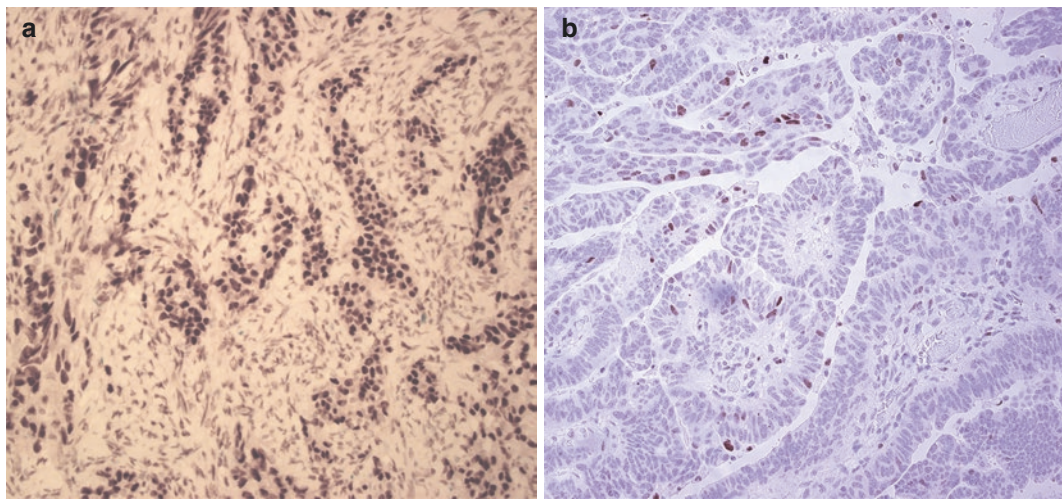

Fig. 5.3 Mutant P53 profiles: (**a**) strong diffuse nuclear expression in tumour cells correlates with nonsense mutation, (**b**) complete absence of expression correlates with nonsense mutation. Expression is seen in the tumour infiltrating inflammatory cells

sion achieved in most patients. However, most patients experience relapse. In recent years it has been shown that *BRCA* gene status influences prognosis and response to chemotherapy, where *BRCA1* and *BRCA2* germline mutations are associated with better prognosis [15]. In addition, targeted therapies, including poly (ADP-ribose) polymerase (PARP) inhibitors, are indicated as maintenance therapy for patients with mutated *BRCA* who experience relapse after response to chemotherapy. Hence determining the *BRCA* gene status has become crucial for personalised targeted therapy, based on *BRCA* mutational status and the treatment received in the first-line setting [16].

Low-Grade Serous Carcinoma (LGSC)

LGSC represents approximately 5% of serous carcinomas. The mean age of patients presenting with LGSC is approximately 50 years [1].

LGSC can have variable architectural patterns including papillary architecture and cell nests (Fig. 5.4). Many tumours show a component of serous borderline tumours (SBT), which is

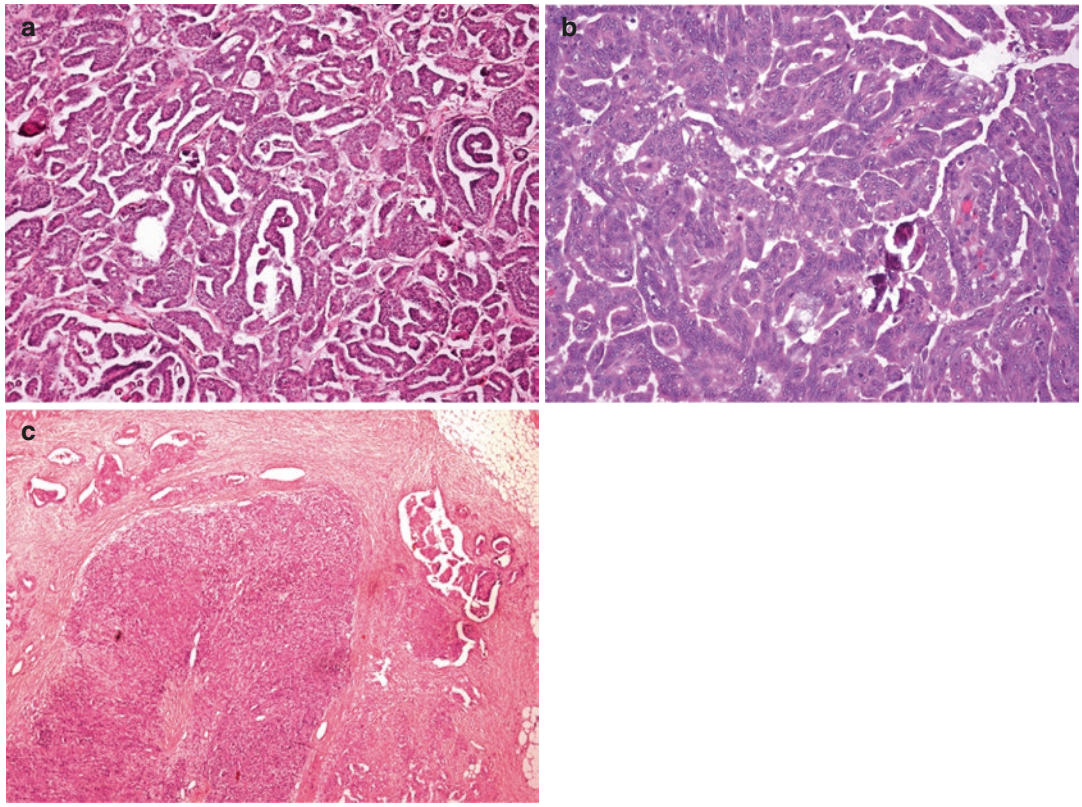

Fig. 5.4 Low-grade serous carcinoma (LGSC): (**a**) LGSC shows predominantly papillae and cell nests. (**b**) Some tumours show areas of transition to HGSC. (**c**) We encountered a case of LGSC with transition to areas of mesenchymal differentiation (carcinosarcoma)

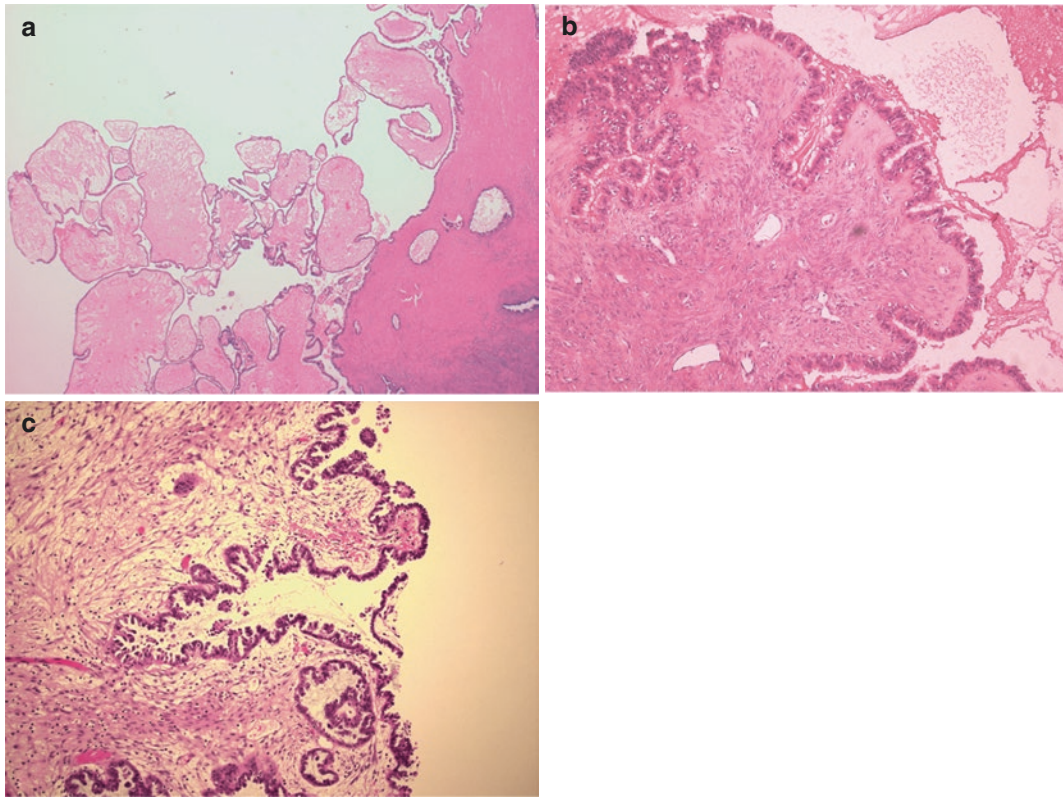

Fig. 5.5 Serous borderline tumour/Atypical proliferative serous tumour: (**a**) The tumours show a hierarchical papillary pattern. (**b**) The cells show crowding and mild cytological atypia. (**c**) Foci of pseudoinvasion and microinvasion may be seen

believed to be the precursor lesion for such tumours [17].

Serous Borderline Tumours

SBT are a challenging group of tumours that usually affect women in the reproductive age group with a mean age of 42 years. They may be unilateral or bilateral and usually confined to the ovaries. Most tumours behave in a benign fashion and are cured by surgical removal, but a minority may recur or progress to LGSC, which may happen up to 20 years post primary presentation and treatment [1].

Tumours show a hierarchical branching pattern of large to progressively smaller papillae ending in detached tufts of cells. The cells show little crowding and cytological atypia [1] (Fig. 5.5).

Foci of invasion may be seen, and if less than 5 mm in greatest dimension are labelled microinvasion (Fig. 5.5), and the tumour is still classified as SBT, as microinvasion does not adversely affect biological behaviour and outcome [18, 19].

Serous Borderline Tumour: Micropapillary Variant

These tumours are characterised by micropapillae with little or no core, which are usually five times taller than they are wide, and emanate directly from large papillae. Some tumours show slit-like glandular or cribriform patterns. The tumour cells are cuboidal to polygonal with some nuclear atypia and low mitotic index (Fig. 5.6).

SBT showing such features focally (<5 mm in confluent growth) and with lesser atypia can be

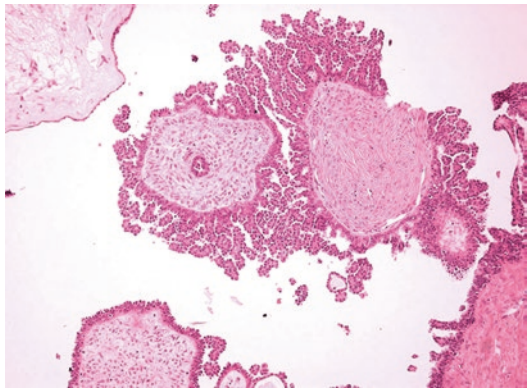

Fig. 5.6 Micropapillary SBT/non-invasive LGSC: Tumours usually show micropapillae with little or no core emanating directly from large papillae

classified as SBT with focal micropapillary features [1].

Immunophenotype and Genetic Profile of SBT and LGSC

The tumour cells express WT-1 [12] and PAX8 [13], ER, PR [20], P53 (wild type pattern) and patchy P16 [11].

Somatic *KRAS* and *BRAF* mutations are present in approximately 50–60% of cases [21].

Peritoneal Lesions Associated with SBT

SBT may be associated with extraovarian lesions, generally known as implants. These are non-invasive lesions present on peritoneal surfaces composed of hierarchical branching papillae or detached clusters of cells associated with non-fibrotic stroma, termed "epithelial non-invasive implants", or embedded in reactive-appearing or dense fibrous tissue, termed "desmoplastic non-invasive implants" [22]. Implants that invade underlying tissue or appear as small, solid nests of cells surrounded by a space, micropapillae and/or cribriform growth behave like LGSC and are hence designated as such [23]. Deposits of SBT may be identified in pelvic lymph nodes and this has no adverse effect on outcome [18] (Fig. 5.7).

Diagnostic Challenges in Serous Tumours

Tumour Typing

The varied architectural patterns seen in HGSC can show morphological overlap with other types of ovarian carcinoma, most commonly high-grade endometrioid carcinoma. In such cases immunohistochemistry can be helpful in tumour typing as most serous carcinomas show expression of WT-1, unlike endometrioid carcinoma, which is usually entirely negative for WT-1. In our experience P16 shows diffuse strong expression in HGSC, but patchy expression of variable intensity in endometrioid carcinoma.

Some serous tumours are difficult to classify as whether high grade or low grade. In addition to morphological assessment, mitotic activity <12/10 HPFs and P53 wild type expression profile favour LGSC.

Although the majority of cases of LGSC and high HGSC are known to develop through different molecular pathways, we and others have seen cases of LGSC progressing to HGSC [24] and even carcinosarcoma (Fig. 5.4).

Assignment of Primary Site of Origin

HGSC is usually diagnosed at an advanced stage where both the fallopian tube and ovary as well as the peritoneum are involved by tumour. Pathologists use their professional judgement and proposed algorithms [25] to designate the primary site of origin based on histological assessment. However, it is difficult in some cases to ascertain the primary site of origin. As tumours arising from all three sites have the same biological behaviour and management protocols, this does not represent a challenge that affects patient management, and all fall under pelvic HGSC. It is on this basis that the latest FIGO staging system is the same for tumours arising from either of the three sites, and it is recommended that tumours that cannot be assigned as of one of the three sites is labelled as undesignated [26].

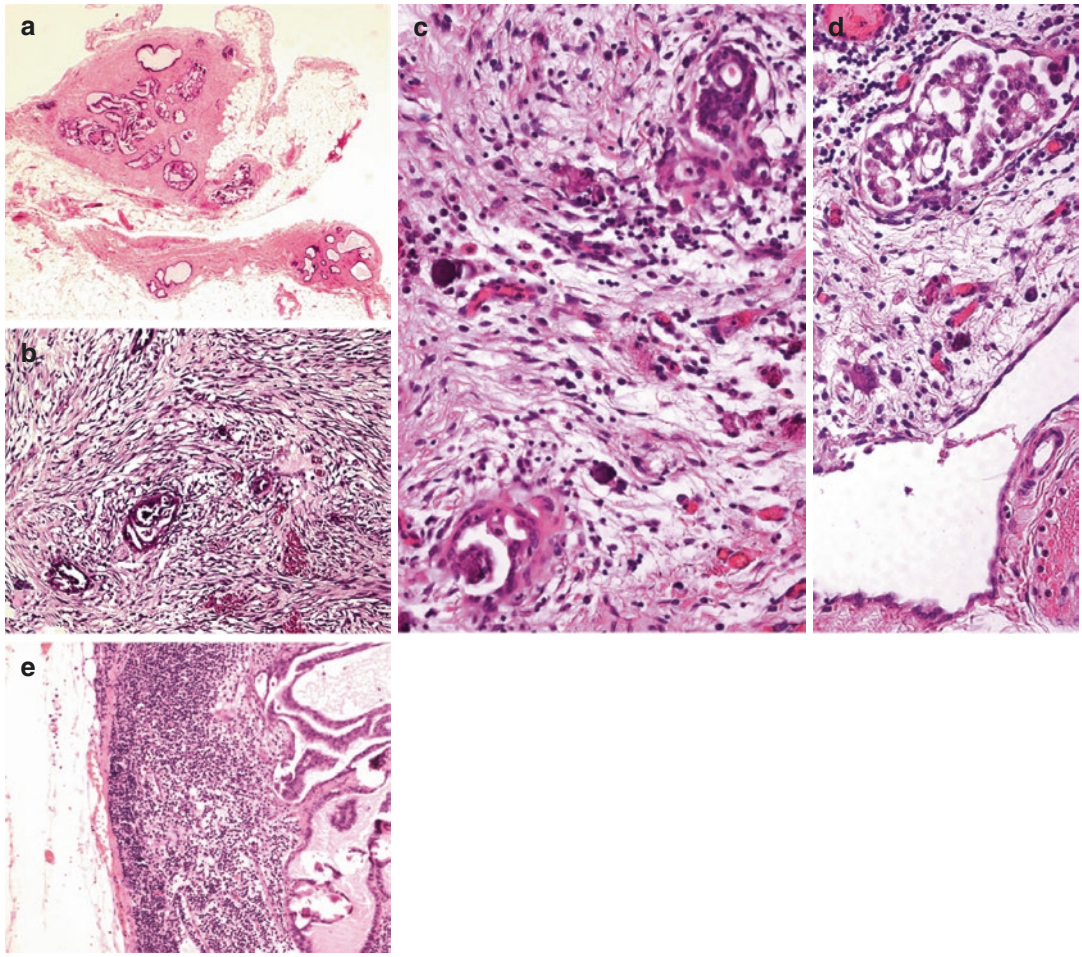

Fig. 5.7 Extraovarian SBT/APST deposits: These include (**a**) epithelial non-invasive implants, (**b**) desmoplastic non-invasive implants, (**c**, **d**) LGSC [formerly designated invasive implants] and (**e**) lymph node deposits

Synchronous Endometrial and Ovarian Serous Carcinoma

Ovarian and endometrial HGSC have similar morphology and immunoprofile [27]. WT-1 is commonly expressed in ovarian serous carcinoma, while it is generally believed that WT-1 is rarely expressed by endometrial serous carcinoma (ESC). We studied the expression of WT-1 in ESC and showed that WT-1 is expressed in 44% or the studied tumours [28]. Hence if positive WT-1 is not helpful in the distinction between ovarian HGSC and ESC in diagnostic peritoneal biopsies for disseminated intraabdominal malignancy or in cases presenting with concurrent endometrial and ovarian serous carcinoma. However, as endometrial serous carcinoma has potential for spread even at low stage, the presence of serous carcinoma in both the endometrium and the ovaries most likely represents ESC with metastatic deposits in the ovaries.

Prediction of Behaviour of SBT

Most SBT have excellent prognosis, but some show recurrence or progression to LGSC. We studied gene expression using Affymetrix HGU133plus2 GeneChip microarrays in a number of LGSC, SBT and benign serous tumours (BST). Unsupervised clustering revealed clear separation of benign and malignant tumours. SBT showed two distinct groups, one clustering with benign and the other with malignant

tumours. The segregation into benign- and malignant-like borderline molecular subtypes was reproducible on applying the same analysis to an independent publicly available data set. This was the first report of molecular subtypes of SBT based on gene expression profiling [29].

Subsequently we profiled the DNA methylomes of LGSC, SBT and BST. Unsupervised hierarchical clustering of DNA methylation levels showed distinction between LGSC and BST, and returned subgroups of SBT with malignant- or benign-like methylation profiles [30].

Our results show a subgroup of SBT can be classified into tumours with benign- or malignant-like molecular profiles. This may help in identifying tumours more likely to progress into LGSC and provide the basis for identification of biomarkers for the malignant potential of SBT.

Mucinous Carcinoma

Mucinous carcinoma represents approximately 3% of primary ovarian carcinoma. The mean age of presentation is 45 years. Mucinous carcinomas may arise from borderline tumours, teratomas or Brenner tumours [1].

The tumour may show confluent glandular/expansile or infiltrative growth patterns. The tumour cells are mucinous cells of gastrointestinal differentiation (Fig. 5.8). Invasive carcinoma with a confluent growth pattern is associated with better prognosis [31].

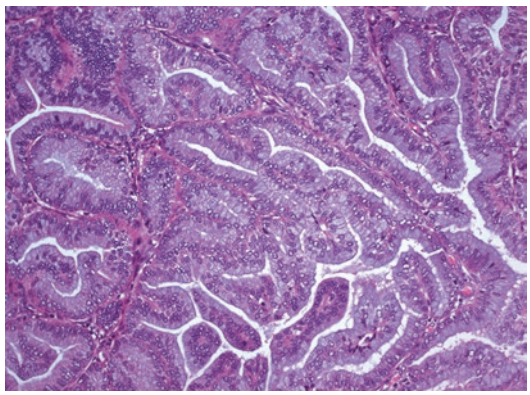

Fig. 5.8 Mucinous carcinoma

Mucinous Borderline Tumour (MBT)

The tumours are composed of gastrointestinal type mucinous cells that show variable degrees of architectural complexity but lack frank stromal invasion. Tumours that include foci of notable nuclear atypia are designated MBT with intraepithelial carcinoma. Survival of women with MBT with intraepithelial carcinoma is 95–100%. Invasive foci of less than 5 mm in greatest dimension are defined as microinvasion and in their presence the tumour is still considered MBT. Tumours with microinvasion may show recurrence in 5% of cases, principally in tumours of FIGO stage IC [32]. If foci of microinvasion show marked cytological atypia, the tumour is best designated microinvasive carcinoma [1].

MBT or carcinomas may contain reactive sarcoma-like mural nodules, foci of anaplastic carcinoma, and sarcomatous nodules [1].

Immunoprofile and Molecular Phenotype

The tumours express CK7 and variably CK20 and CDX2. ER and PR are negative. PAX8 is expressed in 50–60% of tumours [33–35].

Somatic mutations in *KRAS* are present in 30–75% of the tumours [36].

Challenges with Mucinous Tumours

The possibility of metastatic carcinoma should be considered on encountering a mucinous tumour of the ovary especially in cases of bilaterality and cases associated with extraovarian disease, as it is unusual for primary ovarian mucinous tumours to present with extraovarian disease [37]. Metastatic tumours to the ovary can simulate primary ovarian mucinous tumours including benign and borderline features, which may give the false suggestion that the malignant component is arising in a primary ovarian precursor benign or borderline tumour [38].

PAX2, PAX8 and CDX2 could be useful in differentiating primary from metastatic tumours. Most of the metastatic tumours are negative for PAX2 and PAX8 and diffusely positive for CDX2 [39].

Tumours arising from teratomas have an immunoprofile similar to lower gastrointestinal tract tumours being CK7−/CK20+. These are often associated with pseudomyxoma peritonei. The

presence of teratomatous elements helps to make the distinction between such tumours and metastasis from a primary gastrointestinal tumour [40].

P16 is helpful in distinction of primary ovarian mucinous tumours from metastatic cervical carcinoma, where the latter shows strong diffuse P16 expression [41].

Sampling of Mucinous Tumours

Adequate sampling of mucinous tumours of the ovary is crucial since they are typically heterogeneous and can harbour occult foci of carcinoma that can be missed on inadequate sampling. Sampling should be one section per centimetre of greatest tumour dimension in tumours that measure less than 10 cm, focusing on solid or unusual looking areas. In tumours of 10 cm or more, or showing microinvasion or intraepithelial carcinoma, the sampling should be increased to two sections per centimetre of greatest tumour dimension [42].

Endometrioid Carcinoma

Endometrioid carcinoma represents 10–15% of cases of ovarian carcinomas. The tumour usually presents with a mean patient age of 58 years. There is an association with ovarian or pelvic endometriosis in up to 42% of cases. The majority of cases are unilateral. The morphology, immunoprofile and grading are similar to those of endometrial endometrioid carcinoma [1] (Fig. 5.9).

Seromucinous carcinoma is now considered a subtype of endometrioid carcinoma with mucinous differentiation [1].

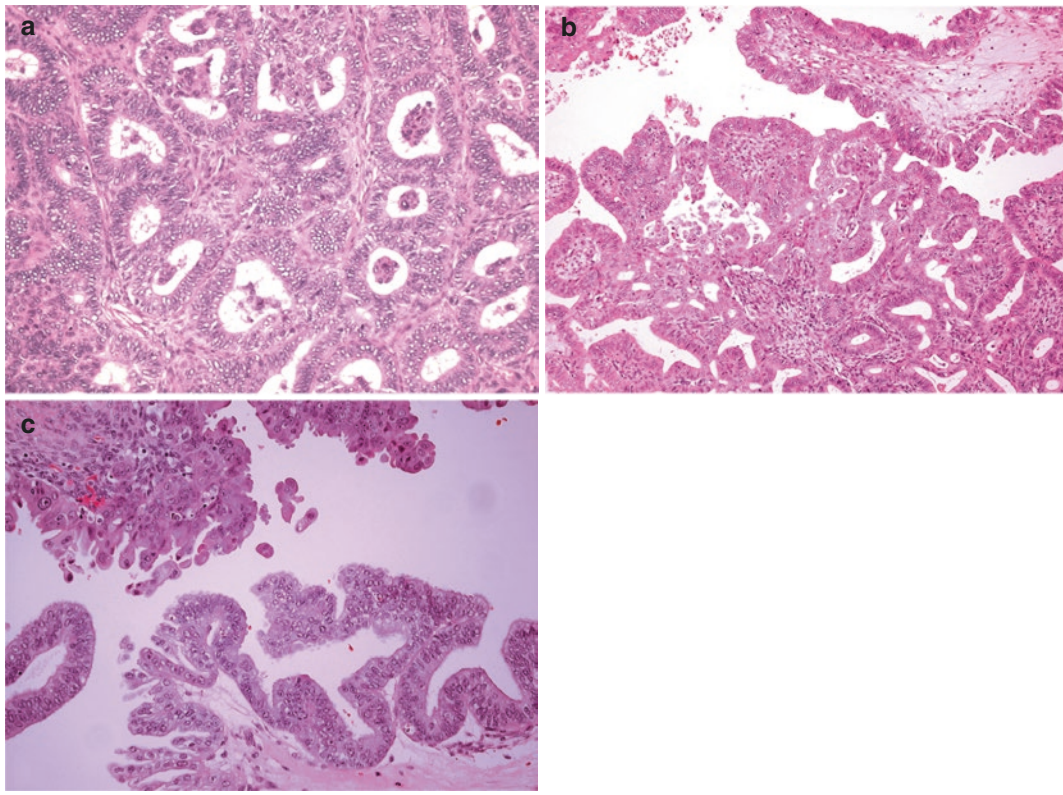

Fig. 5.9 Endometrioid tumours: (**a**) endometrioid carcinoma, (**b**) borderline endometrioid tumour and (**c**) borderline endometrioid tumour with intraepithelial carcinoma

Genetic Profile

The most common genetic abnormalities in endometrioid carcinoma are in the Beta catenin signalling pathway [43], *PTEN* [44], *PIK3CA* [45], and *ARID1A* [46].

Endometrioid Borderline Tumour (EBT)

These represent 0.2% of ovarian epithelial tumours. They are associated with endometriosis in many cases. The average age of patients at presentation is 51 years. The majority of tumours are unilateral.

The tumours have histological features similar to endometrial atypical complex hyperplasia and foci of marked cytological atypia are designated as intraepithelial carcinoma (Fig. 5.9). Invasive foci of <5 mm in maximum dimension are designated as microinvasion [1]. Findings of microinvasion or intraepithelial carcinoma should prompt more extensive sampling to exclude the presence of frankly invasive carcinoma.

Challenges in Endometrioid Carcinoma

Synchronous Endometrial and Ovarian Endometrioid Carcinoma (SEOs)

SEOs occur in 15–20% of cases [47]. The criteria for distinguishing between metastatic carcinoma from one site to the other and two independent primary carcinomas are mainly based on clinicopathological findings. In cases of low-grade endometrial carcinoma associated with hyperplasia and minimal or no myometrial invasion, the ovarian tumour can be regarded as an independent primary, particularly if endometriosis, adenofibroma or an EBT is present [48]. Bilaterality and multinodular growth and vascular invasion suggest ovarian metastasis from a primary endometrial carcinoma.

Organ-confined and low-grade SEOs clinically behave as independent primary tumours rather than a single advanced-stage tumour.

Hajkova et al. performed molecular analysis of SEOs by next-generation sequencing. In all tumours clonal origin was confirmed by at least one shared mutation in *PTEN, AKT1, PIK3CA, KRAS, TP53* and *ARID1A*. Their results showed that all studied SEOs were clonally related, irrespective of their clinicopathological features [49]. Other studies also confirmed this using whole exome massive parallel sequencing and high-depth targeted massively parallel sequencing [50, 51]. However, in current practice only the conventional morphological criteria should be used for the classification and staging of these tumours.

Distinction Between Serous Carcinoma and High-Grade Endometrioid Carcinoma

WT1 and P53 expression are of value in differentiating between grade 3 endometrioid carcinoma and HGSC where the expression of WT-1 and mutant profile of P53 favour HGSC [52]. In our experience, P16 may also be of value as it shows a strong diffuse pattern of expression in serous carcinoma, while in endometrioid carcinoma, the expression is patchy and of variable intensity.

Clear Cell Carcinoma (CCC)

CCC presents in patients with a mean age of 55 years, and is strongly associated with pelvic endometriosis (50–70%). The tumours are typically unilateral.

CCC can show variable architectural patterns, including solid, papillary, and the characteristic tubulocystic pattern. The cells in most cases have clear cytoplasm and feature a hobnail appearance [1] (Fig. 5.10).

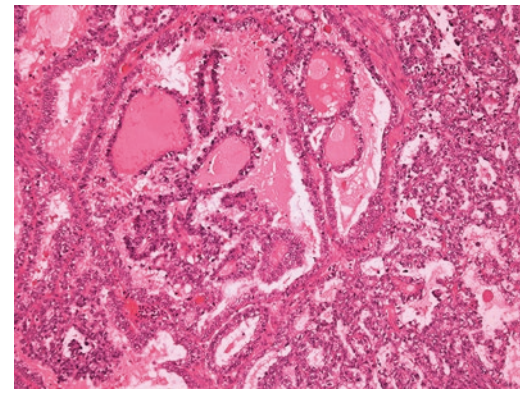

Fig. 5.10 Clear cell carcinoma. The tumour shows glandular, papillary and tubulocystic patterns

Immunophenotype and Genetic Profile

The tumours express Napsin A and are negative for WT-1 [53].

The most common mutations in CCC include mutations in *ARID1A* (46–57%) [46], *PIK3CA* (40%) [45] and *PTEN* (8.3%) [54].

Clear Cell Borderline Tumour (CCBT)

CCBT comprise less than 1% of borderline/atypical proliferative tumours, and thorough sampling is indicated to exclude a clear cell carcinoma component [1].

Challenges in Clear Cell Carcinoma

CCC has overlapping histopathologic features with other ovarian tumours, particularly HGSC and endometrioid carcinoma. Napsin A (positive in CCC) and WT1 (positive in HGSC) are highly sensitive and specific IHC markers for diagnosing ovarian CCC and HGSC, respectively, and for differentiating them from endometrioid carcinomas, which are usually negative for both. These immunomarkers can also be helpful in the identification of the respective components in tumours showing mixed differentiation [53].

Seromucinous Borderline Tumour

These tumours present at the average age of 34–44 years and are associated with endometriosis in about 31–35% of cases [55]. The tumours are non-invasive neoplasms composed most commonly of serous and endocervical mucinous epithelium (Fig. 5.11), but may feature other types of epithelium. Most tumours are confined to the ovary, but some may be associated with implants or lymph node deposits.

Immunophenotype and Genetic Profile

The tumours express CK7 and are negative for CK20 and CDX2. They usually express PAX8, ER and PR and are usually negative for WT-1 [39].

ARID1A mutations occur in one-third of these tumours [56].

Malignant Brenner Tumour

These tumours usually occur in women over 50 years of age. It is an ovarian carcinoma usually of transitional cell type, and in some cases shows squamous differentiation. The diagnosis is supported by the presence of a benign or borderline/atypical proliferative Brenner tumour. Mucinous glandular elements and, more rarely, mucinous adenocarcinoma may coexist with the Brenner component. Most are unilateral [1].

Borderline Brenner Tumour (BBT)

This is a neoplasm of transitional cell type (resembling low-grade non-invasive urothelial neoplasms) displaying epithelial proliferation beyond that seen in benign Brenner tumours and lacking stromal invasion.

BBT are typically unilateral cystic tumours. If there is notable cytological atypia without invasion, these can be diagnosed as BBT with intraep-

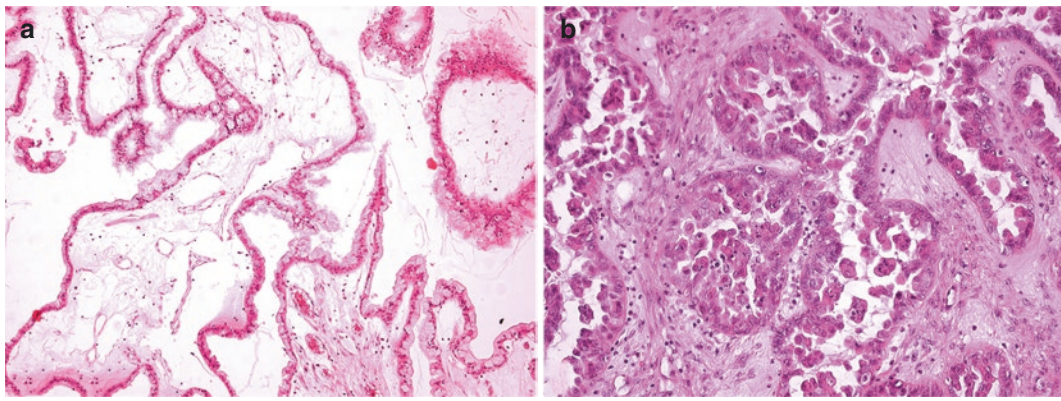

Fig. 5.11 Seromucinous borderline tumour: There are cells showing mucinous differentiation of the endocervical type (**a**) and cells showing serous differentiation (**b**)

ithelial carcinoma. Mucinous metaplasia is often present. A benign Brenner component is nearly always present, and confirms the diagnosis [1].

Immunophenotype

The tumour cells express p63 and GATA3 and are negative for WT-1 [57].

Mesonephric-Like Adenocarcinoma

Mesonephric-like adenocarcinoma is a very rare adenocarcinoma displaying mesonephric differentiation [1].

Immunophenotype and Genetic Profile

Most tumours express GATA3, TTF1, CD10, and PAX8 and are negative for WT1, ER, PR. P53 is wild type [58, 59].

Dedifferentiated and Undifferentiated Carcinoma

Undifferentiated carcinomas are uncommon highly aggressive carcinomas showing no specific differentiation. Dedifferentiated carcinoma shows a differentiated component and an undifferentiated carcinoma [1].

Carcinosarcoma

Carcinosarcoma represents 2% of ovarian malignancies. Most patients present at more than 60 years and with high-stage tumours.

These are tumours of epithelial origin [60] that are biphasic, composed of malignant epithelial and mesenchymal elements (Fig. 5.12). The carcinomatous component is often of serous or endometrioid differentiation. The sarcomatous

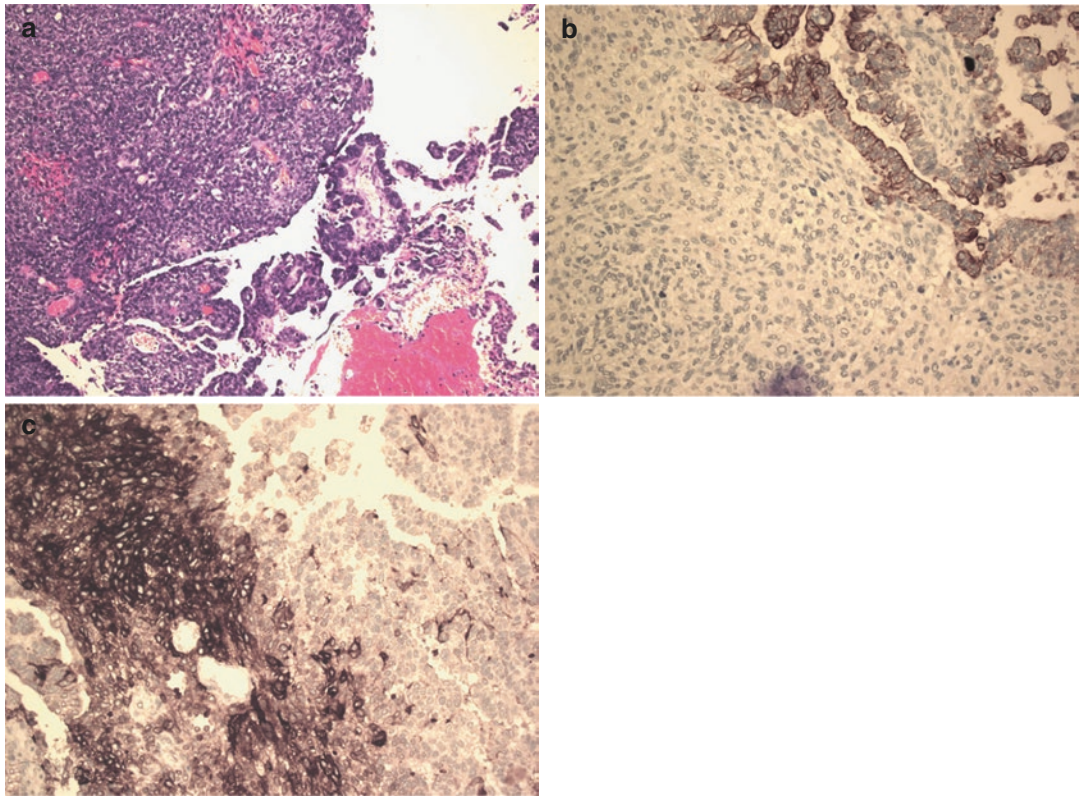

Fig. 5.12 Carcinosarcoma: (**a**) The tumour shows malignant epithelial and stromal components. (**b**) The epithelial component is highlighted by CK 7. (**c**) The homologous stromal component is highlighted by CD10

component can be homologous showing non-specific appearance or heterologous showing specific differentiation, e.g. rhabdomyosarcoma [1].

Mixed Carcinoma of the Ovary

This is carcinoma of the ovary composed of two or more histological subtypes.

Mesenchymal Tumours

Low-Grade Endometrioid Stromal Sarcoma

These tumours mostly occur in women in the fifth and sixth decades and may be associated with endometriosis. Tumours frequently show extraovarian spread at presentation [1]. The tumours have the same morphological features and genetic alteration as in the uterus, including fusions of *JAZF1-JJAZ1 (SUZ12), EPC1-PHF1* and *PHF1* rearrangement [61].

High-Grade Endometrioid Stromal Sarcoma

These are tumours with some evidence of endometrial stromal differentiation, showing high-grade cytological atypia and frequent mitosis. The tumours have the same morphology as in the uterus.

Mixed Epithelial Mesenchymal Tumours

Adenosarcoma

This is a biphasic tumour with malignant mesenchymal and benign epithelial components. Patients present at a mean age of 54 years. Most tumours are unilateral and confined to the ovary at presentation [62].

The stromal component is typically reminiscent of endometrial stromal neoplasia and is CD10, ER, PR positive. The stroma is usually low grade but can be high grade with loss of CD10, ER and PR expression. There can be stromal overgrowth and including heterologous elements displaying rhabdomyomatous differentiation, where tumours are designated adenosarcoma with sarcomatous overgrowth. High-grade stroma and sarcomatous overgrowth are associated with worse prognosis [62].

Sex Cord Stromal Tumours

Pure Stromal Tumours

Fibrosarcoma

These are aggressive tumours, usually presenting in post-menopausal women, and rarely associated with Maffucci syndrome and nevoid basal cell carcinoma syndrome [1].

Steroid Cell Tumour (Lipid Cell Tumour)

These account for 0.1% of ovarian tumours. Tumours present at a mean age of 43 years. Patients may experience androgenic symptoms, oestrogenic symptoms, progestational changes or Cushing syndrome. The tumour cells resemble steroid secreting cells (Fig. 5.13). Approximately 30% of tumours show malignant behaviour, and these usually show size of >7 cm, >2 mitoses/10HPF, necrosis, haemorrhage and notable nuclear atypia [1].

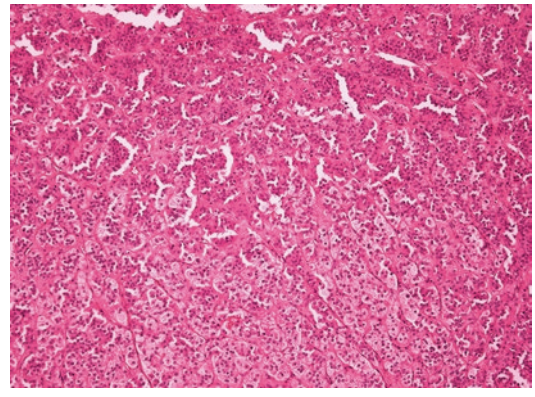

Fig. 5.13 Steroid cell tumour

Immunophenotype

The cells express inhibin, and calretinin and usually Melan-A [63].

Pure Stromal Tumours

Adult Granulosa Cell Tumour (AGCT)

AGCTs are low-grade malignant tumours accounting for <5% of ovarian malignancies. The majority present at over 30 years. Tumours are usually unilateral and confined to the ovary at presentation. The tumours are composed of granulosa cells (Fig. 5.14) and show a variety of architectural patterns [1].

Immunophenotype and Genetic Profile

Tumour cells usually express inhibin, calretinin, WT-1 and CD56. The cells may be positive for cytokeratins but are negative for EMA. The cells may express SMA, desmin, CD99, S-100 protein, ER and PR [64].

More than 90% of tumours have a missense somatic point mutation in the *FOXL2* gene [65].

Juvenile Granulosa Cell Tumour (JGCT)

These tumours account for 15% of GCTs and present at the average age of 15 years.

JGCTs are typically unilateral, and more than 95% of them are confined to the ovary at presentation [1]. The tumours show predominantly sheets of small cells (Fig. 5.14).

Immunophenotype and Genetic Profile

Tumour cells usually express inhibin, calretinin, CD99 and CD56, and may express cytokeratins and EMA (weak and focal) [1].

These tumours do not have *FOXL2* mutation [65].

Sertoli Cell Tumour

The tumour is composed of Sertoli cells most commonly arranged in hollow or solid tubules. The mean age at presentation is 30 years. Some tumours may show malignant behaviour and these usually have a size of >5 cm, >5 mitoses/10HPF, notable cytological atypia and necrosis [66].

Immunophenotype

Tumours usually express WT-1, inhibin, calretinin, SF1, CD99 and cytokeratins, but are negative for EMA, GATA3, CK7 and PAX8. SMA and S-100 are positive in some cases [66].

Sex Cord Stromal Tumour with Annular Tubules

These represent <1% of sex cord stromal tumours and have a distinctive pattern of simple and complex annular tubules (Fig. 5.15).

SCTAT occurs either sporadically or in association with Peutz-Jeghers syndrome (PJS) Sporadic tumours are usually unilateral and have a malignant course in about 20% of cases. Tumours associated with PJS are usually bilateral

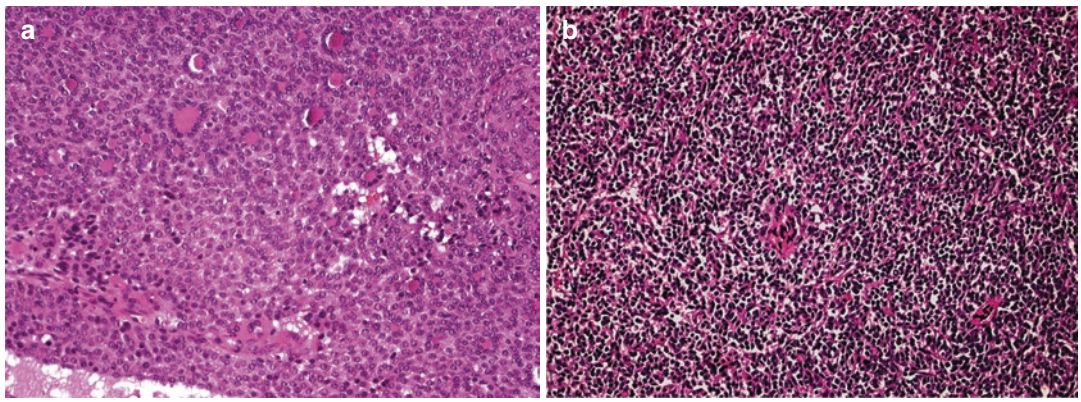

Fig. 5.14 Granulosa cell tumour: (**a**) Adult granulosa cell tumour. (**b**) Juvenile granulosa cell tumour

and multifocal and show a benign course. However, we have reported an unusual case of SCTAT in a PJS patient that showed malignant transformation [67].

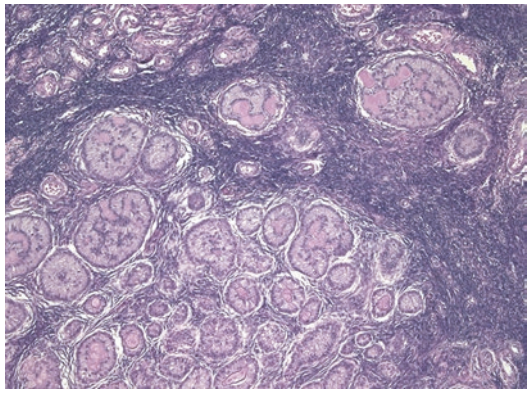

Fig. 5.15 Sex cord stromal tumour with annular tubules

Immunophenotype and Genetic Profile

The tumour cells usually express inhibin, calretinin, WT-1, CD56 and cytokeratins, but are negative for EMA [68, 69].

Germline mutations of *STK11* are seen in tumours associated with PJS [70], but somatic mutations of the *STK11* gene are not encountered in sporadic tumours.

Mixed Sex Cord Stromal Tumours

Sertoli Leydig Cell Tumour

The tumours represent <0.5% of ovarian tumours. The mean age at presentation is 25 years. Most tumours are unilateral, but up to 3% may show extraovarian spread at presentation.

The tumours are composed of Sertoli cells and Leydig cells (Fig. 5.16). Primitive gonadal stroma

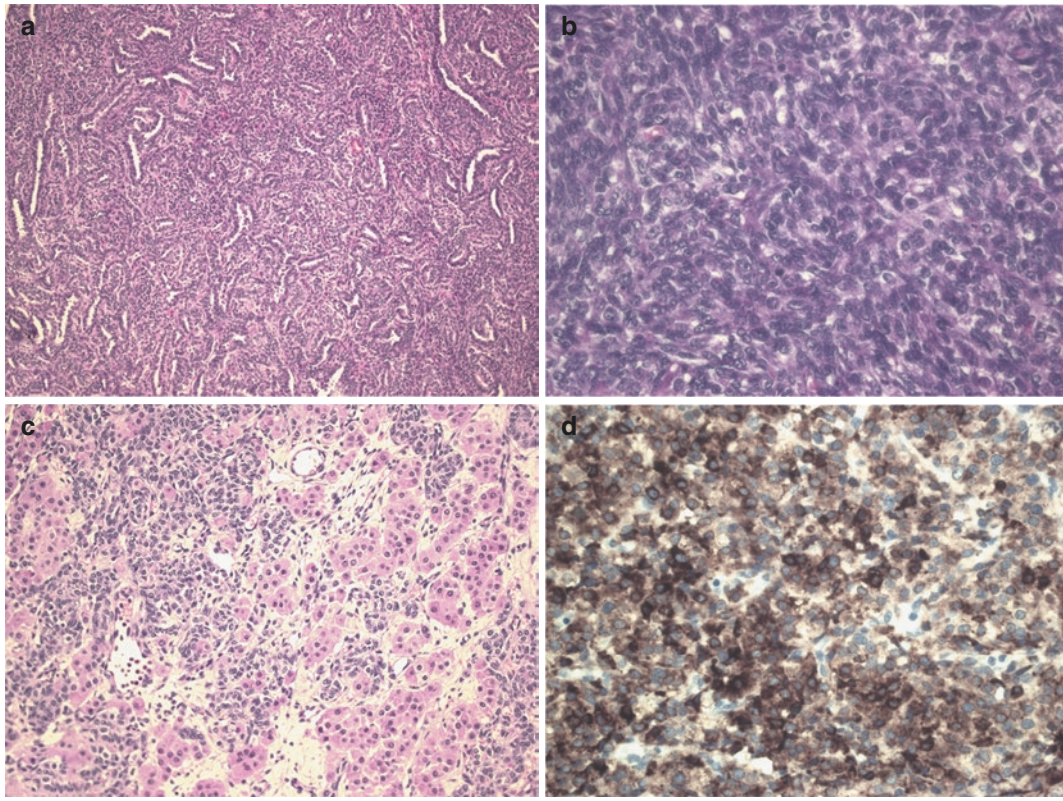

Fig. 5.16 Sertoli Leydig cell tumour: (**a**) Well-differentiated tumour showing well-formed tubules. (**b**) Poorly differentiated tumour with cells arranged in sheets. (**c**) Leydig cells of variable amounts are focally seen. (**d**) The cells express inhibin

and heterologous elements are present in moderately and poorly differentiated tumours. Poorly differentiated tumours and some moderately differentiated tumours may show a malignant course in 60% and 10% of cases, respectively [1].

Immunophenotype and Genetic Profile

Tumour cells express vimentin, cytokeratin, inhibin, calretinin, CD56, WT-1 and usually CD99 [64]. Mucinous epithelium seen in heterologous elements expresses CK7 and CK20.

Mutations in *DICER1* gene mutations are detected in 60% of tumours [71, 72].

Sex Cord Stromal Tumour NOS

Less than <5% of sex cord stromal tumours lack features of specific tumours and are then designated sex cord stromal tumour NOS. These tumours show biological behaviour similar to granulosa and Sertoli Leydig cell tumours [1].

Germ Cell Tumours

Malignant germ cell tumours almost exclusively present in children and young adults in most of the cases.

Immature Teratoma

This is a teratoma containing variable amounts of immature embryonal tissues, characteristically of the neurectodermal type (Fig. 5.17). Immature tissues of ectodermal and endodermal derivation may also be encountered [1].

Immature teratomas are graded from one to three, based on the amount of immature neuroectodermal component (Table 5.3), or using a 2-tier

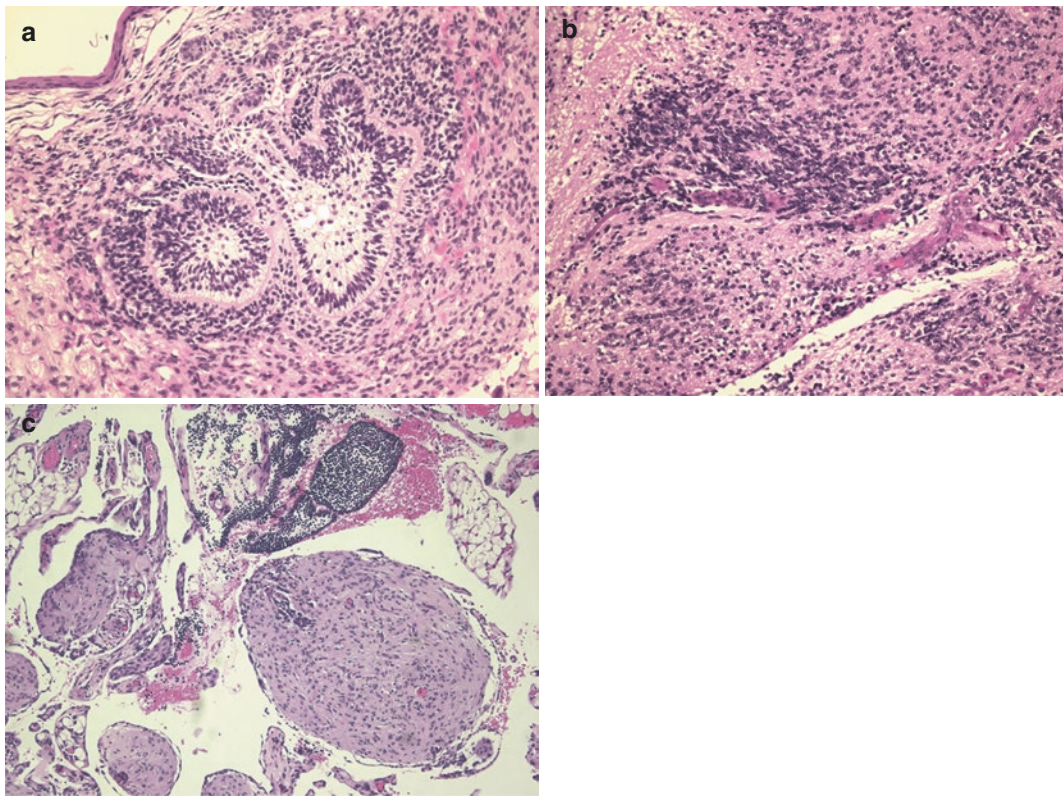

Fig. 5.17 Immature teratoma: Primitive neuroepithelium is a common and diagnostic feature of immature teratoma (**a**, **b**). There may be associated peritoneal nodules of mature glial tissue (**c**)

system into low (grade 1) and high grade (grades 2 and 3) [73, 74].

Some cases may be associated with military nodules of mature glia in the peritoneum, a condition known as gliomatosis peritonei (Fig. 5.17). These may also be present in abdominal lymph nodes. The presence of these nodules of mature tissue does not adversely affect prognosis [1].

Table 5.3 Grading of ovarian immature teratoma using a three-tiered grading system [73, 74]

Grade 1: Tumours with rare foci of immature neuroepithelial tissue that occupy <1 low-power field (40×) in any slide (low grade)
Grade 2: Tumours with similar elements, occupying 1–3 low-power fields (40×) in any slide (high grade)
Grade 3: Tumours with large amount of immature neuroepithelial tissue occupying >3 low-power fields (40×) in any slide (high grade)

Dysgerminoma

Dysgerminoma represents 1–2% of malignant ovarian tumours. About 20% of the tumours are bilateral [1].

Immunophenotype and Genetic Profile

The tumour cells express placental alkaline phosphatase (PLAP), CD117 (c-KIT) [75] (Fig. 5.18), D2-40 [76], OCT-4 [77], NANOG, and SALL4 [78]. The cells may express cytokeratin, but not EMA. *C-KIT* mutations are detected in 25–50% of cases [79].

Yolk Sac Tumour

Yolk sac tumours may present in pure form or as a component of a mixed germ cell tumour. Yolk sac tumours show a variety of architectural patterns [1] (Fig. 5.19).

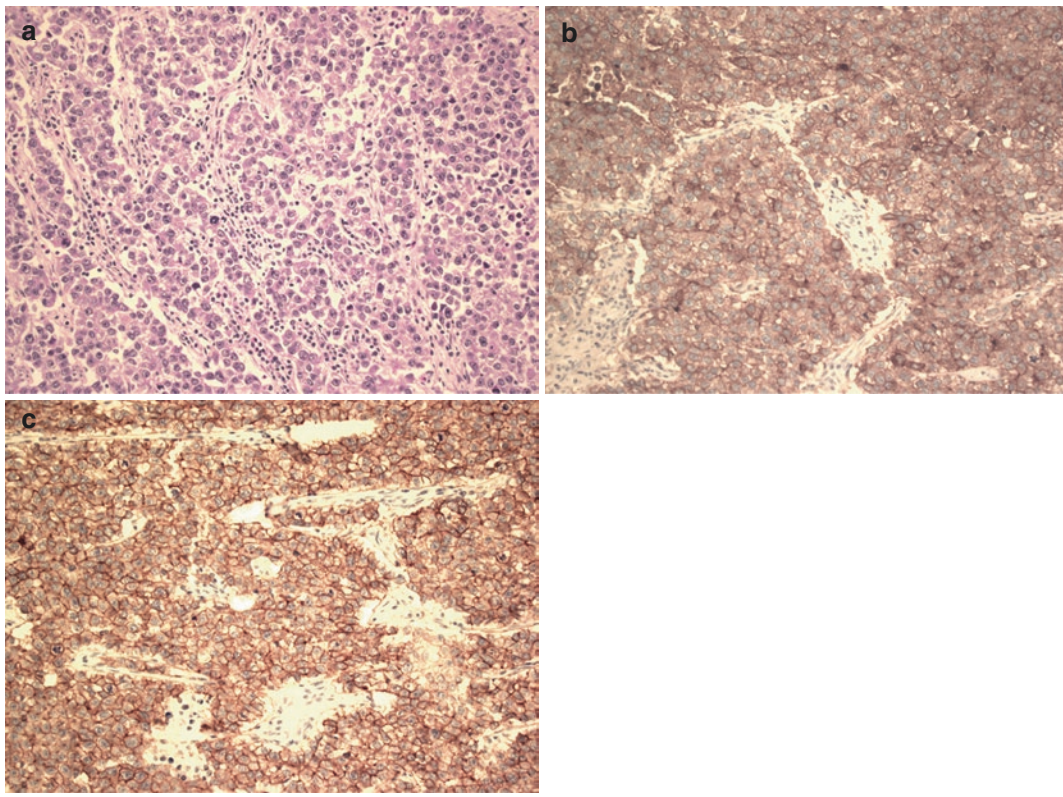

Fig. 5.18 Dysgerminoma: (**a**) Fairly uniform cells are arranged in sheets separated by septa infiltrated by lymphocytes. (**b**) The cells show expression of PLAP and (**c**) c-KIT

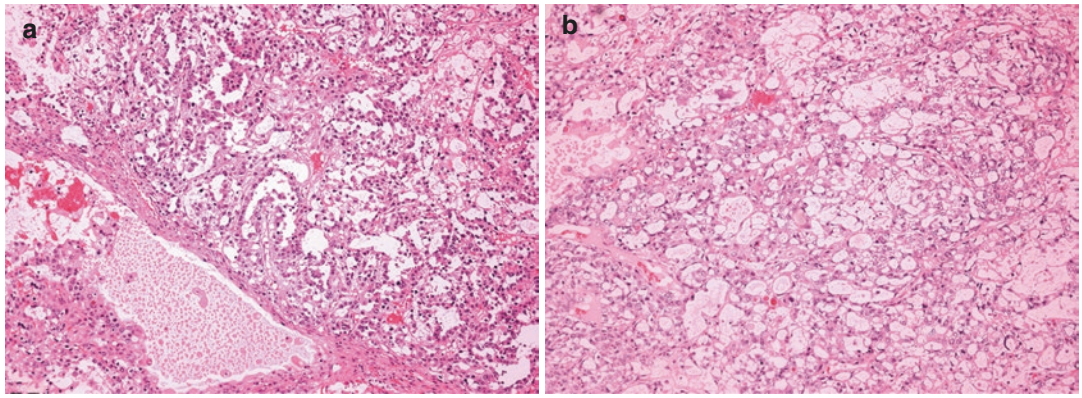

Fig. 5.19 Yolk sac tumour. The tumours show a variety of architectural patterns including the typical Schuller Duval bodies (**a**) and microcystic pattern (**b**)

Immunophenotype

The tumour cells express AFP, glypican 3 and SALL4 [78].

Embryonal Carcinoma

Embryonal carcinoma presents in pure form or as a component of a mixed germ cell tumour.

Immunophenotype

The tumour cells express CD30, OCT4, SALL4, glypican 3 and cytokeratin, but not EMA [78, 80].

Choriocarcinoma

Non-gestational choriocarcinoma accounts for <1% of ovarian malignant germ cell tumours, either pure, as a component in mixed germ cell tumours, or in association with carcinoma [1].

Tumours are composed of cytotrophoblast and syncytiotrophoblast cells that show expression of HCG, which also shows high serum levels [1].

Mixed Germ Cell Tumour

Germ cell tumours containing two or more types of germ cell components are designated mixed germ cell tumours and represent about 8% of malignant germ cell tumours. The percentage of each tumour type affects prognosis [1].

Somatic-Type Tumours Arising from a Dermoid Cyst

Neuroectodermal-Type Tumours

These tumours occur in patients ranging in age between 6 and 69 years. The tumours encompass a differentiated group (includes ependymoma, astrocytoma and oligodendroglioma), a primitive group (includes primitive neuroectodermal tumours, neuroblastoma, ependymoblastoma, medulloblastoma and medulloepithelioma) and anaplastic tumours (Glioblastoma multiforme) [81].

Somatic-Type Tumours Arising from a Dermoid Cyst

Any of the tissue elements present within a dermoid cyst/mature teratoma may undergo malignant transformation. The most common is squamous cell carcinoma. Adenocarcinoma is the second most common malignancy. Most adenocarcinomas arise in gastrointestinal and respiratory epithelium [1]. Sarcomas of different types may occur in mature teratomas [1].

Miscellaneous Tumours

Tumours of Rete Ovarii

Adenocarcinoma of the rete ovarii is a very rare tumour. The tumour shows a predominant retiform pattern with papillary areas and solid tubules [1].

Wolffian Tumour

The tumour is presumed to arise from Wolffian remnants in the adnexal region within the ovary or adjacent to it. Patients are mostly post-menopausal. Tumours are unilateral. While most of these tumours show a benign course, some cases have shown recurrence and malignant behaviour, par-

ticularly cases that originally showed cytological atypia and frequent mitoses [1].

The tumour shows a combination of cysts of variable size giving a sieve-like pattern, retiform, tubules and solid foci. The tumour cells are principally cuboidal or columnar and are usually bland and have low mitotic activity [1].

Immunophenotype

The tumour cells express cytokeratin, vimentin and usually calretinin and WT1, but variable expression of inhibin, CD10, SMA, ER, PgR, c-KIT and EMA [82].

Solid Pseudopapillary Tumour of the Ovary

The tumour shows morphology and immunoprofile identical to the pancreatic counterpart. Tumours were reported over an age range of 17–57 [83].

Small Cell Carcinoma of Hypercalcaemic Type (SSCOHT)

This is an undifferentiated neoplasm that is associated with hypercalcaemia in two thirds of cases. The mean age at presentation is 23 years. SCCOHT was thought to be epithelial, but now there is evidence that this may be a primitive germ cell neoplasm following the identification of cases of SCCOHT associated with germ cell tumours, mainly teratomas. In one study approximately 50% of the studied cases expressed the germ cell marker SALL4, providing additional support to SCCOHT being a primitive germ cell neoplasm [84].

Tumours are usually unilateral, but associated with peritoneal spread in about 50% of cases. In reported familial cases the tumours were often bilateral. The tumour shows predominantly sheets of small cells (Fig. 5.20), but a large cell component of varying proportion may be present [1].

Immunophenotype and Genetic Profile

The tumour cells express WT-1, BRCK, EMA, CD10, neuroendocrine markers and calretinin. TTF1 and inhibin are negative [85].

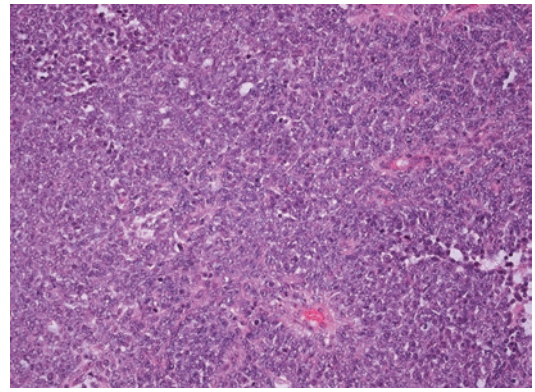

Fig. 5.20 Small cell carcinoma of hypercalcaemic type: The tumour shows a diffuse growth of predominantly small cells

There are inactivating mutations of *SMARCA4* (BRG1), encoding a member of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodelling complex, with concomitant complete loss of its encoded protein SMARCA4 (BRG1) [86]. SCCOHTs may also lack SMARCA2 (BRM), another member of the SWI/SNF complex protein expression. Loss of SMARCA4 protein alone or with loss of SMARCA2, shows high sensitivity and specificity for SCCOHT [87].

Wilms' Tumour (Nephroblastoma)

These tumours have been reported in children and adults in the third and sixth decades [88].

Other Tumours Non-specific to the Ovary

Mesothelial Tumours

Mesothelioma

Mesotheliomas can be bilateral involving the ovarian surface and parenchyma [1]. Mesothelioma may be biphasic (epithelial and sarcomatoid types) or epithelial type. The exclusively epithelial type can have papillary, tubular/glandular and solid patterns and can simulate primary epithelial tumours (Fig. 5.21). On immunostaining, mesothelioma cells usually express

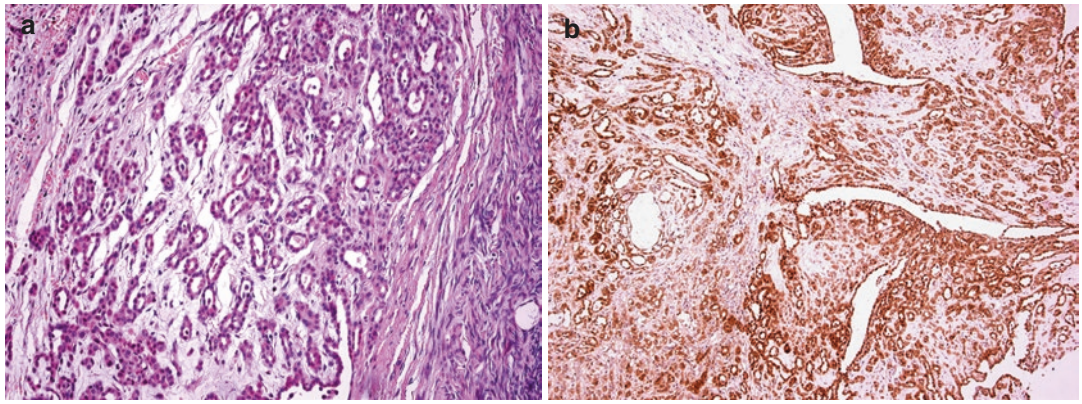

Fig. 5.21 Mesothelioma: (**a**) Epithelial mesothelioma showing glandular architecture can simulate ovarian carcinoma. (**b**) The tumour cells express calretinin

calretinin, CK5/6, WT-1, HMBE1, thrombomodulin, D2-40, and sometimes h-caldesmon, but are negative for BerEP4 and hormone receptors [89].

Soft Tissue Tumours

A variety of malignant soft tissue tumours can rarely arise in the ovary and are reported to include leiomyosarcoma, angiosarcoma, chondrosarcoma, rhabdomyosarcoma, synovial sarcoma and malignant PEComa [1, 90].

Lymphoid and Myeloid Tumours

Less than 1% of lymphomas present with ovarian involvement. The most common primary ovarian lymphoma is diffuse large B-cell type, followed by Burkitt lymphoma and follicular lymphoma, with rare cases of B and T cell lymphoblastic lymphoma. Primary ovarian Hodgkin lymphoma is extremely rare. Primary ovarian plasmacytoma and myeloid sarcoma also very rarely occur [1].

Secondary Tumours

The ovary is one of the sites in which it is not uncommon to have metastatic tumour deposits from primary extraovarian neoplasms. These are most commonly metastatic carcinomas and some of these show morphological overlap with primary ovarian tumours. In some cases, an ovarian mass represents the first manifestation of disease from a clinically occult non-ovarian primary. It is very important that the pathologist is provided by clinical information and history of the presence of an extraovarian tumour in a patient presenting with an ovarian lesion.

Pathologists have to be aware of the features that would raise the possibility of an ovarian tumour being metastatic rather than primary to do the relevant extra tests and seek the relevant clinical history to ascertain the diagnosis as the management would be very different.

In endometrioid tumours the possibility of metastasis from an endometrial primary should be excluded. An adenofibromatous background, squamous differentiation and the presence of a background of endometriosis favour primary ovarian origin. Endometrioid tumours can also show morphological overlap with other primary tumours as colonic adenocarcinoma (Fig. 5.22). Immunostaining can be helpful in making this distinction [91].

Most of the challenging problems in this context are with mucinous tumours. Metastatic mucinous tumours are most commonly from the gastrointestinal tract, but the cervix can also be a primary site of origin. Pathologists are generally aware that an extraovarian primary needs to be clinically considered and excluded in cases of mucinous carcinomas in the ovary. This should

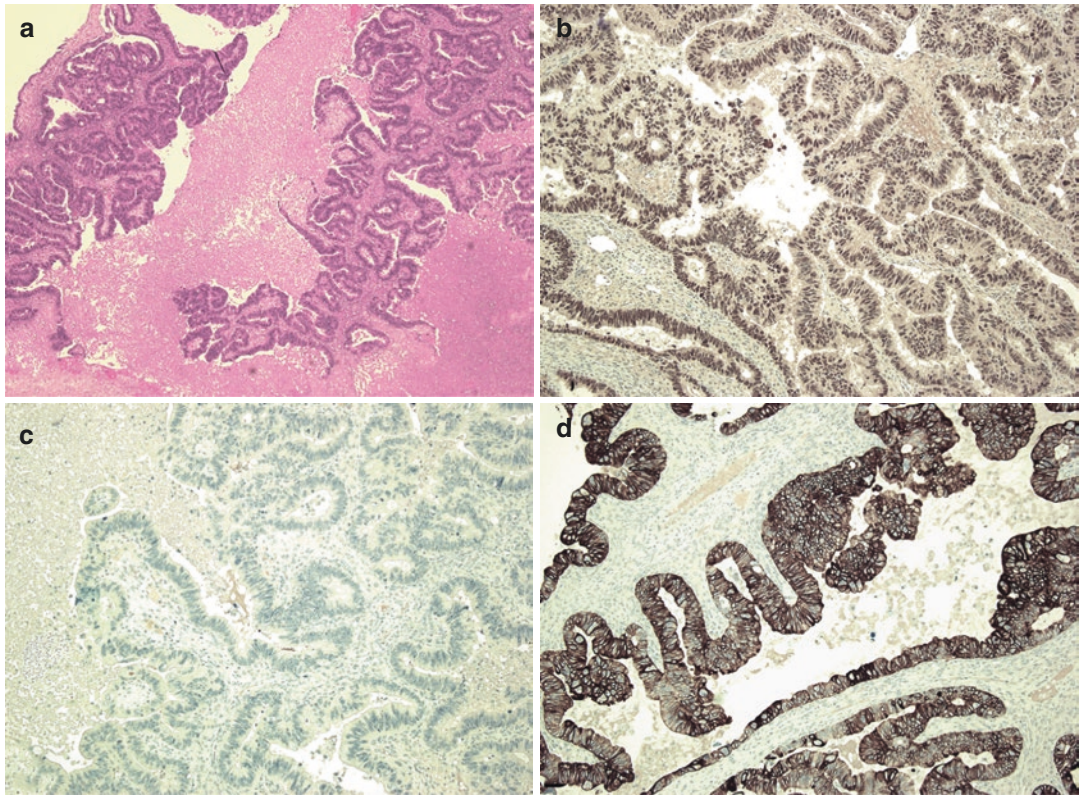

Fig. 5.22 Metastatic colorectal carcinoma. (**a**) The tumour shows the characteristic garland pattern of dirty necrosis with necrotic material and karyorrhectic debris surrounded by viable tumour tissue. (**b**) Tumour cells express CDX2. (**c**) The cells are negative for CK7, (**d**) and positive for CK20

also be the case in mucinous tumours of borderline features as some metastatic tumours may mimic a primary MBT/APMT. Gross pathological features in favour of metastasis are bilateral ovarian involvement with a nodular growth pattern on the surfaces of the ovaries [1].

Carcinomas with signet ring cells are practically indicative of metastatic carcinoma from the gastrointestinal tract (Fig. 5.23), most likely from the stomach [1]. These are bilateral in the majority of cases and are designated Krukenberg tumour [92].

On suspicion of metastatic carcinoma, immunoprofiling can be helpful in confirmation and

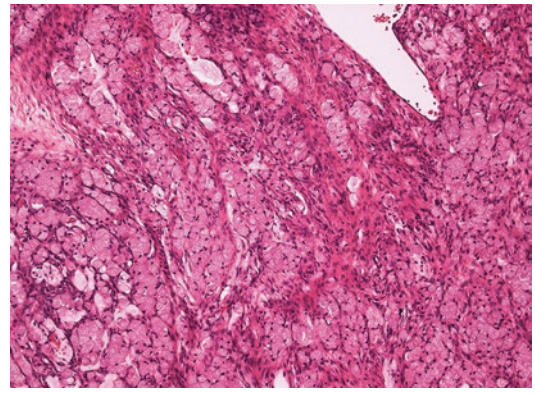

Fig. 5.23 Metastatic signet ring cell carcinoma

Table 5.4 Comparative immunoprofile of adenocarcinomas of different organs

Organ	CK7	CK20	P16	PAX8	ER	PgR	GATA 3
Colorectal and appendix carcinoma	–	+	–/focally +	–	–	–	–
Gastric carcinoma	+/–	+	+/–	–	–	–	–
Pancreaticobiliary carcinoma	+	+/–	–/+	–	–	–	–
Endocervical carcinoma	+	–/+	+ strong diffuse	+	–	–	–
Ovarian endometrioid carcinoma	+	–	+/–	+	+	+	
Ovarian mucinous carcinoma	+	+/–	+/–	+/–	–	–	–
Breast carcinoma	+	–	+/–	–	+/–	+/–	+

identification of the primary site of origin. Table 5.4 summarises the immunoprofile of tumours that commonly metastasise to the ovaries.

Synchronous Tumours of Different Histogenesis

Synchronous/bilateral ovarian tumours of different histogenesis have been reported, including synchronous HGSC and CC in right and left ovaries [93], and synchronous right ovarian endometrioid carcinoma and left ovarian clear cell carcinoma [94]. Immunohistochemistry would be helpful in ascertaining the diagnosis and identifying the different types, which is of relevance as the presence of some tumour types would affect the prognosis.

Hereditary Syndromes

Hereditary predisposition to ovarian cancer represents 15–20% of cases. Most cases are due to germline mutations in BRCA1 (17q21.31) and BRCA2 (13q13.1) genes. BRCA1 mutations confer approximately 50% lifetime risk of ovarian cancer, with earlier age of presentation (49–53 years). BRCA2 is associated with lower risk (11–37%) and older age at presentation (55–58). Mutations in other DNA repair genes of the homologous recombination group, such as *BARD1, BRIP1, PALB2, RAD51C, RAD50, MRE11A* and *NBN*, represent approximately 6% of additional germline mutations detected in ovarian cancer [95].

Lynch syndrome is characterised by germline mutations in mismatch repair (MMR) genes. Patients are at increased risk of developing different malignancies including ovarian carcinoma, most commonly of clear cell and endometrioid types [96]. dMMR is encountered in 13.8% of ovarian endometrioid and 2.4% of clear cell carcinomas [97].

Prognostic Factors in Ovarian Cancer

There are several prognostic factors that influence the outcome of ovarian tumours, which include tumour type, grade, stage, size, mitotic activity, *BRCA* and MMR gene status and patient age. Tumour stage is the single most important prognostic factor in most types of ovarian cancer, with tumours presenting at an advanced stage generally having worse prognosis [1].

The first-line treatment for ovarian cancer in most cases is debulking surgery followed by chemotherapy. In advanced-stage disease the amount of residual tumour after debulking is the most important prognostic factor. Current practice aims at optimal debulking by extensive cytoreductive surgery leaving no residual macroscopic disease [98]. In patients with residual macroscopic disease there is prognostic stratification based on the size of residual tumour tissue (i.e. <1 cm, 1–2 cm, >2 cm) [99].

Frozen Sections in Ovarian Cancer Management

Many ovarian tumours are heterogeneous, and thereby thorough sampling is essential for mak-

ing the correct diagnosis. This should be by taking at least one section per centimetre of the largest tumour dimension. Also with the morphological overlap between different types of primary ovarian tumours and with some extraovarian tumours, there are many situations where ancillary techniques, principally immunophenotyping, are required to ascertain the diagnosis. Both thorough sampling and immunophenotyping are not feasible during intraoperative frozen section assessment of ovarian masses. These represent serious limitations [16, 17], and both the surgeon and the pathologist should be aware of these limitations.

The concordance between frozen section diagnosis and final diagnosis in ovarian tumours overall is reported to be 80–87% [36, 37]. Frozen sections for ovarian tumours are reliable in making the distinction between benign and malignant tumours, but not as much in the distinction between borderline and malignant tumours. The surgeon should be well aware that a diagnosis of borderline tumour on frozen section may change in the final diagnosis. On thorough sampling areas of invasion are identified, resulting in a final diagnosis of carcinoma. This is particularly challenging with mucinous tumours, where concordance between frozen section diagnosis and final diagnosis is reported to be 55–66% [38, 39].

Molecular Inter- and Intratumoral Heterogeneity in Ovarian Cancer

Molecular profiling has revealed intertumour/interpatient heterogeneity in tumours of the same histological subtype in many tumours including ovarian carcinoma. Gene expression profiling studies comparing epithelial ovarian cancer and normal ovarian tissue using RNA microarray analysis showed several distinct molecular subtypes of high-grade ovarian cancer, including immunoreactive, differentiated, proliferative and mesenchymal. These different molecular subtypes correlate with clinical outcome [100–102].

Moreover, molecular profiling has also shown intratumour/intrapatient heterogeneity, where tumours of the same histological subtype from the same patient harvested from different locations, e.g. primary and metastatic, may show differences in molecular profile [103]. HGSC and tumours classified as proliferative subtype also showed significant heterogeneity across multiple anatomic sites [104]. This represents spatial intratumour heterogeneity. This is most likely due to subclonal tumour evolution [105, 106]. Heterogeneity can also be detected in tumours harvested at different time points from the same patient, e.g. at diagnosis and relapse. This is known as temporal intratumour heterogeneity. This is most likely due to selection stress of specific therapeutic regimens [107].

Next-generation/high-throughput sequencing of ovarian carcinomas of different histological subtypes demonstrated the significant genomic variation and the intrinsic diversity of subclonal populations between different regions of the same tumour and/or between synchronous primary and metastatic tumours, in untreated patients and the evolutionary response to treatment [105–109].

Evolutionary models of ovarian cancer predict that, following treatment, resistance emerges either due to outgrowth of an intrinsically resistant sub-clone, or evolves in residual disease under the selective pressure of treatment. These facts need to be considered in clinical practice when a tumour sample is requested for genetic testing or molecular profiling. These facts should also be considered on selection of tissue for translational studies in the context of clinical trials. There may be a case in both scenarios to include tumour tissue from the primary tumour and different metastatic foci, and at different time points in the course of disease. This is to achieve better representation of the potential diversity of molecular profile in the same patient. It may also be a more productive option to choose assays for sequencing tumour cell free circulating DNA from the blood, which may include better representation of the molecular profile of tumour tissue from different foci in the patient, and at different time points in the disease course. This may overcome the limitations of taking samples from one or few tumour foci [110].

Molecular characterisation of ovarian samples from different sites and at different time points is essential for uncovering evolutionary patterns [111]. With tumour evolution over the course of treatment the existence of multiclonal disease and tumour subclonal evolution may compromise the effectiveness of a chosen targeted therapy if emerging subclones with different genomic alterations develop [112]. Selective pressure imposed by treatment may modify the relative proportions of tumour subclones leading to resistance to a chosen targeted therapy [113]. So it may be necessary to revise the tumour molecular profile using serial biomarkers over the course of therapy and to include altered combinations of targeted agents in management of recurrent or chemoresistant tumours depending on the findings. An alternate approach would be to focus therapy at identified targets known to be less affected by clonal evolution in ovarian cancer.

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6 Current Management of Patients with Early-Stage Ovarian Cancer

Samir A. Farghaly

Introduction

Worldwide, the annual number of new patients who have ovarian cancer are about 300,000 and about 200,000 dies of this disease. The American Cancer Society estimates that in 2022, about 19,800 new cases of ovarian cancer will be diagnosed and 12,810 women will die of ovarian cancer in the USA [1]. The mortality rates for ovarian cancer have not improved in 40 years. The other cancers have shown a marked reduction in mortality, due to the availability of early detection tests and improved treatments. Early-stage ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] stages I to IIA) is approximately 30% of patients with ovarian cancer; the disease is restricted to the true pelvis when it is diagnosed. In these early stages, there is a reasonable chance of cure. The standard primary therapy for epithelial ovarian cancer (EOC) involves staged procedures with pelvic and para-aortic lymphadenectomy, followed by adjuvant chemotherapy consisting of carboplatin and paclitaxel. In the literature, lymph node metastasis has been detected in 6–18% and 23–31% of patients with pT1 and pT2, respectively. Systematic resection and pathological examination of retroperitoneal lymph nodes have clinical significance for accurate assessment of staging and prognosis. Systematic lymphadenectomy is not always performed on patients during initial surgery for early-stage disease. This procedure may involve para-aortic lesions, and therefore it may increase surgical morbidity, such as increased operation time, increased blood loss, lymph cyst formation, and edema in the leg. Moreover, the therapeutic value of systematic lymphadenectomy remains controversial, especially in early disease. Following surgery, patients with early ovarian cancer—FIGO stages I to IIA, except stage IA, grade 1—benefit from 3 to 6 cycles of platinum-based chemotherapy, in terms of both overall survival (increase in 5-year survival rate from 74% to 82%; $P < 0.008$) and disease-free survival (increase from 65% to 76%; $P < 0.001$). The protocols of most of the available studies established six cycles of platinum-based chemotherapy. It is also unclear whether combined chemotherapy with carboplatin and paclitaxel is superior to monotherapy with carboplatin (area under the curve [AUC] 5) in early stages. Fertility-sparing surgery (FSS) for women of childbearing age with early-stage ovarian cancer had been discussed over the past 20 years. Preservation of the reproductive tract organs in young women who want to conceive is an understood need. Hysterectomy and bilateral salpingo-oophorectomy have been considered part of the

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initial surgical approach to ovarian cancer, regardless of the stage of the disease. Preservation of the adnexa and uterus is recommended in patients with non-epithelial tumors and epithelial borderline ovarian cancer, in those patients.

Screening for Ovarian Cancer

Routine EOC screening of the general population has not been recommended by any professional society (Table 6.1) [2]. Women who are at high risk for EOC based on *BRCA* mutations or who have a family history of breast or ovarian cancer require a different "screening" approach. There is no evidence that measurement of cancer antigen 125 (CA-125) and transvaginal ultrasonography every 6 months provides a survival benefit, but the National Comprehensive Cancer Network does recommend this strategy for high-risk patients.

Table 6.1 Recommendations for ovarian cancer screening

Professional group	Recommendation
US Preventive Services Task Force	Does not recommend routine screening, concluding that "the potential harms outweigh the potential benefits"
American Cancer Society	Does not recommend routine screening; possible screening for women with a family history of ovarian cancer, although "it is not known how helpful" the tests will be in improving survival
American College of Obstetricians and Gynecologists	Does not recommend routine screening; suggests evaluation of signs and symptoms of ovarian cancer (e.g., pelvic mass, pelvic or abdominal pain, urinary frequency or urgency, increased abdominal size or bloating, or difficulty eating or feeling of fullness)
National Comprehensive Cancer Network	Does not recommend routine screening; recommends screening of high-risk women (i.e., those with either a family history of ovarian or breast cancer or a documented BRCA mutation) with transvaginal ultrasonography and CA-125 measurements every 6 month, starting at the age of 35 years or 5–10 years before the earliest age at diagnosis of ovarian cancer in relatives; recommends strong consideration of risk-reducing prophylactic salpingo-oophorectomy at the completion of childbearing in women with a BRCA mutation

Detection of Ovarian Cancer

Early detection is important to the successful treatment of ovarian cancer. It is estimated that 15% of ovarian cancer is localized to the ovary, 17% is regional, and 62% occurs as distant disease. With tumor spread into the pelvis and upper abdomen, patients often complain of pelvic or abdominal pain or pressure, abdominal swelling, dyspepsia, and early satiety. As the disease progresses, patients note weight loss and increasing pain, and they can develop bowel or urinary tract disorders. Many patients will note a several-month history of vague abdominal discomfort which does not represent marked underlying pathology. A study from the University of Washington [2] noted that ovarian cancer patients' symptoms occurred 20–30 times per month as compared with two to three times for the clinic population. The severity of symptoms was also significantly higher in cancer patients and of more recent onset. The authors also noted that 44% of women with ovarian cancer had a triad of bloating, increased abdominal size, and urinary urgency, as compared with only 8% of clinic controls. They also observed that the important distinction between cases and controls seems to be in the frequency, severity, and duration of the symptoms. Several researchers in the USA and in other countries have found similar results. The same group [2] established a positive symptom index (any of those six symptoms that occurred more than 12 times per month in less than 1 year) and had a sensitivity of 56.7% for early-stage disease and 79.5% for advanced disease. More specificity was 90% for patients older than 50 years and 86.7% for patients younger than 50 years. Ovarian cancer should be included in the differ-

ential diagnosis and testing for the disease should be included in the workup if these symptoms are present.

Diagnosis and Staging

Palpation of an adnexal mass during a pelvic examination is considered a diagnostic evaluation for ovarian cancer. Ultrasound examination is a useful noninvasive diagnostic test. Between 13% and 21% of women undergoing surgery for an adnexal mass will have an ovarian malignancy. Surgical option for management depends on several factors: age, menopausal status, family history, size, and complexity of the mass, associated symptoms, CA-125, unilaterality versus bilaterality, and characteristics on ultrasound. Management may include observation with repeat examination, radiographic imaging, and laparoscopy or laparotomy. The preoperative evaluation of a woman with suspected ovarian cancer includes measurement of CA-125, which is elevated in greater than 80% of patients with advanced EOC. Sensitivity is lower for stage I disease (50%). CA-125 is highest in serous and lowest in mucinous EOC. In addition, CA-125 is not specific for EOC and found to be elevated in endometriosis, pelvic inflammatory disease, endometrial, and pancreatic cancers. Surgery is necessary for the diagnosis, staging, and treatment of EOC. The bulk of the ovarian tumor could be found on peritoneal surfaces. This peritoneal disease results from shedding of ovarian tumor cells into the peritoneal cavity, circulation of these cells throughout the abdomen and pelvis, and its implantation onto the peritoneal surfaces. This is dependent upon the development of sufficient neo vasculature to support cell survival and tumor growth. Optimal surgical cytoreduction before the administration of chemotherapy is a common practice in management of ovarian cancer. Optimal cytoreduction could be achieved by reducing the largest residual tumor nodule that remains after debulking surgery to 0.5 cm or less and greater than 1 cm for suboptimal debulking. The goals of initial surgery in ovarian cancer are to diagnose and stage disease and to provide therapeutic benefit with cytoreduction. Accurate histologic diagnosis and staging are required before systemic treatment is established.

Ovarian malignancies are surgically staged according to the FIGO staging system (Table 6.2). Staging laparotomy includes inspection of the peritoneal cavity, including the parabolic gutters, pelvis, and domes of the diaphragm; total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO); liver palpation and biopsy (if indicated); lymph node sampling; omentectomy; and peritoneal washings. The extent of surgical cytoreduction should be fully documented.

Table 6.2 FIGO staging and prognosis of ovarian cancer

FIGO stage	Characteristics	Stage distribution (%)	10-year survival rate (%)
I	Disease confined to the ovaries		
IA	One ovary, capsule intact, no ascites		
IB	Both ovaries, capsule intact, no ascites	20	73
IC	Stage IA or IB plus ascites or washings, capsule ruptures, tumor on ovarian surface		
II	Disease confined to the pelvis	5	45
III	Disease confined to the abdominal cavity, including surface of the liver; pelvic, inguinal, or para-aortic lymph nodes; omentum or bowel	58	21
IIIA	Negative lymph nodes, plus microscopic seeding of peritoneal surface		
IIIB	Negative lymph nodes, peritoneal implants <2		
IIIC	Positive lymph nodes and/or abdominal implants >2 cm		
IV	Spread to the liver parenchyma, lung, pleura, or other extra-abdominal sites	17	<5

Treatment Options for Early-Stage Ovarian Cancer

Treatment of early-stage ovarian cancer is dependent on the stage of the disease and extent of surgical cytoreduction. Approximately 25% of women with ovarian cancer have disease confined to one or both ovaries (FIGO stage I) or to the pelvis (FIGO stage II). Treatment options for stage 1 and stage 2 ovarian epithelial cancers may include:

1. Surgery: Total hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and surgical staging of the lymph nodes and other tissues in the pelvis and abdomen. Selected premenopausal women in stage I with the lowest-grade tumors in one ovary may be treated salpingo-oophorectomy to preserve fertility.
2. Chemotherapy: Patients with stage IA or B disease, grade 1 (or sometimes grade 2) do not need further therapy after surgery. The higher risk patients (stage IC, stage I/grade 3) are treated with platinum-based chemotherapy to reduce their risk of recurrence.
3. Clinical trials with chemotherapy, radiation therapy, or targeted molecular therapy.

Data from the International Collaborative Ovarian Neoplasm trial 1 (ICON1) and Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) have compared a platinum-containing adjuvant chemotherapy regimen with observation after surgery. They reported over 900 patients with over 4 years of median follow-up; the hazard ratio for recurrence-free survival is 0.64 (95% confidence interval [95% CI], 0.50–0.82; $P = 0.001$) in favor of adjuvant chemotherapy, and the hazard ratio for overall survival (OS) is 0.67 (95% CI, 0.50–0.90; $P = 0.008$) in favor of adjuvant chemotherapy. A subgroup analysis suggested that the benefits of chemotherapy were in non-optimally staged patients, establishing the clinical importance of surgical staging in early-stage ovarian cancer [3].

The Gynecologic Oncology Group (GOG) studies have shown that patients with stage IA or IB disease (limited to one or both ovaries with no ascites and negative peritoneal washings) and with well- or moderately differentiated histology have a 5-year disease-free survival (DFS) rate of 91% and a 5-year OS rate of 94% with surgery alone. This subset of patients is generally not treated with adjuvant therapy. However, it is critical that these patients are fully staged. It has been shown that one-third of apparent early-stage patients will have more advanced-stage disease when full staging is done. Also, it was observed that chemotherapy improves progression-free survival (PFS) for patients with stage IA or IB poorly differentiated disease, stage IC, or stage II disease, and these patients should receive adjuvant chemotherapy [4].

GOG in phase 3 study of patients with early-stage ovarian cancer (GOG protocol 157) compared 3 versus 6 cycles of paclitaxel and carboplatin. The 5-year probability of recurrence was 20.1% for six cycles versus 25.4% for three cycles, a 24% reduction in recurrence risk. But the OS was similar for both regimens and the decrease in recurrence was not statistically significant. In addition, analysis of patients from this trial showed that those with high-grade serous histology had a significantly lower risk of recurrence with six compared with three cycles. Based on these findings, a minimum of three cycles of paclitaxel and carboplatin for patients with early-stage disease who are treated with adjuvant chemotherapy and six cycles for those with high-grade serous cancers is recommended. Four phase III trials (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26, and VELIA/GOG-3005) demonstrated remarkable improvements in progression-free survival with PARP inhibitor therapy (Olaparib, niraparib, or veliparib) for newly diagnosed ovarian cancer. Differences in trial design (treatment and/or maintenance setting; single agent or combination; bevacizumab or no bevacizumab), patient selection (surgical outcome, biomarker eligibility, prognosis), and primary analysis population (intention-to-treat, *BRCA* mutated or homologous recombination deficiency positive) affect the conclusions that can be drawn from these trials [5].

Borderline Ovarian Tumors

Borderline tumors of the ovary are characterized by serous, mucinous, or endometrioid histology type, and lack of stromal invasion. The median age at diagnosis is 45, with greater than 34% of patients being less than 40 years of age. These tumors are managed with TAH and BSO. Twenty-five percent borderline tumors are reclassified as invasive on final review of the histopathology. The surgical management could be limited to unilateral salpingo-oophorectomy with complete surgical staging if patients desire fertility preservation. If the patient has bilateral ovarian tumor, and complete resection can be achieved, ovarian cystectomy is reasonable treatment option.

Complete surgical staging, including exploration of the entire abdominal cavity, peritoneal washings, infrasonic omentectomy, and multiple peritoneal biopsies, is important, as 20% of patients may have noninvasive as well as invasive metastatic implants (Table 6.3).

Malignant germ cell tumors account for 5% of ovarian malignancies, and the median age of affected patients is 19 years. Generally, most of those patients have stage I disease. The management of those patients includes (1) examination and palpation of the ileac and aortocaval nodes with biopsy of abnormal areas intact removal of the tumor, (2) examination and palpation of the omentum with removal of suspicious areas sparing of the fallopian tube if not adherent to the tumor, (3) collection of cytologic washings or harvesting of ascites fluid, and (4) removal of the tumor, (5) sparing the tube and the ovary. It was shown that 90–95% of malignant germ cell tumors of the ovary are curable with the use of postoperative systemic chemotherapy [16] (Table 6.4).

Table 6.3 Oncologic and obstetric outcomes in patients with borderline ovarian tumors undergoing fertility-preserving surgery

Author	Patients	Pregnancies	Live births	Recurrences	Deaths
Zanetta et al. [6]	189	44	N/A	35	0
Lim-Tan et al. [7]	35	8	6	6	0
Morice et al. [8]	44	17	10	9	0
Boran et al. [9]	62	13	10	4	0
Fauvet et al. [10]	162	30	18	27	0
Donnez et al. [11]	16	12	12	3	0
Seracchiolo et al. [12]	19	6	6	1	0
Camatte et al. [13]	17	8	8	9	0
Morris et al. [14]	43	25	16	14	1
Gotlieb et al. [15]	39	22	21	3	0
Total	626	185 (50%)	107 (58%)	111 (18%)	1 (0.2%)

Table 6.4 The obstetric outcomes in patients with malignant germ cell tumors treated conservatively

Author	Patients	Pregnancies	Live births	Recurrences	Deaths
Kanazawa et al. [17]	21	11	9	1	1
Gershenson et al. [18]	71	37	30	10	4
Zanetta et al. [19]	138	41	28	16	3
Perrin et al. [20]	45	8	7	4	2
Tangir et al. [21]	64	47	38	5	3

Biopsy of a normal-appearing contralateral ovary is not recommended as this can result in tissue pelvic adhesion and possible mechanical infertility.

Platinum-Based Chemotherapy for Early-Stage Ovarian Cancer

Adjuvant platinum-based chemotherapy has been established as the optimal of care for women with high-risk early-stage EOC [22]. Gynecologic Cancer Intergroup (GCIG) consensus statement [23] and a Cochrane meta-analysis [22] advocated the use of platinum-based chemotherapy. National Comprehensive Cancer Network (NCCN) [24] guidelines recommend three to six cycles of a carboplatin/taxane combination. The GOG-157 trial [25] and other case series [26, 27] show that carboplatin-paclitaxel (CP) is frequently used as the standard of care for early epithelial ovarian cancer. This is due to concerns about suboptimal surgical staging. The GOG definition of comprehensive surgical staging includes total hysterectomy, bilateral salpingo-oophorectomy, resection of all gross disease, aspiration of free peritoneal fluid, peritoneal washings for cytology, infracolic omentectomy, selective bilateral pelvic and aortic node dissections, peritoneal biopsies from four pelvic locations and bilateral paracolic areas, and right diaphragm cytology or biopsy. The ACTION trial [28] found that only 151 (34%) women were optimally staged. In a study of series of 100 women with apparent early-stage EOC, they underwent a second, comprehensive surgical staging procedure at which 23 were found to have stage III disease [16]. It has been shown that comprehensive surgical staging is critical in all women with early-stage ovarian cancer [29]. It may avoid the need for chemotherapy for some, as subset analysis of the 151 (34%) optimally staged women in the ACTION trial [28] showed no benefit of adjuvant chemotherapy. Most women labeled as having early-stage EOC will have undergone less than comprehensive surgery. Some of these will have occult stage III disease.

It is known that the risk of paclitaxel-related neuropathy increases with cumulative dose [30], and if paclitaxel is used in the initial regimen, the ability to administer sufficient doses to women who relapse will be reduced. This additional toxicity could be justified if there was an overall survival benefit. The ICON three trial [31] compared carboplatin with carboplatin plus paclitaxel. In this trial, 20% of the population had stage I or II disease. There was no benefit in survival either in the trial as a whole or in the 413 women with early-stage disease.

Published studies (Table 6.5) showed 5-year relapse-free survival (RFS) and 5-year overall survival (OS) in patients with early-stage ovarian cancer treated with systemic chemotherapy following comprehensive surgical staging.

The role of chemotherapy in early-stage epithelial ovarian cancer and the completeness of surgical staging are interlinked. The improved survival of women with suboptimal staged, early-stage ovarian cancer noted in ACTION 2003 is likely to be due to chemotherapy-related treatment of occult disease. The National Institute for Health and Care Excellence (NICE) guidelines (NCCC OC 2011) do not recommend systematic lymphadenectomy but advocate lymph node assessment by palpation and sampling of any suspiciously enlarged nodes. It argues that the morbidity of a comprehensive para-aortic lymphadenectomy cannot be justified. In addition, it has been shown that platinum-taxane combination chemotherapy and platinum-based chemotherapy without taxane were effective in prolonging survival with a significant dose–response relationship among patients with late-stage ovarian cancer. Among those with early-stage tumors, platinum-taxane combination appeared more effective than other chemotherapy regimens [29].

Table 6.5 Published studies of adjuvant chemotherapy on early-stage ovarian cancer

Study	Study type	Stage	Systemic therapy	Women	5-year RFS	5-year OS
Young et al. [32]	Prospective/ randomized	Stage IG3/stage II	Melphalan/32P	68/73	80%/80%	81%/78%
Bolis et al. [33]	Prospective/ randomized	Stage IC	Cisplatin/32P	82/79	85%/65%	81%/79%
Trope et al. [34]	Prospective/ randomized	Stage I	Carboplatin/ observation	81/81	70%/71%	86%/85%
Trimbos et al. [28]	Prospective/ randomized	IA–IIA except IA/B G1	Platinum/ observation	224/224	76%**/68%	85%/78%
ICON 1 [3]	Prospective/ randomized	Uncertain benefit immediate chemotherapy	Platinum/ observation	241/236	73%***/62%	79%*/70%
Bell [35]	Prospective/ randomized	I and II except IA/B G1/2	CP × 6/CP × 3	225/232	80%/75%	83%/81%
Bamias et al. [26]	Retrospective/ nonrandomized	I–IIB except IA/b G1	CP × 4	69	79%	87%
Shimada et al. [27]	Retrospective/ nonrandomized	I–II	CAP × 3 or CP × 3	69/31		92% (total group)
Platinum-based adjuvant therapy for early-stage EOC; single or combination chemotherapy (Adams [16])	Retrospective/ nonrandomized	IA–IIC	CP × 6/C × 6	60/35	57%/54%	73%/62%
Adams [16] (Subgroup PS0/1 stage 1)	Retrospective/ nonrandomized	IA–IC	CP × 6/C × 6	33/20	60%/80%	60%/80%

CAP cisplatin 50 mg/m^2, doxorubicin 40 mg/m^2, and cyclophosphamide 400 mg/m^2
*P = 0.03, **P = 0.02, ***P = 0.01

Minimally Invasive Surgery for Patients with Early-Stage Ovarian Cancer

The major deterrents to the general acceptance of laparoscopic staging of EOC have been:

1. Ovarian cancer represents a major surgical challenge, as it entails more extensive surgery than other gynecological cancers.
2. Comprehensive surgical staging is of undoubtful importance, as subsequent treatment plans and prognosis will be determined by the stage of disease.
3. The common and earliest mode of dissemination of ovarian cancer is by exfoliation of cells into the peritoneal cavity.
4. Last, ovarian neoplasms are often cystic masses and thus are prone to intraoperative rupture.

The real possibility of inadequate staging, port-site recurrence, and intraperitoneal spillage has been counted against the use of minimally invasive surgery for surgical treatment of ovarian cancer.

Laparoscopic Surgery for Ovarian Cancer

Results of published studies addressing laparoscopic staging of EOC are listed in Table 6.6.

The search for clear evidence-based data supportive of treatment decisions in EOC remains unclear. Previous trials, involving open surgery for the staging process of EOC, have shown inconsistencies in surgical staging, with a low rate of completely staged patients.

Childers et al. noted a mean operating time of 149 min in patients who did not undergo a hysterectomy during their laparoscopic staging and a mean operating time of 196 min in patients who did undergo a hysterectomy [38]. It has been shown that total hysterectomy in a laparoscopic staging procedure is not justifiable [49, 50]. In women who wish to preserve fertility, it has been reported that leaving the uterus and the remaining ovary seems to be safe [51]. Eltabbakh et al., in a study, performed laparoscopic-assisted vaginal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node sampling in patients staged for endometrial cancer. They reported reduction in operating time and a significant increase in the amount of pelvic lymph nodes harvested [52].

Many gynecologic oncologists are reluctant to adopt laparoscopic staging of ovarian cancer. This is based on doubts about the number of lymph nodes obtained, possible risk of port-site metastases, lack of tactile sensation, and risk of intraoperative mass rupture [39, 41–44, 53, 54].

Nagarsheth et al. demonstrated that the risk of port-site metastases (ranging from 0% to 2.3%) is comparable to the incidence of implantation metastases observed after conventional laparotomy [55, 56]. The risk seems to be higher in patients with recurrent ovarian cancer or primary peritoneal malignancies in the presence of ascites [54, 57].

Intraoperative mass rupture laparoscopic staging procedure of early-stage ovarian cancer is thought to be a risk [58]. Upstaging of the tumor (having a higher stage after secondary staging procedure then presumed after the initial operation) may create the need for adjuvant chemotherapy in patients with early-stage disease [43].

A multivariate analysis reported that accidental capsular rupture did not affect the prognosis in stage I and II ovarian cancer [56].

Vergote et al. reported that tumor rupture during surgery has a negative effect on prognosis [59]. It has been shown that the incidence of iatrogenic rupture of ovarian cancer cysts is similar in the laparoscopy and laparotomy groups [37, 44].

The rate of upstaging reported ranged between 0% [36] and 41.7% [53]. The upstaging rates in laparotomic staging were reported to be ranging from 21.2% [43] to 47% [39].

The complication rate for the laparoscopic staging procedure in early-stage ovarian cancer ranged from 4.2% [53] to 37.5% [60], and the complication rate in laparoscopy is like with laparotomy [41, 42]. It has been noted that laparoscopic-assisted ovarian tumorectomy is a feasible surgical procedure in patients with early-stage ovarian cancer [61, 62].

Postoperative hospital stays for laparoscopic staging ranges from 2 to 10.6 days [53, 60]. Jung

Table 6.6 Studies on laparoscopic surgical staging of early-stage ovarian cancer

Study (*n*)	Time in OR (min)	EBL (mL)	Complications	Conversion	Hospital stays (day)	PLN (*n*)	PALN (*n*)	Upstaging (%)	Follow-up (month)	DFS (%)	Overall survival (%)
Querleu and Leblanc [10, 36]	227	<30	0	0	2.8	–	8.6	11.1	NA	NA	NA
Pomel et al. [11, 37]	313	NA	1 hemoperitoneum, 1 pulmonary embolus	0	4.7	7.5	8.5	10	NA	100	100
Childers et al. [20, 38]	149/196	NA	0	0	1.6	–	–	35.7	NA	NA	NA
Tozzi et al. [22, 39]	176	NA	1 chylous ascites, 1 hematoma, 2 lymphocysts	0	7	19.4	19.6	20.8	46.4 (2–72)	91.6	100
Leblanc et al. [40, 41]	238	NA	1 hematoma, 2 lymphocysts	0	3.1	14	20	19	54 (8–116)	90.5	97.6
Chi et al. [16, 41]	321	235	0	0	3.1	12.3	6.7	10	NA	NA	NA
Ghezzi et al. [17, 42]	377		1 hematoma, 1 lymphedema	0	3	25.2	6.5	27.6	16 (4–33)	100	100
Park et al. [19, 43]	321	231	1 ureter injury, 1 vein injury	0	9.4	13.7	8.9	5.9	17 (5–61)	88.2	94.1
Park et al. [21, 44]	220	240	1 great vessel injury	5.3%	8.9	27.2	6.6	21.1	17 (2–40)	100	100
Colomer et al. [45]	223	NA	1 vein injury (conversion)	5%	3	18	11.3	20	24.7 (1–61)	95	100
Nezhat et al. [35, 46]	229	195	2 lymphocyst	0	2.4	14.8	12.2	19.4	55.9	83.3	100
Lee et al. [26, 47]	228	230	2 umbilical hernias	3.7%	6.4	23.5	9.9	3.8	12 (1–42)	100	100
Schreuder et al. [25, 48]	235	100	2 hemorrhage, 2 port-site hematomas	0	4	8	6	32	43 ± 31.5	92	92

et al. found a mean postoperative stay of 10.6 days. The postoperative stay in the laparotomy control groups ranges from 5.8 to 14.5 days [41, 44].

Port-site metastasis following laparoscopic surgery is well documented. It is noteworthy that if the following protective measures are applied, it will decrease undoubtedly the risk of the development of port-site metastases: trocar fixation, prevention of insufflation gas leaks, rinsing of instruments with 1% povidone-iodine solution, Mini laparotomy protection, rinsing off trocars before removal, closure of all abdominal layers including peritoneum, and rinsing of all wounds with 1% povidone-iodine solution. The issue of insufflation gas, which is used during laparoscopic surgery, is an important one. It has been shown that the use of helium as a laparoscopic insufflation agent for cancer surgery results in less tumor implantation and growth at port sites. Helium significantly slows down cell growth and has a minimal effect on the reduction of pH. These two factors are important in the development of port-site malignancy recurrence [63].

Robotic Surgery for Ovarian Cancer

There are several limitations to laparoscopic-assisted surgery. First, the learning curve is long; second, the hand movements are counterintuitive; third, the long instruments working through a fixed entry point cause small movement.

The da Vinci robotic platform XI (Fig. 6.1) is ideal for robot-assisted laparoscopic surgery in ovarian cancer patients. It consists of three components: the surgeon's console, which directs the movements of the robotic arms, the vision system, and the patient-side cart, which in the latest system has four arms. After placement of port sites and docking the patient-side cart, the surgeon sits at the console and can view the pelvis through a three-dimensional vision system in high definition.

Furthermore, the camera system is stabilized by the robotic platform and easily controlled by the surgeon through foot pedals and arm movements. At the console, the surgeon controls the robotic arms, and the Endo Wrist instruments with natural hand and wrist motions that mimic movements performed in open surgery.

Fig. 6.1 The da Vinci XI Surgical System

There are only a few publications that relate to robotic surgery for ovarian cancer patients. In a case analysis of robotic approach for epithelial ovarian cancer [64], 25 patients that underwent robotic surgical treatment were compared with those treated by laparoscopy and laparotomy. Complete debulking was achieved in 84% of patients in the robotic group, 93% in the laparoscopy group, and 56% in the laparotomy group ($P < 0.001$). The authors noted that optimal debulking is more important than the type of surgical method, as there was no difference in the overall and progression-free survival for robotic and laparotomy patients. To, thoroughly, explore all four quadrants of the abdomen, Magrina et al. [64] have suggested the rotation of operative table and redocking the robot at the patient's head. Also, the authors noted that it was easier to resect paraaortic lymph nodes to higher levels and upper abdominal metastases. Also, the reverse-docking

position was useful when the transverse colon needed mobilization for bowel resection (Fig. 6.1).

Fertility-Sparing Surgery (FSS) in Young Women with Early-Stage Ovarian Cancer

Fertility-sparing surgery for ovarian neoplasms has been used in borderline tumors of the ovary, early-stage malignant ovarian germ cell tumors, granulosa cell tumors, Sertoli-Leydig cell tumors, and ovarian dysgerminomas, with satisfactory fertility and oncological outcomes. The acceptable standard is to implement adequate operative staging to reveal occult advanced disease with acceptable therapeutic results and satisfactory prognosis [65].

According to the guidelines of the American College of Obstetrics and Gynecology (ACOG) in 2007, fertility-sparing surgery for reproductive-age patients with invasive EOC is recommended for highly or moderately differentiated stage IA disease with non-clear cell histology.

The European Society for Medical Oncology (ESMO) in 2008 indicated that fertility-sparing techniques in EOC is recommended in patients with unilateral stage I tumor without dense adhesions with moderate or highly differentiated, non-clear cell histology. The number of published studies related to FSS in young patients with EOC is limited, and the patient's samples are small to allow a consensus regarding the selection criteria of the optimal candidate for FSS.

Borderline Ovarian Tumors

Patients with borderline ovarian tumors (BOTs) are good candidates for FSS, which has shown increased safety and efficacy in those patients.

The standard surgical procedures include total hysterectomy, BSO, peritoneal washings, multiple peritoneal biopsies, resection of implants, omentectomy, and appendectomy (in patients with mucinous BOTs) [64, 66].

Lymphadenectomy is usually not indicated due to the rarity of lymph node metastasis [67–70].

Type of Surgery

Salpingo-oophorectomy in patients with BOTs has been reported to be associated with better oncologic outcome as less-extensive surgery has been associated with higher recurrence rates. However, cystectomy as FSS could be the only option, in some patients, due to previous history of unilateral oophorectomy or salpingo-oophorectomy or bilateral involvement of BOTs.

Several studies have suggested that bilateral adnexectomy in patients with bilateral BOTs was associated with an insignificant increase in recurrence rate. This indicates that cystectomy should be limited to patients with a previous history of unilateral adnexectomy or bilateral BOTs.

The rates of bilateral involvement of BOTs have been reported to be 25–50% for serous-type tumors and 5–10% for mucinous-type tumors [71, 72]. The need for histopathologic evaluation of the contralateral ovary during fertility-sparing surgery is paramount, and wedge biopsy of the remaining ovary may cause mechanical infertility or ovarian failure [73–75].

A study of 14 patients who underwent wedge biopsy of the contralateral ovary found that none was positive, and one patient with normal results had recurrent disease in the remaining ovary [73]. This would indicate that histopathologic evaluation of the normal-appearing contralateral ovary is not helpful in reducing the risk of recurrence in the remaining ovary.

In another study, among all patients who underwent wedge biopsy of the normal-appearing contralateral ovary, none was positive for BOTs, whereas 11 of the 22 patients who underwent cystectomy to remove benign-appearing cysts of the contralateral ovary had BOTs on the contralateral ovary [76]. This illustrates that thorough inspection of the surface of the contralateral ovary and biopsies of suspicious lesions are adequate for screening.

FSS laparoscopic surgery has several advantages over laparotomy. Farghaly [62] described a technique for video laparoscopic fertility-sparing surgery in patients with low malignant potential (LMP) ovarian tumors. This technique was shown to be feasible, accurate, and safe.

Also, two studies [43, 44] have suggested the feasibility, safety, and accuracy of laparoscopic surgery for patients with early-stage epithelial ovarian cancer.

Recurrence rates were found to be similar in patients undergoing laparoscopy or laparotomy and FSS for early ovarian cancer [11, 72, 77–79].

Borderline ovarian tumors with a micropapillary histologic pattern [80, 81] have been associated with more common bilateral ovarian involvement, extraovarian implants, and invasive implants [82, 83]. In a study of 15 patients with that pattern, the rates of bilateral ovarian involvement, extraovarian implants, and recurrence were high [84].

It has been shown, in a study of ten patients with microinvasion, that five of these patients had recurrent disease, all lesions developed on the remaining ovary, and all patients with recurrence were successfully treated [84].

Other Potential Options to Preserve Fertility

Where FSS is not indicated, when the normal ovarian tissue cannot be preserved due to massive bilateral ovarian involvement and only the uterus can be preserved, have several options for fertility preservation. These include embryo freezing, oocyte freezing, and ovarian tissue freezing. Embryo freezing has been shown to offer reasonable success rate of 20–30% [85]. This option could be considered for patients with BOTs, before definitive surgery [86]. In this treatment, a life partner or sperm donor is required, and patients must delay cancer treatment for 2–6 weeks. Oocyte freezing is also a viable option for fertility preservation in patients with BOTs. More than 230 pregnancies from frozen oocytes have been reported worldwide, with live-birth rates per oocyte thawed of 1.9–4.6% [87]. Oocyte freezing does not require a life partner or sperm donor, and it requires a 2–6-week delay in cancer treatment. Ovarian tissue freezing is another option and three pregnancies have been reported [87–89]. A delay in cancer treatment and a life partner or sperm donor is not required. A restoration of endocrine function and embryo development from this technique has been reported, but cancer cells may be transmitted [90]. As of now, the cryopreserved fragments have not been reimplanted [91]. Donor oocytes could be an alternative option for fertility preservation [92, 93].

Oncologic Outcomes After FSS

FSS is a safe treatment option for early-stage ovarian cancer patients with acceptable oncologic safety profile [94]. Satoh et al., in a study of stage I EOC patients who underwent fertility-sparing surgery [50], reported that 8.5% relapsed with 27% of the relapsed patients presenting recurrence in the remaining ovary. In patients with stage IA disease with clear cell histology or stage IC with unilateral ovarian involvement and favorable histology, authors emphasized the need of a complete surgical staging and an adjuvant platinum-based chemotherapy. In other studies, the mean relapse rates were estimated to be around 10% [94–99].

Kajiyama et al. [99] concluded that the outcome of patients with stage IC (surface involvement/positive cytology) was significantly poorer than that of patients with stage IA after FSS.

Zanetta et al. reported that none of the women undergoing bilateral oophorectomy had microscopic foci of cancer in the normal-looking contralateral ovary [94].

It has been shown that the negative impact of unfavorable histology on survival has mainly been related to advanced-stage disease III and IV [100, 101]. The reason for that was increased chemotherapy resistance to carboplatin and paclitaxel regimens, and in stage IA, no adjuvant treatment was necessary.

Reproductive Outcomes After Fertility-Sparing Surgery

Impaired fertility in young women with early-stage ovarian cancer represents a therapeutic challenge. Chemotherapy and surgical treatments often compromise the ovarian function, resulting in infertility and premature menopause [102–104]. The rate of women with successful conception after FSS is approximately 30% of all patients; however, it is higher in women in the childbearing age, ranging from 66% to 100%. It has been shown that only a small percentage of patients required assisted reproductive techniques for a successful conception and pregnancy [50, 94, 105, 106]. The incidence of spontaneous abortions is reported to be between 11% and 33%. In a study by Satoh et al. [50], 5.0% of the patients who received platinum-based chemotherapy presented a persistent secondary amenorrhea up to 224 months after completion of four to six cycles of systemic chemotherapy. 9.1% of the patients who successfully conceived have been stated to receive an infertility treatment before pregnancy. In addition, it has been reported that none of the patients who successfully conceived and gave birth presented any cancer-related problems during the perinatal period, and rates of congenital malformations and abnormal fetal outcomes have been the same as in the general population [50, 107].

Chemotherapy-Induced Gonadotoxicity Following FSS

To decrease chemotherapy-induced gonadotoxicity after FSS, hormonal protection has been utilized to affect the ovarian tissue by pituitary downregulation to enter a state of inactivity and so to make it less susceptible to cytotoxic agents. Several agents have been used, such as GnRH agonists, oral contraceptives, and tamoxifen. Tan et al. applied different doses of triptorelin in combination with busulfan in sexually mature, virgin, female mice. Results have demonstrated a dose-dependent protective effect against gonadotoxic chemotherapy of a gonadotropin-releasing hormone (GnRH) analog on ovarian reserve [107].

All clinical studies assessing the protective effect of GnRH agents have been conducted in patients with hematologic malignancies, breast cancer, and lupus erythematodes chemotherapy and have shown a reduction of premature ovarian failure in patients receiving GnRH analog or OC during systemic chemotherapy [108].

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7 Treatment of Advanced-Stage Ovarian Cancer

Alexandra Lawrence and James Dilley

Introduction

Over 70% of women with epithelial ovarian cancer are diagnosed with advanced-stage disease, FIGO stage III/IV (Table 7.1). Management of these women usually involves a combination of surgery, chemotherapy and palliative treatments. Despite advances in both chemotherapy and surgery, the majority of these women will have disease recurrence and will die from their disease. It is the seventh most deadly cancer in women with 46% survival 5 years after diagnosis [1]. Unlike most other solid tumours, there appears to be a significant survival benefit from surgical debulking of advanced-stage disease. Recent major studies have been conducted to address the timing of surgery with relation to chemotherapy, radicality of surgery, intraperitoneal chemotherapy and use of targeted chemotherapy agents in addition to standard chemotherapy.

Table 7.1 Staging classification for cancer of the ovary, fallopian tube and peritoneum by International Federation of Gynecology and Obstetrics Criteria (FIGO 2014) [2]

Stage I: Tumour confined to ovaries or fallopian tube(s)
IA: Tumour limited to 1 ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB: Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC: Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following: IC1: Surgical spill IC2: Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface IC3: Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal tissues
Stage III: Tumour involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven) IIIA1 (a) Metastasis up to 10 mm in greatest dimension IIIA1 (b) Metastasis more than 10 mm in greatest dimension

(continued)

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Table 7.1 (continued)

IIIA2: Microscopic extra pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retro-peritoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV: Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Diagnosis

Symptoms of advanced-stage ovarian cancer are non-specific, which partially accounts for its late presentation. Women may present with a variety of symptoms such as pelvic or abdominal pain, abdominal distension, early satiety, loss of appetite and urinary symptoms [3]. There may be abnormal findings at pelvic or abdominal examination, or abnormalities found in imaging studies or surgery for other conditions. Commonly women have presented as emergency cases, although this figure is falling in the UK, with an increasing number of women presenting after an urgent suspected cancer referral. Despite this, 36% of women with epithelial ovarian cancer die within the first year of presentation [4]. Ovarian cancer diagnosis may be made after a staging laparotomy for suspected ovarian cancer, image-guided core biopsy, laparoscopic assessment and biopsy or biopsy during other operations. Ascitic or pleural fluid cytology alone is not recommended for diagnosis as it does not provide tissue to classify the grade and type of ovarian cancer and may give false negative results in women with ovarian cancer [5]. Cases of suspected and confirmed advanced-stage ovarian cancer should be discussed by multidisciplinary teams including a gynaecological oncology surgeon, medical or clinical oncologist, radiologist, pathologist, clinical nurse specialist and palliative care team with at least one member having assessed the patient. This multi-professional discussion will ensure that holistic management of women can be planned and pathways of care organised which often involve a coordinated combination of surgery and chemotherapy alongside other hospital and community services.

Surgery in Ovarian Cancer

Surgery has been conducted for women with ovarian cancer since the 1930s and in 1975 Griffiths et al. published a landmark paper demonstrating an inverse relationship between residual tumour diameter after surgery and survival [6, 7]. After the benefits of platinum-based chemotherapy (cisplatin and carboplatin) were established in the 1980s, there have been no randomised controlled studies to compare the outcomes of women receiving and not receiving surgery in addition to chemotherapy and surgery continues to be performed. The timing of initial surgery may be before chemotherapy (primary debulking surgery—PDS) or after chemotherapy (delayed primary surgery—DPS). DPS may be performed during chemotherapy (interval debulking surgery—IDS) or after completion of chemotherapy (delayed debulking surgery—DDS) [8]. Secondary surgery can be offered for recurrent disease. The roles of surgery include diagnosis, staging, cytoreduction and palliation.

In the platinum era the benefit of surgical debulking persisted. In Bristow's meta-analysis of 53 studies including 6885 women with stage III or IV disease, for every 10% in cytoreduction median survival improved by 5.5% [9]. There is uncertainty whether this represents inherent tumour biology or benefit gained from surgical aggression and radicality.

Cytoreduction is classified by the Gynecologic Oncology Group as complete, optimal or suboptimal depending on the volume of residual disease after surgery (Table 7.2) [10]. The benefits of surgery may include (1) resection of areas of tumour

that are poorly vascularised and in which chemotherapy may be less effective, (2) higher growth fraction in well-perfused small residual tumour masses that may be more chemosensitive, (3) treating a smaller volume of disease may need less chemotherapy and reduce the opportunity for resistant tumour clones to develop, (4) resection of drug-resistant tumour cells and (5) host immunocompetence improved with removal of tumour bulk [11]. Complete and optimal debulking rates are higher when women are operated on by gynaecological oncologists in specialised hospitals, compared to general gynaecologists or general surgeons [7, 9, 12]. It remains unclear whether these improved outcomes in optimally debulked women are due to the surgery or patient and disease factors [13].

Cytoreductive Surgery

The aims of cytoreductive surgery are to (1) remove all sites of macroscopic disease, (2) assess areas for microscopic disease spread to allow accurate staging to guide treatment and inform prognosis and (3) minimise morbidity.

Table 7.2 Definitions of cytoreduction

Complete cytoreduction	No visible residual disease
Optimal	All residual deposits <1 cm maximal dimension
Suboptimal	Residual deposits 1 cm or greater

Evaluation of Women for Surgery

The patient should, if possible, be reviewed by a surgical and medical oncologist and then discussed at a multidisciplinary meeting with relevant imaging and blood tests (Table 7.3).

Initial management options include:

1. Primary cytoreductive surgery
2. Laparoscopy ± proceed to primary cytoreductive surgery
3. Image-guided biopsy to establish ovarian cancer diagnosis and proceed to primary cytoreductive surgery
4. Image-guided biopsy to establish ovarian cancer diagnosis and proceed to neoadjuvant chemotherapy
5. Palliative surgery
6. Supportive care ± palliative chemotherapy

The use of image-guided biopsy prior to surgery (option 3 above) is reserved for cases in which the primary cancer is in doubt. Gastric cancer with omental disease, ascites and Krukenberg tumours may masquerade as an ovarian cancer and should be excluded if there is any doubt preoperatively [14].

Table 7.3 Routine preoperative tests for women with advanced ovarian cancer

Type of test	Test
Routine blood tests	Full blood count, renal function, liver function, (including albumin), clotting profile, blood grouping
Tumour markers	CA-125, CEA, CA19-9, (β-hCG, LDH, alpha fetoprotein, inhibin in suspected non-epithelial ovarian cancer)
Imaging	CT thorax, abdomen and pelvis ± MRI pelvis for consideration of fertility preservation or if diagnosis in doubt ± CT PET in secondary surgery
Cardiorespiratory	Electrocardiogram, ± echocardiogram, ± lung function, ± sleep studies, ± CPEX testing with anaesthetic review
Other ±	Colonoscopy, gastroscopy, stoma counselling

Selection of Women for Primary Cytoreductive Surgery

Survival benefit from primary cytoreductive surgery in advanced ovarian cancer is gained for women where complete or optimal cytoreduction can be achieved. The prognosis does not differ according to specific sites of disease within the abdomen [15]. Furthermore, women with tumours that cannot be reduced to less than 1 cm will suffer surgical morbidity but probably derive no survival benefit from surgery [16]. A variety of predictive factors have been assessed. Bristow et al. identified a Gynecologic Oncology Group (GOG) performance status of ≥2, CT features of peritoneal thickening, peritoneal implants (≥2 cm), bowel mesentery involvement (≥2 cm), suprarenal para-aortic lymph nodes (≥1 cm), omental extension (spleen, stomach or lesser sac) and pelvic sidewall involvement and/or hydroureter to be most strongly associated with surgical outcome [17]. Using the scoring system (Table 7.4) in all women with a score of less than 4 optimal or complete debulking was achieved, whereas in those with a score of 4 or greater, 87.5% of women were suboptimally debulked (Fig. 7.1) [17].

Ferrandina et al. validated this approach in a European centre and identified five independent variables: ECOG performance status ≥2, CT findings of peritoneal thickening, peritoneal implants ≥2 cm, bowel mesentery involvement, suprarenal aortic lymph nodes ≥1 cm and diaphragmatic disease (widespread infiltrating carcinomatosis or confluent nodules) [18]. With each of these allocated a score of 1, a predictive

Table 7.4 Final model of predictive index parameters, including 13 radiographic features and GOG performance status >2

Predictive index parameter	Point value	Sensitivity	Specificity	PPV	NPV	Accuracy
Peritoneal thickening	2	71.4% (15/21)	90.0% (18/20)	88.2% (15/17)	75.0% (18/24)	80.5% (33/41)
Peritoneal implants ≥2 cm	2	57.1% (12/21)	95.0% (19/20)	92.3% (12/13)	67.9% (19/28)	75.6% (31/41)
Small bowel mesentery disease ≥2 cm	2	33.3% (7/21)	100% (20/20)	100% (7/7)	58.8% (20/34)	65.9% (27/41)
Large bowel mesentery disease ≥2 cm	2	38.1% (8/21)	90.0% (18/20)	80.0% (8/10)	58.1% (18/31)	63.4% (26/41)
Omentum extension to stomach, spleen, or lesser sac	2	42.9% (9/21)	85.0% (17/20)	75.0% (9/12)	58.6% (17/29)	63.4% (26/41)
Extension to pelvic sidewall, parametria, or hydroureter	2	42.9% (9/21)	85.0% (17/20)	75.0% (9/12)	58.6% (17/29)	63.4% (26/41)
Ascites-large volume (seen on all cuts)	2	38.1% (8/21)	90.0% (18/20)	80.0% (8/10)	58.1% (18/31)	63.4% (26/41)
Performance status ≥2	2	33.0% (7/21)	95.0% (19/20)	87.5% (7/8)	57.6% (19/33)	63.4% (26/41)
Suprarenal para-aortic lymph nodes ≥1 cm	2	23.8% (5/21)	100% (20/20)	100% (5/5)	55.6% (20/36)	61.0% (25/41)
Diaphragm or lung base disease ≥2 cm, or confluent plaque	1	42.9% (9/21)	75.0% (15/20)	64.3% (9/14)	55.6% (15/27)	58.5% (24/41)
Inguinal canal disease or lymph nodes ≥2 cm	1	19.0% (4/21)	100% (20/20)	100% (4/4)	54.1% (20/37)	58.5% (24/41)
Liver lesion ≥2 cm on surface, or parenchymal lesion any size	1	14.3% (3/21)	90.0% (18/20)	80.0% (8/10)	58.1% (18/31)	56.1% (23/41)
Porta hepatis or gallbladder fossa disease ≥1 cm	1	14.3% (3/21)	100% (20/20)	100% (3/3)	52.6% (20/38)	56.1% (23/41)
Infrarenal para-aortic lymph nodes ≥2 cm	1	14.3% (3/21)	100% (20/20)	100% (3/3)	52.6% (20/38)	56.1% (23/41)

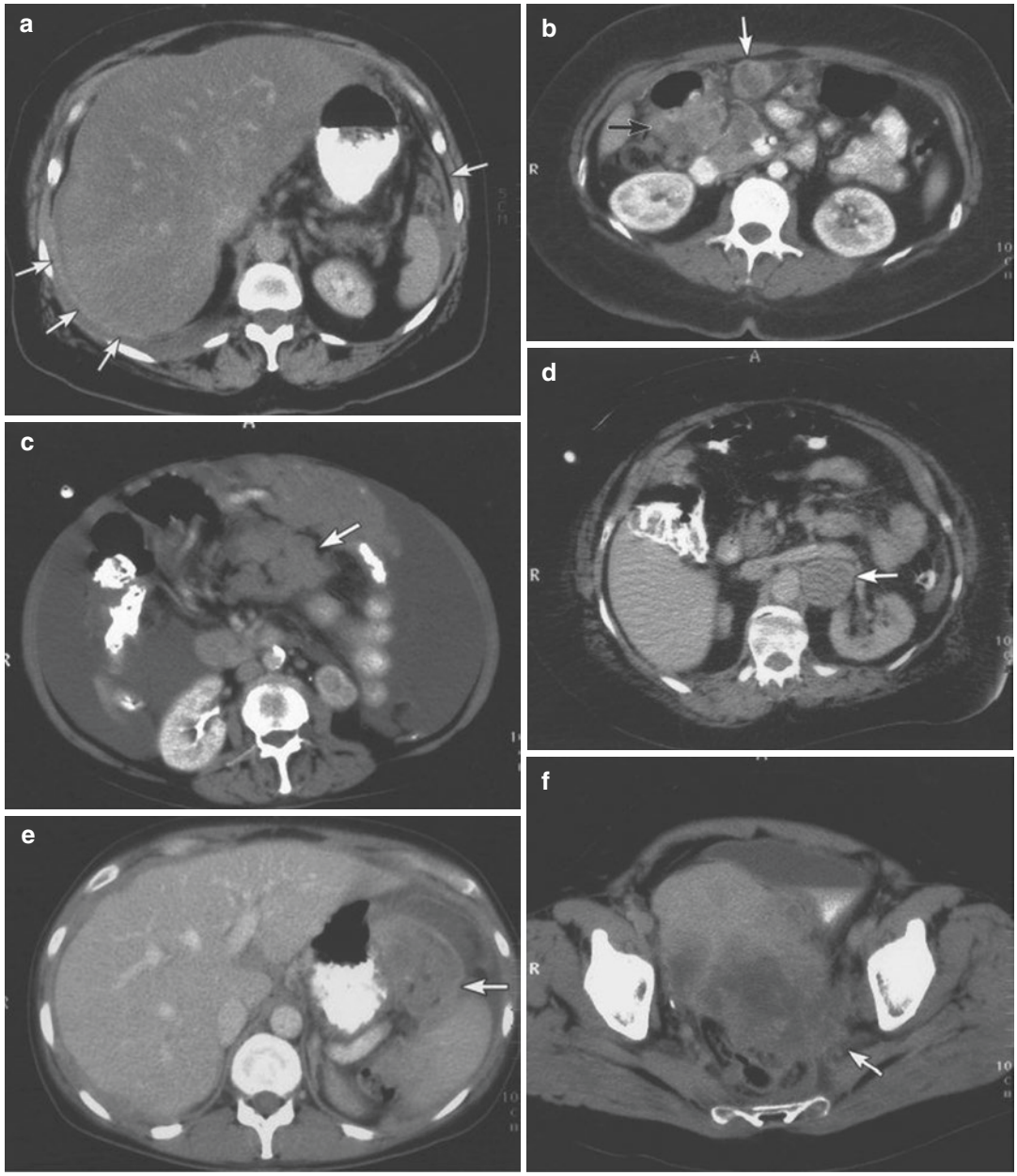

Fig. 7.1 Representative CT findings: (**a**) peritoneal thickening, (**b**) peritoneal implant ≥2 cm and large bowel mesentery disease ≥2 cm, (**c**) small bowel mesentery disease ≥2 cm, (**d**) suprarenal para-aortic lymph node ≥1 cm (the left renal vein can be seen running ventral to the tumour mass), (**e**) omental tumour extension to spleen and (**f**) tumour infiltration of parametrial soft tissue and extension to pelvic sidewall Bristow et al. [17]

index value can be calculated (PIV) with corresponding rates of unnecessary surgery and also inappropriate under exploration.

There is currently no perfect model that can completely predict when complete or optimal debulking may be achieved so that women do not receive unnecessary surgery. Variation between surgeons and centres makes any predictive model difficult to apply universally and the lack of reproducibility of CT interpretation highlights

the caution that should be observed with any model [19]. In particular, radical upper abdominal procedures have been introduced to many gynaecological oncology centres with associated improvements in optimal debulking and survival and will alter rates of optimal and complete debulking [20]. Chi et al. reported a significant increase in cytoreduction, survival and progression-free survival when extensive upper abdominal procedures were performed on women with advanced ovarian cancer [20] (Fig. 7.2).

This often requires close working relationships with hepatobiliary and colorectal surgeons both for preoperative evaluation and intraoperative support. These procedures are associated with significant surgical morbidity and it is essential to audit quality of life alongside disease-specific measures as this approach becomes more widespread. In order to help stratify surgical complexity, Aletti et al. generated the surgical complexity score (SCS) [13] and found that whilst those undergoing more complex procedures had greater morbidity, overall survival was improved. Recently, Philips et al. confirmed findings that the SCS correlates with postoperative complications but also found that multiple bowel resections were a strong predictor of postoperative complications [14].

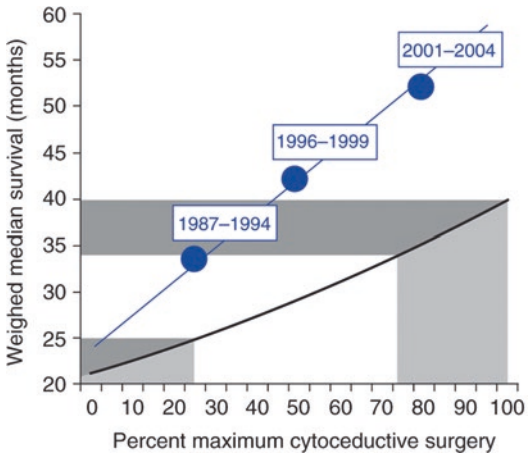

Fig. 7.2 Median overall survival as a function of percent maximum or optimal cytoreductive surgery. Memorial Sloan Kettering Cancer Center survival 1987–2004 superimposed on model by Bristow et al. (Modified with permission Bristow et al. [9])

There is no benefit for routine pelvic and paraaortic lymphadenectomy in women with normal appearing nodes radiologically and intraoperatively even if a complete macroscopic debulk has been achieved. The LIONS study showed no benefit in either overall or progression-free survival and those undergoing lymphadenectomy experienced a higher incidence of postoperative complications [15].

In a small group of women although there may be no survival benefit from primary surgery if optimal debulking is not achieved, surgery may improve symptoms such as those from large ovarian cysts or obstructed bowel and establish the diagnosis [21].

Operative and Perioperative Management

Preoperative evaluation will help determine the likely extent of surgery, in particular, the likelihood of bowel resection, stoma formation and upper abdominal procedures. It is important that any relevant multi-professional support is available if procedures outside the repertoire of the lead surgeon may be performed. For women where a stoma is likely, preoperative stoma siting and counselling are useful not only to ensure a good anatomical location of any stoma but also help with psychological aspects of bowel diversion. Women should also be counselled about the potential benefits and risks of intraperitoneal chemotherapy if optimal or complete debulking is achieved and consent taken for intraperitoneal catheter placement.

Bowel Preparation

The evidence for the use of bowel preparation is stronger in colorectal than gynaecological surgery and is therefore the source of many of the studies; however, they can be considered translatable. Studies in elective colorectal surgery have shown there is no evidence that preoperative mechanical bowel preparation (MBP) reduces the risk of surgical site infection or anastomotic

leak nor does its omission increase reoperation, secondary procedures or length of stay [22–24]. As such, the use of mechanical bowel preparation within an enhanced recovery after surgery (ERAS) setting is discouraged [25]. In cases where the surgeon feels bowel preparation is warranted, preference should be given to preparations that are isosmotic to minimise intravascular volume depletion and electrolyte imbalance. This is particularly important in the elderly [26]. An enema before surgery is also often used to ensure the lower bowel is completely empty. Bowel preparation should not be used in women with bowel obstruction.

Recent evidence has shown that a preoperative oral antibiotic in isolation or in combination with MBP can reduce surgical site infection (SSI) [27–29]. This has led to the World Health Organisation (WHO) recommendation that preoperative oral antibiotics combined with mechanical bowel preparation (MBP) should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery [30]. The majority of studies use a combination of neomycin and either erythromycin or metronidazole for oral antibiotic prophylaxis on the preoperative day.

Enhanced Recovery After Surgery (ERAS)

ERAS protocols aim to facilitate functional outcomes and improve postoperative recovery. They are composed of pre-, intra- and postoperative strategies. Techniques include preoperative counselling and nutrition, surgical site infection bundles, intraoperative goal-directed fluid therapy, multimodal opiate sparing perioperative and postoperative analgesia, early feeding and aggressive postoperative rehabilitation [25]. Currently there is no evidence from high-quality studies to support or refute the use of perioperative enhanced recovery programmes for women with ovarian cancer, although it is associated with shorter length of hospital stay, a reduction in overall health care costs, and improvements in patient satisfaction [31, 32].

Surgery

The goals of the initial surgical procedure are to (1) make a pathological diagnosis of ovarian malignancy, (2) quantify the extent of initial disease, (3) achieve complete cytoreduction and (4) quantify the extent of residual disease. After administration of general anaesthesia, ± epidural anaesthetic and a dose of prophylactic intravenous antibiotics (e.g. 1.2 g co-amoxiclav or 1.5 g cefuroxime and 500 mg metronidazole), the patient is placed in a modified Lloyd Davies position, cleaned, draped and catheterised to facilitate operative exposure from anus to xiphisternum. A midline incision is then performed from the symphysis pubis supraumbilically to allow thorough exploration of the upper abdomen. Upon entering the peritoneal cavity, any ascites present should be aspirated. If no ascites is present, a peritoneal lavage is performed and specimen sent for cytological examination and then all peritoneal surfaces should methodically be inspected. In advanced ovarian cancer this assessment is essential to determine whether optimal or complete cytoreduction is possible. If optimal cytoreduction is not possible, representative biopsies should be taken which may include unilateral oophorectomy or omentectomy and the abdomen closed so that operative morbidity is minimised (Fig. 7.3).

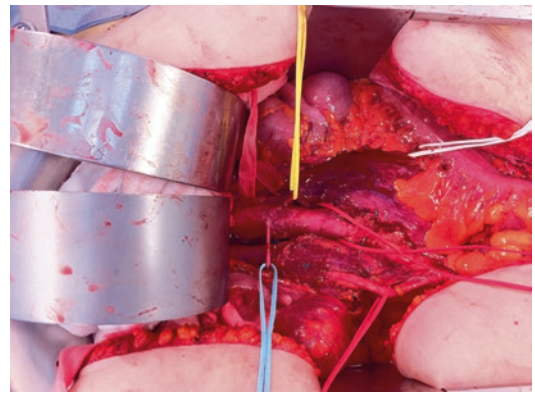

Fig. 7.3 A para-aortic node dissection. White vessel loop marks to left ureter, red loops to right ureter and aortic bifurcation, yellow loop to inferior mesenteric artery and blue loop to anomalous accessory right renal artery supplying lower renal pole

Relative contraindications to an attempt at primary debulking include extensive upper abdominal carcinomatosis, large tumour burden in small bowel mesentery or porta hepatis, extensive suprarenal lymphadenopathy, patient co-morbidity and patient wishes (e.g. declining stoma formation). If ovarian cancer is confirmed, these women should receive adjuvant chemotherapy and be considered for interval debulking surgery. For women where optimal or complete debulking is deemed possible, standard and extended procedures should be performed to achieve cytoreduction and the disease status at the end of surgery clearly documented (Table 7.5).

Table 7.5 Procedures in the management of primary advanced-stage ovarian cancer

Standard procedures
Bilateral salpingo-oophorectomy
Total hysterectomy
Omentectomy
Simple peritonectomy (pelvic, paracolic gutters or anterolateral diaphragmatic area)
Pelvic lymphadenectomy
Infrarenal para-aortic lymphadenectomy
Intraperitoneal port placement
Extended procedures
Radical pelvic dissection
Bowel resection(s)
Bowel anastomosis
Ileostomy/colostomy
Suprarenal para-aortic lymphadenectomy
Diaphragm or other complex peritoneal stripping
Full-thickness resection of diaphragm
Splenectomy
Partial hepatectomy
Partial gastrectomy
Partial cystectomy
Ureteric reimplantation/anastomosis
Distal pancreatectomy
Palliative procedures
Paracentesis
Thoracentesis
Pleurodesis
Anterograde or retrograde ureteric stents
Bowel diversion
Gastrostomy tube
Venous access systems (implanted port or peripherally inserted central catheter line)
Intestinal stents
Inferior vena cava filter

Appendicectomy should be performed unless it is known that the tumour is not mucinous and there is no evidence of metastatic disease to the appendix. If optimal or complete cytoreduction is achieved, consideration should be given to placing an intraperitoneal port for the administration of adjuvant chemotherapy.

Postoperative care is usually on the high dependency or intensive care unit. Fluid balance in particular needs active monitoring and treatment as there are often marked third space fluid losses and depleted intravascular fluid volumes. This is exacerbated with low serum albumin levels. Unless there is a coagulopathy, prophylactic low-molecular-weight heparin should be given. Early mobilisation and physiotherapy reduce the incidence of chest sepsis and thrombosis. Early postoperative feeding has been found to be safe and is encouraged. It can help with faster recovery of bowel function, lower rates of infectious complications, shorter hospital stay, and higher patient satisfaction [25, 33].

Pathological Review

Following surgery all specimens should undergo pathological evaluation and a final stage and histology recorded alongside sites of residual disease.

Chemotherapy

If a diagnosis of ovarian cancer is confirmed, women with advanced-stage disease should be considered for adjuvant chemotherapy. The options include intravenous chemotherapy, combination intraperitoneal and intravenous chemotherapy or a clinical trial. A variety of regimens are used with a platinum agent (carboplatin or cisplatin) and taxane (paclitaxel or docetaxel).

GOG 172 reported an improved median overall survival of 67 months with intraperitoneal cisplatin and paclitaxel compared to 49 months with IV treatment [34] These improvements in survival are associated with greater rates of toxicity and adverse events with less than half of women

tolerating six cycles of IP chemotherapy [35]. The PETROC/OV21 study showed a significant reduction in progressive disease at 9 months with IP carboplatin and paclitaxel over the intravenous route [36].

Several randomised trials have explored hyperthermic intraperitoneal chemotherapy (HIPEC) given at the time of interval debulking surgery. Findings from van Driel et al. reported increased median recurrence-free survival (10.7 months surgery alone vs. 14.2 months in HIPEC) and median overall survival (33.9 months surgery alone vs. 45.7 months in HIPEC) [37]. However findings from the Lim study did not show benefit [38]. This warrants further research and clarification whether any benefit is related to an additional intraperitoneal cycle of therapy or the association with hyperthermia.

Targeted Agents

Two recent trials have reported on the role of the anti-angiogenesis inhibitor bevacizumab (directed against vascular endothelial growth factor) in ovarian cancer (ICON-7, GOG 218) [39, 40]. These trials demonstrate a small improvement in progression-free survival in women who have not been optimally debulked but no improvement in overall survival. It is likely that the major benefit of drugs from these agents will be gained if suboptimally debulked women remain on maintenance bevacizumab until progression.

An exciting development is the use of PARP (poly ADP-ribose polymerase) inhibitors as maintenance treatment. This mechanism of these drugs centres on deficiency in the homologous recombination repair (HRR) pathway, which repairs DNA double-strand breaks [41]. PARP inhibition can result in preferential death of cancer cells when another mechanism for repairing DNA is defective. This deficiency is commonly seen in BRCA-mutated tumours. PARP inhibitors have shown an increase in progression-free survival in BRCA carriers with recurrent disease [29, 42]. More recently PARP inhibitors have shown benefit as maintenance treatment following first-line platinum base chemotherapy in BRCA-mutated advanced ovarian cancer, with the SOLO 1 trial demonstrating a 70% lower risk of disease progression or death compared to placebo [43]. The PRIMA trial showed a progression-free survival advantage of 5.6 months for all women with newly diagnosed advanced platinum-sensitive ovarian cancer with maintenance niraparib over placebo [44]. Tumour testing for HRR deficiency is becoming the standard of care to inform the use of PARP inhibitors in treatment of primary and recurrent ovarian cancer [44].

Neoadjuvant Chemotherapy and Delayed Primary Surgery

In many women with advanced ovarian cancer, optimal or complete cytoreduction cannot be achieved due to patient co-morbidity, pattern of disease, surgical expertise or unwillingness of the patient to undergo extensive surgery (e.g. including stoma formation). Furthermore, in women who respond to chemotherapy, if primary surgery is performed after chemotherapy surgical radicality, complications and side effects may be reduced. Vergote et al. reported outcomes of 632 women with advanced-stage disease (IIC–IV) randomised to primary debulking surgery followed by platinum-based chemotherapy or to neoadjuvant platinum-based chemotherapy (NACT) followed by debulking surgery (delayed primary debulking surgery) after three cycles of chemotherapy. There appeared to be no difference in overall survival between the two groups, and less morbidity in NACT [10]. The study had low rates of complete (19.2%) and optimal debulking (41%) and this may reflect surgical expertise or case selection that limits the universal application of the findings.

Similarly in a non-inferiority trial, the CHORUS study randomly assigned 550 women with suspected stage III or IV cancer to either primary surgery followed by six cycles of chemotherapy or three cycles of chemotherapy, then surgery and a further three cycles of completion chemotherapy [45]. Median overall survival was 22.6 months in the primary-surgery group versus 24.1 months in primary chemotherapy. Severe postoperative complications and deaths within 28 days after surgery were more common in the primary-surgery group than in the primary-chemotherapy group.

Pooled analysis of both of these studies substantiates previous results showing that neoadjuvant chemotherapy and upfront debulking surgery result in similar overall survival in advanced tubo-ovarian cancer. Women with stage IV disease had improved overall survival with neoadjuvant chemotherapy [46]. NACT appears a reasonable approach particularly in women with a high tumour burden, where optimal debulking is unlikely to be achieved, or women with comorbidity that may be improved with chemotherapy such as ascites, pleural effusions and hypoalbuminaemia.

There are limited data to guide management of women who after three cycles of NACT by CT assessment have progressive disease, partial response or mixed response and only suboptimal debulking is felt possible. Delayed debulking surgery can be considered using laparoscopy or mini-laparotomy after six cycles of chemotherapy to assess resectability. In carefully selected patients, optimal and complete debulking can exceed 80% [8].

Laparoscopic and Robotically Assisted Surgery

The advantages of laparoscopic surgery have been well established in gynaecological surgery, in particular reduced surgical morbidity, length of stay, adhesion formation, blood loss and postoperative pain. This has been advanced further with the introduction of robotically assisted surgery that offers the potential for more complex procedures to be performed. In order to allow a full oncological assessment, all peritoneal surfaces should be inspected and retroperitoneal structures palpated if not visualised. Concerns with laparoscopic and robotic surgery include the lack of visualisation of all peritoneal structures, limited haptic feedback, port site metastasis and suboptimal resection. Laparoscopy can be used to assess whether optimal cytoreduction is achievable and a scoring system has been developed [47]. This approach leads to a decrease in the rate of primary cytoreductive surgery but achieves a higher rate of optimal debulking at primary surgery [48]. The MISSION study followed up a selected group of women who had laparoscopic IDS [49]. Complete resection was achieved in 96.6% of women, with the majority of patients being discharged on postoperative day 2. These findings were replicated in a larger study across five cancer centres [50]. Robotically assisted laparoscopic surgery allows more complex dissections to be performed than 'straight stick' laparoscopy due to articulated instruments. Complex urological, gynaecological and exenterative procedures may be performed robotically and these have been applied to ovarian cancer in selected women [51]. Although in a carefully selected cohort, Abitbol et al. have reported positive findings after employing a robotic approach on 57 women undergoing interval debulking surgery. Complete cytoreduction was achieved in all women, with median blood loss being 100 mL and median length of stay one day [52]. It is essential that any novel techniques applied to the management of women with ovarian cancer have multidisciplinary review to ensure that the patient is fully counselled regarding both the risks and benefits of more novel surgical approaches and complications are audited.

Palliative Surgery

Unfortunately, most women diagnosed with advanced-stage ovarian cancer will die from recurrent or progressive disease. Bowel obstruction is the most frequent cause of admission for women with ovarian cancer in their last year of life [53]. Many women can be managed initially with nasogastric suction tube, bowel rest and intravenous hydration. Surgery may also be indicated for enterovaginal and rectovaginal fistulas, as well as for genital and lower gastrointestinal haemorrhage [54].

Surgery can have an important role in palliation of symptoms. The management of bowel obstruction will depend on the disease status of the patient, life expectancy with and without surgery, nutritional and medical status and site/s of obstruction. The goal of any intervention is to improve symptoms and quality of life; it is rarely

appropriate to perform secondary debulking for women with recurrent ovarian cancer causing bowel obstruction.

Women with recurrent ovarian cancer and bowel obstruction have high rates of perioperative mortality and morbidity, but successful palliation can be achieved. Kolomainen et al. reported successful palliation (oral intake at least 60 days postoperatively) in 59 of 90 women (66%) undergoing surgery with only the absence of ascites as a predictor for successful palliation [55].

For distal large bowel obstruction (sigmoid and descending colon), colorectal stents may be considered. This may require balloon dilatation but for a selected group of women, surgery and stoma formation may be avoided [56].

Recurrent or advanced ovarian cancer may cause ureteric obstruction and ureteric stents or a nephrostomy may be considered to relieve obstruction to preserve or improve renal function. For some women with end stage disease, insertion of a stent or nephrostomy may be inappropriate due to their short life expectancy and lack of symptoms. It is important to involve palliative care teams in ongoing management whether or not surgery is considered.

Recurrence

Most women with advanced ovarian cancer experience disease recurrence. For women with platinum-resistant disease whose disease progresses within 6 months of initial platinum-based chemotherapy, the prognosis is poor and there is no role for further surgery outside a palliative setting. Women whose disease recurs over 6 months from the completion of primary platinum chemotherapy have platinum-sensitive disease and have a survival benefit from further chemotherapy.

The DESKTOP (Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer) studies investigated whether this group of women would also benefit from surgery. Predictors for complete resection (positive AGO score) were ECOG performance status 0, FIGO stage I or II at initial diagnosis, absence of residual disease after primary surgery and absence of ascites [57, 58]. In the prospective validation study (DESKTOP-II), preoperative imaging underestimated disease spread in around half of women and overestimated in a quarter. The DESKTOP-III study explored outcomes in women with platinum-sensitive disease, a positive AGO score randomised to secondary cytoreduction and chemotherapy vs. chemotherapy alone. Women who had surgery had a significant increase in progression-free survival from 14 months without surgery to 18.2 with surgery and in time before subsequent therapy was initiated [59, 60]. However, the findings from the GOG-0213 study which randomised women to similar arms as DESKTOP III found that although it is possible to safely perform secondary surgery cytoreduction it did not improve overall survival [61]. This study did not include the AGO score in patient selection. We would therefore recommend restriction of the use of secondary cytoreduction to carefully counselled women with a positive AGO score.

In addition to MRI and CT, laparoscopy and FDG-PET may be used to assess sites and resectability of recurrent disease [62, 63]. Although a midline laparotomy is usually performed for the resection of recurrent ovarian cancer, conventional or robotically assisted laparoscopic surgery may be performed [64].

Intraperitoneal Chemotherapy Ports

Intraperitoneal chemotherapy ports may be placed at the same time as debulking surgery, at a subsequent laparoscopy or under radiological guidance [65]. Complications from port placement include bleeding, catheter blockage, infection and bowel perforation [66].

Novel Surgical Techniques

The introduction of new surgical instruments and techniques has been applied to ovarian cancer. Metastatic deposits may be ablated with radiofre-

quency, argon beam coagulation or microwave ablation [67–69]. These techniques may be applied to minimally invasive surgery or as an adjunct to conventional laparotomy. New tissue sealing and coagulation devices can be used as an alternative to traditional haemostasis with suture and diathermy in order to reduce operating times and blood loss.

Hereditary Susceptibility

Approximately 15–20% of women with high-grade serous cancer will have a germline BRCA1 or BRCA2 mutation. Consequently, diagnosis should trigger genetic testing [70]. If a germline mutation is confirmed, subsequent testing should be offered to first-degree relatives to identify others carrying the mutation and who might benefit from prophylactic surgery or chemoprevention. The estimated cumulative risks of epithelial ovarian cancer at the age of 80 are 44% in BRCA1 and 17% in BRCA2 mutation carriers [71]. Other genes such as RAD51C, RAD51D, BRIP1 and MSH6 are considered to be of moderate penetrance. Although their individual mutation frequency is uncommon (<1% each), cumulatively they might be responsible for about 5% of epithelial ovarian cancers [72]. As such, they should be included in genetic testing panels.

Future Directions

Ovarian cancer remains a major challenge for gynaecological oncologists and advances in surgery and chemotherapy have improved survival for ovarian cancer. Despite medical and surgical progress, most women will die from their disease. As most treatments are therefore ultimately palliative rather than curative, it is essential that quality of life measures are recorded alongside survival. Inequities in survival for women with advanced-stage ovarian cancer persist both within and between countries that need to be addressed to ensure that women have access to optimum therapies [73].

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8 Management of Recurrent Ovarian Cancer

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Introduction

The majority of patients with ovarian cancer will have been diagnosed at stage III/IV. At these advanced stages, the chance of relapse is 80–85% [1]. The management of recurrent ovarian cancer is challenging. The decision regarding the correct treatment modality depends on multiple factors, including the distribution of the recurrent disease, the histological type, the performance status and the co-morbidities of the patient, the previous treatments and their efficacy, the interval from the initial treatment until the relapse as well as the previous toxicities to therapies.

In this chapter, the indications and the role for each of these treatment options are discussed.

Surgery in Recurrent Ovarian Cancer

The theoretical background is similar to that of the primary surgery. Reduced tumour volume might increase the response to chemotherapy due to lower volume of disease, better drug perfusion to the tumour, and less chemo-resistant clones of malignant cells [2]. Moreover, the quality of life of the patients undergoing surgery plus chemotherapy is comparable to that of the chemotherapy only patients [3].

The selection of the patients to undergo secondary debulking is important. The second International Ovarian Cancer Consensus Conference proposed the criteria for optimal candidates (Table 8.1) [4].

Since then, multiple studies aimed to investigate further these criteria. A survival benefit for disease-free interval (DFI) of more than

Table 8.1 Criteria for secondary cytoreduction based on second IOCCC [4]

Criteria for optimal candidates for secondary cytoreduction Second International Ovarian Cancer Consensus Conference (1998)	
1	Disease-free interval >12 months
2	Response to first-line treatment
3	Potentially completely resectable disease (preoperative evaluation)
4	Good performance status
5	Younger age

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36 months (median survival of 56.8 months) compared to 6–12 or 13–36 months (median survival of 25.0 and 44.4 months, respectively) was found in Eisenkop et al. study [5]. Similarly, Chi et al. showed an increasing median survival from 30 months (DFI = 6–12 months) to 39 months (DFI = 13–30 months), while patients with DFI > 30 months had the highest median survival of 51 months [6]. On the other hand, the benefit of the long recurrence-free interval was not confirmed in other studies, as in the study of Zang et al., progression-free interval was found to be independent of survival in a multivariate analysis [7].

The studies were mainly retrospective and heterogeneous, characterised by different inclusion criteria and used terminology [8].

DESKTOP Studies I–III

DESKTOP I OVAR (Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer) was a large multicentre trial on secondary cytoreduction, published by AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) in 2006 [9]. In this study, patients were divided in three subgroups based on the DFI (6–12 months, 12–24 months and >24 months). In a multivariate analysis, DFI was found to be independent of survival [9].

One of the most important findings of DESKTOP I study was based on the proposed AGO score (Table 8.2) [9]. This included the good performance status, the lack of any residual disease after the initial cytoreduction and the absence of ascites. Patients fulfilling all three criteria are considered to have a positive AGO score, and 79% of them had complete cytoreduction. In contrast, only 43% of the patients without all three criteria had complete resection [9].

Table 8.2 AGO score. The score is positive when all three criteria are met [9]

DESKTOP I AGO score	
1	Good performance status (Eastern Cooperative Oncology Group—ECOG = 0)
2	No residual disease after primary surgery (or early FIGO stage, if the residual is unknown)
3	Absence of ascites >500 mL (pre-secondary cytoreduction)

DESKTOP II was a prospective multicentre study, also published by AGO [10]. In this study, the proposed by DESKTOP I score (AGO score) was validated. Half (261) of the 512 patients that were included in the trial had positive AGO score, and out of them, almost half (129) underwent secondary cytoreduction for recurrent ovarian cancer. The rate of complete cytoreduction in these patients was 76% [10]. The score is also used in other studies, showing even higher complete resection rates [11].

The volume of ascites and the extent of the recurrent disease have also been considered critical parameters when deciding on secondary cytoreduction. DESKTOP I study showed that the presence of ascites >500 mL was an unfavourable prognostic factor on survival, on multivariate analysis [9]. This finding was verified in DESKTOP II study [10]. Additionally, patients with less extended disease and especially localised, solitary and small volume tumour are more likely to have a complete secondary cytoreduction and therefore better survival [2, 11].

Preoperative good performance status was also found to be a significant parameter for survival [7, 11]. Patients with ECOG (Eastern Cooperative Oncology Group) score of 0 or 1 had statistically significant better median survival, compared to patients with low performance status (ECOG = 2) (40.5, 24.5 and 15 months, respectively) [7].

Multiple factors have also been included in other models, to identify the optimal candidates. FIGO stage, residual disease after the initial treatment, progression-free interval, ECOG performance status and the volume of ascites have been combined showing a sensitivity of 83.3% and specificity of 57.6%. In this model, complete cytoreduction was achieved in only 20.1% of the high-risk patients, contrary to the 53.4% in the low-risk group [12].

Finally, laparoscopy has also been proposed to evaluate the extent of disease, clarify the indications and identify the appropriate candidates for secondary debulking [13, 14]. The role of mini-

mal invasive surgery as surgical approach technique for secondary cytoreduction is discussed below.

DESKTOP III trial [NCT01166737] was a randomised multicentre study that compared cytoreduction followed by chemotherapy versus chemotherapy alone, in patients with platinum-sensitive recurrent ovarian carcinomas, positive AGO score and platinum-free interval of more than 6 months [15]. Candidates were randomised to either second-line chemotherapy alone (control arm, 203 patients) or to maximum effort secondary cytoreduction followed by chemotherapy (experimental arm, 204 patients) [15]. The primary measured outcome was the overall survival, while secondary outcomes were quality of life and progression-free survival, and the estimated study completion date is in December 2020 [15]. The results of the predetermined interim analysis were presented in the ASCO (American Society of Clinical Oncology) meeting in 2017 [15]. The patients in the experimental arm (secondary cytoreduction followed by chemotherapy) had a median progression-free survival of 19.6 months compared to 14 months of the chemotherapy only group ($p < 0.001$) with acceptable treatment burden [15]. Due to immaturity at the time of the report, the overall survival was kept blinded.

GOG 213 is another ongoing multicentre, open-label, randomised phase 3 trial [16]. The eligible patients had at least 6 months disease-free interval and were randomised to carboplatin + paclitaxel chemotherapy only or to the same combination plus bevacizumab (1:1), every 3 weeks, and as 3 weekly maintenance until disease progression or unacceptable toxicity [16]. The patients of both groups were further randomised to secondary cytoreduction or no surgery (1:1:1:1). The study aimed to determine the role of secondary cytoreduction and bevacizumab in terms of overall survival [17]. While the addition of bevacizumab seems to improve the median overall survival, the analysis regarding the role of secondary cytoreduction is still pending and the completion date is in March 2019 [16, 17].

Finally, the **SOCceR trial** [Surgery for Ovarian Cancer Recurrence, (Netherlands Trial Register number NTR3337)] was a multicentre randomised controlled trial that was aiming to study whether secondary cytoreduction, in addition to the standard chemotherapy, increases the disease-free survival of patients with recurrent ovarian cancer [18]. However, the study was prematurely stopped.

Parameters with Impact to Survival

Surgical outcome, and especially complete cytoreduction to no macroscopically visible disease, seemed to be the strongest predictive factor for survival in the patients undergoing secondary debulking [8, 19]. This finding was confirmed in all multivariate analysis performed [8] and it was achievable in about 40–80% of the patients with a reported survival of 24–50 months [2]. Moreover, optimal cytoreduction to <1 cm of maximum residual disease seemed to still offer some survival benefit [2, 7]. In most series the rate of optimal debulking varied between 40% and 60% and the survival 18–56 months [2]. Additionally, as reported above, when AGO score was used to select patients, the complete resection rate was about 67% (2 out 3 patients). However, in patients with sub-optimal cytoreduction (residual tumour >1 cm), the survival was only 8–27 months. Thus, in situations where complete cytoreduction is not possible, an aggressive surgical approach is not warranted, apart for palliation [2].

All other factors that were tested showed varied results in terms of survival, as were presented in the previous section.

Minimal Invasive Surgery (MIS) for Secondary Cytoreduction

In secondary cytoreduction, similarly to primary surgery, midline laparotomy is usually considered the standard approach. However, recent studies aimed to clarify the potential role of minimal invasive techniques (laparoscopy, robotic surgery) in the surgical management of recurrent ovarian cancer. These studies showed that both

laparoscopy and robotics are feasible and safe approaches for secondary cytoreduction, in well-selected patients, having the perioperative advantages of the MIS and comparable oncological outcome [20–25]. To the best of our knowledge there are no specific criteria to select for MIS; however, single and localised disease, lack of extensive adhesions as well as the experience on the use of MIS techniques and surgeon's preference seem to be important parameters [21, 23, 25–27].

The Role of Tertiary Cytoreduction in Recurrent Ovarian Cancer

The available data regarding the role of debulking beyond the secondary cytoreduction—third, fourth cytoreduction—is very limited. This is mainly based on retrospective studies with a very wide heterogeneity in terms of inclusion criteria, measured outcome and adjuvant treatment [28–33]. It is difficult to easily clarify the selection criteria for the suitable candidates for tertiary cytoreduction [33]. Similarly, it is difficult to identify the parameters with impact to survival [33].

Despite the above limitations, most of the studies, including the two largest and recent [28, 29], showed a survival benefit for the patients with at least optimal cytoreduction after tertiary debulking [29–31].

It is important to note that patients with recurrent disease after secondary debulking often have exhausted all non-surgical treatments (chemotherapy, targeted therapies, etc.) and tertiary cytoreduction could be the only available option [33]. Since there is a lack of clear inclusion criteria for such a surgery, benefits of cytoreduction should be balanced against the potential risks, especially in elderly and morbid patients [33].

Systemic Treatment for Recurrent Ovarian Cancer

For patients in whom secondary cytoreductive surgery is not appropriate, treatment with systemic chemotherapy is the treatment of choice, with a view to controlling disease-related symptoms and improving overall survival. The choice of chemotherapy is dependent on the length of time to relapse and determined by platinum sensitivity. Until recently, the platinum-free interval (PFI) had been the main marker to classify tumours as 'platinum-sensitive' or '-resistant' based on a 6-month cut-off from the last platinum-based therapy [34]. This historic definition, which was derived in an era when there were limited treatment options other than platinum re-challenge, was recently dropped at the Fifth Ovarian Cancer Consensus Conference of the GCIG [34]. It was agreed that the 6-month cut-off could not reliably predict those patients that would gain further benefit and those that would not. For example, not all patients with a PFI greater than 6 months respond to further platinum with objective responses between 47.2% and 66% [35, 36]; similarly a PFI less than 6 months does not predict platinum resistance with responses rates of 29% with both weekly carboplatin/paclitaxel and carboplatin/gemcitabine [37, 38]. The recently published ESMO-ESGO consensus guidelines suggest the definition of platinum resistance should be therapy-orientated [39], and as such this group should be defined as those patients have progressed while receiving platinum-based chemotherapy or experienced a symptomatic relapse soon after the end of the last platinum-based chemotherapy. Patients who are considered platinum sensitive should be re-challenged with platinum chemotherapy, with combination chemotherapy having been shown to be advantageous over single-agent platinum [35, 36, 40]. The addition of the anti-angiogenesis drug bevacizumab to platinum-based therapy and then as maintenance therapy should be considered in those without any contraindication, as it has been demonstrated to improve the progression-free survival (PFS) compared to chemotherapy alone in both the OCEANS and GOG213 trials [16, 41].

Patients with proven platinum resistance or early relapse should be considered for sequential non-platinum therapy (weekly paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan). As with platinum-sensitive relapsed dis-

ease, the addition of bevacizumab has a proven benefit with respect to improved response rate, progression-free survival and improvements in quality of life [42] and should be combined with chemotherapy where possible.

One of the most notable recent advances in the management of recurrent ovarian cancer is the introduction of oral poly adenosine diphosphate–ribose polymerase (PARP) inhibitors as maintenance therapy following a response to platinum-based chemotherapy [43–47]. PARP inhibitors interfere with single-strand DNA repair. They trap PARP protein onto DNA at sites of single-strand DNA breaks. When this trapped PARP is encountered by the DNA replication machinery, it leads to stalling of the replication fork, collapse and the generation of a double strand break, which cannot be repaired in cells with defective homologous recombination, such as *BRCA1/2* mutated cells [48].

Initial indications for PARP inhibition were limited to *BRCA1/2* mutated tumours characterised with olaparib receiving the first license from the EMA as maintenance treatment of recurrent *BRCA1/2* mutated epithelial ovarian cancer. Emerging data supports an extended scope for PARP inhibitor use and this has been reflected with the recent approval by both the FDA and EMA for niraparib, olaparib and rucaparib as maintenance therapy for all patients, treated with two or more prior chemotherapy regimens who have responded to platinum therapy, regardless of *BRCA1/2* status [43–47, 49–51]. Olaparib, niraparib and rucaparib all delay progression following platinum-based chemotherapy in high-grade ovarian cancer with benefit seen in all groups of patients [43–46]. The median PFS from randomisation ranges from 16.6 to 21 months for *BRCA*1/2 mutant populations and 8.4–10.8 months for *BRCA1/2* wild-type/all comer populations [43–47].

To date, no benefit has been observed in overall survival (OS), but with long-term follow-up in the original olaparib study (Study 19), 10% of patients remained on olaparib for over 6 years without evidence of tumour progression [52]. Despite impressive prolongation in PFS, disease relapse remains almost inevitable, even within the *BRCA1/2* mutant population, and combination strategies are required to overcome resistance.

Olaparib and rucaparib have additional licenses as monotherapy for recurrent *BRCA1/2* mutant ovarian cancer [51, 53]. Response rates of between 31% and 41% in *BRCA1/2* mutation carriers and up to 21% in *BRCA* wild-type patients have been demonstrated with olaparib monotherapy [54, 55]. Similarly, with rucaparib monotherapy, there was an overall response rate of 53.8% in *BRCA1/2* mutated patients [56].

Conclusions

The management of recurrent ovarian cancer is complex and a multidisciplinary approach is required for optimal patient outcome. Patient factors such as performance status and co-morbidities should be considered alongside disease characteristics including treatment-free interval, response to prior therapy, disease distribution and histological subtype.

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9 Overview of Ovarian Cancer Chemotherapy

Kylie Klein, Mary Dandulakis, and Dana M. Roque

Principles of Cytotoxic Chemotherapy

Cell Cycle, Growth Kinetics, Log Cell Kill

Growth of a tumor has been described by Gompertz in which a period of exponential growth is followed by plateau, dictated by available resources and tumor size [1]. Administration of chemotherapy kills a constant fraction of cells (first-order kinetics); therefore, the potential for remission may relate to the number of tumor cells at the time of initiation, thus underscoring the effect on prognosis of surgical debulking to no residual disease prior to adjuvant therapy [2]. Cytotoxic chemotherapy preferentially affects cells with faster growth rate of tumor cells relative to normal cells; this also explains toxicity to normal cells with renewing properties (e.g., bone marrow, gastrointestinal epithelium, skin).

The cell cycle consists of gap (G1, preparation for synthesis), synthesis (S, DNA synthesis), gap (G2, preparation for mitosis), and mitosis (M, cellular division). Cell cycle-specific agents active in the treatment of ovarian cancers include microtubule-bindings agents (M-phase; taxanes, vinca alkaloids, epothilones) and anthracyclines/camptothecins (S-phase). Platinums and alkylating agents are generally considered cell cycle-independent drugs.

Resistance Mechanisms

The likelihood of response to initial adjuvant platinum/taxane-based chemotherapy is between 60% and 80% [3]. Ovarian cancers are currently believed to exhibit intratumoral heterogeneity. Clonal populations with certain characteristics may survive exposure to certain agents, much like the selection which breeds antibiotic resistance. Specific mechanisms that have been implicated for agents important to ovarian cancer include impaired activation (doxorubicin-decreased p450, gemcitabine-decreased deoxycytidine kinase, alkylating agents-decreased microsomes), increased efflux via MDR1 or ABCG2, enhanced inactivation via increased glutathione/thiols (alkylating agents, platinums), induction of more efficient repair

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(alkylating agents, platinums), decreased uptake (gemcitabine, platinums), and target modifications (taxanes-β-tubulin, gemcitabine-ribonucleotide reductase, camptothecins-topoisomerase I, etoposide/anthracyclines-topoisomerase II) [4]. Recurrences that arise 12 months following last platinum exposure are definitively *platinum-sensitive*; those which arise between 6 and 12 months are considered *partially platinum-sensitive*. Tumors that recur within 6 months of platinum exposure are regarded as *platinum-resistant*. Disease that grows during platinum therapy is *platinum-refractory*, and portends a prognosis as short as 6 months in response to chemotherapy in the absence of bevacizumab [5].

Routes of Administration

Intravenous

Vesicants and Antidotes

A vesicant is a drug capable of local tissue necrosis upon extravasation. Many chemotherapeutic drugs are classified only as irritants, but can function as vesicants as the volume of the extravasated agent increases. Vesicants should be administered through a central venous catheter, which reduces the likelihood of extravasation to approximately 1.5–5% [6–8]. A higher rate of extravasation despite central venous access has been identified with increasing body mass index (BMI) and chronicity of the catheter [7, 9]. Extravasation of a vesicant produces local irritation followed by desquamation and discoloration. Among agents commonly administered for ovarian cancer, anthracyclines and vinca alkaloids are notable vesicants, whereas platinums, taxanes, alkylating agents, epothilones, gemcitabine, camptothecins, epipodophyllotoxins, gemcitabine, and bleomycin are generally considered irritants. Treatment of extravasation reaction in many cases involves administration of cold/heat four times daily for 24–48 h [10] and antidote if available [11], with possible Plastic Surgery consultation. Cold to induce vasoconstriction can be applied for all drugs except epipodophyllotoxins and vinca alkaloids, where vasodilation seems to facilitate diffusion. Dexrazoxane (1000 mg/m^2 in the first 6 h followed by 1000 mg/m^2 at 24 h then 500 mg/m^2 at 48 h) via an alternate large vein or dimethylsulfoxide (DMSO) 50% topical every 8 h for 7 days may neutralize anthracycline extravasation. Hyaluronidase is thought to facilitate dispersion of the drug and can be given at 150 U/mL distributed evenly via several injections at the extravasation site for vinca alkaloids and taxanes. Carboplatin and cisplatin extravasation can be addressed with distribution of 2 mL of 4% sodium thiosulfate subcutaneously; oxaliplatin extravasation has been treated with oral corticosteroids. In all cases, analgesia should be administered as needed.

Hypersensitivity and Alternate Formulation: Nanoparticles and Liposomes

Hypersensitivity reactions manifest in the form of shortness of breath, flushing, changes in blood pressure, rash, or back pain, among other symptoms. These are thought to be mediated by mast cells/basophils (paclitaxel) and IgE (platinums). Without steroids and antihistamines, hypersensitivity to the cremophor diluent of water-insoluble paclitaxel would affect nearly one-third of all recipients [12]; steroids and antihistamines decrease this rate to 2–4%. Patients with mild to moderate reactions can undergo treatment with additional steroids and antihistamines prior to rechallenge at a slower rate. Severe reactions should undergo rechallenge in an inpatient intensive care unit setting with desensitization protocol [13]. Nanoparticle albumin-bound paclitaxel (Abraxane) is a water-soluble alternate formulation which has superior efficacy to cremophor formulations of paclitaxel in breast cancer and activity in ovarian cancer in the front-line setting [14]. Its volume of distribution is greater and clearance is faster. The recommended three-weekly dose is 260 mg/m^2 IV.

Carboplatin hypersensitivity generally develops after 6 cycles or more [15], is associated with germline BRCA status as well as OS compared to non-hypersensitive patients irrespective of BRCA status, and can be addressed with similar desensitization protocols [16, 17].

Liposomal encapsulation is another technique to alter pharmacokinetics and drug properties.

Liposomes are phospholipids used to encapsulate drug, which may also be pegylated to prevent phagocytosis and elimination by circulatory cells. Pegylated liposomal doxorubicin has a longer half-life and decreased volume of distribution relative to the free drug, resulting in enhanced concentrations of drug within the tumor. Unlike the parental formulation, pegylated liposomal doxorubicin does not act as a vesicant and results in minimal cardiotoxicity; the dose-limiting toxicities are palmar-plantar-erythrodysesthesia (PPE), followed by stomatitis.

Intraperitoneal Chemotherapy

Intraperitoneal (IP) chemotherapy was originally investigated as a salvage measure for control of ascites in the 1950s [18]. In general, IP administration of chemotherapy allows a greater concentration of drug to bathe the site of disease, while simultaneously minimizing systemic toxicity. The IP concentration of cisplatin, for example, can be 10–20-fold higher when given IP compared to intravenous (IV). The most extensively studied agents for IP delivery include cisplatin, paclitaxel, docetaxel, 5 fluorouracil, and pemetrexed [19]. Agents with larger molecular weights will dwell in the cavity for a longer period of time but may suffer from poor penetration into the tumor. Some authors have described penetration of paclitaxel to 80 call layers [20]. A number of studies [19] have shown benefit relative to adjuvant IV therapy for newly diagnosed patients. A Cochrane review including 8 studies and 2026 women demonstrated improved hazard ratios (HR) for death (0.81, 95% CI 0.7–0.9) and recurrence-free interval (HR 0.78, CI 0.7–0.86) [21]. Uptake by practitioners of IP chemotherapy has been overall poor. Catheter-related complications such as infection, blockage, and leakage occur in as many as one-third of patients [22]. Administration is associated with increased peritoneal irritation and requires specialized resources not available at all centers. During therapy, patients are rotated in lateral decubitus to allow distribution of drug. Currently, National Comprehensive Cancer Network (NCCN) guidelines include the following regimen for optimally debulked stage II–III disease: IV paclitaxel 135 mg/m^2 over 3 or 24 h day 1 with cisplatin 75–100 mg/m^2 IP day 2, and IP paclitaxel 60 mg/m^2 day 8 every 21 days for 6 cycles as an accepted alternative to IV carboplatin and paclitaxel [23]. All recommendations based on the NCCN Guidelines are category 2A unless otherwise noted. The NCCN Guidelines define category 1 as high-level evidence and uniform NCCN consensus, category 2A as lower-level evidence and uniform NCCN consensus, category 2B as lower-level evidence and NCCN consensus that the intervention is appropriate, and category 3 as any level of evidence and major NCCN disagreement that the intervention is appropriate [23].

Hyperthermic Intraperitoneal Chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) involves instillation of cytotoxic agents heated to approximately 42 °C and infused for 60–120 min at the time of debulking. Closure with moderate pressure optimizes drug distribution. In a recent phase III trial, van Driel and colleagues [24] assigned patients with stage III disease who responded or had stable disease after 3 cycles of neoadjuvant carboplatin AUC 5–6 and paclitaxel 175 mg/m^2 to receive HIPEC with cisplatin 100 mg/m^2 or not at the time of optimal interval debulking followed by three additional cycles of carboplatin/paclitaxel. The group that received HIPEC exhibited a hazard ratio for death/recurrence of 0.5–0.87 ($P = 0.003$); median overall survival (OS) was 45.7 versus 33.9 months, respectively. Grade 3 toxicities were not significantly different. HIPEC in this fashion was found to be cost-effective based on an ICER of €28,299/QALY (quality-adjusted life year) [25]. At present, the NCCN states that HIPEC can be considered at the time of interval debulking surgery for stage III disease [23]. In some series, HIPEC has been associated with complications in as many as 44% of cases. ASA (American Society of Anesthesiologists) score, blood loss, performance status, large bowel resection, postoperative serum albumin levels, and nutritional status correlate with higher risk for postoperative infectious complications. Surgical site and bloodstream infections contained candida in 22% of instances [26].

Dosing in Obesity

Current estimates suggest that more than one-third of individuals in the United States have a BMI exceeding 30 kg/m^2 [27]. In the past, chemotherapy dosing was capped in obese populations given concern for excessive toxicity at large doses. Data have suggested that obese patients were under-treated in nearly 40% of instances, resulting in compromised rates of recurrence and mortality [28]. The American Society of Clinical Oncology has recommended since 2012 dosing based on actual rather than ideal weight [29].

The Food and Drug Administration (FDA) recommends capping creatine clearance at 125 mL/min [30]. Though direct methods for measurement of creatinine clearance exist, they are cumbersome. The Gynecologic Oncology Group (GOG) suggests use of the Cockcroft-Gault formula for estimated creatinine clearance (CrCL): (140 − age)(weight in kg)/72/serum creatinine. Actual body weight is utilized for women with BMI < 25 kg/m^2; adjusted body weight is used for women with BMI ≥ 25 kg/m^2. Adjusted body weight is derived from (0.4)(actual − ideal) + ideal. GOG recommends a minimum creatinine of 0.7 mg/dL. NRG-GY022/DT1833 is a study under development to assess carboplatin clearance predictors, as the original data for the current standard of care were in actuality based on very few women [31]. The Calvert formula is used to calculate dose as follows: mg = (25 + CrCL) × desired area under the curve (AUC). AUC refers to plasma concentration over time, which is specific pharmacokinetic parameter influenced by a variety of individual patient factors beyond clearance, such as gender, metabolizing agents, and transporters, among others.

Mechanisms and Toxicities of Commonly Employed Agents

Platinums

Platinum chemotherapeutic agents primarily exert their antineoplastic effect via the creation of intrastrand and interstrand DNA cross-links. Their mechanism is similar to alkylating antineoplastic agents such as cyclophosphamide, but they do not operate via an alkyl group [32]. Platinum agents covalently link DNA nucleotides within a single strand of DNA (intrastrand) or between strands of double-stranded DNA (interstrand), typically by way of the nucleic acid base guanine [33]. The cross-linking prevents DNA replication, transcription, and likely translation as well, essentially bringing the functionality of a cell to a standstill. This leads to cell cycle arrest and apoptosis [32]. While this is one mechanism by which platinum-derived chemotherapeutic agents exert their antineoplastic force, there are likely other mechanisms of action that have yet to be completely delineated. Cytotoxic activity has also been attributed to interactions with mitochondrial DNA as well as instigation of endoplasmic reticulum stress, which both can activate apoptotic pathways [34].

Three primary platinum agents relevant to treatment of gynecologic malignancies include cisplatin, carboplatin, and oxaliplatin. When platinum is administered with paclitaxel, the latter is traditionally infused first to reduce sequence-specific myelosuppression.

Cisplatin

Cisplatin, the prototypic platinum chemotherapeutic agent, was first synthesized in 1893, although it was not until the 1960s before its antineoplastic properties were recognized. Research supports its primary mechanism of action to be via cross-linking of purine bases, specifically at the N7 position of guanine/adenine [33]. While it is used extensively in oncology for treatment of a plethora of cancers including sarcomas, gynecologic as well as testicular tumors, and head/neck neoplasms, it has a significant cytotoxic profile [35]. Cisplatin is water-soluble with 90% bound to protein. Renal excretion of cisplatin is associated with significant nephrotoxicity up to 20 days after the dose is given. Other side effects include nausea and vomiting, which combined with the nephrotoxicity can lead to significant electrolyte imbalances. Myelosuppression is not an uncommon side effect. Neuronal damage is common both centrally and peripherally, leading to periph-

eral neuropathy, ototoxicity/tinnitus, encephalopathy and in severe cases seizures as well as residual motor deficits. Neuropathy is irreversible in 30–50%. Although rare, vascular events have been associated with cisplatin including myocardial infarction, stroke, and arteritis. As with many chemotherapy agents, cisplatin is associated with ovarian failure [32, 36].

Carboplatin

Carboplatin is a derivative of cisplatin and structurally differs from cisplatin only in that it has a bidentate dicarboxylate group whereas cisplatin has two chloride ligands [33]. It is believed that its primary mechanism of action is similar to cisplatin and produces the same kind of cross-linking as cisplatin. It does differ significantly in its kinetic profile [32, 33]. While it binds DNA at a slower rate than cisplatin, it also has an overall lower reactivity. The lower reactivity produces fewer protein-carboplatin byproducts, which are a primary way that carboplatin or cisplatin is excreted. This translates into carboplatin being excreted at a slower rate and therefore having longer lasting effects than cisplatin [33]. It is overall less potent than cisplatin. Carboplatin is also associated with fewer side effects than cisplatin, particularly with respect to renal toxicity and emetogenicity. It can have severe myelosuppressive effects; thrombocytopenia is its dose-limiting toxicity. Carboplatin has been associated with the development of hypersensitivity reactions [32, 36], usually after administration of more than 6 cycles, which can generally be overcome with desensitization protocols.

Oxaliplatin

Oxaliplatin, most commonly utilized in colorectal, gastric, and pancreatic cancers, is characterized by a 1,2-diaminocycloheane carrier ligand [32, 37]. While it is believed that its mechanism of action is similar to cisplatin and carboplatin, including forming cross-links between guanine nucleic acid bases of adjacent nucleotides, oxaliplatin is typically considered more cytotoxic than cisplatin. It can be effective in tumors that have become cisplatin or carboplatin resistant [38]. One possible mechanism for its increased efficacy includes the production of larger oxaliplatin-DNA adducts, secondary to the large 1,2-diaminocycloheane carrier, which are more problematic for DNA repair pathways to correct [32, 38]. Unfortunately, ovarian cancers upregulate genes encoding the nucleotide excision pathway, which is a DNA repair pathway more adept at correcting the interstrand and intrastrand cross-links created by oxaliplatin, theoretically limiting its potential impact in treating cisplatin/carboplatin-resistant ovarian chemotherapy [36]. Similar to carboplatin, oxaliplatin is associated with less nephrotoxicity relative to cisplatin. It also exhibits fewer myelosuppressive effects than cisplatin or carboplatin. Dose-limiting toxicity is neurotoxicity; other side effects include hypersensitivity reactions and nausea/vomiting. Neurotoxicity frequently resolves within 3–4 months of its discontinuation and is typically more reversible than the neurologic effects associated with cisplatin [32, 36].

Microtubule-Binding Agents

Microtubules are an essential component to a variety of cellular functions. These dynamic hollow heterodimers composed of alpha- and beta-tubulin subunits are fundamental in constructing the mitotic spindle and orchestrating successful cellular divisions. Additionally, they organize and support the interior of the cells and act as the scaffolding necessary to move organelles from one area of the cell to another [39]. In oncology, microtubules have been a particularly successful target in limiting tumor growth, as well as initiating tumor cell apoptosis. Microtubules are defined by their dynamic growth through beta and alpha tubule non-covalent dimerization that can lead to rapid elongation as well as rapid shortening [40]. During mitosis, microtubules, comprising the mitotic spindle, rapidly elongate and shorten in a highly choreographed mechanism to enable the attachment of the microtubule to the kinetochores of the chromosomes and thereby correctly allocating chromosomes during cellular division [41, 42]. If during any step of mitosis, the mitotic spindle is unable to form or

the microtubules are unable to attach to the chromosomes, apoptosis can be initiated [41]. Additionally, research suggests that some microtubule-targeting agents can depolymerize microtubules involved in the support of vasculature, thereby interrupting the blood supply to the tumor [43]. There are two primary mechanisms through which microtubules are targeted by chemotherapy drugs: the first by depolymerizing agents such as vinca alkaloids, and the second via microtubule-stabilizing agents, which includes the taxanes and epothilones [40].

Taxanes

Paclitaxel is an extract discovered in 1971 from the bark of the Pacific yew tree that preceded the discovery of docetaxel, a synthetic derivative of an extract from the European yew tree, in the 1980s [40, 44]. Both drugs exert their antitumor properties by binding the beta-tubulin subunits of the microtubule, thereby effectively stabilizing the tubulin polymer and preventing the dynamic elongation and shortening that is essential to microtubule function [40]. While their mechanism of action is similar, due to differences in their pharmacokinetics, paclitaxel and docetaxel ultimately have slightly different overall effects on the cell cycle. Paclitaxel has a higher affinity for the mitotic spindle during the G2 and M phase of the cell cycle, while docetaxel may act more specifically on centrosomes during the S phase in addition to the G2 and M phase of the cell cycle [44]. One side effect common to both drugs, which is actually secondary to the solubilizing agents, includes hypersensitivity reactions mediated by the release of histamines from basophils. In many circumstances these reactions can be prevented by pre-medicating with steroids and antihistamines [45]. The dose-limiting toxicity of paclitaxel is peripheral neuropathy; other side effects include myalgias, onycholysis, neutropenia, and transient bradycardia. Docetaxel is often considered less neurotoxic; dose-limiting toxicity is neutropenia. Additionally, fluid retention is common and can lead to pleural effusions as well as ascites. Other side effects for docetaxel include stomatitis and both drugs are associated with nausea and vomiting as well as diarrhea [44, 45].

Epothilones

The epothilones are a group of microtubule-stabilizing agents derived from myxobacterium, a bacterium found in soil. They are believed to act in a mechanism similar to that of paclitaxel, although their exact mechanism of action remains elusive [40]. There is also evidence to suggest that in addition to inhibiting the mitotic spindle, epothilones induce apoptosis by weakening intracellular microtubules [46]. Epothilones can be effective in taxane-resistant cancers and ixabepilone, an epothilone B analog, in clinical trials has been shown to have antitumor activity in platinum- and taxane-resistant ovarian cancer. There are two mechanisms by which ixabepilone and more largely epothilones possibly evade the resistance mechanisms that limit taxane utilization. Firstly, epothilones are not good substrates of the active transport pump p-glycoprotein, which is upregulated in many cancers to prevent accumulation of chemotherapeutic agents. Secondly, mutations in beta-tubulin converting it from the constitutively expressed class I beta-tubulin to class III beta-tubulin or upregulation of class III beta-tubulin, alter the binding site of the taxanes, essentially reducing affinity. This adaptation in the beta-tubulin structure does not impact the binding affinity of epothilones [46, 47].

Topoisomerase Inhibitors

The enzyme topoisomerase functions to unwind deoxyribonucleic acid (DNA) that becomes supercoiled during replication, transcription, and repair. It involves inducing a break in the DNA strand followed by untangling then sealing of the interruption. Topoisomerase inhibitors target this enzyme by preventing the re-ligation of the DNA strand breaks through stabilization of the cleavable complex. Without this process, breaks accumulate leading to arrest of cell division in the late S or early G2 phase [48] and ultimately cancer

cell apoptosis [49]. Type I topoisomerase cuts a single strand of DNA without utilizing adenosine triphosphate (ATP) while type II topoisomerase cuts both strands through ATP-dependent hydrolysis [50].

Etoposide

Etoposide is a semisynthetic derivative of podophyllotoxin. It specifically inhibits type II topoisomerase. Myelosuppression is the dose-limiting toxicity. Adverse effects include mucositis, alopecia, gastrointestinal, hepatotoxicity, hypersensitivity reaction, and secondary leukemia [50–53]. Hypotension can occur if administered too rapidly.

Topotecan and Irinotecan

Camptothecin, an extract from the tree *Camptotheca acuminata*, has antineoplastic effects [54, 55]. Due to its notable toxicity, the semisynthetic derivatives topotecan and irinotecan were developed [54, 55]. For topotecan, the dose-limiting toxicity is myelosuppression [53, 54]. Other adverse effects include alopecia (75%), fatigue, and gastrointestinal, stomatitis, dyspnea, and asthenia [53, 56–58]. For irinotecan, dose-limiting toxicities are myelosuppression and gastrointestinal, particularly diarrhea [54, 59, 60]. Bodurka noted fatigue to also be a dose-limiting toxicity [60]. Irinotecan is a prodrug, converted to its active form (SN38) by deesterification in the liver.

Nucleoside Analogs

Nucleoside analogs become incorporated into tumor cell DNA during the S, or DNA synthesis, phase of the cell cycle by imitating endogenous nucleosides. This results in an error that inhibits further DNA synthesis and ultimately causes tumor cell apoptosis.

Gemcitabine

Gemcitabine undergoes intracellular conversion to become active metabolites gemcitabine diphosphate and gemcitabine triphosphate. The former functions by blocking ribonucleotide reductase, an enzyme responsible for synthesizing DNA precursors. The latter inhibits DNA polymerase, thus preventing DNA assembly. Myelosuppression is the dose-limiting toxicity [53, 61]. Cardiac, pulmonary, and thrombotic microangiopathy toxicities can develop with cumulative doses [53]. Other adverse effects are hepatotoxicity [61], flu-like symptoms, vomiting, and edema [53, 62].

Capecitabine and 5-Fluorouracil

Capecitabine is an oral prodrug that undergoes metabolization to 5-fluorouracil (5-FU) through the action of thymidine phosphorylase. Within tumors, higher levels of thymidine phosphorylase exist in comparison to normal tissue [63]. 5-FU subsequently blocks thymidylate synthetase, which is responsible for synthesizing the pyrimidine thymidine. Without thymidine, DNA synthesis cannot continue. Inhibition of ribonucleic acid (RNA) synthesis also occurs by 5-FU, incorporation into RNA, in place of uridine. Dose-limiting toxicities of capecitabine are palmar-plantar erythrodysesthesia (PPE) and diarrhea; myelosuppression, nausea, vomiting, hepatotoxicity, stomatitis, and fatigue are less common adverse effects [64–66]. With 5-FU, toxicities include PPE, gastrointestinal, mucositis, myelosuppression [63, 67], cardiovascular [68, 69], and neural [70].

Folate Antimetabolites

This class of chemotherapeutics binds dihydrofolate reductase in order to impede conversion of dihydrofolate to tetrahydrofolate. Additionally, they inhibit thymidylate synthetase. This blocks production of purine and thymidine nucleic acids, and subsequently prevents DNA synthesis. Folate antimetabolities are cell cycle specific for the early S phase. Leucovorin rescue leads to selective reactivation of dihydrofolate reductase in normal cells to reduce toxicities [71]. Methotrexate and pemetrexed target rapidly dividing cells, and hence their antineoplastic effects.

Methotrexate

Administration is either IV or intramuscular (IM). The dose-limiting toxicities are myelosuppression and mucositis [72]. Other adverse effects include diarrhea, rash, alopecia, eye disorders, pleuritic chest pain, nephrotoxicity, and hepatotoxicity [71, 73, 74].

Pemetrexed

In addition to the mechanisms of action described above, pemetrexed also inhibits glycinamide ribonucleotide formyltransferase and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase, other enzymes involved in purine synthesis. The dose-limiting toxicity is myelosuppression [75, 76]. Other notable toxicities include mucositis, alopecia, fatigue, and gastrointestinal [77–79]. Toxicity can be reduced through folic acid (400–1000 μg po qday beginning 7 days prior to infusion) and cobalamin (1000 μg IM 7 days prior to infusion and every 3 cycles) supplementation without affecting antineoplastic activity [75, 78].

Antineoplastic Antibiotics

A number of antineoplastic antibiotics are derived from the *Streptomyces* fungus.

Doxorubicin

Doxorubicin is an anthracycline antibiotic with at least three proposed mechanisms of action: (1) intercalation with DNA, thus preventing replication; (2) inhibition of topoisomerase II, hindering DNA replication and leading to cell apoptosis; and (3) generation of free radicals resulting in DNA and cell membrane damage. It has cell cycle specificity for the late S phase. Myelosuppression is the dose-limiting toxicity. It is also associated with cardiotoxicity, alopecia, nausea, vomiting, and mucosal ulcerations [57].

The pegylated formulation of doxorubicin involves a polyethylene glycol coating and liposomal encapsulation. This increases drug dissemination into tumor cells. Given the difference in formulation, pegylated doxorubicin is affiliated with a different set of toxicities, including palmar-plantar erythrodysesthesia, myelosuppression, and stomatitis [57, 80] as discussed earlier.

Bleomycin

This antineoplastic antibiotic intercalates with guanine/cytosine-rich portions of DNA. It then binds with iron-oxygen complexes leading to an oxidative reaction. Free oxygen radicals are generated that result in breakage of DNA strands. The cytotoxicity is cell cycle specific for the M and G2 phases [81]. Bleomycin is associated with dose-limiting pulmonary toxicity [82]. The mix of oxidative damage and inflammatory cytokines can cause endothelial damage of the lung vasculature and subsequent fibrosis, as well as fever. Pulmonary toxicity is more common with cumulative doses >400 U and is related to deficiency in deactivating enzymes. Other associated toxicities are nausea, vomiting, stomatitis, and alopecia [83, 84].

Actinomycin D

In a similar manner, actinomycin D intercalates with guanine-cytosine rich areas of DNA inhibiting DNA, RNA, and protein synthesis. It demonstrates cell cycle specificity for the G1 phase. Toxicities include vomiting, stomatitis, alopecia, as well as hepatic, dermatologic, and hematologic side effects [85–87].

Vinca Plant Alkaloids

Vinblastine, vincristine, and vinorelbine are isolated from the *Vinca rosea* plant. By binding to proteins of the mitotic spindle, they impede microtubule assembly. Metaphase, and thus mitosis, cannot proceed making them cell cycle specific for the M phase. There may also be a role in disrupting nucleic acid and protein production. Between vinblastine and vincristine, minimal differences in their capacity to inhibit bovine tubulin polymerization were found [88]. Given their similar efficacy in blocking tubulin but differing toxicity profiles, other mechanisms of action may exist [88].

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid. In contrast to the other vinca alkaloids, it is associated with a reduced impact on axonal microtubules. This theoretically may result in less neurotoxicity (Burger 1999); however, in platinum-resistant ovarian cancer the most common reason for discontinuation is still worsening of pre-existing paresthesias rather than other adverse effects [89]. Myelosuppression, nausea, vomiting, constipation, and stomatitis are also prevalent [89–91].

Vinblastine

With vinblastine, the dose-limiting toxicity is typically myelosuppression [88]. Common toxicities include vomiting, neuropathy, and constitutional [92].

Vincristine

In general, vincristine is considered to have a mild toxicity risk. Neurotoxicity is the most common adverse effect [88] followed by nausea in women treated for a refractory gynecologic malignancy. For vincristine, neural, myelosuppressive, cranial nerve palsies, and gastrointestinal toxicities are common.

Alkylating and Alkylating-Like Agents

The primary mechanism of action for this class involves adding an alkyl group to nucleic acids. As a result, fragmentation, cross-linking, and mispairing occur. This hinders synthesis of DNA, RNA, and protein, culminating in cell apoptosis. The alkylating agents do not demonstrate cell cycle specificity. Among various chemotherapy classes, alkylating agents are gonadotoxic and very commonly precipitate ovarian failure [93, 94].

Cyclophosphamide

For cyclophosphamide, toxicities include myelosuppression, hemorrhagic cystitis, cardiac [51], and alopecia [95]. Dose adjustments are indicated with hematologic toxicity and hemorrhagic cystitis. At lower doses, the hematologic toxicity is platelet-sparing. At higher doses, mesna co-administration functions to chelate the toxic byproduct acrolein, thereby reducing urothelial toxicity [51]. It generally has reduced neurotoxicity compared to ifosfamide.

Ifosfamide

Ifosfamide is a synthetic analog of cyclophosphamide. The dose-limiting toxicities are hemorrhagic cystitis and renal tubular necrosis [51]. As with cyclophosphamide, mesna is used to minimize hemorrhagic cystitis [96]. Other toxicities include hematologic and encephalopathy [96]. The risk for neurotoxicity increases with poor nutritional status, as it is albumin-bound [97].

Mitomycin C

Mitomycin C is activated into an alkylating agent. In addition to the mechanisms of action described above, it has the capacity to generate free radicals similar to the other antineoplastic antibiotics [98]. Of the toxicities, myelosuppression most commonly occurs and is dose limiting while skin necrosis from extravasation, cardiac, pulmonary, renal, and hepatic toxicities are less common [51, 99–101].

Therapeutic Principles for Advanced-Stage Epithelial Histologies

High-Grade Serous and Advanced Clear Cell

High-grade serous carcinoma (HGSC) is the most prevalent form of ovarian cancer. It typically presents with insidious symptoms such as vague pain or bloating in the sixth and seventh decades of a woman's life, with a mean age of diagnosis of 63 years. HGSC is typically associated with significant omental and peritoneal metastatic disease at the time of diagnosis secondary to poor tests for early detection. HGSC is histologically distinguished by marked nuclear atypia, with nuclei that can be as large as 50 μm in diameter, as well as a large proportion of abnormal mitotic cells and necrosis [36]. It is considered a

separate entity from low-grade serous ovarian carcinoma (LGSC) and is not merely a natural progression of LGSC into a more malignant disease. Tubal intraepithelial carcinoma represents the origin of HGSC in a number of instances. In other cases, HGSC appears to arise from serous ovarian inclusion cysts [102]. Either way, HGSC is genetically distinct from LGSC. High-grade tumors are characterized by TP53 mutations, a molecule dubbed the "guardian of the genome" due to its diverse and massively important task of monitoring DNA repair as well as cell division and apoptosis. BRCA1 and 2 mutations are prevalent in both sporadic and hereditary forms of the cancer. It has a low frequency of KRAS and BRAF mutations, which are associated with LGSC [102].

While HGSC can present with areas containing clear cell features on histology, ovarian clear cell carcinoma is a distinct malignancy with a similarly poor prognosis. It presents most commonly in the fifth and sixth decades of life with symptoms of bloating and pelvic pain and a predominance in Asians [36, 103]. It is more commonly associated with thrombotic events as well as paraneoplastic hypercalcemia compared to other forms of ovarian cancer. There is a distinct correlation between endometriosis and development of clear cell ovarian carcinoma, and up to 1/3 of clear cell ovarian tumors are found within areas of endometriosis [36, 102].

NCCN First-Line Agents: Adjuvant Therapy Following Primary Debulking Surgery

Ovarian cancer is a surgically staged disease by total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and peri-aortic lymphadenectomy, and peritoneal biopsies. Traditionally, surgical cytoreduction has been the initial step in ovarian cancer treatment [23, 104], though neoadjuvant chemotherapy followed by interval debulking and at least 3 cycles of postoperative chemotherapy is an accepted approach for patients with extensive disease or medical contraindications to immediate surgery such as venous thromboembolism. Even in the absence of gross IP metastatic disease, peritoneal fluid should be sent for cytology as well as random biopsies from the pelvis, paracolic gutters, and diaphragm. Para-aortic lymph node sampling as high as the renal vessels as well as pelvic lymph node dissection of the common iliac vessels extending to the external iliac vessels, the hypogastric vessels and at least to the obturator nerve had been considered standard of care [23], though this dogma has recently been called into question.

Metastasis in ovarian cancer tends to be confined to the intra-abdominal space with the mechanism of spread established to be from exfoliation of cells from areas of tumor tissue into the peritoneal fluid that then implant at distant sites, making peritoneal washings important [104]. In 1975, Dr. Thomas Griffiths published a seminal paper proving that patients who had less than 1.5 cm of residual macroscopic disease after surgery had improved survival rates compared to those with larger areas of residual disease [105]. Subsequent studies by Hoskins et al. in 1994 bolstered this data by establishing that in patients were optimal tumor debulking was unable to be achieved, those with residual tumor diameters of less than 2 cm had improved survival outcomes compared to those with larger diameter residual disease. This research also suggested that there is no significant difference in survival outcomes for patient based on stratification of gross residual disease diameter for diameters larger than 2 cm [106]. Further research suggests that even patients with unresectable liver metastases have improved survival outcomes with extrahepatic tumor debulking to less than 1 cm. The GOG continues to define optimal tumor debulking as less than 1 cm of gross residual disease, though the goal of cytoreductive surgery is debulking to no residual disease.

Following surgical treatment, adjuvant chemotherapy is recommended for stage II–IV epithelial ovarian pathologies regardless if all macroscopic disease has been resected. There are two broad approaches to administration: IV versus IV with concomitant IP chemotherapy [23].

Intravenous Regimens

Carboplatin and Paclitaxel

Evolution of the 3-Weekly Regimen

After 1996, the IV chemotherapeutic protocol for advanced-stage ovarian cancer transitioned from cyclophosphamide with cisplatin to cisplatin with paclitaxel based on results of GOG 111. In this study, patients with advanced ovarian cancer and greater than 1 cm of residual disease after cytoreductive surgery who received cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 every 3 weeks had a statically significant improved progression-free survival (PFS) compared to the group treated with cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2 every 3 weeks. Participants in the cisplatin and paclitaxel arm experienced a 17.9-month PFS compared to 12.9 months in the group treated with cyclophosphamide plus cisplatin [107]. This trial was further corroborated by a European-Canadian trial that showed statistically significant improved survival and a favorable side effect profile [108]. GOG 158 compared carboplatin plus paclitaxel versus cisplatin plus paclitaxel in optimally cytoreduced advanced-stage epithelial ovarian cancer. The results showed that both regimens were equally effective, but that the carboplatin regimen was associated with significantly fewer renal, gastrointestinal as well as hematologic toxicities [3]. Currently, the approved 3-weekly IV regimen is 175 mg/m^2 paclitaxel administered over 3 h followed by AUC 5–6 carboplatin administered over 1 h every 3 weeks for 6 cycles.

Dose Density

The Norton-Simon hypothesis maintains that the relationship between drug concentration and anticancer effect is not always linear [109], and that front-loading drug in high doses may fail because more drug may not equate to enhanced killing. According to this theory, chemotherapy is most effective when cells are growing rapidly, so administration during the initial period of regrowth is predicted to be most favorable. In this model, to target regrowth of tumor populations it is imperative to administer an effect dose over as short a time period as possible.

The results of several large studies comparing dose-dense regimens, defined as carboplatin AUC 6 on cycle day 1 followed by paclitaxel 80 mg/m^2 on cycle days 1, 8 and 15 every 3 weeks for 6 weeks, versus conventional carboplatin/paclitaxel regimens have been conflicting [23]. A randomized control trial was completed in the United States comparing these regimens with or without the addition of bevacizumab. In patients who received bevacizumab, there was no difference in PFS between the two groups when considered as intention-to-treat. There were statistically significant differences in toxicity, and patients who received the dose-dense regimen were more likely to experience sensory neuropathy [110]. The long-term results from a randomized, controlled open-label trial by the Japanese Gynecologic Oncology Group (JGOG) published in 2013 had different results. In that study, the dose-dense regimen was associated with a statistically significant PFS, as well as an OS benefit. The patients were followed for an average for 76.8 months, and those who received the dose-dense regimen had a 28.2-month PFS compared to a 17.5-month progressions-free survival with a hazard's ratio of 0.76 and a *P*-value of 0.0037. Additionally, median OS was 100.5 months in the dose-dense group and only 62.2 months for the conventional group with a hazard ratio of 0.79 and a *P*-value of 0.039 [111]. A subsequent European trial showed similar results to those of the American group. The European trial included patients undergoing neoadjuvant. Overall, there was no statistical difference in PFS between dose-dense and the 3-week dosing. There were also no statistically significant differences in side effects between the two groups [112]. A fourth clinical trial performed in France and Italy compared carboplatin plus paclitaxel every 3 weeks to a modified dose-dense regimen of carboplatin AUC 2 mg/mL plus paclitaxel 60 mg/m^2. Any woman with stage IC–IV ovarian cancer who had not received prior chemotherapy was included in this randomized

control trial. The results also failed to show a significant difference between the two treatment regimens and the side effect profile was similar if not slightly better for the dose-dense protocol [113]. NCCN guidelines currently include paclitaxel 80 mg/m^2 on day 1, 8, and 15 with carboplatin AUC 5–6 on day 1 every 3 weeks for 6 cycles as a primary treatment option for stage II–IV disease following cytoreductive surgery [23]. For the elderly or individuals where there is a concern for increased toxicity the regimen can be adjusted to 60 mg/m^2 paclitaxel over 1 h and carboplatin AUC 2 over 30 min weekly for 18 weeks [23].

Bevacizumab in the Front-Line Setting

There is evidence to suggest that the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, to carboplatin/paclitaxel is beneficial in patients at a higher risk of disease progression [114, 115]. There have been two major randomized controlled clinical studies involving a 3-week dosing regimen of carboplatin with paclitaxel for 6 cycles with bevacizumab. The bevacizumab was continued as 3-week cycles in both trials as maintenance. In both trials there was an estimated PFS benefit approaching 4 months, although in one trial the benefit was primarily seen in patients with an increased risk of progression [114, 115]. The bevacizumab patients demonstrated higher rates of side effects including hypertension and gastrointestinal manifestations [114, 115], and no improvement in OS. NCCN recommended options for using bevacizumab in the first-line setting for treatment of stage II–IV disease include the addition of bevacizumab 7.5 mg/kg day 1 for up to 18 cycles to paclitaxel 175 mg/m^2 IV and carboplatin AUC 5–6 on day 1 for 5–6 cycles (21-day cycle), or bevacizumab 15 mg/kg day 1 of cycle 2 and continuing for up to 22 cycles, to paclitaxel 175 mg/m^2 IV and carboplatin AUC 6 on day 1 for 6 cycles (21-day cycle) [23]. Bevacizumab may be particularly beneficial in women with massive ascites, for stage IV disease, and following suboptimal debulking.

Carboplatin and Docetaxel

Docetaxel at 60–75 mg/m^2 IV with carboplatin AUC 5–6 IV every 3 weeks for 6 total cycles is a regimen recommended by the NCCN as a first-line chemotherapy option for stage II–IV HGSC [23]. This regimen has been primarily studied in patients with recurrent ovarian cancer that is paclitaxel resistant. The first trial to study the potential utility of this regimen was published in 2002 as GOG 126-J and was developed in response to research proving the utility of docetaxel in paclitaxel-resistant breast cancer [116]. This study involved 60 patients and showed a statistically significant response in 22.4% of patients with about a 2.5-month duration of response [116]. Additional studies including one comprised of 36 patients and second comprised of 25 patients continued to show a survival benefit with ORRs, defined as complete or partial responses, of 67% and 72%, respectively [117, 118]. Grade 3 or 4 neutropenia was the predominant side effect in all of the trials, although there was only one associated death among the three trials. Other side effects included diarrhea as well as carboplatin hypersensitivity reactions [116–118]. Docetaxel may have less neuropathy than other taxanes.

Carboplatin and Pegylated Liposomal Doxorubicin

Another first-line chemotherapy option for stage II–IV HGSC is carboplatin AUC 5 with pegylated liposomal doxorubicin 30 mg/m^2 every 4 weeks for 6 cycles [23]. In 2012, an international randomized control trial (CALYPSO) compared carboplatin-paclitaxel to carboplatin-pegylated liposomal doxorubicin in patients with platinum-sensitive recurrent ovarian cancer. The primary end point was PFS which showed a statistically significant difference favoring doxorubicin of 11.3 months compared to 9.4 months in the paclitaxel arm. There was no statistically significant difference in OS [119]. While the authors of this trial argued that pegylated liposomal doxorubicin is superior to paclitaxel secondary to reduced neurotoxicity side effects and reduced carbo-

platin hypersensitivity reactions, a Cochrane meta-analysis demonstrated that the regimen is associated with more severe anemia and thrombocytopenia compared to paclitaxel [119, 120].

Intravenous and Intraperitoneal

Ovarian cancer even in advanced stages tends to be confined to the peritoneal cavity. Secondary to this observation, beginning in the 1950s there was interest in directly introducing chemotherapeutic agents to ovarian tumor sites via IP therapy. Multiple trials comparing different chemotherapeutic combinations of IV/IP formulations have been examined [121]. In 1994, a small randomized trial was published comparing IP cisplatin with IP etoposide to IV cisplatin with IV cyclophosphamide; this determined that these regimens were comparable in terms of survival as well as side effect profile in stage II–III ovarian cancer patients as adjuvant therapy [122]. A study published in 1999 compared IV carboplatin with IV cyclophosphamide to IP carboplatin with IV cyclophosphamide and determined that both regimens were equivocal in terms of time to progression and median survival, but that the IP group was associated with significantly fewer hematologic side effects [123]. Similar results were published in 2000 in a study that compared IV cisplatin to IP cisplatin. Both regimens were comparable in terms of survival but the IP regimen was associated with fewer hematologic toxicities [124]. Another study published that same year hinted at a potential benefit to IP formulations of cisplatin or IV cisplatin when patients received concomitant IV epidoxorubicin and IV cyclophosphamide to the cisplatin. The median OS was 67 months for the IP group and 51 months for the IV group. Additionally, median PFS was 42 months in the IP group and 25 months in the IV group. This study was unable to prove that these results were statistically significant though and there were notable compliance issues in the IP group [125]. The pivotal GOG 172 study published in the *New England Journal of Medicine* in 2006 established a statistically significant benefit of IP administration of paclitaxel and cisplatin over IV administration alone. The study compared a regimen of IV paclitaxel with IV cisplatin to a regimen of IV paclitaxel with IP paclitaxel and IP cisplatin in patients with optimally cytoreduced surgery and stage III epithelial ovarian or peritoneal cancer. Specifically, the regimen was 135 mg/m^2 IV paclitaxel given over 24 h on day 1 followed by either 75 mg/m^2 IV cisplatin or 100 mg/m^2 IP cisplatin on day 2 with 60 mg/m^2 of IP paclitaxel on day 8 in the IP arm. The median time of survival was 49.7 months in the IV only group and 65.6 months in the IP group. Additionally, PFS was 18.3 in the IV only group and 23.8 months in the IP group. Both of these results were statistically significant. The IP group was associated with significantly worse hematologic, metabolic, gastrointestinal, and neurologic side effects. Additionally, only 42% of patients initially randomized to the IP group were able to complete all six cycles [126]. Despite the impressive survival outcomes, secondary to the significant side effect profile and the need for inpatient administration, this regimen of IP/IV combination chemotherapy was not readily adopted by clinicians. In an effort to mitigate the side effects and create an outpatient regimen, another trial published in 2012 studied a modified regimen of 135 mg/m^2 IV paclitaxel given over 3 h on day 1 followed by 75 mg/m^2 IP cisplatin on day 2 and 60 mg/m^2 of IP paclitaxel on day 8 given every 21 days for 6 cycles. The outcomes were similar to those of GOG 172 with the median PFS time found to be 29 months and OS to be 67 months, but there was improved toxicity and compliance. Eighty percent of patient completed 4 cycles, while 56% completed all 6 cycles [127]. GOG 252 compared three regimens (outlined in Table 9.1) and failed to illustrate significant differences in median PFS among the three arms for individuals with no visible disease after tumor debulking in stage 3 epithelial cancer [128]. The NCCN does suggest an IP/IV regimen as a first-line chemotherapy option for stage II–IV epithelial cancer patients outlined in Table 9.2 [23].

Table 9.1 Chemotherapy Arms in GOG 252

	Arm 1	Arm 2	Arm 3
Paclitaxel IV	80 mg/m^2 IV over 1 h days 1, 8, 15	80 mg/m^2 IV over 1 h days 1, 8, 15	135 mg/m^2 IV over 3 h days 1
Paclitaxel IP			60 mg/m^2 IP day 8
Carboplatin IV	AUC 6 IV on day 1		
Carboplatin IP		AUC 6 IP on day 1	
Cisplatin IP			75 mg/m^2 IP day 2
Bevacizumab IV	15 mg/kg IV day 1 beginning on cycle 2	15 mg/kg IV day beginning on cycle 2	15 mg/kg IV day beginning on cycle 2

[a] Cycles were 3 weeks long
[b] Carboplatin, cisplatin, and paclitaxel were continued for 6 total cycles in each arm regardless if IP or IV
[c] Bevacizumab was started on cycle 2 and continued for 22 cycles

Table 9.2 NCCN IP/IV Regimen

	Paclitaxel IV	Cisplatin IP	Paclitaxel IP
Day 1	135 mg/m^2 over 3 or 24 h		
Day 2		75–100 mg/m^2	
Day 3			60 mg/m^2

[a] Cycle were 3 weeks long
[b] Regimen continued for 6 cycles

Neoadjuvant Therapy and Interval Debulking

Primary cytoreductive surgery can be associated with significant morbidity especially in patients presenting with a significant disease burden and comorbidities. Neoadjuvant chemotherapy (NACT) was introduced as a tactic to reduce the disease burden prior to surgery, thereby reducing the extent of surgery required to obtain optimal or as optimal as possible surgical resection. A randomized controlled trial was conducted in Europe and published in 2010. The results indicated that 3 cycles of platinum-based chemotherapy as NACT followed by interval debulking surgery and a minimum of 3 further cycles of platinum-chemotherapy was non-inferior to primary cytoreductive surgery followed by adjuvant therapy. Overall, the most important predictor of survival remained maximum resection of disease during surgery whether it was interval or primary debulking surgery [129]. Other studies continue to suggest non-inferiority of NACT with interval debulking surgery and some research even suggests it may improve survival in women with stage IV disease [130]. NACT may be associated with less surgical morbidity, and particularly beneficial in women with tumors >5 cm. A confirmatory study by JGOG (0602) is ongoing [131]. Overall, there is limited data regarding IV/IP regimens as neoadjuvant chemotherapy options. A phase II randomized clinical trial demonstrated comparable toxicities, but it was underpowered to detect any differences in PFS. Currently, NCCN guidelines recommend that any of the primary IV regimens recommended for adjuvant treatment of stage II–IV disease can be used for neoadjuvant therapy before interval debulking surgery but cautions against using bevacizumab as it may been associated with delayed postoperative healing and should be held 6 weeks prior to surgery. IV/IP regimens are not discouraged in NCCN guidelines but are cautioned regarding limited evidence. Lastly NCCN recommends that at minimum 6 cycles of chemotherapy be completed, with a minimum of 3 after interval debulking surgery [23].

Therapeutic Considerations for Other Epithelial Histologies

Carcinosarcoma

Biology and Surgical Approach

Carcinosarcoma, also called mixed malignant Müllerian tumor, comprises an amalgamation of malignant epithelial (carcinoma) and mesenchymal (sarcoma) cells. This histological type exhibits a poor prognosis due to its particularly aggressive nature. The 5-year survival rate ranges from 6% to 39% [132]. Up to 82% of carcinosarcomas of the female genital tract demonstrate p53 positivity, and in both the epithelial and mesenchymal constituents, the same muta-

tion in p53 can be found [133]. While applying CA 125 level to assessing chemotherapy response is not fully validated in carcinosarcoma, it may be applicable [134].

Irrespective of age and stage, patients with ovarian carcinosarcoma should undergo complete surgical staging and maximal cytoreduction (Fig. 9.1). Given the aggressive nature of carcinosarcoma, fertility sparing surgery is not recommended. The FIGO (Federation Internationale de Gynecologie et d'Obstetrique) staging system mirrors that of other ovarian cancers. Many retrospective assessments demonstrated the significant utility of optimal cytoreductive surgery in terms of prognosis [134–147]. While the role of surgical debulking has not consistently conferred a statistically significant prognostic advantage [132, 148–154], it remains the goal.

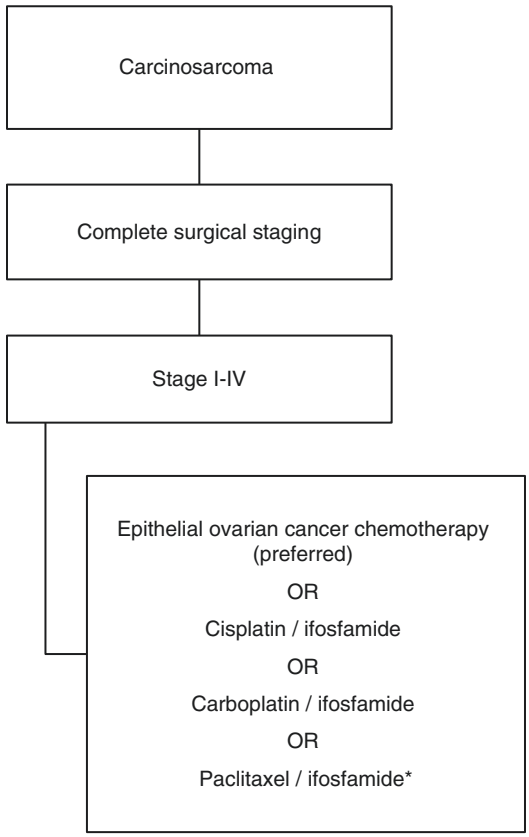

Fig. 9.1 Ovarian carcinosarcoma management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *Category 2B. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

Chemotherapy

For primary chemotherapy in patients with carcinosarcoma, the NCCN recommended category 2A options include the IV and IP/IV epithelial regimens (preferred), carboplatin/ifosfamide, and cisplatin/ifosfamide [23]. Paclitaxel/ifosfamide is a category 2B option [23]. Utilization of platinum-based regimens is associated with improved outcomes [138, 142, 143, 155, 156]. The ORRs for various platinum-based regimens are 20–85% [134, 138–140, 143, 144, 150, 152, 157–162].

Taxane and platinum combination chemotherapies produce an ORR ranging from 50% to 72% [139, 145, 153, 163] and median overall survival between 18 and 53 months [139, 144, 145, 153, 154, 156, 163] (Table 9.3). Superiority of paclitaxel/platinum to other platinum-based regimens (cisplatin/ifosfamide, cisplatin/adriamycin, cyclophosphamide/adriamycin, or etoposide/ifosfamide) was demonstrated by statistically significant improved outcomes for median PFS (35 vs. 12 months) and OS (53 vs. 21 months) [144]. Some retrospective studies comparing paclitaxel/carboplatin to cisplatin/ifosfamide showed significantly inferior PFS and OS of the former (PFS: 12 months vs. not reached at 28 months; at 2 years, 55% vs. 81% alive); however, the outcome differences were not conferred to individuals with advanced-stage disease [142]. Other retrospective studies described improved outcomes with cisplatin/ifosfamide although not necessarily reaching statistically significance [154, 156]. For cisplatin/ifosfamide, the ORR was reported as 89% [164]. Despite these findings, the ifosfamide/cisplatin regimen has also been associated with a truncated duration of response and substantial toxicity [164]. Table 9.4 describes reported outcomes of platinum/ifosfamide treatment. Recently, results of GOG 261,

Table 9.3 Taxane with platinum chemotherapy in ovarian carcinosarcomas

Study	Sit 2000	Duska 2002	Rutledge 2006	Leiser 2007	Silasi 2008	Chun 2011	Rauh-Hain 2011	Brackmann 2016
Regimen	Paclitaxel/ Carboplatin	Paclitaxel/ Platinum	Paclitaxel/ Carboplatin	Taxane/ Platinum	Paclitaxel/ Carboplatin	Paclitaxel/ Platinum	Taxane / Platinum	Paclitaxel/ Carboplatin
Number of participants	6	28	16	30	4	18	50	13
Stages involved	I–III	I–IV	I–IV	II–IV	III, IV	I–IV	III, IV	–
Median number of cycles	7	6 (range 3–8)[a]	6	6[b]	6.5 (range 6–9)	6 (range 2–9)	6 (range 1–8)	–
Overall response rate (CR + PR)	–	72%	–	63%	–	–	62%	–
Median PFS	–	9 months	12 months	12 months	6 months	35 months	11 months	9.4 months
Median OS	19 months	27.1 months	–	43 months	38 months	53 months	24 months	18.3 months

CR complete response, *PR* partial response, *PFS* progression-free survival, *OS* overall survival

[a] Number of cycles not available for all patients

[b] Average, rather than median, number of cycles for taxane and platinum, respectively

Table 9.4 Outcomes of ifosfamide with platinum chemotherapy in ovarian carcinosarcoma

Study	Sit 2000	Rutledge 2006	Crotzer 2007	Silasi 2008	Brackmann 2016
Regimen	Platinum/Ifosfamide	Cisplatin/Ifosfamide	Cisplatin/Ifosfamide/Mesna	Cisplatin/Ifosfamide	Paclitaxel/Ifosfamide
Number of participants	8	11	9	6	8
Stages involved	II–III	I–IV	II–IV, unstaged	III, IV	–
Median number of cycles	6	6	6 (range 4–6)	6 (range 2, 6)	–
Overall response rate (CR + PR)	–	–	89%	–	–
Median PFS overall	–	Not reached (28+ months)	10 months	13 months	7.8 months
Median OS overall	23 months	–	17.1 months	51 months	19.6 months
Survival by year	–	81% at 2 years	33% at 2 years	83% at 3 years	–

CR complete response, *PR* partial response, *PFS* progression-free survival, *OS* overall survival

a randomized phase 3 trial of paclitaxel plus carboplatin versus paclitaxel plus ifosfamide in chemotherapy-naive patients with stage I–IV, persistent or recurrent carcinosarcoma of the uterus or ovary, were reported in abstract form [165]. Carboplatin/paclitaxel was not inferior to ifosfamide/paclitaxel for OS, and demonstrated longer PFS and similar quality of life and neurotoxicity. Many now accept carboplatin/paclitaxel as a new standard regimen for women with carcinosarcoma.

Low-Grade Serous and Borderline Tumors with Invasive Implants

Biology and Surgical Approach

Low-grade serous carcinoma (LGSC) arises from the gradual progression from serous cystadenoma to borderline tumor to invasive carcinoma [166–168]. It does not progress to HGS disease and instead is a discrete entity [166, 169]. The poor chemoresponsiveness of LGSC may be attributed in part due to its indolent growth [170]. While borderline tumors lack stromal invasion, both non-invasive and invasive pelvic/peritoneal implants are possible. Table 9.5 outlines the histological classification of serous ovarian tumors by the World Health Organization (WHO) [171].

In contrast to high-grade serous, LGSCs commonly possess KRAS, BRAF, or ERBB2 mutations while lacking mutations in the p53 and BRCA genes [166–168]. Additionally, estrogen and progesterone receptor positivity is significantly greater in LGSC [172]. While CA 125 was elevated in a reported 86% of patients [173], normalization is not indicative of prognosis [168]. The management of low-grade serous and borderline ovarian tumors is outlined in Figs. 9.2 and 9.3, respectively.

Table 9.5 WHO histological classification of serous epithelial tumors

Serous epithelial tumors	
Cystadenoma	Benign
Adenofibroma	Benign
Surface papilloma	Benign
Borderline	Borderline
Low grade	Malignant
High grade	Malignant

Due to the relatively chemoresistant nature of LGSCs, comprehensive staging and optimal cytoreductive surgery are critical [174]. Staging of LGSCs follows the same FIGO system as other ovarian cancers. Residual disease in stage III and IV LGSC significantly worsens PFS and OS [175, 176]. For borderline epithelial tumors, fertility-sparing surgery remains an option regardless of the presence of implants as long as the remaining ovary and/or uterus are grossly normal-appearing [177, 178].

Adjuvant Treatment

Postoperatively, stage IA and IB LGSC are safely observed [23]. Several options exist for stage IC, including IV platinum-based chemotherapy [179] for 3–6 cycles, hormonal therapy (category 2B), or observation (category 2B) [23]. Of these, only platinum-based therapy is considered category 2A [23]. For stages II–IV, platinum-based chemotherapy [180] for 6 cycles or hormonal therapy exist as options, the latter of which is category 2B [23]. Active platinum-based chemotherapy options are the same as those used as first-line IV regimens for HGSC. Because LGSCs do not exhibit the same degree of chemosensitivity as HGSC, alternative therapies have been explored [170, 176, 181, 182]. Response rates, PFS, OS to platinum is outlined in Table 9.6. Romero et al. caution against oncluding that chemotherapy should not be administered in LGSCs, particularly given the improvement in CA 125 value and acceptable proportion of disease remaining stable in these studies [183].

Following platinum-based chemotherapy in stage II–IV disease, either surveillance or hormonal maintenance therapy are reasonable. Hormonal maintenance therapy was associated with significantly improved PFS (64.9 months versus 26.4 months, $P < 0.001$), relative to observation alone, but OS was comparable [184]. Acceptable hormonal approaches include aroma-

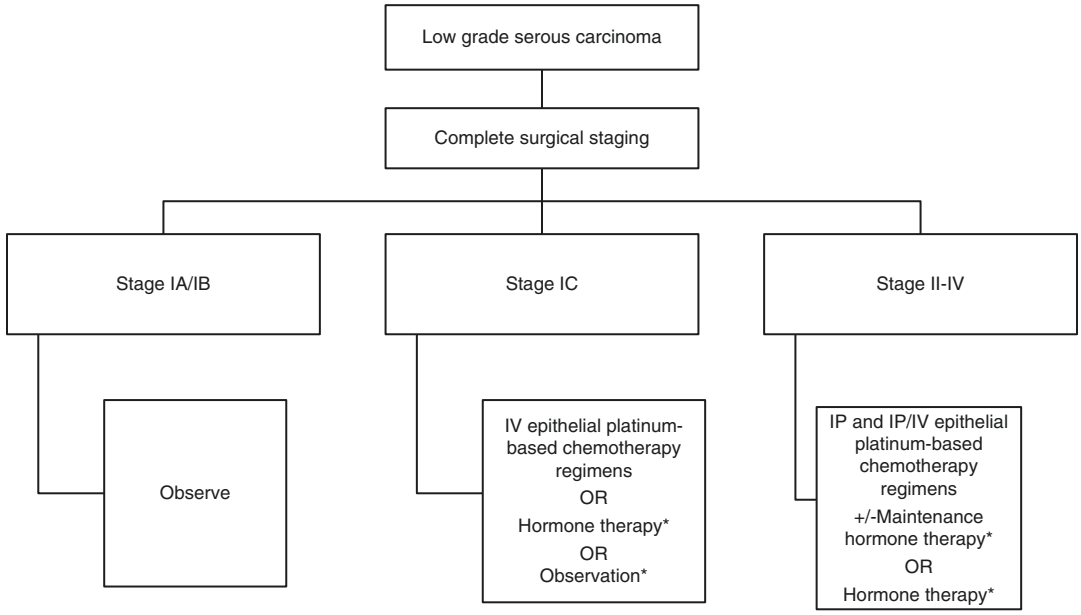

Fig. 9.2 Low-grade serous ovarian carcinoma management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *Category 2B. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

tase inhibitors (anastrozole, letrozole, exemestane), leuprolide acetate, and tamoxifen.

Ovarian borderline epithelial tumors with invasive implants and prior complete surgical resection can be managed in the same manner as LGSCs [185]. If complete surgical staging was not performed, the next step involves undergoing a CT with contrast of the chest, abdomen, and pelvis to assess for residual disease [23]. In those without residual disease, surveillance only is appropriate. Management of residual disease then can be directed by desire for fertility preservation coupled with cytoreductive surgery. Even though restaging procedures resulted in an upstage rate of 14.8–17%, they did not impact recurrence rates or overall survival [186–188]. If invasive implants are present, then preferred therapy proceeds along the same guidelines as for LGSC [178, 185]. With evidence of residual disease, observation rather than surgery is considered category 2B in the NCCN Guidelines in those without invasive implants or unknown invasive implants but category 3 in those with invasive implants noted at prior surgery [23]. In contrast, the Gynecologic Cancer InterGroup (GCIG) Consensus Review does not recommend any adjuvant therapy regardless of stage or invasive implants [189].

Mucinous

Biology and Surgical Approach

Mucinous ovarian tumors include the following histological subtypes based on the WHO classifi-

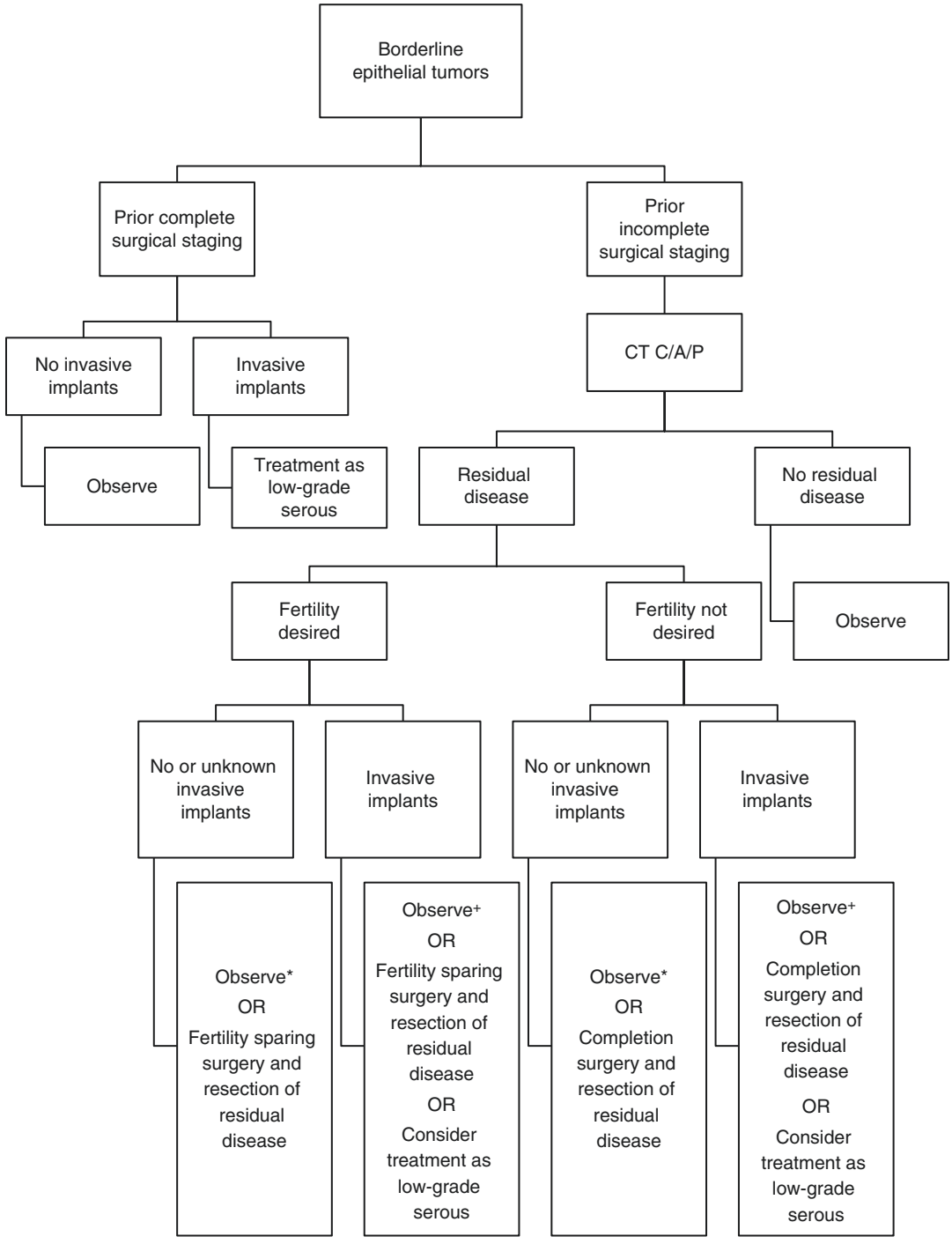

Fig. 9.3 Borderline ovarian tumor management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *CT C/A/P* computed topography with contrast of the chest, abdomen, and pelvis. *Category 2B. +Category 3. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

Table 9.6 Chemotherapy outcomes in low-grade serous ovarian carcinoma

Study	Gershenson 2006	Schmeler 2008	Gershenson 2009	Schmeler 2011	Grabowski 2016	
Regimen	Platinum based	Platinum based	Variety	Primarily platinum based	Platinum/ Paclitaxel	
Classification	Stage II–IV	Neoadjuvant	Recurrent	Peritoneal	LGSC	HGSC
Participants	112	25	58	48	39	80
Median number of cycles	6	–	6	6	6	6
Response rate (CR + PR)	80%[a]	4%	3.7%	–	23.1%	90.0%
Disease free at completion of chemotherapy	52%	–	–	33%	–	–
Median PFS	19.5 months	–	29.0 months	30.5 months	–	–
Median OS	81.8 months	56.1 months	87.1 months	107.6 months	–	–

CR complete response, *PR* partial response, *PFS* progression-free survival, *OS* overall survival
[a]15% of the patients were evaluable; 38% of patients underwent second look surgery: microscopically negative disease in 5%, microscopically positive disease in 33%, macroscopically positive disease in 64%

cation scheme: cystadenoma, adenofibroma, borderline, and carcinoma (Table 9.7) [171]. Of these, only the last is malignant. Mucinous ovarian carcinomas (MOCs) are exceedingly rare and occur at a median age of 52 years [190]. A majority present at an early stage. As many as 64% will be diagnosed in stage I [191], with a 5-year OS of 92%. Response to chemotherapy is poor, and 5-year OS is only 13% for stage IV disease [191]. As opposed to HGSCs, MOCs tend to possess more KRAS than p53 mutations and lack association with BRCA [166, 192–194]. Tumor markers include carcinoembryonic antigen (CEA), CA19-9, CA 125 as well as the ratio of CA 125:CEA [192].

With MOC, establishing the tumor as an ovarian primary versus a metastasis remains challenging. The gastrointestinal (GI) tract, including colon and appendix, is the most common primary site that metastasizes to the ovary [195, 196]. Fifty-seven percent to 63% of mucinous carcinomas initially categorized as an ovarian primary were reclassified as metastatic to the ovary [197]. Since MOCs are particularly difficult to differentiate from metastatic adenocarcinomas, upper and lower GI endoscopy is necessary to further evaluate for a GI primary.

Management of mucinous ovarian carcinoma first involves complete surgical staging following the FIGO system [23]. Suspicion for a primary GI malignancy metastatic to the ovary must be high when navigating this histology; therefore, it is prudent to also examine the stomach, small intestine, large intestine, and pancreas. With mucinous histology, an appendectomy has traditionally been performed, but with overall low yield for metastatic mucinous appendiceal carcinoma [198, 199]. Appendectomy may be reserved for instances of grossly abnormal appearance or pseudomyxoma peritonei [198–200]. However, the GCIG maintains this position is still debated [192].

The continued utility of lymphadenectomy rather than palpation-directed dissection in MOCs has been questioned. Lymph node dissection was not associated with improved outcomes in disease grossly confined to the ovary [201] or of early stage [202]. For clinically suspected stage I and II MOC, 0.8% were upstaged due to lymph node metastases [203]. A higher rate of 1.7% for lymph node metastases discovered in clinically suspected stage I disease was reported but did not translate to increased mortality [204]. In stage I and II MOC, lymphadenectomy can be excluded in grade 1 and 2 disease unless preoperative radiology or intraoperative palpation otherwise reveal lymphadenopathy [205]. A statistically significant difference between lymph

Table 9.7 Outcomes of platinum-based chemotherapy in mucinous ovarian carcinoma versus control with either serous histology or a composite of various histologies

Study	Regimen	Group	Participants	Stages	Response rate	Median PFS	Median OS
Hess 2004	Platinum based	MOC	27	III, IV	26.3%	5.7 months	12.0 months
		Control (Composite)	54	III, IV	64.9%	14.1 months	36.7 months
		P value	–	–	$P = 0.01$	$P < 0.001$	$P < 0.001$
Pectasides 2005	Platinum based	MOC	47	III, IV	38.5%	11.8 months	33.2 months
		Control (Serous)	94	III, IV	70%	20.0 months	38
		P value	–	–	$P = 0.001$	$P = 0.18$	$P = 0.46$
Winter 2007	Paclitaxel/Platinum	MOC	34	III	–	10.5 months	14.8 months
		Control (Serous)	1392	III	–	16.9 months	45.1 months
		P value				$P = 0.006$	$P < 0.001$
Shimada 2009 [4]	Platinum-based	MOC	24	–	12.5%	–	–
		Control (Serous)	189	–	67.7%	–	–
		P value	–	–	–	–	–

PFS progression-free survival, *OS* overall survival
Response rate = complete response + partial response

node sampling versus complete dissection has not been shown [192, 203].

Since the v1.2017 update, the NCCN Guidelines have included fertility-sparing surgery in select stage IA–IC mucinous ovarian carcinomas [23]. Evidence demonstrated a lack of significant difference in PFS and OS between fertility-sparing and radical surgery in those with mucinous carcinoma grossly confined to the ovaries [206]. Stage IA and IC epithelial ovarian carcinoma treated with fertility sparing surgery did not significantly alter survival outcomes [207] and 5-year OS was 98% [208]. The need for comprehensive surgical staging in clinical stage I disease has been disputed due to lack of significant difference in PFS and OS [209]. For instances of advanced disease, the principle of cytoreductive surgery is standard of care [193, 210].

Adjuvant Therapy

Necessity of adjuvant therapy in MOCs depends on the stage. Stage IA and IB MOCs are observed due to the overall low recurrence risk and lack of significant decrease in recurrence risk after adjuvant treatment [166, 194]. For stage IC, either observation or a variety of chemotherapy options exist [23]. Stage II–IV requires chemotherapy [23].

The chemotherapy options for stages II–IV include IV and IP/IV platinum-based regimens recommended for serous EOC, leucovorin/5-FU/oxaliplatin (FOLFOX4) ± bevacizumab, or capecitabine/oxaliplatin ± bevacizumab for 3–6 cycles [23, 194], as fashioned after GI literature. All regimens containing bevacizumab are category 2B options in the NCCN Guidelines [23]. Initial research addressed epithelial ovarian cancers as a whole rather than by distinct histological subtypes. Thus, platinum-based therapy utilized in serous EOCs was applied to MOCs; however, when analyzed as a discrete subtype, MOCs were noted to have a relatively poor response to platinum. In comparison to other histological subtypes, MOCs demonstrated a significantly worse response rate, PFS, and OS to platinum-based regimens (Table 9.7) [210–213]. Highlighting the parallels between MOCs and gastrointestinal cancers, application of 5-FU, leucovorin, oxaliplatin, and capecitabine has been incorporated into MOC therapy. A prospective trial that assessed the regimen FOLFOX4 in platinum-resistant and taxane-pretreated ovarian cancer [214], while not exclusive to mucinous histology, showed an ORR of 29% and median OS of 10.1 months [214].

In a mouse xenograft model of MOC, the chemotherapy duo 5-FU and oxaliplatin demonstrated improved survival in cell lines resistant to paclitaxel/cisplatin [215]. Subsequently a prospective, randomized trial attempted to investigate oxaliplatin/capecitabine ± bevacizumab versus paclitaxel/carboplatin ± bevacizumab, but due to poor accrual secondary to the rarity of disease, it closed prior to reaching statistical significant enrollment [216]. Based on this composite of findings, preferred regimens for stage IC–IV include oxaliplatin with 5-FU or capecitabine ± bevacizumab for 6 cycles [166] and oxaliplatin/capecitabine ± bevacizumab for 3–6 cycles [194]. Overall, very limited evidence exists to direct chemotherapy regimens in MOCs (Fig. 9.4).

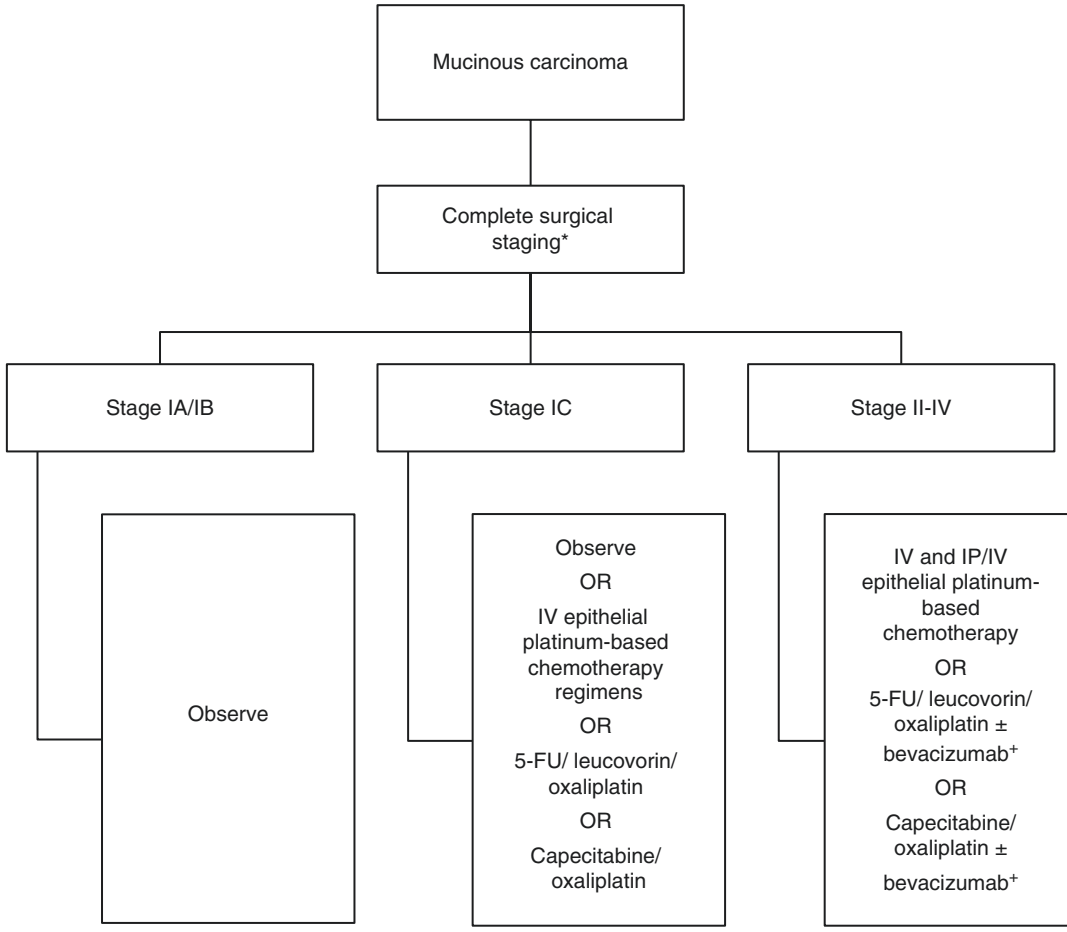

Fig. 9.4 Mucinous ovarian carcinoma management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *Fertility sparing surgery is an option for stage I disease. +Use of bevacizumab is supported by category 2B evidence. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

Therapeutic Principles for Germ Cell Tumors

Biology and Surgical Approach

The name ovarian germ cell tumor (OGCT) reflects their derivation from primitive ovarian germ cells. OGCTs include the following histological subtypes based on the WHO classification system: mature teratoma, dysgerminoma, yolk sac (also called endodermal sinus) tumor, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma, immature teratoma, and mixed germ cell tumor (Table 9.8) [171]. Of these, only the mature teratoma is classified as benign. Since certain histological subtypes produce specific tumor markers, their serum detection can aid in diagnosis, planning, and surveillance (Table 9.9). Elevations in tumor markers correlate with poor prognosis, as do stage and yolk sac histology [217–222]. Spread occurs via the lymphatic system, bloodstream,

Table 9.8 WHO histological classification of ovarian germ cell tumors

Germ cell tumors	
Mature teratoma	Benign
Dysgerminoma	Malignant
Yolk sac tumor	Malignant
Embryonal carcinoma	Malignant
Polyembryoma	Malignant
Non-gestational choriocarcinoma	Malignant
Immature teratoma	Malignant
Mixed germ cell tumor	Malignant

Table 9.9 Serum tumor markers for ovarian germ cell tumors

Histology	LDH	AFP	hCG
Dysgerminoma	+	–	±
Yolk sac tumor	+	+	–
Embryonal carcinoma	±	±	+
Polyembryoma	–	±	+
Non-gestational choriocarcinoma	±	–	+
Immature teratoma	±	±	–
Mixed germ cell tumor	±	±	±

LDH lactate dehydrogenase, *AFP* alpha-fetoprotein, *hCG* human chorionic gonadotropin

and peritoneal dispersion. Overall, OGCTs are considered to be chemotherapy sensitive.

Surgical staging of OGCTs adheres to the same FIGO system as other ovarian tumors. Considering the chemosensitive nature and predilection for young women, the surgical approach of OGCTs first involves determining the patient's fertility goals (Fig. 9.5). The general fertility-sparing approach applies not only to the pediatric/adolescent population but also to women of reproductive age. Additionally, utilization of fertility-preserving methods is not contingent upon surgical stage [23]. For those with advanced-stage disease (stage II–IV), fertility sparing methods combined with adjuvant chemotherapy yield survival rates comparable to those seen in standard surgery, ranging from 88% to 100% at a mean follow-up of 52–86 months [220, 223–225].

The strategy of comprehensive staging with suspected early-stage disease has been questioned [226–228]. An alternative method of evaluation lymph nodes and the omentum with selective removal has been proposed to lower operation time, blood loss, and complication rate without compromising PFS/OS [229]. However, numerous other studies found that lack of comprehensive surgical staging was significantly associated with disease recurrence [220, 221, 230]. Additionally, performing surgical restaging resulted in a change of stage for 43% of patients [231]. Optimal cytoreductive surgery in advanced-stage disease is associated with improved outcomes [217, 220, 232]; however, thorough cytoreductive surgery in patients with histologies other than immature teratoma has been questioned [231].

Etoposide, Cisplatin, w/wo Bleomycin

Following surgery, adjuvant chemotherapy is generally recommended for OGCTs with the exception of stage I dysgerminomas and stage IA, grade I immature teratomas (Fig. 9.5). In these situations, observation is acceptable given their excellent prognosis [23, 233].

The regimen of bleomycin, etoposide, and cisplatin (BEP) emerged as the primary therapy for OGCTs due to superior outcomes in advanced and incompletely resected disease as well as toxicity profile. Data from University of Texas MD Anderson Cancer Center (UTMDACC) in 1990 demonstrated no disease progression in 96% of participants after 3–6 cycles for a median follow-up of 22 months [234]. In 1994, the GOG compiled a multi-institutional single-arm prospective trial to further assess outcomes associated with BEP for 3 cycles [235]. In contrast to the UTMDACC study, eligibility criteria included complete tumor resection. At a median follow-up of 39 months, 97.8% remained clinically free of disease [235]; however, while second-look surgery in a subset of these patients revealed 82.6% without evidence of tumor, six participants had a mature teratoma or gliomatosis peritonei, while two had an immature teratoma [235]. The phenomenon of growing teratoma syndrome involves regression to a benign, mature teratoma following chemotherapy. It can resemble disease progression although tumor markers are usually

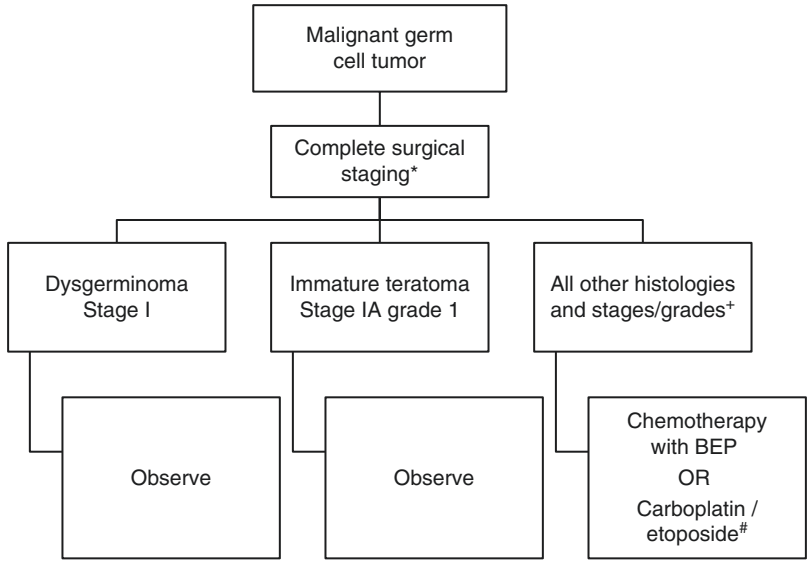

Fig. 9.5 Malignant ovarian germ cell tumor management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *BEP* bleomycin/etoposide/cisplatin. * Fertility-sparing surgery and comprehensive staging is an option for appropriate patients. +Includes embryonal tumor, endodermal sinus tumor (yolk sac tumor), dysgerminoma (stage II–IV), immature teratoma (Stage 1, grade 2/3; or stage II–IV), nongestational choriocarcinoma. #For select patients with stage IB–III resected dysgerminoma for whom minimizing toxicity is critical. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

negative. When this occurs, surgical resection is standard [236].

Due to the infrequency of OGCTs, extrapolation from testicular germ cell tumors (TGCT) has further guided management. For stage I nonseminomatous TGCTs at high risk of relapse, two cycles of BEP resulted in no recurrence for 99% of participants [237]. In good prognosis testicular disease, no significant difference in DFS or OS between 3 versus 4 cycles of BEP was detected [238]. Additionally, the dosing schedule originally developed at Indiana University (bleomycin 30 U IV q week, etoposide 100 mg/m^2 days 1–5, and cisplatin 20 mg/m^2 days 1–5 every 21 days) remains the mainstay of treatment as a less dose-intense regimen yielded worse overall survival in good prognosis testicular disease [239]. An abbreviated BEP regimen consisting of a 3 day cycle every 3 weeks for three total cycles (completely resected stage I–III) or four total cycles (incomplete resected or stage IV) OGCTs showed no evidence of disease in 96% of participants at a median follow-up of 5 years [240]. The goal of this modified regimen was to reduce adverse effects, including febrile neutropenic episodes and delays in treatment. An attempt at substituting cisplatin in the BEP regimen with carboplatin lead to statistically significant inferior outcomes for TGCTs in terms of complete response and survival [241]. Conversely, the combination of carboplatin/etoposide was used in completely resected stage IB to III dysgerminoma with no instances of disease recurrence at a median follow-up of 7.8 years [242]. The role of neoadjuvant BEP in advanced-stage disease followed by fertility-sparing surgery demonstrated a response rate of 91.3% [243]. Despite these nuances in tailoring adjuvant chemotherapy for OGCTs, BEP remains the standard of care.

Therapeutic Principles for Sex Cord Stromal Tumors

Biology and Surgical Approach

Sex cord stromal ovarian tumors (SCSTs) derive from the sex cords (granulosa and Sertoli cells) and stroma (fibroblast, theca, and Leydig cells) surrounding oocytes. This group of tumors include the following histological subtypes based on the WHO classification scheme: fibroma, thecoma, Leydig cell, granulosa cell, Sertoli cell, and Sertoli-Leydig [171] (Table 9.10). Certain histological subtypes are associated with steroid hormone production, which can aid in diagnosis due to the effects of excess estrogen or androgens (Table 9.11). SCSTs account for 2% of all ovarian cancers [191] with an average age at diagnosis of 50 years [190]. At the time of diagnosis, 64% of cases are stage I [191]. The 5-year cause-specific survival is 98% for stage I and 41% for stage IV disease [191]. Spread likely occurs via hematogenous and direct extension [244]. Overall SCSTs possess an indolent nature with late recurrence, generally around 4 years but can surpass 20 years [245–250].

Table 9.10 WHO histological classification of sex cord stromal ovarian tumors

Pure stromal tumors	
Fibroma	Benign
Thecoma	Benign
Leydig cell tumor	Benign
Steroid cell tumor	Benign, malignant
Fibrosarcoma	Malignant
Pure sex cord tumors	
Juvenile granulosa cell tumor	Borderline
Sertoli cell tumor	Borderline
Sex cord tumor with annular tubules	Borderline
Adult granulosa cell tumor	Malignant
Mixed sex cord stromal tumors	
Well differentiated Sertoli-Leydig	Benign
Moderately differentiated Sertoli-Leydig	Borderline
Poorly differentiated Sertoli-Leydig	Malignant

If clinical suspicion points to SCST, then determining a patient's fertility goals preoperatively is important. Oophorectomy of the involved ovary is necessary, but preservation of the contralateral ovary and uterus remains an option for most women who desire fertility-sparing surgery [248, 251]. Restriction of fertility-sparing surgery to only stage IA [252], IA and IC [23, 253], or early-stage disease has also been proposed [249, 254]. Some conflicting data showing statistically significant inferior outcomes in PFS and OS after fertility-sparing surgery exist [255]. If the uterus remains in situ and the SCST creates an environment of estrogen excess, then endometrial sampling should be performed to evaluate for resultant endometrial hyperplasia or cancer. After completion of childbearing, resection of the uterus and remaining ovary should be addressed.

Otherwise, comprehensive surgical staging for SCSTs abides by the same principles and FIGO system as other ovarian tumors [248, 252, 256] with the exception of lymphadenectomy [257]. Given the rarity of lymph node metastases in SCSTs [256], the necessity of lymphadenectomy can be guided by gross evaluation regardless of surgical stage [244, 250, 257, 258]. Women who underwent a primary surgery involving only an ovarian cystectomy or unilateral oophorectomy likely require a secondary surgery to perform peritoneal staging, which can still employ fertility-sparing methods [246, 248, 258]. The most consistently reported prognostic factor in these tumors is stage, thus highlighting the importance of comprehensive peritoneal surgical staging [245, 248–250, 254, 259, 260]. This is

Table 9.11 Serum tumor markers for sex cord stromal ovarian tumors

Histology	AFP	E2	Inhibin	AMH	Testosterone	Androgen	DHEA
Granulosa cell	–	±	+	+	±	–	–
Sertoli-Leydig cell	±	±	±	–	±	±	±

AFP alpha-fetoprotein, *E2* estradiol, *AMH* anti-Müllerian hormone, *DHEA* dehydroepiandrosterone

particularly crucial in presumed stage I disease since fertility-sparing surgery and observation may be utilized [250].

Chemotherapy

BE(P)

Based on the NCCN guidelines, postoperative therapy for SCSTs is shown in Fig. 9.6 [23]. Low-risk stage I disease can be observed [251, 253, 257]. For stage I intermediate-risk (e.g., heterologous elements) and high-risk (e.g., stage IC, poorly differentiated, size greater than 10–15 cm), either observation or platinum-based chemotherapy is an option [261, 262]. Therapy for stage II–IV SCST involves platinum-based chemotherapy [228, 250]. Alternatively, radiation therapy can be considered for limited-extent stage II–IV disease [263–265]. The chemotherapy regimens recommended for SCSTs include carboplatin with paclitaxel (preferred) or EP with or without bleomycin (category 2B) at the doses described for OGCTs [266–271].

For the BEP regimen, ORR ranges from 83% to 90% for a median of 4–5 cycles [266–268, 271]. In the original publication, two treatment-related deaths due to bleomycin toxicity led to a dose reduction without additional fatalities [267]. The recommended number of cycles is 3–4 [262]; however, 6 cycles demonstrated a 5-year disease-free survival of 100%, whereas fewer than 6 cycles resulted in a rate of 50% [257].

Carboplatin/Paclitaxel

Given the toxicities and marginal activity associated with BEP in the early studies, UTMDACC

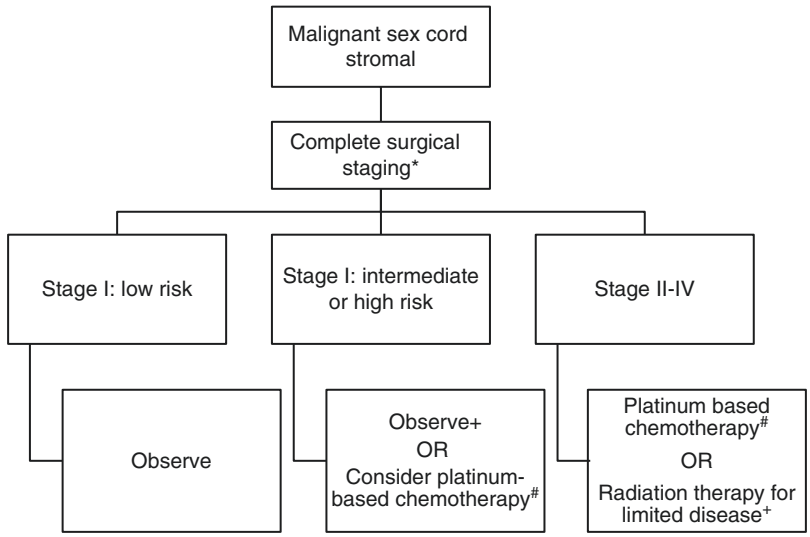

Fig. 9.6 Malignant sex cord stromal ovarian tumor management per NCCN guidelines; all recommendations are category 2A unless otherwise noted [23]. *Fertility sparing surgery is an option for patients with stage IA/IC disease. +Category 2B. #Acceptable options include BEP (etoposide and cisplatin +/- bleomycin) or paclitaxel/carboplatin. (*Adapted with permission from the NCCN Guidelines® for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way*)

Table 9.12 Outcomes of taxane use in sex cord stromal ovarian tumors at UTMDACC [1]

	Newly diagnosed without measurable disease	Newly diagnosed with measurable disease	Recurrent disease without measurable disease	Recurrent disease with measurable disease
Histologies involved	Granulosa cell, unclassified	Granulosa cell	Granulosa cell	Granulosa cell, unclassified
Stages involved	I–III, unstaged	I–III, unstaged	I, III, unstaged	I–III, unstaged
Chemotherapy regimen	Paclitaxal with cisplatin or carboplatin	Paclitaxal with cisplatin or carboplatin	Paclitaxal with cisplatin or carboplatin	Variety of taxane based[a]
Median number of chemotherapy cycles	6 (range 3–6)	3.5 (range 1–6)	6 (range 6–9)	5 (range 1–12)
Number of participants	9	2	7	30
No disease at completion of chemotherapy	8/9 = 89%	–	6/7 = 86%	–
Overall response (CR + PR)	–	1/2 = 50%	–	13/30 = 43%
Median PFS (median FU)	NR (52+ months)		34.3 months	19.6 months
Median OS (median FU)	NR (52+ months)		NR (90.3+ months)	NR (100.7+ months)

CR complete response, *PR* partial response, *PFS* progression-free survival, *FU* follow-up, *OS* overall survival, *NR* not reached

[a]Paclitaxel with cisplatin or carboplatin, paclitaxel only, docetaxel, paclitaxel/liposomal doxorubicin/cisplatin, cyclophosphamide/docetaxel

retrospectively explored the use of taxanes in treating SCSTs [270]. Refer to Table 9.12 for details on chemotherapy regimens, outcomes, and toxicities. This study divided participants into four groups based on presence of measurable disease and new diagnosis versus recurrence. In all of the groups, OS was not reached at a median follow-up of 52–101 months. No treatment-related deaths occurred, and hematologic was the most common toxicity.

This same set of taxane data was then used to retrospectively compare outcomes to UTMDACC patients who received BEP [271]. In comparing the BEP and taxane groups, a statistically significant difference was not reached in terms of ORR, PFS, OS, and toxicities (Tables 9.13 and 9.14). While the threshold did not meet statistical significance, the authors concluded that BEP use in recurrent disease seemingly demonstrated a higher response rate compared to taxanes [271]. However, they argued that taxanes lead to a more durable response as well as less severe toxicity that lacked clinical sequelae [271]. The GOG is currently conducting the first prospective, randomized trial comparing BEP to carboplatin with paclitaxel in SCSTs [272].

Table 9.13 Outcomes of BEP versus taxane-based chemotherapy for sex cord stromal ovarian tumors at UTMDACC

	Newly diagnosed + BEP[a]	Newly diagnosed + Taxane[b]	*P*-value	Recurrent disease + BEP[a]	Recurrent disease + Taxane[c]	*P*-value
Histologies involved	Granulosa cell	Granullosa cell, unclassified	*P* = NS	Granulosa cell, unclassified	Granulosa cell, unclassified	*P* = NS
Stages involved	I–III, unstaged	I–III, unstaged	–	I, III, unstaged	I–III, unstaged	–
Number of participants	11	11	–	10	35	–
Median number of cycles	4 (range 1–6)	6 (range 1–6)	*P* = NS	–	–	*P* = NS
Overall response rate (CR + PR)	82%	82%	*P* = 1	71%	37%	*P* = 0.677
Median PFS (median FU)	46.1 months	NR (52+ months)	*P* = 0.213	11.2 months	7.2 months	*P* = NS
Median OS (median FU)	97.2 months	NR (52+ months)	*P* = 0.994	NR (87.2+ months)	NR (94+ months)	*P* = NS

CR complete response, *PR* partial response, *PFS* progression-free survival, *FU* follow-up, *OS* overall survival, *NS* not significant, *NR* not reached

[a] BEP regimen: bleomycin 15 units on day 1, etoposide 100 mg/m^2 days 1–5, and cisplatin 20 mg/m^2 days 1–5, administered intravenously every 3 weeks

[b] Taxane regimen: paclitaxal with cisplatin or carboplatin

[c] Taxane regimen: paclitaxel with cisplatin or carboplatin, paclitaxel only, docetaxel, paclitaxel/liposomal doxorubicin/cisplatin, or cyclophosphamide/docetaxel

Table 9.14 Toxicities of BEP versus taxane-based chemotherapy for sex cord stromal ovarian tumors at UTMDACC

Toxicity	BEP	Taxane based	
Grade 4 Neutropenia	2	4	
Febrile neutropenia	–	2	
Myelodysplasia requiring bone marrow transplantation	–	1	
Grade 2 anemia	–	1	
Grade 2 thrombocytopenia	–	1	
Hypersensitivity		1	
Bleomycin pulmonary fibrosis	3	–	
Palmar-plantar erythrodysesthesia	–	1	
Treatment-related death	–	–	
Number of individuals who experienced toxicity greater than grade 2	5/21 = 24% patients	7/44 = 16% patients	P = NS

BEP bleomycin/etoposide/cisplatin, *NS* not significant

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Management of Epithelial Ovarian Cancer with Peritoneal Metastases

10

Paul H. Sugarbaker

Introduction

Ovarian cancer is a disease in which major improvements in survival should be expected over the next 3–5 years. Unfortunately, early diagnosis or prevention of this disease has not meaningfully improved. However, multiple new and improved treatment strategies are being rationally organized to optimize the treatments. The tools that the oncologist and surgeon have to deal with disease are significantly more sophisticated than those available for other abdominal and pelvic malignancies. First, the tumor marker, CA125, is of great help to monitor the progression of disease or response as brought about by successful treatments. These tumor markers are used along with the abdominal and pelvic CT scan. Second, the most modern surgical approach which seeks to achieve a complete visual clearance of the abdomen and pelvis of ovarian cancer has successfully evolved over the last two decades. Peritonectomy procedures and visceral resections are combined to achieve an R0 status within the abdomen and pelvis. Third, not only can surgery result in a complete response, but also the cancer chemotherapy with cisplatin and paclitaxel show a remarkable response as compared to other abdominal and pelvic malignancies. These drugs can be applied intraoperatively with heat (hyperthermic intraperitoneal chemotherapy—HIPEC), early postoperatively as instillations into the peritoneal space (early postoperative intraperitoneal chemotherapy—EPIC), or long-term through an intraperitoneal port (normothermic intraperitoneal chemotherapy—NIPEC). This combination of complete surgical removal of the disease combined with regional drug delivery may offer the best opportunity for cure of a disease rarely amenable to long-term survival in the past. All of these treatments need to be individualized for a particular patient who will have special requirements. Finally, molecular diagnosis and treatment must be blended in to the surgery with cancer chemotherapy to maximize benefits. A surge forward in the improved management of ovarian cancer is possible in the future and is a current reality.

Intraperitoneal Administration of Anticancer Drugs Showed the Potential for Control of Small Peritoneal Nodules

The rationale for use of chemotherapy administration directly into the peritoneal space seems to have emanated from pharmacologic research in chronic ambulatory peritoneal dialysis [1]. It was recognized that some drugs would be especially

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appropriate for prolonged retention within the peritoneal space based on their molecular structure [2]. It was Dedrick and colleagues at the American National Institutes of Health who called attention to the potential benefits of intraperitoneal administration of cancer chemotherapy agents especially in ovarian cancer [3]. High concentrations within the peritoneal space after intraperitoneal administration as compared to drug levels within the plasma resulted in a markedly enhanced exposure of cancer nodules on peritoneal surfaces. Jones and colleagues recognized that a high volume of intraperitoneal chemotherapy solution (belly bath technique) was necessary to adequately distribute the drugs [4]. Ozols and colleagues investigated the pharmacokinetics of intraperitoneal doxorubicin and McVee and colleagues the possible benefits of intraperitoneal cisplatin [5, 6]. Because of a large molecular size and hydrophobic surface, cancer chemotherapy agents were shown to have a slow clearance from the peritoneal compartment through the lining of the abdomen and pelvis to the body compartment. Also, metabolism of the cancer chemotherapy in the body compartment was at all points in time faster than clearance from the peritoneal space. This resulted in a much greater concentration times time (area under the curve) of drug in the peritoneal space as compared to concentration times time measured in the blood. This results in an increased therapeutic effect on cancer nodules on the peritoneal surface and a reduced systemic toxicity. With continued efforts to identify drugs appropriate for intraperitoneal chemotherapy administration, an extended list of possible chemotherapy agents and their pharmacologic advantage following intraperitoneal administration has been defined [7].

Complete Visible Removal of Cancer from the Abdomen and Pelvis as the Goal for Cytoreductive Surgery

A second essential part of a new and improved treatment strategy for primary or recurrent ovarian cancer is a new and more technically demanding approach to surgery. No longer should optimal ovarian cancer surgery be defined by resection to nodules 1 cm in diameter. The goal of optimal cytoreduction is resection to macroscopic residual (absence of visible) disease. This revised approach to ovarian cancer surgery requires peritonectomy procedures in areas where peritoneal metastases are present [8]. When viscera are involved, organ resection is required. In order for this surgery not to interfere with subsequent chemotherapy administration, it must be performed with no mortality and a low morbidity.

The peritonectomy procedure required in almost all ovarian cancer patients is the pelvic peritonectomy. With a low extent of disease within the pelvis this is a hysterectomy, salpingo-oophorectomy, and pelvic peritoneal stripping. If disease is more extensive, then a rectosigmoid colon resection is required to clear the pelvis of disease [9]. Usually, with a rectosigmoid colon resection a low colorectal anastomosis can be performed in the absence of a diverting ileostomy [10].

The next most frequent cytoreductive procedure is the greater omentectomy. This may be performed with or without splenectomy depending upon the extent of disease. For complete cytoreductive surgery the entire greater omentum is resected along with the gastroepiploic vessels ligated on the greater curvature of the stomach [9].

Subdiaphragmatic peritonectomy of the liver surface and right subphrenic peritoneum is the third most frequently required procedure. This proceeds with peritoneal stripping of the undersurface of the right hemidiaphragm and a Glisson's capsulectomy. Both procedures are performed with high-voltage electrosurgical dissection. If the resection is going to require removal of the central tendon of the right hemidiaphragm, entrance into the right pleural space should be avoided until all cytoreduction is complete and thorough irrigation of the abdominal and pelvic spaces has occurred. Then, with the abdomen and pelvis as clear of tumor cell contamination as is possible, resection of the full thickness involvement of the hemidiaphragm should proceed. Also, if HIPEC is being used, washing of the right

pleural space should occur with diaphragm closure after the completion of HIPEC.

Other cytoreductive surgical procedures may include stripping of the undersurface of the left hemidiaphragm, lesser omentectomy with peritoneal stripping of the omental bursa, and cytoreduction of the small bowel and its mesentery. The goal of this surgery is complete visible clearance of the abdomen and pelvis of all ovarian cancer but an absence of adverse events that will delay subsequent chemotherapy [9].

Perioperative Chemotherapy Following Best Efforts at Surgery

Following the surgical procedure a judgment regarding the adequacy of the cytoreduction is indicated. If the cytoreduction is suboptimal with visible tumor nodules remaining behind, regional approaches to chemotherapy are unlikely to be of benefit. Patients with suboptimal cytoreduction should go on to receive systemic chemotherapy as soon as possible postoperatively. However, with adequate debulking, randomized controlled studies suggest that hyperthermic intraperitoneal chemotherapy is of benefit to patients following complete cytoreduction. Spiliotis and colleagues in 2014 reported the first randomized controlled trial regarding HIPEC in patients with recurrent epithelial ovarian cancer [11]. They used cisplatin at 100 mg/m^2 and paclitaxel at 175 mg/m^2 for 60 min at 42 °C in 60 patients. In their second group of 60 patients, the cytoreduction was not followed by perioperative chemotherapy. Both groups received systemic chemotherapy postoperatively. The overall survival in the HIPEC group was 26.7 months versus 13.4 months in the non-HIPEC group ($p = 0.006$). In both groups of patients, survival was improved when the peritoneal cancer index was less than or equal to 15.

Van Driel and colleagues reported in 2018 a randomized controlled study in 250 patients, all of whom received neoadjuvant chemotherapy with 3 cycles of carboplatin and paclitaxel [12]. Randomization to either receive or not receive HIPEC was performed at the time of surgery that resulted in no visible disease measuring 10 mm or less in diameter. Half of the patients received hyperthermic intraperitoneal chemotherapy with cisplatin at 100 mg/m^2. After 4.7 years of follow-up, 89% of patients who had cytoreductive surgery only had an event of disease recurrence as compared to 81% of patients with surgery plus HIPEC. Also, 62% of the patients in the surgery only group died of progressive disease as compared to 50% of patients in the surgery plus HIPEC group ($p = 0.02$ for survival and $p = 0.003$ for progression-free survival). Adverse events of grade III or IV were reported in 30 patients (25%) in the surgery only group and in 21 patients (27%) in the surgery plus HIPEC group ($p = 0.76$).

Several other randomized controlled trials testing HIPEC in primary ovarian cancer resection, HIPEC after interval resection, or HIPEC with recurrent ovarian cancer are currently in progress [13].

Survey of HIPEC Regimens for Ovarian Cancer

Although the goals for cytoreductive surgery are quite straightforward, the regimens for HIPEC used after optimal cytoreduction have not been standardized at this point in time. Three cisplatin-based regimens are currently in use. These regimens are appropriate for primary cytoreduction, interval cytoreduction, or cytoreduction of recurrent ovarian cancer. The Sugarbaker regimen uses a moderate dose of cisplatin plus doxorubicin intraperitoneally and ifosfamide systemically. The National Cancer Institute of Milan uses similar doses of doxorubicin and cisplatin. Both these groups use a 90-min HIPEC treatment. The French HIPEC treatment for ovarian cancer is cisplatin 80 mg in 3 L of NaCl for 60 min [14]. In the Van Driel study, cisplatin was used at 100 mg/m^2 with thiosulfate protection for the HIPEC procedure lasting 120 min. Fifty percent of the cisplatin was infused initially, 25% at 30 min, and the final 25% at 60 min for a total of a 90-min peritoneal cisplatin lavage (Table 10.1).

Table 10.1 Cisplatin-based regimens for ovarian cancer. (From Ref. 14 with permission)

Sugarbaker Regimen
1. Add cisplatin to 2 L 1.5% dextrose peritoneal dialysis solution
2. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution
3. Dose of cisplatin is 50 mg/m^2 and doxorubicin is 15 mg/m^2 for 90-min HIPEC treatment
Intravenous Chemotherapy
4. Add ifosfamide 1300 mg/m^2 to 1 L 0.9% sodium chloride. Begin continuous IV infusion over 90 min simultaneous with intraperitoneal chemotherapy
5. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 15 min prior to ifosfamide infusion
6. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 4 h after ifosfamide infusion
7. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 8 h after ifosfamide infusion
National Cancer Institute Milan Regimen
1. 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin for 90-min HIPEC treatment
2. Chemotherapy solution 4–6 L based on capacity of the peritoneal space
RENAPE—French HIPEC for Ovarian Cancer
1. Cisplatin 80 mg in 3 L 0.9% sodium chloride at 42 °C for 60 min
Dutch HIPEC for Interval Cytoreduction
1. Cisplatin 100 mg/m^2 in abdomen filled by saline with 50% at time 0, 25% at 30 min, and 25% at 60 min
2. Thiosulfate 21 g/m^2 over 6 h

Intraperitoneal Paclitaxel

Paclitaxel is a cell cycle-specific drug so that its use within the peritoneal space over a prolonged time period should optimize the responses. Mohamed and Sugarbaker explored the pharmacology of intraperitoneal taxanes in 2003 [15]. They used intraperitoneal paclitaxel in ovarian cancer patients as EPIC. Starting on the first postoperative day, paclitaxel 20–40 mg/m^2/day was instilled into the peritoneal space for 5 days in a row. The difference in plasma concentrations of paclitaxel and intraperitoneal concentrations of paclitaxel after intraperitoneal drug administration was approximately 1000. Certainly, paclitaxel is one of the chemotherapy agents with activity towards ovarian cancer that is well suited for intraperitoneal drug administration.

Normothermic Intraperitoneal Chemotherapy Long-Term for Optimally Cytoreduced Ovarian Malignancy

Following cytoreduction with HIPEC one can insert an intraperitoneal port safely with excellent long-term functional results [16]. The port is placed just prior to the abdominal closure. Antiadhesion agents are recommended between bowel loops and between bowel loops and the abdominal and pelvic sidewalls. Approximately 80% of intraperitoneal ports can be expected to function for at least 5 cycles of NIPEC.

The clinical use of long-term normothermic intraperitoneal chemotherapy gained marked visibility in January of 2006 as a result of the NCI clinical alert. A meta-analysis of eight trials comparing intraperitoneal with intravenous platinum-based chemotherapy showed an average 21.6% decrease in risk of death with IP therapy. This translated into a 1-year increase in overall median survival. This analysis was based primarily on survival benefits for IP chemotherapy observed in three randomized controlled trials. This was the study of Alberts et al. of 546 patients reported in 1996, the efforts of Markman et al. reported in 2001 of 462 patients, and the efforts of Armstrong et al. reported in 2006 on 416 patients [17–19]. The modified GOG-172 Armstrong regimen currently recommended administration through an intraperitoneal port is shown in Table 10.2.

Table 10.2 Modified GOG 172, Armstrong regimen for optimally debulked stage 3 ovarian cancer. (From Ref. 14 with permission)

• Intravenous paclitaxel 135 mg/m^2 over 3 h on day 1
• Intraperitoneal cisplatin 75 mg/m^2 in 1 L normal saline plus additional intraperitoneal saline as tolerated on day 2
• Intraperitoneal paclitaxel 60 mg/m^2 in 1 L normal saline plus additional intraperitoneal saline as tolerated on day 8
• Repeat every 3 weeks for 6 cycles

Literature Support of Cytoreduction to Microscopic Disease Plus Long-Term Intraperitoneal Chemotherapy as a Strategy to Maximize Survival in Ovarian Cancer

Landrum and colleagues collected data on 428 patients with stage III ovarian cancer who underwent optimal cytoreduction followed by intraperitoneal paclitaxel plus cisplatin chemotherapy [20]. Predictors for progression-free survival were histology, surgical stage, and residual disease post-cytoreduction. For patients receiving intraperitoneal chemotherapy (n = 428), 36% of patients had no residual disease with a progression-free survival of 43.2 months and a median overall survival of 110 months. These investigators concluded that patients with no residual disease following primary surgery treated with adjuvant intraperitoneal-based chemotherapy have survival measures that exceed any rates previously seen in this group of patients (Fig. 10.1).

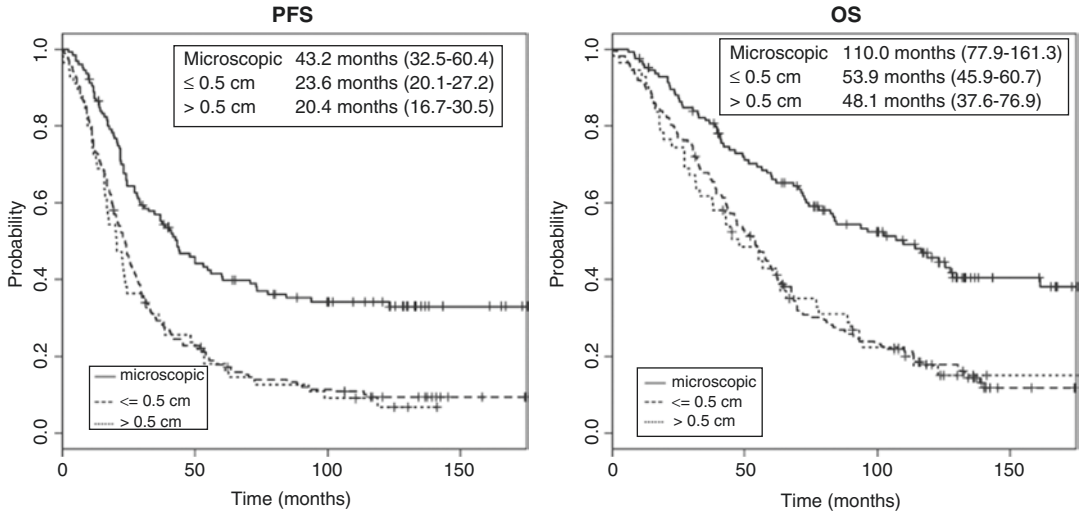

Fig. 10.1 Progression-free (PFS) and overall survival (OS) curves for patients treated by intraperitoneal chemotherapy stratified by residual disease following primary cytoreductive surgery. Median PFS and OS for patients with microscopic residual disease were 43 months and 110 months, respectively. (From Ref. 21 with permission)

Conclusion

In this approach to advanced stage ovarian cancer a clinical pathway to select patients for an optimal outcome is possible. As shown in Fig. 10.2, patients who are healthy and by CT of chest, abdomen, and pelvis suggested to have the possibility of complete cytoreduction, upfront surgery is planned [21]. If indeed there is optimal debulking, these patients should go on to receive HIPEC and then long-term combined intraperitoneal and intravenous chemotherapy. Alternatively, patients with large volume ovarian cancer at the time of presentation may be treated with neoadjuvant chemotherapy [22]. This usually involves three cycles of carboplatin plus paclitaxel. In the responder patients the clinical pathway would suggest benefit from cytoreduction and HIPEC if indeed the cytoreduction is adequate for the activity of hyperthermic intraperitoneal chemotherapy. Patients with interval cytoreduction may profit from a preoperative laparoscopy in order to make an assessment regarding the possible completeness of cytoreductive surgery [23].

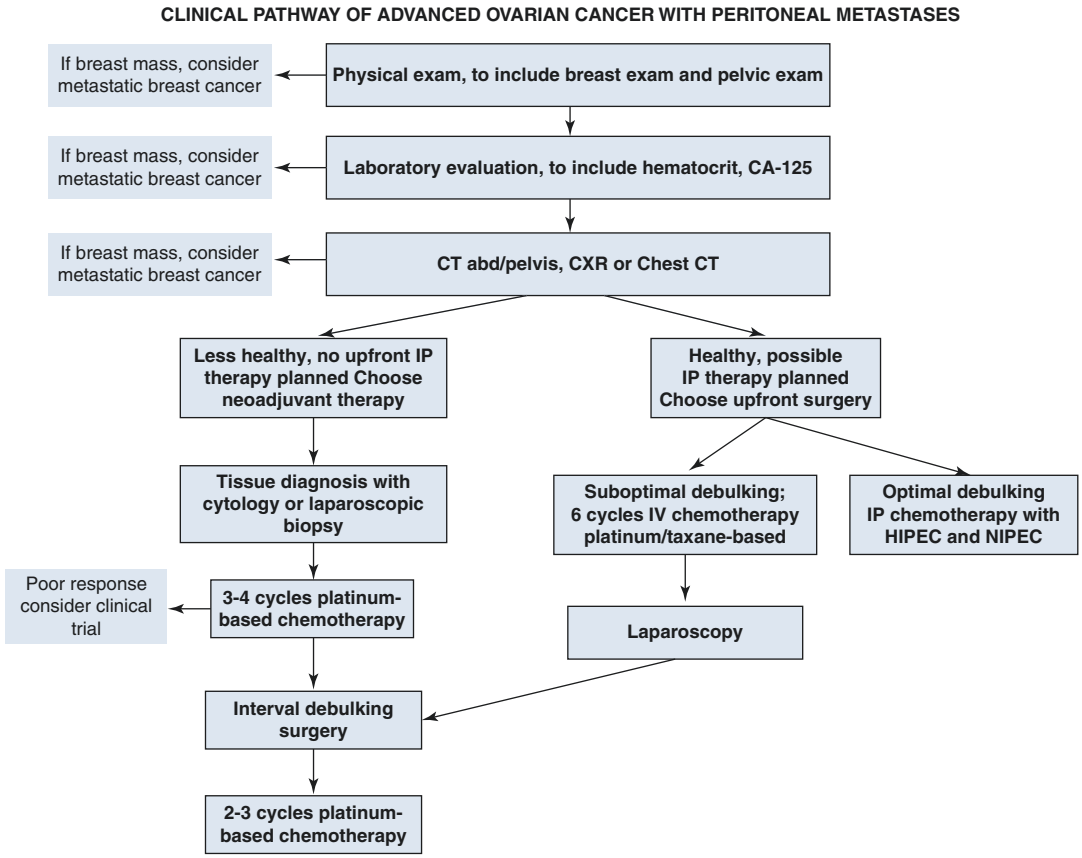

Fig. 10.2 Clinical pathway of advanced ovarian cancer with peritoneal metastases. (Modified from Ref. 22 with permission)

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Targeted Molecular Therapy for Ovarian Cancer Patients

11

Samir A. Farghaly

Introduction

Over 300,000 women are diagnosed with ovarian cancer each year worldwide, and this disease was responsible for an estimated 200,000 deaths per year worldwide in 2018. The American Cancer Society estimates that in 2021, about 21,410 new cases of ovarian cancer will be diagnosed and 13,770 women will die of ovarian cancer in the USA. Ovarian cancer is the most common cause of death from cancers of the female genital tract [1, 2]. The high case fatality rate results from the frequent diagnosis of epithelial ovarian cancer at an advanced stage: 75% of all cases are diagnosed as stage III or IV, where the disease has spread throughout the abdomen [3, 4]. Patients with advanced-stage disease have a 5-year survival of 29%. There are only a limited number of chemotherapeutic agents with reasonable effectiveness against epithelial ovarian cancer. Most patients develop recurrent disease, which commonly acquires chemoresistance. The identification of the genes and their protein products in ovarian cancer that contribute to the malignant phenotype has increased our knowledge of human tumorigenesis. There are several cell surface receptors, signaling pathways, and nuclear proteins, which are possible targets for molecular therapeutic approach. Targeting specific cellular mechanisms associated with ovarian tumorigenesis and progression may serve to improve oncologic outcome and limit toxicity in patients with ovarian cancer. The standard therapy involves a combination of optimal cytoreductive surgery with chemotherapy that consists of a platinum agent and a taxane compound [5]. The response rate of the standard regimen for ovarian cancer exceeds 80%, but about 70% of patients with advanced ovarian cancer experience recurrence within 5 years, and they die because their cancer disease becomes resistant to platinum and taxane [6, 7]. Most of these patients are subsequently treated with other agents, such as liposomal doxorubicin, gemcitabine, topotecan, or etoposide. The overall response rates to these other drugs are 10–25% [8]. So, targeted molecular therapy is needed to improve oncologic outcome for patients with advanced and recurrent ovarian cancer. The ideal molecular target ought to be differentially expressed by the tumor, have a potential chemosensitive molecular site, and be necessary for the viability of the cancer cell. The molecular heterogeneity of ovarian cancer compared with other disease sites has made the successful transfer of molecular agents into the ovarian cancer treatment feasible [9]. Ovarian cancer has been recognized to possess a multitude of molecular abnormalities any of which

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may play a role in ovarian cancer proliferation and survival. The understanding of the complex pathways of growth deregulation in gynecologic cancers has provided us with a basis for the application and testing of novel therapies [10, 11].

Antiangiogenic Therapy

There are several reasons for using antiangiogenic therapy. First, all solid tumors require increased tumor angiogenesis to facilitate growth and metastasis, and therefore inhibitors may have activity across a variety of malignancies. Second, the development of resistance is rare, because the primary target is normal endothelial cells. Third, side effects are relatively mild and limited.

One of the major mediators of tumor angiogenesis is VEGF. In ovarian cancer, microvessel density, intratumoral VEGF, and VEGF receptor (VEGFR) expression have been associated with a poor prognosis, suggesting that angiogenesis should be considered a target for novel therapies. It is established that VEGF and several antiangiogenic mediators, including platelet-derived growth factor and fibroblast growth factor (FDF), serve as mediators of tumor angiogenesis (Fig. 11.1). VEGF was noted to be overexpressed in primary ovarian neoplasms and in the ascites and plasma of ovarian cancer patients. VEGF was characterized and was found to inhibit tumor growth in vivo in several cancers, including rhabdomyosarcoma, glioblastoma multiforme, leiomyosarcoma, and prostate cancer [5].

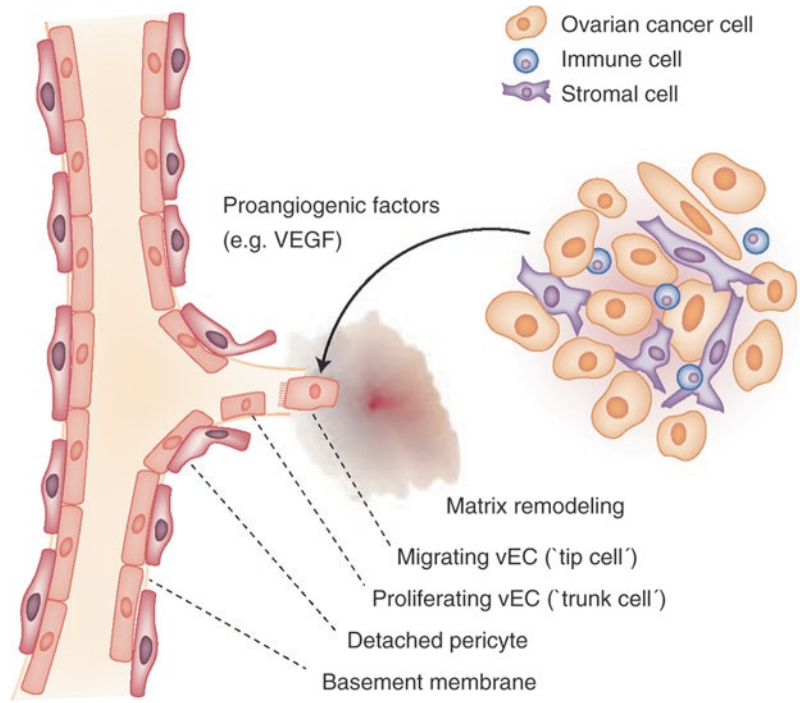

Fig. 11.1 Mediators of tumor angiogenesis

Antiangiogenic Agents

Bevacizumab

Bevacizumab is a recombinant, humanized, monoclonal immunoglobulin G1 antibody targeted at VEGF-A, which is approved for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma [12]. This antibody binds to and neutralizes all forms of VEGF-A, which suppresses growth of tumors and inhibits progression of metastatic disease [13, 14]. Also, anti-VEGF drugs enhance the effects of chemotherapeutic agents by improving the structure and function of tumor vessels [15]. Two phase II studies of bevacizumab monotherapy conducted on patients with recurrent ovarian or primary peritoneal cancers found response rates of 15.9–21.0% [16, 17]. Also, in one of those studies, gastrointestinal perforation (GIP) was observed in 5 of 44 (11.4%) patients who had been treated with three or more regimens [17]. Bevacizumab was evaluated combined with first-line chemotherapy (paclitaxel + carboplatin) for ovarian cancer [18, 19]. Two phase III studies, the Gynecologic Oncology Group (GOG) 218 and the International Collaborative Group for Ovarian Neoplasia (ICON) 7, examined the combined effects with bevacizumab and standard chemotherapy (paclitaxel + carboplatin) in a first-line/adjuvant chemotherapy setting and results are shown in (Table 11.1) [20, 21]. The Ovarian Cancer Education Awareness Network (OCEANS) trial evaluated the efficacy of bevacizumab in combination with carboplatin and gemcitabine in patients with recurrent, platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancers after frontline, platinum-based therapy [22]. In this study, PFS for the bevacizumab arm was significantly longer than for the placebo arm (median PFS, 12.4 vs. 8.4 months). Grade 3 or higher hypertension and proteinuria occurred more frequently in the bevacizumab arm. A multicenter, open-label, randomized, two-arm, phase III trial, AURELIA, was conducted on patients with ovarian, primary peritoneal, or fallopian tube cancers resistant to platinum [23]. It was observed in this study that chemotherapy plus bevacizumab significantly improved PFS (median PFS, 6.7 vs. 3.4 months) and overall response rate (30.9% vs. 12.6%) compared to chemotherapy alone. Hypertension ≥ grade 2 (11.1% vs. 3.9%) and proteinuria (6.4% vs. 0.5%) occurred more frequently in the bevacizumab arm. GIP was observed in 1% patients in the bevacizumab arm.

Cediranib

Cediranib is a potent inhibitor of tyrosine kinase of VEGFR-1, VEGFR-2, and VEGFR-3 and c-Kit that competes for the ATP-binding site within the receptor kinase domain [24, 25]. In a phase II studies, patients with recurrent ovarian, fallopian tube, or peritoneal cancers were treated with cediranib, and 17.4% of patients showed a partial response [26]. Grade 3 hypertension was observed in 46% of patients. No GIP or fistulas were observed.

Pazopanib

Pazopanib inhibits tyrosine kinase of VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-α, PDGFR-β, and c-Kit. It has been approved for renal cell carcinoma and soft tissue sarcoma [27]. A CA-125 response was observed in 31% of patients with median response duration of 113 days during a phase II trial of pazopanib for the treatment of recurrent ovarian, fallopian tube, and primary peritoneal carcinomas [28]. The most common adverse events, noted in this trial, were elevated grade 3 alanine aminotransferase and γ-glutamyl transpeptidase, fatigue, and diarrhea.

Table 11.1 Phase III trials of bevacizumab in ovarian cancer

Trial	Patients	Treatment	Median PFS (M)	Median OS (M)	Selected adverse events	Reference
First line						
GOG 218	1873					[19]
Arm 1	625	CP	10.3	39.3	1.2% GI events (G ≥2), 7.2% HT (G ≥2), 5.8% VTE (any grade)	
Arm 2	625	CP + Bev	11.2	38.7	2.8% GI events (G ≥2), 16.5% HT (G ≥2)***, 5.3% VTE (any grade)	
Arm 3	623	CP + Bev → Bev	14.1*	39.7	2.6% GI events (G ≥2), 22.9% HT (G ≥2)***, 6.7% VTE (any grade)	
ICON7	1528					[20]
Arm 1	764	CP	17.4		1.3% GI events, 0.3% HT, 1.7% VTE	
Arm 2	764	CP + Bev → Bev	19.8*		2.1% GI events, 6.2% HT, 4.3% VTE	
Second line						
OCEANS	484					[21]
Arm 1	242	CG	8.4	35.2	0.4% HT, 0.9% proteinuria, 2.6% VTE	
Arm 2	242	CG + Bev	12.4*	33.3	17.4% HT***, 8.5% proteinuria***, 4.0 VTE	
AURELIA	361					[22]
Arm 1	182	Chemotherapy alone	12.6		2.2% TEE	
Arm 2	179	Chemotherapy + Bev	30.9**		2.8% TEE	

Investigator selected chemotherapy (pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel)

PFS progression-free survival, *M* months, *OS* overall survival, *GOG* Gynecologic Oncology Group, *ICON* International Collaborative Group for Ovarian Neoplasia, *CP* carboplatin plus paclitaxel, *Bev* bevacizumab, *CG* carboplatin plus gemcitabine, *GI events* gastrointestinal events, *G* grade, *HT* hypertension, *VTE* venous thrombosis, *TEE* thromboembolic events

*$P < 0.0001$, **$P < 0.001$, ***$P < 0.05$ versus chemotherapy alone

[a] Selected adverse events (grade ≥3), except for GOG 218 trial

Classical Transgene Delivery

Over the past several years, there has been an increased understanding of the mechanisms behind transgene delivery. Efficient full gene(s) delivery to a mammalian cell involves several steps: delivery of genes to target cells, cellular entry, endosome escape, and integration into the nucleus [28, 29]. No single gene transfer system has been developed that can effectively fulfill the requirements for all the features noted above. A combination of multifunctional nonviral gene transfer systems may satisfy the requirements for efficient gene delivery. Cationic gene carriers can facilitate the cellular entry of DNA by interacting with the negatively charged cell surface [29, 30]. Endosomal escape is achieved by including components that induce membrane fusion at low pH or block pH lowering inside the endosome in the DNA-carrier complex. PEI is a cationic polymer that serves as an effective vehicle for in vivo gene delivery in many tissues. It facilitates effective DNA binding and protection, combined with the capability to escape the endosome due to its proton buffering ability with resultant osmotic swelling and endosomal disruption [29]. PEI has been shown to be an efficient transfection agent for ovarian carcinoma cells by intraperitoneal injection [31]. Several studies indicated that PEI-mediated transgene expression was dose dependent and transient, with maximal transgene expression observed during 48 h immediately following transfection [32]. DNA was detectable in small amounts after 72 h, indicating probable degradation and clearance [31]. This would indicate that development of nonviral gene transfer technologies that can support chromosomal integration and persistent gene expression in vivo is desirable. Transposon-mediated DNA delivery systems have shown to allow the development of a new generation of vectors for human gene therapy and mammalian [33]. Transposon-based systems have been proven to be effective integrating nonviral vectors that can mediate long-term in vivo transgene expression [34]. It has been shown that SB transposons are an efficient intratumoral gene transfer vector for glioblastoma multiforme and was delivered using PEI as gene transfer reagent. The investigators of these two studies observed a marked antitumor activity as reflected by reduced tumor vessel density, inhibition of tumor growth, and tumor elimination in up to 50% of nude mice [34, 35]. In other studies, a more active transposon was used [33–42], combined with PEI to deliver HSV-TK gene into ovarian cancer xenografts. Further studies are needed to determine how PB transposon performs in vivo in the long term. In addition, the potential safety issues from insertional disruption/deregulation in genome needed to be addressed.

DNA Vectors

Adenoviruses are well-understood vectors for gene therapy. Human adenovirus serotype 5 (Ad5) is a reasonable vector to use, as it is not associated with a serious disease [43]. It has several advantages: it is well characterized, it is not restricted to infecting only dividing cells, and it can be grown in high titers with relative biologic stability allowing it to be administered systemically. Early clinical trials utilizing no replicative adenoviruses demonstrated the feasibility and potential utility of adenoviral-based gene therapy strategies for the treatment of malignancy. *While the initial adenoviral-based trials utilized no replicative vectors, subsequent studies investigated the potential of conditionally replicative adenoviruses (CRAd) for the treatment of cancer. These viral agents are designed to infect cancer cells specifically, replicate selectively within these cells, and then to spread* laterally to other cancer cells. A key element of CRAd development is to replicate in cancer cells selectively, without damaging normal host cells. CRAds have thus been engineered to selectively replicate within tumor cells using two broad strategies. The first employs deletion of part of the E1A or E1B genome to prevent replication in normal cells but allow replication in tumor cells with genetic defects that complement the deleted viral genome functions. The second employs a tumor-selective promoter (TSP) to drive the expression of genes involved in viral replication selectively in tumor cells. An

example of the first strategy is the E1B-negative adenovirus (*dl*1520), Onyx-015 [44–51]. In this approach, the *E1B-55 k* gene of Onyx-015 was deleted, resulting in a virus that would replicate selectively within p53-deficient tumor cells. These viruses expressed the E1A protein, which overrode the block imposed by p53 in infected cells, resulting in apoptosis of normal cells, in addition to tumor cells. ONYX-015 demonstrated notable results in both in vitro and in vivo studies but had limited effects in human clinical trials for ovarian cancer. Bischoff et al. demonstrated that ONYX-015 was capable of efficient, selective replication in p53-deficient human tumor cells [52]. Heise et al. demonstrated in vivo correlation in three nude mouse–human ovarian carcinomatosis xenograft models [53]. Clinical studies of patients with head and neck cancer demonstrated safety and efficacy, but Vasey et al. failed to demonstrate similar results in ovarian cancer patients. Fifteen of the 16 study patients were taken from the study because they developed progressive disease [54].

Enhancing Vector Infectivity

The major limitation of gene-based therapies lies within the vector systems. As most patients have been previously exposed to Ad5, there is high level of immunity to the virus with preformed antibodies. In addition, primary tumor cells have low levels of the coxsackie and adenovirus receptor (CAR) relative to their cell line counterparts [55–57]. For the adenovirus vector to facilitate expression of the therapeutic gene in target cells, three steps must occur: first, the adenovirus must attach to the above receptors; second, it must be internalized into the cell; and third, it must transfer the gene to the nucleus where it can be expressed. The adenovirus binds to the primary high-affinity CAR receptor and to the integrins αυβ3 and αυβ5 using two capsid proteins, the fiber and penton base, respectively. The carboxy-terminal (C-terminal) knob domain of the adenovirus fiber protein is the ligand for attachment to CAR [58–60]. It has been demonstrated that adenovirus infection is dependent upon the C-terminal knob [61]. After attachment, the adenovirus is internalized using receptor-mediated endocytosis. This is reliant upon the interaction of the Arg-Gly-Asp (RGD) sequences in the penton base with the integrins αυβ3 and αυβ5 [62]. After internalization, the virus enters the cytosol via a pH-induced conformational change. The virus then localizes to the nuclear pore and is translocated into the nucleus of the host cell. One method of improving adenoviral tropism in low CAR-expressing cells such as ovarian cancer cells is by replacing the serotype knob to utilize a different receptor other than CAR. It has been shown that the knob domain of serotype 3 binds to CD46 and possibly CD80 and CD86, instead of CAR [63–65]. The 5/3 mutated adenovirus incorporates the alternate fiber knob domain from serotype 3 increasing the cytopathicity of a CRAd [66]. In another study, Ad5/3 has been shown to enhance tumor cell destruction in an orthotopic murine model of ovarian cancer [67] by a Δ24 CRAd with the Ad5/3 fiber chimera. Another method to improve transduction of the adenovirus is by utilizing fiber peptide modifications [67]. Ad fiber protein can enhance transduction in ovarian cancer cells by overcoming the low CAR expression. However, this method has been limited by the fact that the addition of more than 27 amino acids or more to the C-terminal end of the fiber will inhibit trimer formation [68]. X-ray crystallography showed that the HI loop is exposed on the fiber knob of the adenovirus and will allow the addition of up to 83 amino acids without affecting replication [69]. Incorporation of the RGD motif into the HI loop as compared to the C-terminus exhibited an increased level of gene transfer in in vitro studies [70, 71], and it also retargeted viruses to ovarian cancer cells that were previously resistant to adenovirus infection [56]. These tropism modifications have been incorporated into the context of CRAds, and infectivity enhancements have been achieved [72].

Achieving Selectivity with Tumor-Specific Promoters

The use of tumor-specific promoters (TSPs) is a strategy to drive viral E1 expression increasing tumor specificity. This strategy showed improved efficacy and tumor specificity [73]. TSPs have also been incorporated into CRAds. This CRAd demonstrated efficient replication and oncolysis in vitro and therapeutic efficacy in murine models of ovarian cancer [73]. Other TSP examples include CXCR4 and survivin. *CXCR4* is a chemokine receptor gene that plays a role in progression and metastasis in ovarian cancer cells. A CRAd modified to include a CXCR4 TSP (CRAd–CXCR4. RGD) has demonstrated improved viral infectivity and tumor specificity in both established ovarian cancer cell lines and in primary ovarian cancer tissue samples [49]. Survivin is a protein that inhibits apoptosis, allowing the survival and progression of cancer cells [74]. In addition, CRAd showed a decreased hepatic uptake [75].

Armed CRAds

CRAds killing ability can be enhanced by constructing an "armed" entity [76]. Several aspects must be considered when constructing an "armed" CRAd. The adenoviral genome can only encapsulate approximately 105% of the wild genome, or 38 kb; therefore, the size of any insert is limited [77]. In addition, the efficacy of the virus is dependent upon replication, and the insertion of a transgene should not interfere with this critical feature. CRAds can be armed with a variety of transgenes that directly enhance the killing of the cancer cell. The most used transgenes that affect cell killing are the "suicide genes" that encode prodrug-converting enzymes that convert nontoxic prodrugs into toxic metabolites. These metabolites then diffuse away from the expressing cell and kill neighboring cells as a "bystander effect." An early example of this system is the herpes simplex virus thymidine kinase/ganciclovir (HSV-TK/GCV), which replaces the *E1B-55 k* gene with HSV-*tk*. This system is very dependent on the *E1B-55 k* gene as well as the amount of ganciclovir given. Another system is CD-5-FC that converts prodrug 5-FC into 5-fluorouracil (5-FU) which can be incorporated into both RNA and DNA, making it toxic to both dividing and nondividing cells [78]. CRAds constructed with short hairpin RNAs directed against vascular endothelial growth factor (VEGF) and/or interleukin 8 have also demonstrated improved antitumor efficacy [56, 57]. Immunomodulatory transgenes are designed to stimulate the immune system into recruiting immune cells to the site of the tumor and to enhance the cells' proliferation and activation. Examples of immunomodulatory CRAds include CRAds armed with TNFα, IFN-γ, and IL-4 [79–84].

Incorporating Imaging into CRAds

An ideal noninvasive monitoring system would emit a signal that directly correlated with the level of viral replication, would be associated with the packaging of the virions to allow detection, and would be continued in viral progeny. To be effective, the system would have to minimally disrupt the replication and spread of the virus. An early approach at noninvasive imaging included positron emission tomography (PET)-directed thymidine kinase as a reporter of oncolytic herpes simplex replication [85]. There are three broad categories of reporters used to monitor the systemic distribution of CRAds in vivo. The first category consists of secreted reporters that are soluble proteins not existent in low levels in serum [86]. The second category of reporters allows the cells to be directly visualized by arming the CRAds with imaging molecules [64–67]. A third system consists of reporters that have been incorporated into the viral capsid. This allows visualization of the viral particle itself [68]. For example, the expression of human somatostatin receptor subtype 2 (SSTR) can be followed by intravenous administration of radiolabeled somatostatin [87].

Cellular Delivery of CRAds

Therapeutic agents often have decreased efficacy in vivo compared to in vitro studies due to physiologic variants. The accurate delivery of these agents to the target tissue can enhance their therapeutic efficiency and decrease toxicity. There are several delivery systems including liposomes, microspheres, synthetic polymers, and protein DNA complexes [87, 88]. Human mesenchymal stem cells have been utilized to improve the delivery of an Ad 5/3 CXCR4 CRAd to pulmonary metastasis in a murine model of advanced breast cancer [89].

Immunotherapy for Ovarian Cancer

The available scientific data suggest that immunotherapy for ovarian cancer (OC) could be effective. Ovarian cancer cells express tumor-associated antigens against which specific immune responses have been detected. The tumor immune surveillance plays an important role in clinical outcomes in OC, as manifested by the correlation between survival and tumor infiltration with $CD3^+$ T cells.

Animal studies and human clinical trials have demonstrated that therapeutically induced tumor-specific immunity is an efficient methodology to treat human cancer based on facts that support this concept. Tumors generally can prevent tumor-specific immunity from eliminating tumors by inducing tumor-specific tolerance or inflammation. The effective immunotherapy for ovarian cancer will have to surmount these obstacles for optimal effectiveness. It is worth noting that ovarian cancer immunotherapies have had less success in ovarian cancer than in most other immunogenic tumor types such as NSCLC and melanoma. Strategies are being adapted to improve the efficacy of immunotherapy application to ovarian cancer, including selecting patients based on immune profiling, such as MSI-H/dMMR, HRD, and combining ICI with other therapeutics.

Cancer Vaccines

Vaccines have been the main approach to ovarian cancer immunotherapy, as with many other types [90–93]. Vaccines have limited efficacy as monotherapy in patients with advanced and recurrent ovarian cancer. Some studies' results provide encouragement for vaccine development and optimization for use. Sabbatini et al. [94] noted that patients vaccinated with monovalent or heptavalent vaccines against carbohydrate epitopes experienced significantly longer time to progression and higher progression-free survival rates. Also, vaccination with anti-idiotype ACA-125 resulted in CA-125-specific antibodies and was associated with prolonged survival [95]. Carcinoembryonic antigen–MUC-1–TRICOM poxviral-based vaccines were used in 16 patients, including three of them being ovarian cancer patients. Immune responses to MUC-1 and/or carcinoembryonic antigen were seen after vaccination in nine patients. A patient with clear-cell ovarian cancer and symptomatic ascites had a radiographically and biochemically clinical response [96]. The limitation in vaccine development in ovarian cancer is due to the lack of well-characterized rejection antigens and by notable molecular heterogeneity of the disease. HER2 is a rejection antigen, and it may also serve as a rejection antigen in ovarian cancer [97, 98]. Vaccination against HER2 has resulted in sustained antigen-specific T cell, humoral immunity, and epitope spreading in patients with ovarian cancer [99]. NY-ESO-1 is a bona fide ovarian cancer rejection antigen, and it is expressed in less than 30% of ovarian cancers [100, 101]. A viable alternative to vaccines is whole-tumor antigen vaccines created using tumor cells, autologous tumor lysate, or tumor-derived RNA [102–104]. The advantages of these vaccines are the opportunity to induce immunity to a personalized and broad range of antigens, which could minimize the development of tumor escape variants; the inclusion of yet unidentified tumor rejection antigens; no HLA haplotype restriction; and the simultaneous administration of MHC class I and

class II epitopes which could prove beneficial for immunologic memory. In a meta-analysis, it was found that 8.1% of patients vaccinated with whole-tumor antigen had notable clinical responses, while 3.6% of patients vaccinated with molecularly defined tumor antigens had objective clinical responses ($P < 0.001$, χ^2 test) [105]. An intracavitary delivery of a viral oncolysate vaccine generated with ovarian cancer cell lines infected with influenza A virus showed objective clinical responses [106, 107]. Delivery of autologous tumor cells infected with Newcastle disease virus showed the same response [108]. HSV-infected tumor cells used directly or pulsed on dendritic cells have been shown to stimulate marked antitumor immune response in the mouse, which was better than utilizing ultraviolet-irradiated tumor cells [109–111]. Using mature dendritic cells (DCs) with whole autologous tumor lysate, 50% of patients demonstrated remission inversion [112]. The use of DC/tumor cell fusion demonstrated to be able to induce antitumor cytotoxic T-lymphocyte activity in vitro [113]. There is a concern about the use of whole-tumor vaccination which relates to the inclusion of many self-antigens, as it could drive tolerogenic responses (i.e., expand Treg) rather than cytotoxic lymphocyte responses. It has been shown that DCs can be polarized ex vivo with the use of interferons, Toll-like receptor agonists, or p38 mitogen-activated protein kinase inhibitors to stimulate cytotoxic lymphocytes and Th17 [114]. The limitation of cancer vaccines is since it is unable to elicit an overwhelming T cell response. In addition, it has been shown that immune modulation through blockade of the endothelin B receptor markedly increases the efficacy of weak vaccines by reversing the inhibitory function of tumor endothelium and enabling homing of tumor-reactive T cells [105, 115]. Moreover, it was observed that, depletion of Treg is a critical maneuver to enhance vaccine therapy [116]. Recently, improvements in vaccine development have shown more promising clinical benefits in patients with ovarian cancer.

Adoptive T Cell Therapy

The advantages of TIL-based adoptive therapy include the presence of spontaneously occurring T cells with avidity against tumor which have escaped thymic deletion, the use of a polyclonal population of T cells, and the natural selection of patients whose tumor microenvironment is already conducive to T cell homing. Incremental lymphodepletion through high dose non-myeloablative chemotherapy and added whole-body radiation was studied. Regression of metastatic tumors was observed, with 16% complete response and 72% objective response rates in recent reports with maximal lymphodepletion and radiation [117, 118]. In another study, it was shown that adoptive immunotherapy is a viable methodology and can control tumors of all sizes [119]. It was reported that patients who received adjuvant therapy with adoptive transfer of tumor-derived lymphocytes expanded ex vivo with IL-2 had a 3-year disease-free survival rate of 82.1%, and the control group had 54.5% [120, 121]. In melanoma trials, it was shown that TILs persisted 2 months after infusion in patients who exhibited tumor regression and were characterized by a less differentiated phenotype ($CD27^+$ $CD28^+$ $CD45RA^+$ but $CD62L^-$ $CCR7^-$) and longer telomeres [122–126]. It has been argued that the use of memory rather than effector cells may be more efficacious for adoptive transfer [127], and this was confirmed by mouse models [128]. June et al. [129] described the development of a next-generation K562-based aAPC platform capable of expressing multiple gene inserts, including human lymphocyte antigen (HLA)-A2, CD64 CD80, CD83, CD86, CD137L (4-1BBL), and CD252 (Ox40L), and several T cell supporting cytokines. Rosenberg et al. [118] have demonstrated the clinical feasibility, safety, and preliminary efficacy of redirecting T cells of patients with melanoma using a TCR specific to the melanoma antigen MART-1. Adoptive transfer of TCR-transduced cells in 15 patients resulted in durable engraftment at levels exceeding 10% of

peripheral blood lymphocytes for at least 2 months after the infusion. In addition, high levels of circulating engineered cells at 1 year after infusion was observed in two patients who demonstrated regression of metastatic melanoma lesions. TCR-based engineering represents a reasonable strategy for ovarian cancer therapy as TCRs recognize HLA-A2 restricted epitopes from known ovarian cancer antigens such as NY-ESO-1 and p53 [130–133]. Optimization through selection of naturally occurring or recombinant high-affinity receptors, engineering to prevent recombination with endogenous TCR, and the use of lentiviral vectors have been developed [134]. Genetic modification to recognize antigens in an MHC-unrestricted fashion using chimeric antigen receptors (CARs), fusion genes encoding an extracellular domain that specifically binds to tumor epitopes through a single-chain variable fragment (scFv) antibody, linked to intracellular signaling modules that mediate T cell activation has been developed [129, 135, 136]. The tumor-binding function of CARs is usually accomplished by the inclusion of a scFv antibody, containing the V_H and V_L chains joined by a peptide linker of about 15 residues in length. The universal targeting vectors can be constructed, as the scFvs bind to native cell surface epitopes and bypass the requirement for MHC restriction [137, 138]. Several CARs targeting diverse tumors have been developed [129, 139–142], and some of the ovarian tumor antigens and CAR investigated in vitro and in vivo in T lymphocytes are FBP [143, 144], MUC-1 [144], HER2, and mesothelin [145].

Antibody-Based Immunomodulation

Modulating immune checkpoints by activation of effector cells, depletion of Tregs, or activation of professional APCs could improve the therapeutic efficacy of vaccines or adoptively transferred T cells. The development of functional antibodies has enabled effective immune modulation as shown in Fig. 11.2.

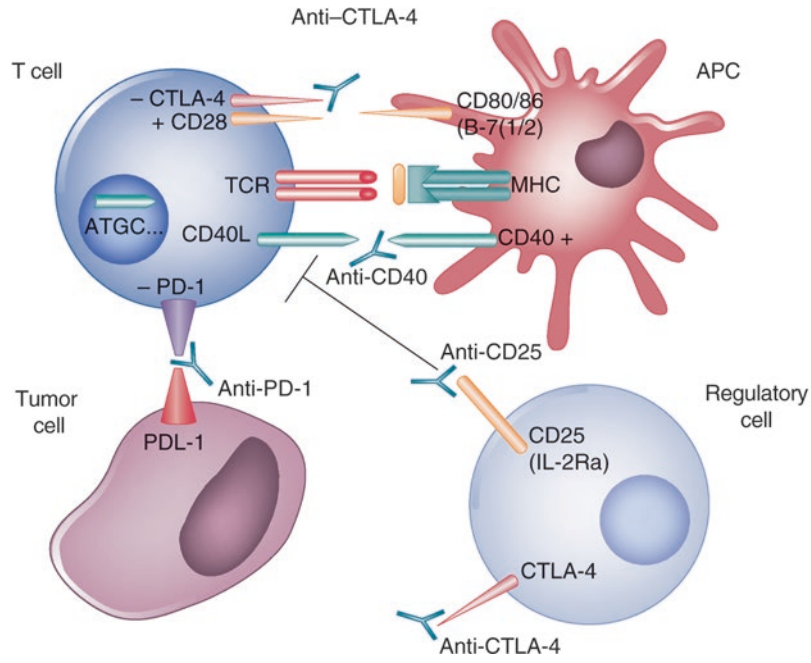

Fig. 11.2 Improved therapeutic efficacy of vaccines or adoptively transferred T cells can be achieved by modulating immune checkpoints, including activation of effector cells by blocking CTLA4 or PD-1; depletion of regulatory T cells by use of low-dose oral or intravenous cyclophosphamide or through targeting the interleukin-2 (IL-2) receptor α chain, also known as CD25; or activation of professional antigen-presenting cells (*APCs*) by stimulation with CD40 ligands

Dendritic Cell Activation

The main mechanism of immune stimulation by CD40 ligands is the activation of DCs resulting in increased survival, upregulation of molecules, and secretion of critical cytokines for T cell priming. This promotes antigen presentation, priming, and cross-priming of $CD4^+$ and $CD8^+$ effector T cells. It was observed that agonistic anti-CD40 antibody is well used in combination with vaccines or Toll-like receptor agonists [146, 147], as it can accelerate the deletion of tumor-specific cytotoxic lymphocytes [148]. It was noted that ovarian cancers express the CD40 receptor [149–153] and respond to CD40 agonists with apoptosis and growth inhibition in vitro and in vivo [152, 154, 155].

Effector T Cell Activation

T cell activation is triggered through the T cell receptor by recognition of the cognate antigen complexed with MHC. CTLA-4 blockade activates CD4 and $CD8^+$ T effector cells by removing an inhibitory checkpoint on proliferation and function [156], and combination of direct enhancement of Teff cell function and inhibition of Treg activity is important for mediating the therapeutic effects of anti-CTLA-4 antibodies during cancer immunotherapy [157].

Most of clinical data to date have emerged from studies in patients with melanoma [158], where CTLA-4 blockade has yielded notable responses. It has been shown in patients with ovarian carcinoma, previously vaccinated with granulocyte–macrophage colony-stimulating factor modified, irradiated autologous tumor cells (GVAX) and received ipilimumab (1 month to 3 years after GVAX), that tumor regression correlated with the $CD8^+$/Treg ratio [159]. PD-1 is a negative regulator of lymphocyte activation, which binds PD-L1 and PD-L2 ligands. PD-L1 is expressed on many tissues. Ovarian carcinoma cells, tumor-infiltrating tolerogenic DCs, and myeloid-derived suppressor cells express PD-L1 [160, 161]. It was observed that expression of PD-L1 by tumors conferred resistance to immunotherapy in mice [162], while antibodies blocking PD-L1 or PD-1 enhanced the efficacy of immune therapy [162, 163]. A phase I study using PD-1-blocking antibody showed the antibody to be safe and well tolerated in patients with hematologic malignancies [164].

Treg Depletion

$CD4^+$ $CD25^+$ $Foxp3^+$ Treg is responsible for maintaining peripheral tolerance by inhibiting T cell activity. Several Treg-depleting strategies have been investigated [117, 164–168]. One of these strategies was the use of low-dose oral or intravenous cyclophosphamide [117, 169]. It was shown that the use of anti-CD25 monoclonal antibody before vaccination led to complete tumor rejection and establishment of extended immunity with no side effects [117, 170]. Also, it was observed that administration of anti-CD25 resulted in transient reduction in $CD4^+$ $CD25^+$ Treg in patients with metastatic melanoma [171]. Denileukin diftitox, a fusion protein of IL-2 and diphtheria toxin that targets CD25-expressing cells, was used in patients with melanoma, ovarian cancer, and renal cell carcinoma [172–175]. It was observed that these conjugates were immunogenic and induced neutralizing antibodies. In addition, daclizumab, which is humanized immunoglobulin G1-kappa monoclonal antibody that binds specifically to CD25 [176], has been used in autoimmune disorders [177, 178], acute graft-versus-host disease [179], and in patients with cancer with $CD25^+$ T cell malignancies [180]. The advantage of daclizumab is that it is well tolerated and has a half-life of 20 days [181]. Moreover, daclizumab was found to be compatible with effective vaccination [182]. As above, the assumption is that innovative immunothera-

peutic strategies offer the promise of enhancing host antitumor responses which may improve clinical outcomes in women with ovarian cancer. While many preliminary phase I/II studies have demonstrated induction of antitumor responses, currently there is no clinically effective antigen-specific active immunotherapy available for patients with ovarian cancer. Ongoing investigation may help to define the role of immunotherapy alone or in combination with other treatment strategies in the treatment of ovarian cancer patients. These trials may determine a role for immunotherapy in the treatment of ovarian cancer.

Epithelial Growth Factor Receptor Targeting Therapy

The epithelial growth factor receptor (EGFR; also known as Her or ErbB) family of receptor tyrosine kinases has been shown to have oncogenic characteristics in several human cancers. It was suggested that members of the EGFR family, such as ErbB3, may have a role in promoting the growth and proliferation of human ovarian cancer cells. The EGFR family of receptor tyrosine kinases consists of four closely related family members: EGFR (Her1), ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (Her4) [183]. These cytoplasmic membrane-bound receptors share a common extracellular ligand-binding domain and a single transmembrane domain, followed by an intracellular tyrosine kinase domain and a C-terminal non-catalytic signaling tail. Signaling through these receptors is typically mediated by homodimerization or heterodimerization with other family members. Binding of the ligand with the extracellular domain of its corresponding receptor induces a structural reconfiguration of the receptor, promoting exposure of dimerization domain [184, 185]. The EGFR family members can be activated by unphysiological stimuli (e.g., oxidative stress, UV, and γ-irradiation), by other receptor tyrosine kinases (MET, insulin-like growth factor-1 receptor, or tyrosine kinase receptor B), or by G protein-coupled receptors and adhesion proteins [186].

Epithelial Growth Factor Receptor (Her1)/ErbB2 (Her2) in Ovarian Cancer

Siwak et al., *in a review* [187], noted that epithelial growth factor receptor amplification and activating mutations have been reported in a small percentage of ovarian cancer cases (4–22% and <4%, respectively). The EGFR overexpression rate varies from 9% to 62%. Increased EGFR expression has been correlated with poorer patient outcomes. Several small molecule inhibitors that block EGFR kinase activity (e.g., gefitinib and erlotinib) have been explored. There are two phase II clinical trials on gefitinib (Iressa or ZD1839) as a single agent in treating platinum-refractory or -resistant ovarian cancer. No complete response was observed in either trial. In one trial, 37% of the patients had stable disease for over 2 months while none of the patients had a partial or complete response. In the second trial, 4 out of 27 patients had progression-free disease for over 6 months, and 1 of these 4 patients had an objective response. Erlotinib (Tarceva, OSI Pharmaceuticals, Long Island, NY, USA), another small molecule inhibitor of EGFR, demonstrated a 6% partial response rate in a multicenter phase II trial with EGFR-positive ovarian cancer patients with taxane- and/or platinum-refractory or -resistant disease. In a phase II study, 56 patients demonstrated no improvement in pathological CR rates compared with historical experience with erlotinib added to carboplatin and paclitaxel in the first-line therapy for ovarian cancer [187]. An additional study comparing the combination of erlotinib, and the antiangiogenic agent bevacizumab also did not show any improvement compared with bevacizumab alone. Also, vandetanib, a small molecule inhibitor of VEGFR and EGFR signaling, did not demonstrate significant clinical benefit in recurrent ovarian cancer [188]. Monoclonal antibodies that bind directly to the extracellular domain of EGFR to block EGFR activation or reduce surface EGFR levels have also been tested. The objective clinical response of these therapeutic antibodies, such as cetuximab (Erbitux, ImClone LLC, Bridgewater, NJ, USA) and matuzumab (EMD7200), in ovarian cancer was limited [185]. Early studies suggested that Her2 overexpression

in ovarian cancer was a frequent event; but other studies using techniques validated in breast cancer suggest that Her2 overexpression and amplification frequency in ovarian cancer is a rarer event [189]. Overexpression of Her2 has been associated with poor prognosis in some studies but not others. This discrepancy may be explained by differences in the criteria and methods used to assess Her2 overexpression. A phase II trial with trastuzumab (Herceptin, Genentech, Inc., South San Francisco, CA, USA), a humanized anti-Her2 monoclonal antibody, reported a low (7%) partial response rate with only a 2-month progression-free interval in recurrent ovarian cancers overexpressing Her2 [190]. In a phase II multicenter open-label trial, CI-1033 (Canertinib, Pfizer, Inc., New York City, NY, USA), an irreversible pan-EGFR family inhibitor, was shown to have no activity in unscreened patients who have failed previous platinum-based chemotherapy [191]. A phase I trial combining carboplatin and lapatinib (Tykerb, Tyverb, GlaxoSmithKline, plc, London, UK), an EGFR–Her2 dual inhibitor, was performed in unscreened patients with platinum-sensitive recurrent ovarian cancer [192]. In this trial, 27% of patients had a partial response and another 27% had stable disease.

ErbB3 (Her3) in Ovarian Cancer

ErbB3 has been reported to be amplified [191, 193] and overexpressed in epithelial ovarian cancers [193–197]. Overexpression of ErbB3 has been reported to correlate with poorer overall prognosis [194]. Several truncated ErbB3 isoforms composed of the extracellular domains of the protein have been described in ovarian cancer cell lines, but the functional significance of these remains unclear [195]. In addition, ErbB3 has been recently characterized as having a marked role in mediating resistance to EGFR, and Her2-directed therapies in other solid malignancies [196]. Sergina et al. [197] demonstrated that in gefitinib-resistant Her2-overexpressing breast cancer cell lines, ErbB3 activation is increased, through increased localization of ErbB3 to the cytoplasmic membrane. Engelman et al. [198] demonstrated that ErbB3 activation by MET amplification could overcome resistance to gefitinib in EGFR-mutant non-small cell lung cancer cell lines. Inhibition of AKT has been demonstrated to upregulate ErbB3 expression and phosphorylation, so that ErbB3 may have a role in mediating resistance to PI3K/AKT pathway inhibitors [199]. A humanized monoclonal antibody that binds to the extracellular domain of Her2 and blocks its heterodimerization with ErbB3 and other EGFR family members, pertuzumab (2C4), has been studied. Pertuzumab treatment demonstrated a 4.3% partial response in platinum-refractory and -resistant patients. The median progression-free survival in the eight pHer2+ patients (tumors demonstrated positively for pHer2 by an ELISA assay) was 20.9 weeks as compared with 5.8 weeks in the pHer2 patients (P = 0.14), [200]. In a clinical trial conducted using the combination of pertuzumab with gemcitabine versus gemcitabine alone for ovarian cancer patients [200], there was no significant difference seen in the outcome between the two arms. However, a subset analysis demonstrated a potential benefit in progression-free survival to gemcitabine plus pertuzumab in patients with low ErbB3 expression by mRNA (hazard ratio 0.32; 95% CI 0.17–0.59; P = 0.0002). Signaling through the ErbB3 pathway has been reported to correlate with expression of its natural ligand, neuregulin-1 (NRG1) in both ovarian cancer cell lines and in primary human ovarian cancer cells [201]. Moreover, expression of NRG1 has been observed in 30–83% of ovarian carcinomas [201, 202].

ErbB4 (Her4) in Ovarian Cancer

The role of ErbB4 in cancer is not clearly understood. Conflicting reports regarding the potential transforming activity of ErbB4 have been published, which may partly reflect the unique mechanism of ErbB4 signaling. ErbB4 is spliced into multiple isoforms, some of which are further processed by tumor necrosis factor-α-converting enzyme and γ-secretase to generate a soluble ErbB4 intracellular domain that has a BH3 homologous region that can distribute to both the nucleus and the cytoplasm [203]. Nuclear-localized ErbB4 intracellular domain may act as a transcription co-activator, whereas the cyto-

plasmic/mitochondria-localized ErbB4 intracellular domain may act as a BH3-only protein and induce apoptosis in tumor cells [203]. In breast cancer, cytoplasmic ErbB4 independently predicted for improved patient survival [203]. ErbB4 somatic mutations have been detected in 19% of melanoma patients [204] and in several cancer types, but at a lower frequency: 1–5% [205]. It has been shown that ErbB4 is weakly expressed in adult ovarian surface epithelium [206]. In addition, early studies suggested that ErbB4 expression is either absent or decreased in some ovarian cancers when compared with normal ovarian tissues [206, 207]. In several studies, using either IHC, RT-PCR, or Western blotting techniques have demonstrated the presence of ErbB4 in a high percentage of ovarian tumors [208, 209], and RT-PCR has detected at least four different ErbB4 splice variants in both established and primary ovarian cancer cell lines [208]. Gilmour et al. [208] reported that tumors of serous histology tend to express higher levels of ErbB4 than that of the endometrioid subtype, and Steffensen et al. [210] found that ErbB4 expression is significantly higher in epithelial ovarian cancer tumors as compared with borderline/benign ovarian tumors or normal ovaries. Somatic mutations in the intronic regions of ErbB4 have been detected in ovarian cancers [209]. The clinical significance of ErbB4 in ovarian cancer is currently unknown. It is noteworthy that established ovarian cancer cell lines that express high ErbB4 protein level have all been derived from platinum-refractory tumors, raising the possibility that ErbB4 expression may be related to platinum therapy resistance [208].

Poly (Adenosine Diphosphate Ribose) Polymerase (PARP) Inhibition Therapy

It was reported that *BRCA1*-deficient and *BRCA2-deficient* cells were sensitive to poly (adenosine diphosphate ribose) polymerase (PARP) inhibition when compared to wild-type or heterozygous mutant cells [211, 212]. These findings highlighted the clinical potential of PARP inhibitors to treat patients with *BRCA1/2*-associated breast and ovarian cancers. The activity of PARP inhibitors has been examined in selected subsets of breast cancer and epithelial ovarian cancer.

PARP Family of Enzymes

PARPs are a family of enzymes which catalyze poly adenosine diphosphate (ADP)-ribosylation of target proteins in a wide variety of eukaryotes [213]. PARP1 is the most abundant and well-characterized PARP enzyme, accounting for more than 90% of ADP-ribosylation occurring in cells [214, 215]. PARP1 and PARP2 are the only PARP enzymes that are activated by DNA damage and that facilitate DNA repair [216, 217]. It was shown that mice generated to lack either PARP1 or PARP2 has hypersensitivity to ionizing radiation and alkylating agents [218, 219]. Improved understanding of the biology and function of the other PARPs may aid interpretation of the mechanism of PARP inhibition and long-term therapy implication.

PARP1 Role in DNA Repair

PARP1 plays a critical role in the repair of DNA single-strand breaks (SSB) via the base excision repair (BER) pathway. DNA damage due to peroxidation, irradiation, and DNA-damaging chemicals such as chemotherapy stimulates the catalytic activity of PARP1 [220, 221]. PARP1 is recruited to the damaged DNA by two zinc finger motifs in the DNA-binding domain of PARP1 binding to DNA SSB, thus activating the BER machinery to repair the SSB [217, 222]. PARP1 has also been implicated in the two major pathways for the repair of DNA double-strand breaks (DSB): homologous recombination (HR) and nonhomologous end joining (NHEJ) [222]. Genomic instability was observed in HR-deficient cells treated with PARP inhibitors [224].

Structure of Common PARP Inhibitors

AZD2281 (olaparib) and ABT-888 (veliparib) are both p.o. formulations. AZD2281 has an IC for PARP1 of 5 nmol/L, and ABT-888 inhibits PARP1 and PARP2 with a K_i of 5.2 and 2.9 nmol/L, respectively [225–227]. BSI-201 (iniparib) was described as having PARP inhibitory activity, but iniparib does not appear to inhibit PARP1 and 2 [227, 228].

Use of PARP Inhibitors in BRCA1/2 Mutations

Carriers of germline mutations in *BRCA1* or *BRCA2* are at a high risk of developing breast cancer (85% lifetime risk) and ovarian cancer (54% lifetime risk) and are also predisposed to developing pancreatic, prostate, and male breast cancer [229–232]. *BRCA1* and *BRCA2* are classified as tumor suppressor genes, as the wild-type *BRCA1* and *2* alleles are lost in the tumor, with the retention of the mutant allele [223]. *It has been shown that BRCA1* is important for DNA repair, transcriptional regulation, and chromatin remodeling [233]. The function of *BRCA2* appears to be limited to DNA recombination and repair processes [234, 235]. Cells deficient in either *BRCA1* or *BRCA2* repair these lesions using alternative mechanisms, alternative homology-directed repair pathway, and SSA and potentially by the error-prone microhomology-mediated sub-pathway of NHEJ [224, 236–238]. In *BRCA1*-deficient cells, both GC and SSA are impaired, and DSBs are repaired by the error-prone NHEJ pathway [236, 239, 240]. *In BRCA2 deficiency*, repair by GC is impaired. Synthetic lethality occurs when the combination of two genetic alterations results in a lethal phenotype [241]. The original model for explaining the antitumor effects of PARP inhibitors in *BRCA-deficient* tumors postulated a synthetic lethal interaction between PARP inhibition and the DNA repair defects present in *BRCA*-deficient tumor cells (Fig. 11.3). The inhibition of PARP1 prevents cells from responding to endogenous DNA damage through BER, which results in persistent DNA SSB and, in turn, leads to DNA replication fork collapse and increased formation of DSB [242, 243].

Efficacy of PARP Inhibition Therapy in BRCA-Deficient Tumors

The mechanism of PARP inhibitor-induced cytotoxicity appears to be more complex than it was thought. Patel et al. [224] demonstrated that downregulation of X-ray repair cross-complementing 1 enzyme in *BRCA2*-deficient cells failed to produce synthetic lethality. According to the BER-dependent model, if accumulated DNA damage were responsible for mediating PARP inhibitor action, HR-deficient cells would be expected to depend on alternate DSB repair pathways such as NHEJ for survival. It has been shown that PARP inhibitor-induced genomic instability is driven by the activation of NHEJ and that disabling NHEJ using genetic and pharmacological approaches impaired the genomic instability and lethality of PARP inhibition in HR-deficient cells [224]. These findings support an NHEJ-dependent model whereby PARP inhibition leads to defective BER and the aberrant activation of NHEJ in HR-deficient cells.

PARP Inhibitors Resistance

Each PARP inhibitor has a separate chemical structure with diverse off-target effects [244]. So, the utilization of a secondary PARP inhibitor could be beneficial in a resistant tumor. Among the resistance mechanisms identified, restoration of homology-directed DNA repair is frequently observed in vitro and in vivo. The restoration of BRCA activity starts from BRCA-deficient and chemosensitive cells because of several mutations

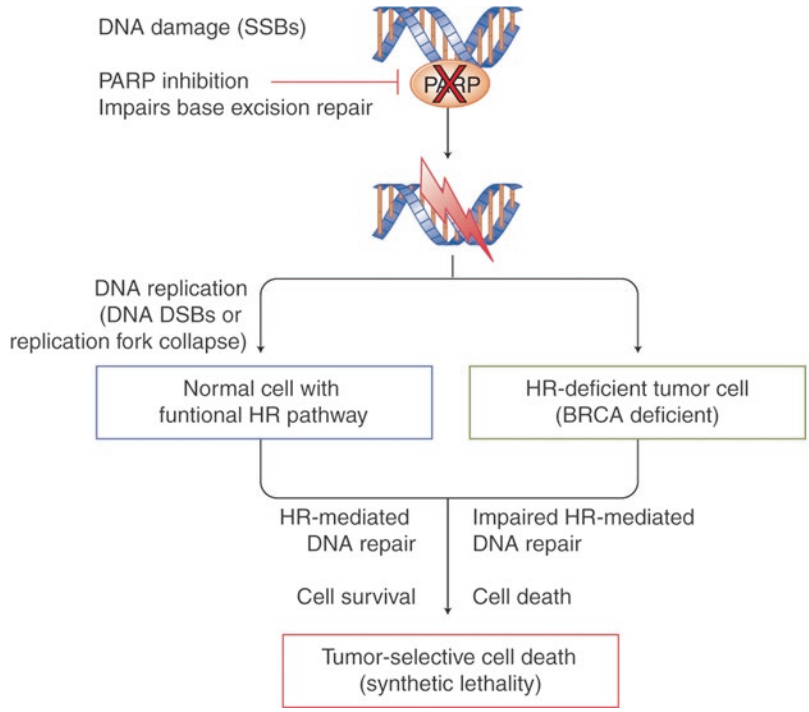

Fig. 11.3 Inhibition of base excision repair (BER) is responsible for poly ADP ribose polymerase (PARP) inhibitor-induced lethality in homologous recombination (HR)-defective cells. The original model for explaining the antitumor effects of PARP inhibitors in BRCA-deficient tumors postulates a synthetic lethal interaction between PARP inhibition and DNA repair defects in BRCA-deficient tumor cells. PARP inhibition prevents cells from responding to endogenous DNA damage through BER. This result in persistent DNA single-strand breaks (SSB), which lead to fork collapse and the increased formation of double-strand breaks (DSB) when they encounter a DNA replication fork. Under normal circumstances, DSB are repaired by the error-free gene conversion pathway

that are induced by platinum agents. This initial restored clone expands in the setting of treatment-specific selective pressure [245]. Compensatory mutations have also been detected to confer PARP inhibitor resistance. TP53-binding protein 1 (53BP1) maintains the balance between HR and NHEJ [246]. Loss of 53BP1 function by either mutation or downregulation accelerates the BRCA1-independent end resection and provides PARP inhibitor resistance [247]. It has been shown that the inactivation of downstream factors of 53BP1-mediated repair, typically RIF1 and REV7, may lead to the restoration of DNA end resection, and consequently promotes homology-mediated repair [248]. This PARP inhibitors resistance can be reverted by the ABCB1 inhibitors verapamil, elacridar, and tariquidar [249]. Currently, there are several ongoing combination clinical trials seeking to reduce and inhibit PARP inhibitor resistance up front.

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12 Ovarian Cancer in the Pediatric Population

Anne C. Fischer

Introduction

Although ovarian tumors are the most frequent neoplasm of the female genital tract in childhood, they are actually an uncommon type of childhood cancer, accounting for only 1% of all malignancies in children (<17 years) [1, 2]. An ovarian mass can be due either to nonneoplastic or neoplastic processes. Nonneoplastic conditions include many hormonally induced masses, follicular cysts, corpus luteal cysts, and endometriomas (chocolate cysts of intraovarian endometriosis), spanning a broad spectrum of hormonally active masses. Neoplastic processes include the spectrum of both benign tumors, such as mature cystic teratomas, as well as malignant tumors that range from being highly malignant to having only a low malignant potential, such as the borderline serous tumors. Historically management was to remove all ovarian masses in children given the concern of an underlying malignancy. Given the low risk of malignancy in the pediatric population, risk stratification is being popularized to better apply a more conservative fertility-sparing approach to decision-making [3, 4].

Generally these tumors are classified into three main pathologic categories—germ cell, sex cord–stromal, and epithelial tumors. The predominant pediatric ovarian tumors are germ cell tumors (GCT) in contrast to epithelial tumors primarily seen in adults. GCTs are a diverse group of tumors and include embryonic and extraembryonic tumors. Benign GCTs include mature teratomas and gonadoblastomas. Malignant GCTs include immature teratomas, as well as endodermal sinus tumors, also called yolk sac tumors, embryonal carcinomas, polyembryomas, and choriocarcinomas. Less frequent, non-germ cell tumors include sex cord–stromal tumors and epithelial tumors. Sex cord–stromal tumors include thecoma–fibroma, Sertoli–Leydig cell tumors, and juvenile granulosa cell tumors.

Though uncommon in children, the clinical spectrum of ovarian tumors ranges from largely benign mature teratomas to life-threatening, widely metastatic cancers. Pain was the most common symptom, although the presence of an abdominal mass was frequent as were other nonspecific symptoms. Precocious puberty and/or increasing abdominal girth may present concurrently. Abdominal and endocrine symptoms should raise the index of suspicion. Torsion is actually infrequently associated with an underlying malignancy: historically, torsion was incorrectly presumed to be secondary to an underlying mass.

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Studies have reported a wide variability in malignancy rates in ovarian masses in girls, depending on the inclusion criteria of the study, the type of referral center, and the number of surgical resections for benign ovarian masses, such as for functional cysts, torsions, and dermoids seen. Therefore the risk of malignancy in these different populations is highly variable depending on the same aforementioned factors.

Ultrasound is 100% accurate in localizing any process to the ovaries; however, its specificity is lacking and has not been conclusively able to distinguish benign from malignant neoplasms. Almost all neoplasms present as unilateral masses and rarely are metastatic at diagnosis. Fortunately, ovarian malignancies in children are frequently found at an early stage and most children with ovarian malignancies respond favorably to chemotherapy with few recurrences given the profound impact that platinum-based therapies have had on this diagnosis. The option of conservative surgical therapy depends on the stage of disease at the time of diagnosis. Only recently have efforts been more concerted to be less extirpative to balance the need for effective treatment with conservation of ovarian function and fertility, despite ovarian preservation being the putative dogma.

Incidence

Ovarian neoplasms are uncommon in children and account for 1% of all malignancies in pediatric patients less than 17 years of age, although they are the most common pediatric gynecologic tumor [1, 2]. The literature is replete mainly with case series, given the limited number of cases seen annually at any center. The overall incidence of an ovarian mass in childhood approximates 2.6 cases/100,000 cases per year, whereas the incidence of those that are tumors may vary from ~10% to 20% [5, 6]. The true incidence of malignant ovarian tumors was not known in the pediatric population given the wide range of reported malignancy rates in different case series.

Our analysis of the Surveillance, Epidemiology, and End Results (SEER) 2008 database, the largest cancer database in the USA, identified 1037 pediatric ovarian tumors diagnosed over three decades from 1973 to 2005 [7]. The SEER program of the National Cancer Institute (NCI) is compiled from 17 population-based cancer registries, encompassing 26% of the US population. The analysis of all malignant pediatric ovarian tumors in the SEER database demonstrated an age-adjusted tenfold increase in cancer incidence with each decade of life. The age-adjusted incidence of malignant pediatric ovarian tumors was 0.102 per 100,000 per year in children younger than 9 years of age, 1.072 per 100,000 in children aged 10–19 years of age, and 11.446 per 100,000 in adult women older than 20 years of age (Fig. 12.1).

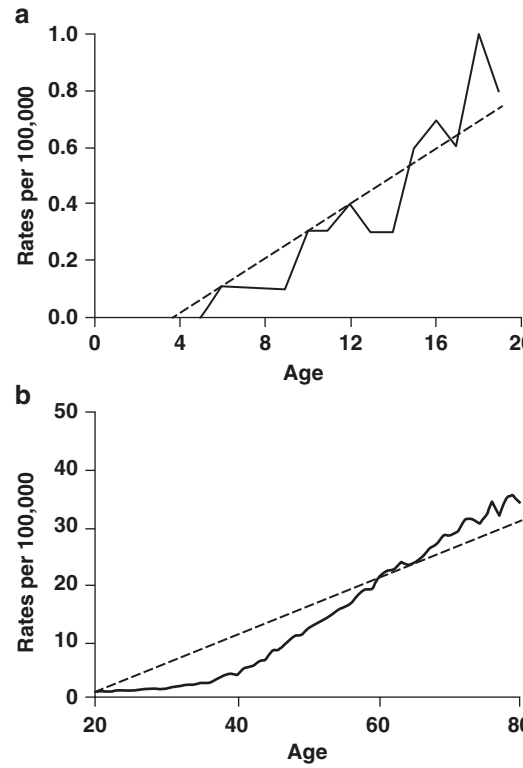

Fig. 12.1 Age-adjusted incidence rates (2000 standard U.S. population) of ovarian tumors for ages (**a**) less than 20 years and (**b**) greater than 20 years. Solid line represents rate per 100,000 per year. Broken line represents best-fit straight line. (From Brookfield et al. [7]; with permission)

Epidemiological Aspects

The low percentage of malignancies overall among ovarian masses, which encompass functional cysts, benign masses, and neoplasms, was demonstrated in several large case series. Three centers, Dallas Children's Medical Center, Children's Hospital of Philadelphia, and Texas Children's Hospital, reviewed a total of 424, 251, 102 ovarian lesions, respectively, over ~15-year period. Each series reported approximately a 10% malignancy rate among all presenting ovarian lesions [5, 8, 9]. Variations in the incidence of neoplasms reported in any case series is likely impacted by age cutoffs and referral patterns for an ovarian mass presenting to those institutions. For instance, a typical ovarian cyst may be managed locally and not at the referral center in contrast to the management of a solid ovarian mass. The mean age of patients with a malignancy was similar to those with a nonneoplastic lesion [5, 8, 9] but can nonetheless be impacted by the referral patterns at a given institution.

Most in the SEER database analysis of pediatric ovarian malignancies were Caucasian (76.6%), presented with local disease (57.4%) and were treated with surgery (79.3%). Out of all the malignancies identified, 10% presented in patients ≤9 years of age, 28.2% in those between 10 and 14 years of age, and the remaining 61.7% presented in teens 15–19 years of age [7].

What is more salient to a specific patient is *how frequently is a mass malignant*, out of all ovarian lesions presenting at a specific age. This last metric is more clinically applicable in the evaluation of a newly diagnosed ovarian mass. The percentage of malignancies among all ovarian lesions varies by age; the subset aged 1–8 years had the highest percentage (22%) of malignant neoplasms among ovarian lesions in comparison to 10% seen in older girls [8]. This finding was further substantiated by a threefold greater odds ratio for malignancy in the 1–8-year group compared to the 15–19-year olds [8].

Anatomic Aspects of Ovarian Masses

As stated, ovarian masses include neoplastic and nonneoplastic lesions. Ovarian germ cell tumors are the most common malignancy in children, whereas epithelial cell tumors are the least common. The significance of this difference anatomically is the fact that most pediatric tumors present at a low stage, and even those at more advanced stages present with localized spread as opposed to gross metastases. A majority of adult ovarian cancers are epithelial neoplasms, derived from the coelomic epithelium covering the surface of the ovary so the tumor can spread widely throughout all surfaces in the peritoneal cavity; they are not locally contained, requiring extensive staging and debulking procedures to mitigate against potential spread.

There are assumptions, often slow to correct, made about the malignant potential in nonneoplastic conditions such as torsion. The resultant ovarian enlargement resulting from the venous engorgement secondary to torsion is assumed to contain an underlying malignant component. Historically, it was presumed that all ovaries containing any lesion discovered in children, even the increase in ovarian volume due to venous engorgement, should be removed surgically for concern of malignancy. Given better imaging and risk stratification using serum tumor markers, a conservative fertility-sparing approach to the management of ovarian masses has been advocated.

Ovarian Masses Associated with Torsion

Torsion is most commonly associated with pathologically normal ovaries [10, 11]. Ovarian enlargement or a discrepancy in ovarian volume is the most characteristic ultrasound (US) finding in torsion and is merely the end result of progres-

sive edema and venous congestion. Previous reports have shown no underlying ovarian pathology was found in over half the cases [10–12]. Given the abdominal location and fair amount mobility of the ovary in a child with the long utero-ovarian ligament, the normal adnexa are at risk of torsion. Torsion of the ovary usually occurs with the twisting of the associated fallopian tube (adnexal torsion) around the broad ligament; although, in very rare cases the ovary rotates just around the mesovarium, or the fallopian tube rotates around the mesosalpinx in an isolated fashion. If this diagnosis is not detected in a timely fashion, then the twisting results in a compromised blood supply to the vascular pedicle, venous engorgement with distortion of the ovarian anatomy and subsequent infarction of adnexal structures leading to necrosis and peritonitis. A dual blood supply is likely the reason why Doppler ultrasonography is not sufficient alone in the diagnosis of torsion [13]. However, a dual blood supply exists in only 56% cases; 40% of ovaries are supplied by the ovarian artery alone and 4% by the uterine artery [14].

Ovarian masses associated with pain had torsion in 42% of the time, whereas those presenting as an asymptomatic mass were found to have a malignancy in 26% of cases [5]. Torsed ovaries are associated with a markedly lower overall malignancy rate of 0.5–1.9% compared with the typical 10% malignancy rate reported for all ovarian masses, in the Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) [11] and in the largest reported case series (682 patients) [10]. The anatomic distortion from the edema of venous congestion can confound decision-making intraoperatively, resulting in an inappropriately more aggressive use of oophorectomy in the acute setting. Torsed ovaries should be "detorsed" laparoscopically with conservation of the ovary despite an ischemic or necrotic appearance with follow-up US surveillance. US can best detect a potential mass persisting when the venous congestion has been resolved in 1–2 months [15, 16]. The contralateral tube and ovary should be assessed as well at the time of laparoscopy and the affected tube and ovary "detorsed." The affected side should also have a suture to shorten the utero-ovarian ligament if that is found to be unusually elongated, causing the torsion. There were historical theories regarding blood clots and emboli being released from detorsion that have proven to be unfounded: there was no diagnosis of pulmonary thromboembolism in any ovarian-related hospitalization in the KID database [11]. Ovarian salvage rates exceed 90–95% in follow-up studies despite the ovary being black at the time of detorsion [17].

Ovarian Cysts in a Changing Hormonal Milieu

Functional cysts are normal physiologically and most resolve spontaneously in 1–2 months. Most ovarian cysts <3 cm are normal follicles and require no surveillance. They can vary with the development and hormonal milieu of the patient. They include follicular, corpus luteum, and theca-lutein types, all of which are benign and self-limited. Simple cysts result from the persistence of a maturing follicle that does not ovulate or involute.

Ovarian cysts are the rule in 98% of newborn girls and over 20% are larger than 9 mm [18]: nearly all simple cysts resolve. Although a neonatal simple cyst >2.5 cm is considered pathologic, surveillance is done to ensure regression since most simple cysts >4–5 cm will resolve with the maturation of the hypothalamic-pituitary-ovarian axis. Most resolve by 4 months up to 12 months of age due to withdrawal of maternal hormonal stimulation [19]. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels peak in the newborn at 3–4 months of age and then reach prepubertal levels at 2–3 years of age [20]. Even large cysts, up to 8.7 cm, can spontaneously resolve. Resolution of a large cyst typically can take up to 10–12 months, which can be concerning for the risk of torsion [21, 22]. Serial ultrasound is used for surveillance and to ensure regression. Cysts that are >5 cm or increasing in size or persist longer than 4 months meet the criteria for proceeding with exploration with the intent on salvage [23]. A neonatal cyst can be managed by laparoscopy although a

minilaparotomy may be required. Alternatively consideration of aspiration of a postpartum cyst has been advocated to temporize and decrease the risk of torsion while waiting for its decrease in size with a waning hormonal milieu [24]. The majority of antenatally diagnosed ovarian cysts have actually torsed before the first postnatal US, so ovarian salvage of perinatal torsions is unexpected [23]. Viable ovarian tissue has been shown to recover in a case of perinatal torsion over time, supporting consideration of nonoperative intervention [23].

The management of large simple cysts if increasing in size, >5 cm, or causing symptoms, then a laparoscopic ovarian cystectomy is preferred given the high recurrence rate after only a cyst aspiration. Both the wall and the fluid should be sent to pathology and cytology, respectively. Simple cysts are best treated with fenestration as opposed to aspiration which is fraught with recurrences; complex cysts should be treated with cystectomy with the goal to maximize preservation of ovarian tissue. Large cysts that are asymptomatic may resolve and can be surveilled. The decision for expectant management is substantiated by concern of the high likelihood of oophorectomy, as the outcome of acute surgical intervention, as opposed to preservation of ovarian function if surgical intervention is avoided [25]. Expectant management can be considered in those cysts that are (1) ovarian in origin, (2) have no associated mass besides debris and septa, (3) have normal tumor markers (alpha-fetoprotein [AFP] and β-human chorionic gonadotropin [β-HCG]), and (4) are asymptomatic [25]. Although the risk of malignancy is essentially nonexistent, most surgeons advocate the removal of complex cysts to prevent complications of bleeding and rupture.

Ovarian cysts are least common in prepubertal girls due to a low hormonal milieu. Cysts <1 cm are considered normal, requiring no further evaluation. Larger cysts require further evaluation given any association with sexual precocity. The persistence of any ovarian cyst or a complex cyst in the prepubertal child warrants surgical resection. Nonfunctional ovarian cysts will present as nonresolving cystic masses, and although rare, benign cystic epithelial tumors, such as serous and mucinous cystadenomas, do occur. These can be asymptomatic, and require excision since they are low-grade tumors, and are typically laparoscopically resectable [26].

Most common in adolescence, ovarian cysts typically present up to 3 cm in diameter and resolve in the second half of the menstrual cycle. Dysfunctional ovulation causes a persistence of the functional cyst which then can continue to enlarge: those cysts that measure >6 cm can take up to 3 months to resolve [27]. Complex cysts typically result from hemorrhage into the functional cyst but should raise a concern for a dermoid or other neoplasms, so tumor markers, serum AFP, and β-HCG should be measured. Those cysts that persist over 3–6 months, increase in size, exceed 6 cm, or are symptomatic require intervention. A laparoscopic cyst aspiration (with cytologic analysis of the aspirated fluid) or cystectomy (with pathologic sampling of the cyst wall) should be performed. A laparoscopic cystectomy with preservation of the remaining ovarian base is preferred over an aspiration, due to a high rate of recurrence following aspirations and repeated surgical interventions [28].

Histopathologic Types of Tumors

The clinical spectrum of ovarian tumors is varied. Malignancies are classified into three main histopathologic categories, reflecting the three gonadal cell types with neoplastic potential—the *primordial germ*, *stromal*, *and epithelial* cells. Primordial germ cells give rise to GCTs which are the most common type of pediatric ovarian malignancy. Less commonly, the cells of the sex cords can develop into stromal tumors, such as ovarian granulosa cell tumors or Sertoli–Leydig cell tumors, or mixtures of these components. The coelomic epithelium covering the ovary may evolve into epithelial neoplasms, which are the most common cell type seen in adults.

The SEER database analysis of pediatric ovarian tumors best demonstrates the distribution of tumor histology as is shown in Fig. 12.2 [7]. Table 12.1 shows a corresponding list of the histopathologic classification of pediatric ovar-

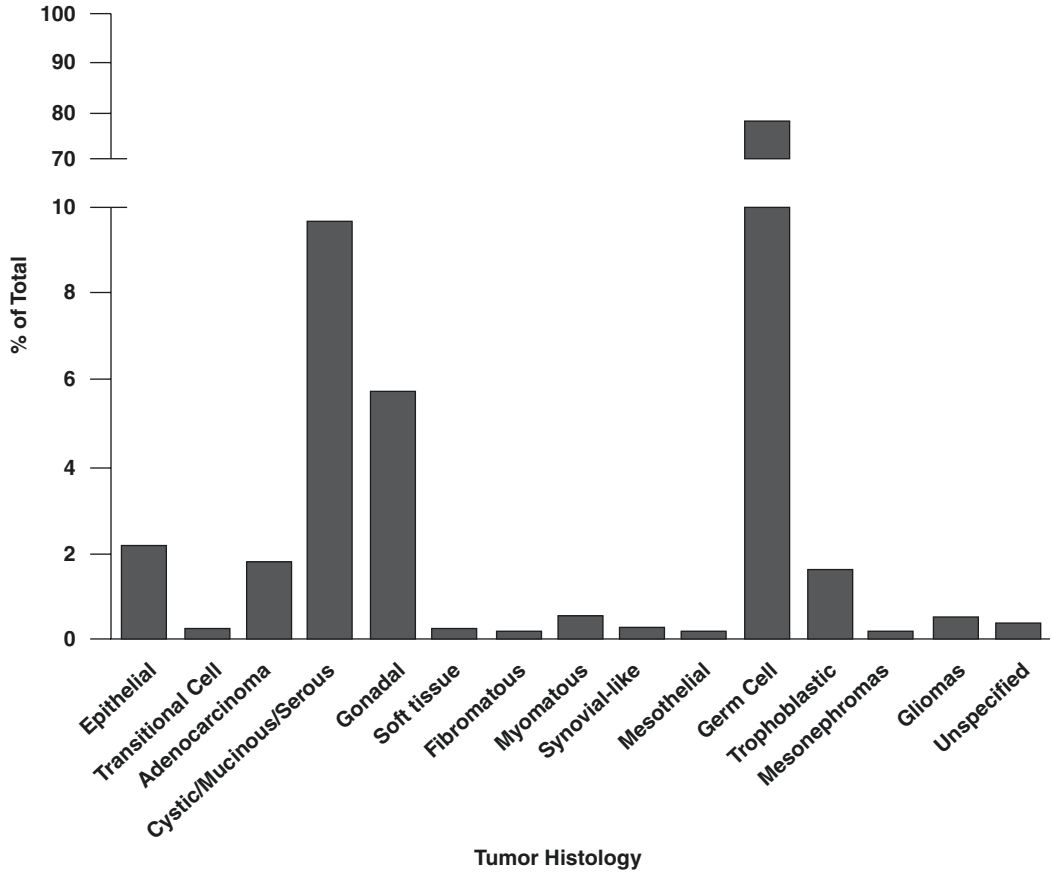

Fig. 12.2 Distribution of tumor histopathology shown as a percentage of total ovarian tumors in SEER database study. (From Brookfield et al. [7]; with permission)

Table 12.1 World Health Organization classification of tumors of the ovary

Germ cell tumors	Surface epithelial stromal tumors	Sex cord–stromal tumors
Mature cystic teratoma	Serous cystadenoma	Juvenile granulosa cell tumor
Immature teratoma	Mucinous cystadenoma	Sertoli–Leydig cell tumors
Dysgerminoma	Borderline tumors	Sclerosing stromal tumor
Mixed germ cell tumors	Cystadenocarcinoma	Sex cord tumor with tubular annules
Yolk sac tumor		Fibroma
Choriocarcinoma		Thecoma

From Lala et al. [29] with permission

ian tumors [29]. Germ cell neoplasms were the most common tumor identified across all ages, constituting nearly 80% of all ovarian tumors in every age group of the pediatric population (Fig. 12.2). The incidence of ovarian GCTs increases around age 8 years of age and peaks in adulthood [30]. The distribution of tumor histopathology included germ cell tumors (77.4%) and serous or mucinous cystic neoplasms (9.6%) which accounted for the majority of pathologic types of malignancies [7]. Sex cord–stromal neoplasms were the next frequent, accounting for 5.7% which in other reports constituted up to 12.3% of all tumors [1].

Malignant Germ Cell Tumors

GCTs account for typically 75–80% of all neoplastic pediatric ovarian masses in most series [7], demonstrated in Fig. 12.3. As the primordial germ cell, they arise from the fetal yolk sac, but can express different tumor markers with different malignant potentials [31]. Their malignant potential can vary, from (1) the stage of germ cell development at tumorigenesis, as well as by (2) the tumor microenvironment secondary to the location of the clone. Their heterogeneity stems from the variations in the developmental age, histopathology, and malignant potential of the primordial germ cell. The lineage of GCTs determined from the timing of tumorigenesis in germ cell development is best shown in Fig. 12.4 [31, 32]. The primordial germ cells that remain undifferentiated become dysgerminomas. Germ cells that undergo some degree of differentiation before becoming neoplastic either differentiate into *embryonic* tumors (embryonal carcinoma or teratoma) or *extraembryonic* tumors (endodermal sinus tumors or choriocarcinoma) [31].

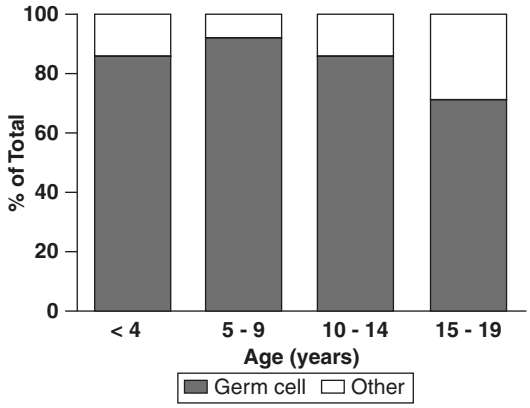

Fig. 12.3 Germ cell tumor shown as a percent of total ovarian tumors by age group. (From Brookfield et al. [7]; with permission)

Teratomas

Teratomas are the most common type of GCTs and are either **mature** (benign), **immature** (contain malignant potential), or **malignant**. The mature teratoma is composed of mature representative tissue from all three germ layers:

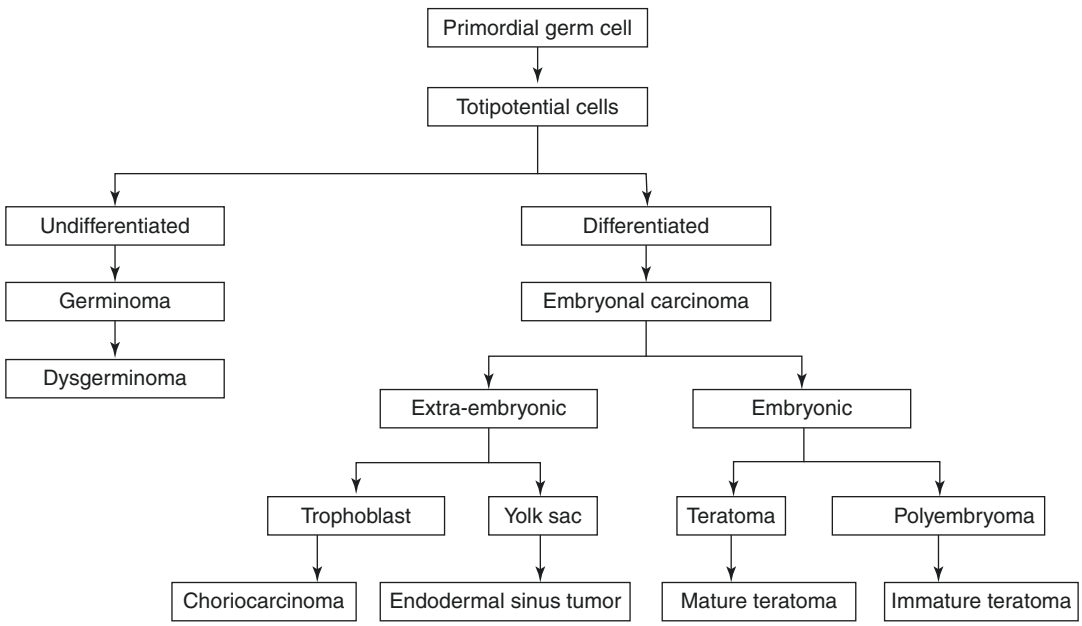

Fig. 12.4 Histologic derivation of ovarian germ cell tumors from primordial germ cell. (Teilum et al. [31] and Strickland et al. [32], with permission)

ectoderm, mesoderm, and endoderm. Immature teratomas have a gross similar appearance to that of a mature teratoma but uniquely have various foci of immature tissues present, usually neuroepithelium. The younger the patient is, the more likely the teratoma is an immature germ cell type [33]. Immature teratomas in children behave in a malignant fashion only if they are clinically advanced (advanced stage) or contain foci of malignant germ cell elements (yolk sac tumor). Clusters of yolk sac tumor may be very small and associated intimately with immature neural tissue and thus do not stain avidly for AFP and are overlooked. These foci of immature elements are assumed to be responsible for the metastatic potential of an immature teratoma.

All grading systems quantify *the degree of immaturity* in the lesion. Immature tumors are graded from I to III based on the amount of neuroepithelium or the degree of immature elements present in the mass (see Table 12.2) [34, 35]. Grade I is the most differentiated with the least risk of malignancy, and grade III is the least differentiated with the greatest risk of malignancy. Norris et al. added a quantitative aspect to the degree of immaturity and showed that the stage and *grade of the primary teratoma* are related to prognosis [34]. Complete resection of an immature ovarian teratoma is standard therapy with close surveillance. These patients had a 4-year EFS and OS of 97.7% and 100% [36].

Table 12.2 Grading of immature ovarian teratomas

Grade 0	All tissues mature; no mitotic activity
Grade 1	Some immaturity but with neuroepithelium absent or limited to 1 low-power microscopic field; no more than one focus in a slide
Grade 2	Immaturity present; neuroepithelium common but no more than 3 low-power microscopic fields in one slide
Grade 3	Immaturity and neuroectoderm prominent; no more than 4 low-power fields per section

Norris et al. [34] and Mahajan et al. [35], with permission

The grade of the primary tumor is a critical determinant of prognosis [37]. The most important risk factor for relapse is also grade in an analysis by the Malignant Germ Cell International Consortium reviewing 7 pediatric trials [38]. Adjuvant chemotherapy did not decrease the risk of relapse. The histologic level of differentiation is determined by the presence of immature elements: the more immature neural elements result in a higher histologic grade which correlates with a more aggressive biology of the tumor in adults [38]. This grading of the extent of immature lesions has shown potential prognostic significance only in adults, and chemotherapy is required to reduce recurrences in adults with this aggressive phenotype. In contrast, an intergroup study of Children's Oncology Group and the Pediatric Oncology Group examined the need for adjuvant therapy in children and concluded that surgery alone is an adequate treatment for an immature teratoma, even in the presence of an elevated AFP suggestive of a component of yolk sac tumor [36].

Five-year survival for pure immature teratomas by histologic grade was 81%, 60%, and 30% for grades I to III, respectively [37]. Survival among pure immature teratomas has shown 74% 5-year survival for all grades of stage I and 38% survival for stages II and III [34]. Many teratomas are associated with the presence of peritoneal implants of mature glial tissue, *gliomatosis peritonei*, which is a distinct entity and does not change tumor stage or alter prognosis.

Germinomas

Malignant dysgerminomas arise from the primordial *undifferentiated* germ cells and are the most common pure germ cell malignancy in the ovary, accounting for 50% of malignant ovarian GCTs [39, 40]. They can occur in dysgenetic gonads, those abnormal gonads containing gonadoblastoma [41], or phenotypic females with karyotypic abnormalities. The majority of pure dysgerminomas present as stage I disease and are highly

responsive to chemotherapy and radiation and are histologically identical to a seminoma in males. Bilateral disease occurs in 10–15% of cases [42]. The 10-year survival rates for a dysgerminoma confined to one ovary and treated with surgery is 92%; however, there is a noted 17% recurrence rate and 6% mortality rate [42].

Yolk Sac Tumor (Endodermal Sinus Tumor)

Endodermal sinus tumor, also called a yolk sac tumor, is of extraembryonic germ cell origin and is the second most common pure GCT [32]. It is typically associated with elevations of AFP [33] (see Table 12.3) and has an aggressive biology with peritoneal spread and metastases to the liver, lung, and brain [43, 44]. There are four general histopathologic patterns but these patterns are not clinically relevant. The "pseudopapillary or festoon" pattern and "microcystic or reticular" pattern are the most common. The "solid" pattern is usually found only focally and can resemble embryonal carcinoma; the "hepatoid" pattern closely resembles fetal liver and is a variant of the "solid" pattern. The fourth pattern is the "polyvesicular vitelline" pattern.

Endodermal sinus tumors can be associated with gonadoblastomas in some cases. Gonadoblastomas are benign tumors typically and occur exclusively in phenotypic females with at least a portion of the Y chromosome; thus, they present clinically as male pseudohermaphrodites and have dysgenetic gonads. Germinomas frequently develop with gonadoblastomas [41].

Table 12.3 Tumor markers associated with ovarian malignancies

α-Fetoprotein[a]	Yolk sac tumor
	Immature teratoma
	Embryonal carcinoma
	Mixed germ cell tumor
	Sertoli–Leydig cell tumor
β-Human chorionic gonadotrophin	Choriocarcinoma
	Embryonal carcinoma
	Dysgerminoma
Inhibin	Juvenile granulosa cell tumor
Lactate dehydrogenase[a]	Dysgerminoma

From Lala et al. [29] with permission
[a]Sometimes test positive in children with mature cystic teratoma

Mixed Cell Tumors: Embryonal Carcinoma and Choriocarcinoma

Mixed GCTs contain multiple malignant cell types and carry the phenotypic biology and diagnosis of the "worst" acting cellular element. They constitute up to 30% of malignant GCTs and peak at 15–19 years of age [45]. Both embryonal carcinoma and choriocarcinoma are rare in isolation but are more commonly seen in mixed tumors: both produce β-HCG, and embryonal carcinoma can produce precocious puberty. The two histopathologic forms of embryonal carcinoma—the pseudotubular and papillary patterns—can be confused with yolk sac tumors, but the cells are AFP-negative and lack the eosinophilic hyaline globules characteristic of yolk sac tumors. Embryonal carcinoma stains positive for CD30 by immunohistochemical staining.

Choriocarcinoma also rarely occurs as a pure lesion, and when it appears in infants, it represents metastases from maternal or placental gestational trophoblastic primary tumor [46, 47]. These tumors are very friable and hemorrhagic and require the presence of two cell types—cytotrophoblasts and the syncytiotrophoblasts—which stain for β-HCG for diagnostic confirmation. Multiagent chemotherapy is used for therapy after surgical resection and staging.

Polyembryoma is a very rare malignant lesion with a poor prognosis, occurring as a component of a mixed lesion. Both AFP and β-HCG can be elevated and also this tumor presents often with symptoms of precocious puberty [48].

Non-germ Cell Tumors

Non-germ cell tumors include both sex cord–stromal tumors (stromal histology) and the epithelial tumors (epithelial histology). Tumors of

epithelial or stromal cells of origin each accounts for the remaining 15–20% of ovarian malignancies that are not germ cells.

Sex Cord–Stromal Tumors

Sex cord–stromal tumors include Sertoli–Leydig cell tumors and juvenile granulosa cell tumors, arising from the stromal components of the ovary and are hormonally active and constitute 15% of pediatric ovarian tumors.

Juvenile granulosa cell tumors, constituting 2/3 of pediatric sex cord–stromal cell cases, have a malignant potential based on the granulosa cells present, although the juvenile subtype follows a benign clinical course unlike the adult subtype. The pure granulosa tumor is highly malignant, mixed tumors are less malignant, and the pure thecoma is benign. The majority (>95%) develop in postpubertal girls with estrogen excess and can be associated with pseudo-precocious puberty in 80% of girls with breast enlargement, vaginal bleeding, and galactorrhea [49, 50]. Menstrual irregularities and swelling are the presenting symptoms. Most cases are limited to the ovary at presentation with <5% being bilateral so that a unilateral salpingo-oophorectomy and appropriate staging is usually adequate therapy. Serum inhibin levels are associated with determining recurrence. Prognosis is excellent with 84–92% survival. Tumors with a higher mitotic activity have a poorer response.

Sertoli–Leydig cell tumors, arrhenoblastomas, are rare and account for <0.5% of all malignant ovarian neoplasms [51] but 20% of the sex cord–stromal cell tumors [52]. The less well-differentiated and retiform histologies are most commonly found in children, most often localized to the ovary, and represent a low-grade malignancy. Clinically they present with androgen excess, amenorrhea, precocious puberty in young children, and hirsutism or virilization in adolescents. An elevated AFP is associated with this tumor [53]. Prognosis depends on the stage and degree of differentiation of the tumor and mitotic index; usually it is a low-grade malignancy, so a unilateral salpingo-oophorectomy with staging is sufficient. Multiagent chemotherapy is utilized for advanced, metastatic, or recurrent disease [54].

In stromal cell tumors, mitotic activity in conjunction with tumor stage correlates with patient outcome. Tumors with >20 mitoses per high-power field (HPF) had an event-free survival (EFS) that was half of those with <20 mitoses per HPF [55]. Those tumors with high proliferative activity are the high-risk category and difficult to treat.

Epithelial Tumors

Less than 20% of ovarian tumors in childhood are derived from the surface epithelium of the ovary and are rare to present before menarche [56]. The histologic subtypes in children are limited to serous or mucinous tumors which can be characterized as benign, borderline (of low malignant potential), or malignant. Approximately 84% of epithelial lesions in two case series were benign or of low malignant potential [9, 57].

Cystadenoma is an epithelial tumor filled with mucin (pseudomucinous) or cystic fluid (serous cystadenoma) and account for 10–20% of ovarian tumors usually after menarche. Mucinous and serous cysts can be removed laparoscopically with preservation of the ovary. Cystadenomas are usually benign with 7% being borderline and 4% being malignant [58–61]. Borderline tumors are indolent and can be bilateral. Borderline epithelial tumors are defined as neoplasms with varying nuclear atypia that lacks stromal invasion of the ovary and occur three times more frequently in children than adults [61]. For a stage IA borderline tumor, a unilateral salpingo-oophorectomy is appropriate for the affected one ovary. Biopsying the contralateral ovary and staging are important. They have more favorable prognosis than higher-grade carcinomas. They can present locally extensive and proper workup would require applying the proper operative staging of epithelial tumors using adult guidelines since they are an epithelial pathology, as opposed to the pediatric guidelines designed for germ cell tumors.

Adenocarcinoma of the ovary is very rare, presenting as two cases in a 40-year center review, and has very poor outcomes [45, 62, 63].

Metastatic Disease to the Ovary

Lymphoma can be a primary ovarian tumor [64] or metastatic to the ovary. Leukemia can relapse with subsequent ovarian enlargement masquerading as an ovarian tumor [65]. Gastric carcinoma also can metastasize to the ovary [66].

Molecular Pathology of Ovarian Tumors

Mature Teratomas

Ovarian mature GTCs are thought to arise primarily from benign germ cells in meiosis and not from a malignant transformation of the germ cell. The entry into meiosis of primordial germ cells is a gradual process that continues until birth. Over 95% of mature ovarian teratomas are karyotypically normal with only 5% showing gains of a single whole chromosome [67, 68]. Analysis of molecular loci has shown that the majority has entered but not completed meiosis and thus is diploid [67].

Immature Teratomas

Immature and mature teratomas appear to have a different mechanism of origin and thus represent different biologic entities rather than occurring along the same spectrum of maturation. The origins of immature teratomas appear to come from meiotic stem cells and others from mitotic cells, implying a failure of early meiotic arrest [69], whereas mature teratomas originate from germ cells entering but not completing meiosis, a normal process of maturation. The frequency of chromosomal abnormalities is higher in immature teratomas than mature teratomas. Chromosomal analysis suggests that immature ovarian teratomas of premeiotic origin show a greater malignant potential and deviations in karyotype suggest a worse prognosis [70, 71]. The majority of patients with cytogenetically abnormal immature teratomas have recurrent disease. In contrast, those with karyotypically normal immature teratomas have remained disease-free [69–71].

Malignant Ovarian Germ Cell Tumors

Immature teratomas may develop genetic changes found in malignant teratomas which correlate with the histologic malignant transformation of malignant GCTs. Malignant ovarian teratomas are presumed to originate from the malignant transformation of a germ cell. The genetics of malignant ovarian teratomas are similar to those of testicular tumors with similar ploidy and genetic features. Malignant teratomas often are aneuploid and 75% may contain the isochromosome 12p, i(12p), common in malignant testicular teratomas [72]. Other genetic features include 42% and 32% have gains of chromosomes 21 and 1q, respectively, whereas 25% and 42% have loss of chromosomes 13 and 8, respectively [73–75].

The association between sex chromosomal abnormalities and the development of GCT is well established. Individuals with 46XY and 45X/46XY gonadal dysgenesis have a 10–50% risk of developing a gonadal germ cell tumor [76].

Dysgerminomas, in particular, are associated with abnormal karyotypes in phenotypic females: 46XY as in gonadal dysgenesis or complete androgen insensitivity, or 45X/46XY as in mixed gonadal dysgenesis.

Clinical Presentation

Although rare in presentation, ovarian tumors must be included in the differential diagnosis of abdominal pain or an abdominal mass in female children. Pain is the most common symptom, although the presence of an abdominal mass was frequent and other symptoms are often nonspecific. Precocious puberty and increasing abdomi-

nal girth are also suspicious for an underlying ovarian malignancy. The symptoms of abdominal pain and increased girth, with nausea and vomiting, also typify appendicitis, which is the primary diagnosis that causes the majority of these operations being performed on an emergency basis without a complete workup or tumor markers. Exquisite tenderness may suggest peritoneal irritation from rupture or torsion of the mass.

The largest case series of ovarian masses analyzed differences in presentation between those that are benign or malignant masses [8]. Perimenarchal patients tend to have a greater number of benign lesions such as cysts and neoplasms, while those younger patients that are hormonally quiescent are less likely to present with an ovarian mass at all. The greatest percentage of malignancies in all ovarian lesions was in those patients aged 1–8 years, with malignancy being present in up to a quarter of the time. As a result, a higher index of suspicion for malignancy is needed in the patient aged 1–8 years, as indicated by a threefold increase in the odds ratio. Conversely, it is exceedingly rare for a child less than 1 year to have a malignant neoplasm [8, 77, 78].

The presenting symptoms of patients with malignancies can significantly overlap with those with benign conditions. Complaints of an abdominal mass or precocious puberty are statistically more often associated with an underlying malignancy [9, 77, 78]. Precocious puberty in the setting of a mass can be associated with sex cord–stromal tumors, including Sertoli–Leydig cell tumors, and GCTs, such as embryonal carcinoma and polyembryoma. Evidence of unusual hormonal activity is more often associated with either estrogen production from a juvenile granulosa cell tumor or androgen production with resultant virilization from a Sertoli–Leydig cell tumor [79, 80]. Not infrequently, a similar level of hormone production can be seen with autonomously functioning benign follicular cysts [25]. In contrast, over 50% of epithelial tumors in children present as asymptomatic masses incidentally detected [9].

A recent largest single institution review analyzed the features of benign ovarian masses compared to malignancies to best unravel the diagnostic dilemma of an ovarian mass on presentation. The findings and odds ratios suggestive of a potential malignancy included masses in those aged 1–8 years of age, a chief complaint of a mass or precocious puberty, imaging findings of a mass greater than 8 cm, or a mass that is solid in character (shown in Table 12.4) [8]. Laboratory investigations showing elevated β-HCG, AFP, or cancer antigen 125 (CA-125) were worrisome for malignant neoplasm but are not definitive if normal.

Table 12.4 Characteristics suspicious for malignancy

Adnexal masses with extra-ovarian spread
Ultrasonically suspicious masses >8 cm
Thick cyst wall by ultrasound
Lengthened utero-ovarian ligament
Numerous vessels starting from the mesovarium with a comb-like pattern
Peritoneal metastasis
External ovarian vegetations
Intracystic vegetations

Adapted from Hayes-Jordan [81] with permission

Management Strategy

Evaluation

The workup involves comprehensive exam, preoperative imaging, and testing for serum tumor markers, and if they are abnormal, then consult with a pediatric oncologist. Preoperative imaging will often reveal a pelvic mass, easily detected by US, computed tomography (CT) scan, or magnetic resonance imaging (MRI), depending on the initial complaints prompting the radiologic evaluation. Malignant masses were thought of those greater than 5 cm [57, 77], whereas others advocate the use of >8 cm to be the size cutoff for concern of malignancy [81]. In a case series, all malignancies exceeded 6 cm, whereas ≥8 cm allowed for a statistically significant odds ratio with the greatest accuracy (Table 12.4) [81, 82]. The caveat is that using the 8-cm cutoff, two of 46 malignancies (4.3%) would have been missed by size alone [8].

Radiologic studies are not always able to distinguish benign lesions from malignancies. Classically, solid masses are thought to have a higher risk of malignancy, although heterogeneous and cystic masses can also harbor underlying malignant neoplasm [5]. Solid masses, either by ultrasound or by CT scan, had the highest frequency (33–60%) of malignancy; solid features were only evident in 14–15% of all malignancies [8]. Conversely, the majority of radiologic reads identified either a heterogeneous or cystic mass, which were associated with malignancy in only 15–20% and 4–5% of the time, respectively, which is consistent with previous reports [83]. While findings of a cystic lesion may be relatively reassuring, heterogeneous masses should still be approached with a heightened suspicion for malignancy, especially if additional concerning factors are present.

If an ovarian mass >8 cm is seen on preoperative imaging, serum levels of AFP, β-HCG, and CA-125 should be evaluated before surgery, and a chest CT scan should be obtained to rule out metastatic disease. If signs of precocious puberty are apparent, then FSH, LH, estradiol, and lactate dehydrogenase (LDH) serum levels should be obtained.

Tumor Markers

β-HCG, AFP, and CA-125 are all potential serum tumor markers for ovarian malignancies. GCTs will often produce AFP and/or β-HCG, depending on their subgrouping (see Table 12.3) [84]. Dysgerminomas can result in elevations of serum lactic dehydrogenase (LDH), β-HCG, or CA-125 [84]. Yolk sac and Sertoli–Leydig cell tumors are both associated with AFP elevations. CA-125 is most commonly associated with epithelial type tumors [9]. However, the caveat is that tumor markers do not exclude the possibility of malignancy when they are not elevated.

Thus, tumor markers are not definitive measurements preoperatively but are of greatest value, if elevated, in the ability to monitor postoperatively for complete resection of disease, as well as to detect relapse [85, 86]. Tumor markers should be drawn preoperatively whenever possible, but elevations can still be detected immediately postoperatively due to the relatively long half-lives of both AFP and β-HCG [85].

Operative Management

Operative Staging

Proper staging at the time of surgery is critical in determining the need for postoperative chemotherapy; cisplatin-based adjuvant chemotherapy has markedly improved the long-term survival in GCTs. Over 80% of ovarian neoplasms in any pediatric age group are GCTs [7]. In contrast, adult ovarian malignancies are primarily epithelial. This difference explains the two different staging systems since epithelial spread requires sampling of many peritoneal surfaces and more extirpative surgery for clearance or debulking. In contrast, most germ cell tumors often present at a low stage and will have visible evidence of local spread, so the staging system for GCTs is focused on sampling what is visibly abnormal. Surgical staging for GCTs need not be as extensive as epithelial ovarian tumors; however, peritoneal cytology is critical to determine stage. Thus, the modified International Federation of Gynecology and Obstetrics (FIGO) staging is best utilized for GCTs [84], and the American Joint Committee on Cancer (AJCC) and FIGO staging for primary ovarian carcinoma is utilized for epithelial-based tumors in children as in adults (see Table 12.5) [87, 88].

The surgical incision is based on the size of the mass to remove it without rupture and the best means to accomplish an appropriate staging procedure. Often this entails a transverse Pfannenstiel skin incision with vertical fascial incision depending on the size of the tumor and likelihood of malignancy. Intraoperative staging entails (1) sampling ascites for cytology, (2) lymph node sampling, (3) omentectomy, and (4) peritoneal biopsies with (5) assessment of the contralateral ovary. The steps of lymph node dissections, biopsies of peritoneal surfaces, and an omentectomy, which are standard in the staging in adults, are usually omitted in pediatric germ

Table 12.5 Children's Oncology Group staging of GCTs

Stage	Extent of disease
I	Limited to ovary, peritoneal washings negative for malignant cells; no clinical, radiographic, or histologic evidence of disease beyond the ovaries. The presence of gliomatosis peritonei does not result in changing stage I disease to a higher stage. Tumor markers normal after half-life decline
II	Microscopic residual or positive lymph nodes <2 cm; peritoneal washings negative for malignant cells. The presence of gliomatosis peritonei does not result in changing stage II disease to a higher stage; tumor markers positive or negative
III	Lymph node involvement (metastatic nodule) >2 cm; gross residual or biopsy only; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells; tumor markers positive or negative
IV	Distant metastases, including liver

Adapted from Von Allmen [84] with permission

cell cases, unless visible involvement is noted. There is no adverse impact on survival given this modification of staging for pediatric GCTs, and thus the new guidelines omit the need for these steps 2–4, listed above, without evidence of gross disease [77]. These new guidelines apply to presumed GCTs.

Epithelial tumors should be staged according to adult staging guidelines since lymph nodes are positive in up to 38% of FIGO stage I epithelial tumors [88] without obvious tumor involvement. Bilateral biopsies are important since lymph node metastases are not clinically evident or visibly obvious.

Surgical Management

Ovarian lesions can be approached from a vertical midline incision or a Pfannenstiel approach with a vertical fascial opening depending on the size of the tumor and ability to adhere to staging guidelines for ovarian tumors. It is often impossible to know at the time of surgery if the lesion is malignant or neoplastic at all. First, pelvic washings or fluid taken for cytologic analysis, then all peritoneal surfaces, the contralateral ovary, the omentum, and pelvic and periaortic lymph nodes should be examined visually and manually. Any lesions or concerning findings needs to be sent for pathologic evaluation. Malignancy is staged according to the COG staging systems (unless FIGO guidelines are needed for epithelial tumors). The grade and stage of the disease are determined by the final pathologic analysis. Gliomatosis peritonei which are peritoneal implants of mature glial tissue is a nonmalignant entity and should not upstage the tumor. Tumor size, stage, and histologic grade are all critical in predicting survival.

Laparoscopy is controversial and discouraged by the Children's Oncology Group, since it is essential to remove the tumor intact to avoid the upstaging associated with rupturing the tumor or violating the capsule intraoperatively [84]. A careful intraoperative manual inspection is also critical. Laparoscopic-assisted approach with a wound protector and plastic bag glued to the ovarian cyst and containing it are other options now under COG review.

When a mixed cystic and solid mass is encountered at laparoscopy or laparotomy, careful inspection is critical to best differentiate if the mass is benign or potentially malignant. Adnexal masses with extra-ovarian spread, ovarian masses >8 cm in diameter, with peritoneal metastases, and external ovarian or intracystic vegetations can predict malignancy with 100% sensitivity (see Table 12.4) [84, 85].

Tumor markers can guide surgical decision-making. If tumor markers are elevated, after incidental detection of an >8-cm solid or mixed mass, then a staging laparotomy should proceed and unilateral oophorectomy or salpingo-oophorectomy. Oophorectomy should be done if signs of precocious puberty exist. If tumor markers are normal and there are no clinical signs of precocious puberty, then excision of the mass >8 cm with an attempt at ovarian salvage to spare the ovary is warranted.

Recommendations for specific pathologies is discussed below.

Active surveillance without adjuvant chemotherapy is sufficient for Stage I GCT (including dysgerminoma and nondysgerminatous GCT). Relapse is high at 50% but salvage at relapse confers OS >95% [84].

Platin-based chemotherapy regimens have increased OS to >85% survival. Carboplatin- versus cisplatin-based chemotherapy is being actively assessed in trials for decrease in toxicity and if there is a similar survival in nondysgerminatous GCTs and advanced dysgerminoma [84].

Immature teratomas are graded from 1 to 3 based on the degree of immature neural elements. Most immature teratomas with a reassuring grade and cell type are typically treated with a unilateral salpingo-oophorectomy and a staging procedure. If the tumor is a distinct encapsulated teratoma, then the ipsilateral fallopian tube can be preserved. Surgery alone is curative even in the presence of elevated levels of AFP or microscopic foci of yolk sac tumors since chemotherapy is used for postoperative cases of relapse [36]. For metastatic or recurrent disease, multiagent chemotherapy is utilized: the response to chemotherapy is excellent in the settings of a recurrence [36, 89, 90]. Extensive GCTs usually require multiple biopsies to confirm extent of disease without resecting vital structures since multiagent chemotherapy is very effective in reducing the extent of disease at the second-look procedure if planned after four rounds of chemotherapy to achieve a complete response.

Since most dysgerminomas have stage I disease, surgery alone is advised. Close follow-up and surveillance is instituted. Approximately 8–15% of dysgerminomas are bilateral, and thus suspicious areas on the contralateral ovary are biopsied. Lymphatic spread typically involves pelvic and para-aortic lymph nodes, so ipsilateral nodes should be sampled to stage the patient. If the dysgerminoma is greater than stage I disease, then cytoreductive surgery to remove all operable tumor is advised, followed by multiagent chemotherapy [39, 91].

Therapy for endodermal sinus tumor involves a staging laparotomy and unilateral salpingo-oophorectomy, unless intraperitoneal and hematogenous spread have resulted in presentation at a higher stage.

Embryonal carcinoma, mixed GCTs, and choriocarcinoma all typically require a staging laparotomy with unilateral salpingo-oophorectomy and postoperative multiagent chemotherapy to reduce recurrence.

Borderline and malignant epithelial tumors typically are managed with conservative therapy since they present early. Thus, they are managed with (1) a unilateral salpingo-oophorectomy for stage IA borderline tumors involving one ovary, (2) staging, and (3) biopsy of the contralateral ovary with a serous cystadenoma or if suspicious as in cases of a mucinous cystadenoma. Conservative management of stage II or III borderline tumors can also allow for preservation of fertility. However, in the rare case of an invasive tumor with peritoneal spread, patients presenting with more advanced stages should be managed as adults with staging laparotomy, cytoreductive surgery, and multiagent chemotherapy [58, 84, 89]. They may require total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Fertility-Sparing Approaches

Malignant ovarian neoplasms in children arise predominately from the germ cell element of the ovary. Although the characteristics of each tumor type (germ cell, stromal, epithelial) differ, the majority of malignant ovarian tumors present at a low stage and can be treated with fertility-sparing surgery.

Given that most lesions present as an ovarian mass without clear evidence of being a malignancy, most advise ovarian-sparing operations for all benign-appearing lesions with normal tumor markers [5]. If the mass is secondary to torsion, then laparoscopic detorsion is first done, even if the ovary is ischemic or necrotic in appearance, and then surveillance by US is done to ensure the mass does not persist and that there is return of ovarian function [15, 16]. If the tumor is a bilateral teratoma, then an attempt to enucleate a lesion on one ovary is attempted to

preserve fertility. Typically in a mature teratoma, if a fallopian tube is not involved and the tumor is clearly encapsulated, then the fallopian tube is preserved. Although oophorectomy has been the traditional treatment for teratomas, many authors report no adverse sequelae from resection of the mass alone in mature teratomas [5, 92, 93]. The resection can be done laparoscopically, and the incidence of recurrent mature cystic teratomas in adults following cystectomy alone is 3–4% [94]. In patients <40 years who had multiple or bilateral mature cystic teratomas resected, such as dermoids, there is a 2–3% incidence of developing subsequent germ cell tumors [94].

Chemotherapy

Cisplatin-based adjuvant chemotherapy has vastly improved survival of GCTs of the ovary even in advanced cases with a dramatic improvement over the last few decades. Chemotherapy is required to manage those tumors that present spreading beyond the confines of the ovary.

Platin-based chemotherapy regimens have increased OS to >85% survival. Active surveillance without adjuvant chemotherapy is sufficient for Stage I GCT (including dysgerminoma and nondysgerminatous GCT). Relapse is high at 50% but salvage at relapse confers OS >95% [35, 84].

The current management with bleomycin, etoposide, and cisplatin has improved event-free survival (EFS) and overall survival (OS) for stage I GCTs to 95.1%. Patients with stage II disease have EFS and OS of 87.5% and 93.8% with four cycles of standard cisplatin, etoposide, and low-dose bleomycin [95]. High-dose cisplatin does not improve survival but is associated with more toxicity, so carboplatin is being tested to replace cisplatin. Carboplatin- versus cisplatin-based chemotherapy is being actively assessed for decrease in toxicity and similar survival in nondysgerminatous GCTs and advanced dygerminoma [96, 97].

Stromal cell tumors with high mitotic activity remain a challenge to treat. Those with mitoses >20 HPF have an EFS of 48% compared to those <20 mitoses HPF with an EFS of 100% [55]. The majority present at a low tumor stage, and prognosis is excellent, but for those with a higher proliferative activity, taxanes are being combined with cisplatin-based therapy to better improve outcomes.

Although the specific histopathologies of each tumor type in pediatric ovarian malignancies differ, the majority of malignant ovarian tumors present at a low stage and can be treated with fertility-sparing surgery. Platinum-based chemotherapy regimens have improved the outcome for that small subset that present with advanced stages of disease. Proper staging is critical to identify that small subset for best targeted chemotherapy.

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Quality of Life in Women with Ovarian Cancer

13

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Introduction

Ovarian cancer and its treatment can have a profound impact on health-related quality of life (HRQL) in both the short and long term. Understanding these impacts is essential for evaluating the effects of treatment from the patient's perspective, as well as for managing the care of individual patients. HRQL can be assessed for research purposes or within clinical practice, and if availed of fully, can form a key component of patient-centred care. HRQL data from clinical research can help to guide improvements in clinical practice as well as to advise patients about the possible impact of treatment, thereby assisting patients to make informed decisions about treatment. The assessment of HRQL within clinical practice can aid communication between the treating clinician and the patient about the issues that are affecting the patient's quality of life. This, in turn, can help the clinician to be more adept at both identifying and managing patient problems. In this chapter, we introduce key terminology and discuss how ovarian cancer and its various treatments affect patients' HRQL in terms of the disease symptoms, treatment side effects and broader impacts on physical and psychological functioning.

Terminology and Definitions: HRQL and PROs

A definition of *health-related quality of life* (HRQL) that is useful for clinical research and health services research is:

> *Health-related quality of life (HRQL) is a multidimensional construct encompassing perceptions of both positive and negative aspects of dimensions, such as physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment* [1].

A fundamental component of this definition is that HRQL is a *multidimensional* concept that includes both core domains and symptoms that differ as a function of the disease type and treatment. It is also a *subjective* phenomenon, meaning that the patient's appraisal of their functioning

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and symptoms is preferable to that of a proxy such as a clinician or family member [2].

Apart from patients' symptoms and functioning, many other aspects of a patient's experience of disease and treatment can have an impact on their HRQL. For example, patients' satisfaction with care, their unmet needs for information or support services, and their psychological adjustment to illness can also negatively affect their HRQL.

A related umbrella term is *patient-reported outcome (PRO)*. This term emerged to solve the difficulty of finding a universal and all-encompassing definition of HRQL and its related concepts. A PRO is defined as:

> *A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else* [3].

As an umbrella term "PRO" does not shed light on what is measured in any specific case, but emphasises that the patient provides the assessment. PROs can be symptoms (e.g. pain, anxiety, nausea, fatigue), aspects of functioning (e.g. physical, emotional, sexual, social), or multidimensional constructs (e.g. HRQL). For the purpose of this chapter, the PRO of interest is HRQL.

How Ovarian Cancer Affects HRQL

High-grade serous ovarian cancer is the most common subtype of ovarian cancer and the most lethal of all gynaecological cancers. Although women with early-stage disease (stage 1A or 1B) have an excellent prognosis, the majority (up to 70%) of women are diagnosed at an advanced stage and less than half of these women will survive beyond 5 years [4]. Unfortunately, following initial treatment, the majority of women will develop a recurrence and with each recurrence the chance of cure diminishes. Throughout all phases of the disease and treatment trajectory, ovarian cancer and its treatments can have wide-ranging impacts on HRQL. Importantly, the value women with ovarian cancer place on different types of treatment outcomes is likely to vary, and the extent to which women will be willing to compromise their HRQL for possible survival gains will differ, particularly as the disease progresses [5].

Although ovarian cancer has often been characterised as a "silent disease" because many women only present with signs and symptoms at an advanced stage of the disease, there is increasing evidence that women with ovarian cancer do have recognisable symptoms before diagnosis [6]. One of the most commonly reported symptoms is abdominal pain, but many women also report abdominal bloating, feeling full quickly, difficulty eating and in some cases urinary symptoms [6]. Some women may also experience abnormal vaginal discharge and postmenopausal bleeding before diagnosis [7].

Receiving a diagnosis of ovarian cancer is often a traumatic shock to patients and causes considerable distress, especially because many women often misattribute their symptoms to other less serious conditions [8]. Many patients experience additional distress after treatment as surgery and chemotherapy can cause burdensome side effects including a number of physical symptoms and physical changes (see section on Treatment-Specific HRQL: Symptoms and Side Effects of Treatment). Some side effects and changes may persist long after treatment ends, such as psychosexual problems. These physical and psychological disturbances can adversely affect HRQL and impact on women's ability to perform their usual daily tasks and activities.

Surgery to remove or reduce the extent of the cancer may be preceded and/or followed by adjuvant chemotherapy. For a minority of women with ovarian cancer, treatment can be curative or result in long-term survival, but for the majority treatment is palliative and intended to slow down or reverse cancer growth and reduce the symptoms caused by the disease. Although palliative treatment may extend survival, it may also induce side effects. PROs are particularly important within a palliative context, and in these contexts may be suitable primary endpoints [9]. This is particularly true for clinical trials of patients with platinum-resistant/refractory ovarian cancer,

where the impact of treatment on HRQL and symptom benefit should ideally be used as co-primary endpoints with traditional endpoints such as progression-free survival and overall survival [10].

Proximal Versus Distal Effects on HRQL

Figure 13.1 provides a graphical depiction of how the symptoms of ovarian cancer and the side effects of its treatments may affect a woman's functioning and HRQL. Proximal effects occur directly as a consequence of the disease and/or treatment [11], such as the symptoms of ovarian cancer (e.g. abdominal pain and bloating) and the side effects of treatment (e.g. nausea, skin rash). In turn, these symptoms and side effects may affect the woman's functioning and overall HRQL (i.e. cause distal effects). A diagnosis of ovarian cancer, its treatment and recurrence can impact psychological well-being directly (i.e. proximally) or indirectly via disease and/or treatment-related symptoms and loss of functional ability.

It is important to consider the proximal and distal effects of disease and treatment when deciding which PRO instrument to use in ovarian cancer research or clinical practice. The more proximal an outcome is to the disease or treatment, the more likely it is to detect treatment effects [11]. In contrast, the more distal an outcome is, the more likely it is to be affected by other factors that are external to the treatment [11]. For this reason, a proximal outcome such as abdominal symptoms may be an appropriate key PRO for an ovarian cancer clinical trial, and a suitable questionnaire must be found. *Good candidates are described in* section "Choosing a PRO Instrument", *along with the general principles guiding instrument selection*. The AURELIA trial illustrates the use of patient-reported abdominal symptoms as the key PRO in a Phase III trial for platinum-resistant ovarian cancer, along with more distal aspects of HRQL as secondary PROs [12].

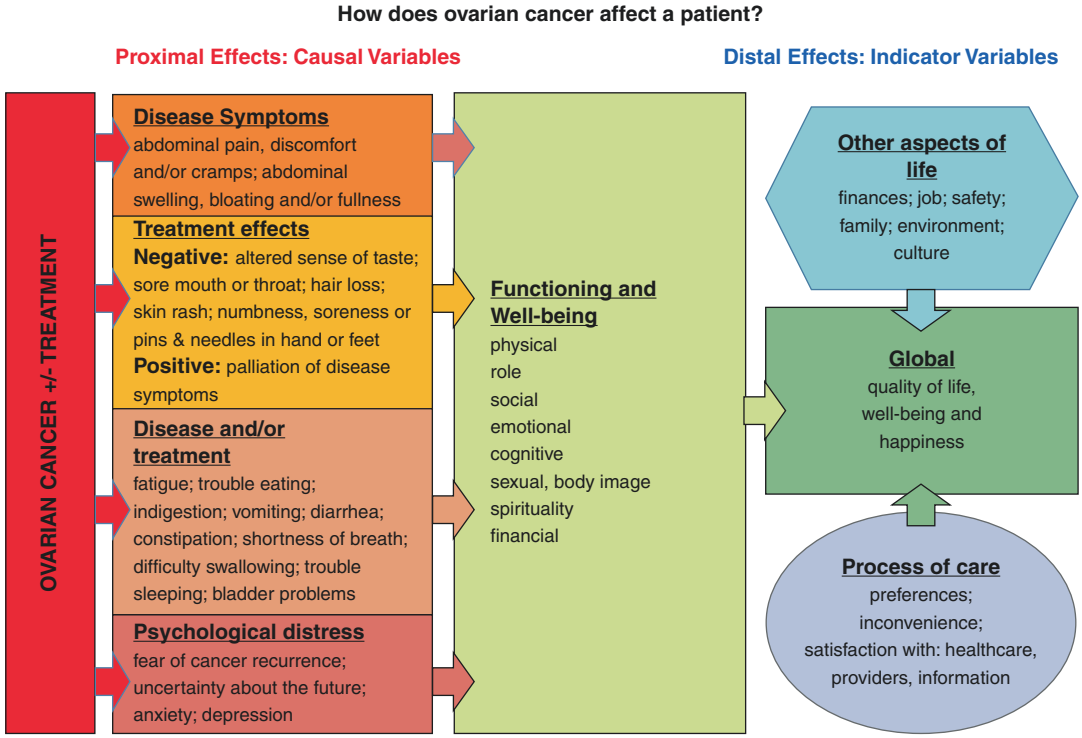

Fig. 13.1 Ovarian cancer effects on HRQL

Treatment-Specific HRQL: Symptoms and Side Effects of Treatment

The main treatment modality for most women with primary ovarian cancer is cytoreductive surgery and chemotherapy. The goal of first-line treatment is to eradicate or reduce the volume of disease, without severely compromising HRQL [13]. Unfortunately, despite high remission rates following first-line treatment, 80% or more will develop recurrent disease [14]. Women with recurrent disease may undergo repeated cycles of chemotherapy so careful consideration of the impact of treatment on HRQL is needed to ensure that the benefits of treatment outweigh the toxicities. Patient reports of the side effects of treatment and their impact on HRQL are paramount for understanding the risks versus benefits of treatment from the patient's perspective.

Surgery

The mainstay of treatment for all stages of ovarian cancer is cytoreductive surgery. This involves comprehensive surgical staging as well as a total abdominal hysterectomy and bilateral salpingo-oophorectomy to remove the uterus and cervix along with the fallopian tubes and ovaries. Depending on the extent of disease, surgery may also involve omentectomy, lymph node dissection and bowel, liver or spleen resection [15]. The extent of successful tumour cytoreduction following surgery is considered to be the most important prognostic factor for long-term survival [15]. For premenopausal women, cytoreductive surgery renders women infertile (*the impact of loss of fertility and early onset menopause on young women is described in* section "Psychological Impact"). Only very selected young women with early-stage disease and specific histological subtypes may be eligible for fertility-sparing surgery [16].

Although a number of studies have examined the impact of chemotherapy on the HRQL of women with ovarian cancer, relatively few studies have examined the direct impact of cytoreductive surgery alone (and not in combination with chemotherapy) on PROs. One study, which assessed PROs in women with suspected primary ovarian cancer pre- and 1 month post-surgery, indicated that the most common post-operative complications reported after surgery were wound infections, fever and sepsis, followed by ileus, nausea and vomiting [17]. After surgery (i.e. prior to chemotherapy) patients report severely impaired HRQL as evidenced by high levels of fatigue, anxiety and depression and lower scores on all functioning domains [18].

A longitudinal cohort study of women with early- and late-stage ovarian cancer that underwent standard or extensive cytoreductive surgery found that global HRQL (that is, based on questions that asked directly about "quality of life" rather than specific aspects of it) deteriorated from baseline to 3 months after surgery in both the standard and extensive surgery group [19]. Notably, the women that had extensive surgery reported greater deterioration in global HRQL, functioning and symptom scores than women who had standard surgery [19].

In circumstances where optimal cytoreduction (i.e. zero residual disease) is not considered achievable because of a very large bulk of disease or because patients are unfit for surgery, neoadjuvant chemotherapy (NACT) may be administered first to reduce tumour volume followed by interval debulking surgery. One trial (EORTC GCG 55971) compared the impact of primary debulking surgery (PDS) versus interval debulking surgery (IDS) after NACT on HRQL and found that survival and HRQL were similar in both treatment arms [20]. All patients showed a clinically relevant improvement (>10 points) in global HRQL, role functioning, and social functioning during and after treatment independent of the treatment arm. Another study compared the symptom burden and functional recovery of women undergoing PDS or IDS following NACT and found that there were no significant differences in the symptoms reported by women both in the immediate in-hospital period and in the extended post-hospital discharge period [21]. However, irrespective of the timing of the surgery in relation to chemotherapy, women that under-

went intermediate or high complexity surgery reported more nausea, fatigue and greater interference of symptoms with their mood and daily activities [21].

Chemotherapy

Chemotherapy before or after surgery is standard treatment for all women with ovarian cancer except for a small minority with selected subtypes of early-stage disease and favourable histology, for whom adjuvant chemotherapy is not recommended [22]. The standard chemotherapy is a platinum-taxane combination regimen [22]. Bevacizumab may also be added to combination chemotherapy in women with advanced disease who have significant residual disease at the completion of surgery.

Women with ovarian cancer may experience a number of treatment-related symptoms during chemotherapy. Common physical symptoms include hair loss, altered sense of taste, sore mouth or throat, skin rash, fatigue, nausea or difficulty swallowing [23]. In a qualitative study, women who had received first-line chemotherapy described hair loss as the most distressing physical symptom of the ovarian cancer experience because it led to a loss of sense of self and altered body image, and served as a reminder of their illness and potential for an early death [24]. Sexual dysfunction and intimacy issues are also prevalent during chemotherapy and there is evidence that patients report significantly worse menopause-related symptoms and body image during first-line chemotherapy compared to women who have already received multiple lines of chemotherapy [25].

Long-term side effects of chemotherapy include pain and fatigue, which can persist years after treatment has ended [26]. Peripheral neuropathy is a debilitating long-term side effect which can persist in 50% of women with ovarian cancer who receive chemotherapy even up to 12 years after the end of treatment [27]. The platinum and taxane-based chemotherapies used for ovarian cancer damage predominantly sensory nerves, manifesting as tingling or numbness in the hands and/or feet [28, 29]. Consequent fine-motor dysfunction causes difficulties in daily tasks such as typing, holding objects securely, doing up buttons and putting on braziers and necklaces. Lower limb problems with balance and walking lead to slips, trips and falls and reduced ability to exercise [30].

Apart from physical symptoms, women receiving chemotherapy may also experience considerable psychological distress. A study among women with recurrent ovarian cancer found that all women reported high levels of anxiety and depression throughout the course of chemotherapy. However, levels of anxiety significantly decreased during active chemotherapy whereas levels of depression did not. Notably, both anxiety and depression were associated with poor HRQL on all functioning and symptom domains, both at baseline and during active chemotherapy [31].

Importantly, chemotherapy can also affect the HRQL of patients positively, by alleviating symptoms and slowing, halting or reversing deteriorations in functioning. Among women with recurrent disease and poor prognosis, chemotherapy can help to manage symptoms by reducing abdominal swelling, bloating, and/or fullness; abdominal pain, discomfort, and/or cramps; and anxiety [23]. Furthermore, in a study by Doyle et al., women with advanced ovarian cancer receiving second-line chemotherapy reported improved emotional functioning even though clinical data indicated that only a minority of patients benefited from treatment in terms of tumour shrinkage [31]. This raises the issue of whether the treatment itself or the hope provided by having the treatment led to these favourable outcomes. It is especially important for women with recurrent disease receiving palliative chemotherapy that these positive effects are carefully balanced against the possible adverse effects to determine the potential value of the treatment for individual patients.

Chemotherapy is usually administered as an intravenous (IV) infusion; however, in selected patients with stage III ovarian cancer whose tumour was optimally debulked, intraperitoneal (IP) chemotherapy may be given by infusion of

the chemotherapy drug directly into the peritoneal cavity. A meta-analysis of nine clinical trials which examined whether adding a component of the chemotherapy regime into the peritoneal cavity affects survival and HRQL revealed that IP chemotherapy prolonged both overall and progression-free survival [32]. However, IP chemotherapy was associated with greater toxicity in terms of pain, fever, gastrointestinal problems and infection than the IV route [32]. Thus, the decision to use IP chemotherapy should be made on a case-by-case basis, weighing up the potential for survival gains and individual tolerance of toxicities.

After chemotherapy for ovarian cancer, women attend regular follow-up appointments for disease surveillance. At follow-up, patients typically receive a clinical examination and a blood test for the ovarian cancer tumour marker CA-125 to monitor treatment response and detect any recurrence. Findings from the MRC OV05/EORTC 55955 trial indicated that asymptomatic patients who attained a complete response after first-line treatment, and received early second-line treatment on the basis of elevated CA-125 levels alone, had no survival benefit and poorer HRQL compared to women who received delayed second-line treatment after recurrence was detected through clinical examination [33]. Thus, findings from this trial indicate that among women who had complete response to first-line treatment, further treatment is not indicated by rising CA-125 levels alone, and can be safely delayed until symptoms or signs of tumour recurrence develop [20]. To this end, a decision aid has been developed to assist asymptomatic women with rising CA-125 levels to make informed decisions about when to initiate second-line treatment [34].

Targeted Therapy

Bevacizumab is a targeted therapy that belongs to a class of drugs called angiogenesis inhibitors. Bevacizumab attaches to a protein called vascular endothelial growth factor (VEGF) which inhibits cancer growth. The AURELIA trial found that adding bevacizumab to standard chemotherapy for women with recurrent platinum-resistant ovarian cancer achieved an approximate doubling of the proportion of patients who experienced a 15% improvement in patient-reported abdominal symptoms [12]. Better outcomes with bevacizumab were also achieved for global QOL and physical, role and social functioning. More recently, a review of randomised phase III trials evaluating the effectiveness of a combination of bevacizumab plus standard chemotherapy for first-line treatment of advanced ovarian cancer reported both clinical and HRQL benefits of bevacizumab. Specifically, the review concluded that bevacizumab extends progression-free, but not overall, survival and improves patient-reported abdominal symptoms in women with recurrent ovarian cancer [35].

Targeted therapy using inhibitors of the enzyme poly ADP ribose polymerase (PARP) is another type of therapy which is increasingly being used in the management of ovarian cancer. PARP inhibitors are used both as a single-agent treatment for relapsed ovarian cancer as well as for maintenance therapy after chemotherapy to prolong the duration of response or the disease-free interval following chemotherapy. For example, olaparib has been shown to be effective at prolonging progression-free survival after second-line platinum-based chemotherapy, especially among patients with a BRCA1/2 mutation [36]. Current evidence indicates that maintenance treatment with olaparib is well tolerated and has no adverse effects on HRQL among patients with recurrent ovarian cancer who responded to their most recent platinum-based therapy compared to a placebo tablet [37, 38]. Furthermore, the SOLO2 trial demonstrated that olaparib maintenance therapy resulted in clinically meaningful patient-centred benefits in terms of higher TWiST scores (defined as time without significant symptoms of toxicity) and quality-adjusted progression-free survival compared with placebo [38]. However, PARP inhibitors have been shown to result in patient-reported adverse effects such as low-grade fatigue, nausea and vomiting [38].

Psychological Impact

Ovarian cancer and its treatment are aggressive by nature, which is often very distressing for the woman. From initial diagnosis through acute treatment to survivorship, psychological distress is significantly more common among women with ovarian cancer than healthy women [39]. Many patients report symptoms of anxiety and depression and some even report symptoms of post-traumatic stress disorder [39, 40]. In qualitative interviews, patients describe the experience of diagnosis and treatment for ovarian cancer and the potential for an early death as an existential assault that severely affects the patient and her relationships [40]. A prospective cohort study examined predictors of psychological distress among ovarian cancer patients and found that higher symptom burden, lower optimism and receiving specialist mental health treatment were all associated with depression and anxiety, whereas lower social support was only predictive of patient anxiety [40].

Due to its high rate of recurrence, women with ovarian cancer commonly report fear of cancer recurrence (FCR) [41]. A systematic review of FCR in ovarian cancer patients revealed that FCR was a significant concern for both younger and older women at both early and advanced stages of the disease [41]. Women report feeling distressed about the possibility of recurrence both during and post-treatment, and report FCR to be particularly prevalent during follow-up examinations [41]. FCR is associated with patients' anxiety about death and dying as well as uncertainty about their future. Many ovarian cancer patients report not receiving adequate support for their FCR [41].

Loss of Fertility and Early Menopause

While the minority of women diagnosed with ovarian cancer are young, treatment can have life-changing consequences including infertility and early onset of menopause. For premenopausal women, treatment can result in infertility through the surgical removal of the reproductive organs and the administration of chemotherapy drugs that are toxic to the ovaries. Most premenopausal women will experience abrupt menopausal symptoms after cytoreductive surgery or chemotherapy [42]. These menopausal symptoms may include hot flashes, mood changes, and vaginal dryness or atrophy [43]. Apart from the physical symptoms and mood changes caused by early menopause, the loss of fertility can also have a profound psychological impact, particularly on women who had wanted to have children. For young women who are not eligible for fertility-sparing surgery, losing fertility following treatment can be very difficult to cope with and feelings of depression, grief and stress are common [44]. This emotional difficulty may be compounded by the fact that these women have to cope with the loss of fertility while also preparing for or already dealing with chemotherapy-induced toxicities. Furthermore, for some young women, infertility may be unexpected because they were unable to take in or recall all of the information they received about the side effects of treatment during the consultation with their oncologist [45], potentially exacerbating the subsequent emotional distress.

Psychosexual/Sexual Function (Problems Preventing/Interfering with Ability to Have Sex)

Sexual function is an important aspect of women's HRQL. Unfortunately, sexual dysfunction is common after surgical cytoreduction and chemotherapy [42]. As a result, many women experience issues with sexuality and intimacy after treatment, which can adversely affect their personal relationships [42]. Ovarian cancer survivors report lower levels of sexual pleasure and higher levels of sexual discomfort than age-adjusted controls from the general population [46]. When attempting sexual intercourse, ovarian cancer survivors experience more problems with vaginal dryness, discomfort and pain compared to healthy women [47]. Ovarian cancer survivors also report significantly less interest in sex, with more than 50% reporting a lack of

sexual desire compared to only 25% of healthy controls [46]. Several factors have been identified which predict worse sexual function among ovarian cancer survivors including increasing age, poorer mental health status and having undergone premenopausal oophorectomy and chemotherapy [46].

Supportive Care Needs of Women with Ovarian Cancer

A cross-sectional descriptive study sought to identify the supportive care needs of women with ovarian cancer of variable stages of disease and treatment who attended a comprehensive outpatient cancer centre [48]. Eight of the top ten most frequently reported unmet needs were psychosocial. These included FCR (72%) or fear of cancer spreading (70%), concerns about the worries of those closest to them (58%), uncertainty about the future (56%), feelings of sadness (50%), changes in usual routine and lifestyle (50%), worry that the success and/or failure of their treatment are beyond their control (48%), and feeling depressed or down (46%) [48]. Two unmet physical needs frequently reported were lacking energy (56%) and not being able to do the things they used to do (52%) [48]. A literature review of the social and psychological needs of ovarian cancer survivors further identified sexual activity and sexual satisfaction as frequently reported unmet needs as well as distress, anxiety and depression [49]. The review further indicated that younger ovarian cancer survivors were more likely to have greater distress and lower HRQL compared to older survivors [49]. Together, these findings highlight the need for targeted early intervention among ovarian cancer patients to address and support these unmet needs.

Individualised nurse-led supportive care interventions may help to manage patients' physical and psychological symptoms and improve the HRQL of women with ovarian cancer. In a pilot randomised controlled trial (RCT) that examined the effects of an interactive web-based symptom management intervention, which facilitated direct communication between women with recurrent ovarian cancer and a dedicated nurse, women reported decreased symptom severity and lower distress after the intervention [50]. Another study of the provision of nurse-led follow-up versus conventional medical follow-up found that ovarian cancer patients who had received individualised nurse-led follow-up reported higher satisfaction and HRQL [51]. In addition, an 8-week comprehensive care programme consisting of group education, self-help group support, home-based exercise and relaxation was found to be an effective nursing intervention for improving the HRQL of ovarian cancer survivors [52].

Exercise and lifestyle interventions may also help to promote the physical and psychological well-being of ovarian cancer patients. After a 12-week exercise intervention during chemotherapy consisting of 90 minutes of low to moderate exercise per week, participants reported significant improvements in their fatigue, mental health and HRQL [53]. Similarly, another study demonstrated that women with ovarian cancer that participated in an individualised walking intervention during chemotherapy reported improvements in physical symptoms and physical functioning following the intervention [53]. Although these studies suggest that exercise may be beneficial for women receiving chemotherapy, future RCTs are needed to confirm these preliminary findings. To address this gap, a phase III RCT (ECHO trial) is currently recruiting 500 patients in Australia to evaluate the effect of exercise during chemotherapy on the physical well-being of women receiving first-line treatment for ovarian cancer.

Impact on Partners/Caregivers

Ovarian cancer is not only distressing and burdensome for patients, but also significantly impacts family members, who are often required to take on the role of caregiver and to provide emotional and practical support as well as physi-

cal care to the patient. Given that ovarian cancer is a disease characterised by multiple recurrences and many lines of chemotherapy, the need to provide prolonged support and care to women with ovarian cancer can put considerable strain on the women's partner or caregiver's own functioning and HRQL over time.

In a qualitative study, the spouses of women with ovarian cancer described the emotional, psychological, and social impact of living with a partner with ovarian cancer [54]. Specifically, the spouses expressed the emotional devastation of the initial diagnosis, the ovarian cancer becoming a new focus/priority, changes to the marital relationship and the burden of providing support and having to rely on other family members [54]. A longitudinal study of women with ovarian cancer and their partners provided further insights into how the ovarian cancer experience affects women and their spouses over time [55]. While the women reported consistently compromised emotional well-being across a 3-year period, their husbands only reported worse emotional well-being at year 3. Insomnia, fatigue, and worry were problematic for both members of the couple over time, with no significant differences between women and their spouses, except that the women experienced more insomnia 3 months post-treatment [55]. These findings underscore the impact ovarian cancer has on women and their partners and underline the need to assess both the patients and their partners HRQL.

Another longitudinal study examined the HRQL of caregivers of women with ovarian cancer during the last year of life [56]. Findings revealed that caregivers had significantly lower mental and physical HRQL than population norms and demonstrated that caregiver distress and unmet needs increased throughout the year [56]. The highest unmet needs in the last year of life were difficulties managing concerns about prognosis, fear of cancer spread, balancing the patients' and their own needs, the impact of caring on work, and making decisions in the context of uncertainty [56]. Optimism, social support, higher unmet needs, the physical well-being of the caregiver, time to death, but not patient HRQL, emerged as significant predictors of caregiver mental well-being and distress [56]. These findings highlight the need to provide increased support to caregivers, particularly during the end-of-life phase.

Why Assess HRQL in Patients with Ovarian Cancer?

There is now wide-spread support from clinical trials groups, cancer institutes, drug regulatory bodies and the pharmaceutical industry for incorporating information about the possible impact of treatments on HRQL into the treatment decision-making process [3, 57–60]. This is particularly true in ovarian cancer, given the potential benefits and risks associated with treatment.

Reasons for Assessing HRQL in Ovarian Cancer Clinical Trials and Clinical Practice [2, 9, 61–63]

- Baseline HRQL serves as an independent prognostic factor for survival and locoregional control.
- In some cases, HRQL may be more sensitive and/or responsive to treatment effects than clinical measures of toxicity.
- HRQL data may provide clinicians useful information when communicating with patients about their expectations and assist the patient and clinician in treatment decision-making through better understanding of treatment benefits and risks during the acute and survivorship phases (e.g. impact of chronic side effects).
- Information about potential impacts on HRQL may help patients make decisions about treatments with their clinician, and make informed decisions based on what others have experienced (i.e. the possible and likely treatment effects).
- PROs can be used to help identify the patients who are most likely to benefit from psychosocial interventions.

How is the HRQL of Patients with Ovarian Cancer Assessed?

Historically, clinicians may have informally assessed the impact of ovarian cancer and treatment on patients' HRQL by simply asking the patient. However, there would likely be large variation in whether and how a range of possible questions are asked as well as how patients respond. A more standardised approach enables more reliable quantification, statistical analysis and comparison. This is achieved by administering validated questionnaires which include unambiguous questions about issues that are relevant to the patient, and a standard set of response options. So, for example, one question might be "In the past week, have you had abdominal pain?" and there might be four response options: "none at all", "a little", "quite a bit" or "very much". A related set of questions (e.g. about abdominal symptoms) are typically combined into a scale (based on the average scores of the component items). This scoring is codified in a scoring algorithm. The questionnaire, along with the algorithm for scoring the patients' responses into summary scores for analysis and reporting, is referred to as a PRO instrument or measure.

This approach draws on psychometric traditions by measuring complex variables broken down into their component parts. Each question (item) may ask about a specific issue, e.g. "have you had abdominal pain?"; this is the "item stem". The stem has a corresponding rating scale, which is referred to as the "response options". Generally, the response options are in the form of a Likert scale, i.e. where 1 = "none at all" and 4 = "very much". This step attaches a numerical value to each response. Items may be grouped with similar items, which together, tap into a larger construct, thereby providing a scale score. For example, the EORTC QLQ-C30 has five items assessing different aspects of physical functioning that are combined to provide a scale score for physical function. Alternatively, a scale may only be comprised of a single item. Any number of domains may be assessed in a single PRO instrument. In other words, the PRO instrument may assess only one domain (unidimensional) or several (multidimensional).

Given that HRQL is subjective and that ideally the patient should be the one to interpret each question, patients usually self-complete PRO instruments. This practice helps to reduce the bias that can be introduced when questions are discussed with other individuals. However, in some circumstances assistance may be necessary, such as when a patient is too fatigued or unable to read or speak the language of the questionnaire. As well as being quick and straightforward to use in research, PRO instruments are advantageous because they yield results that are directly comparable between studies. However, there are always limitations to the information that an instrument, or a battery of instruments, can provide.

Choosing a PRO Instrument

There are a large number of instruments available to assess HRQL and other PROs, which makes it difficult for researchers to select appropriate instruments. This can be particularly problematic when more than one available instrument may seem applicable to the research context. To address this difficulty, researchers should consult clinicians, patients and the available literature to determine which issues are most relevant to their particular research question and treatment context [64]. Researchers should also consult databases such as PROQOLID [65], which catalogue a large number of PRO instruments, to help them to identify candidate instruments that assess the important domains of interest. These instruments should then be carefully reviewed to determine whether the questions they pose address the patients' issues in a meaningful way (i.e. whether they have content and face validity for the research context). The scoring method should also be reviewed to determine whether the instrument produces a score for the issue/s of importance to the research study. The literature should be consulted to determine whether the studies which

validated the instrument were methodologically sound (*refer to the* section "What Makes a Good Instrument" described in this chapter), or whether more validation work is needed. It is also important to consider whether criteria for a clinically important difference or clinical cut-offs have been established to allow for clinically meaningful interpretation of the data [66]. Finally, a pilot study in which patients from the population of interest self-complete the instrument can also be a useful to assess the suitability of an instrument.

Key Questions to Consider When Selecting a PRO Instrument

1. Is the PRO instrument intended for use in research or clinical practice?
2. Which issues are important to the particular research and treatment context?
3. Does the PRO instrument cover all the issues that matter in a given context?
4. Does the PRO instrument have evidence for important psychometric properties: validity, reliability, responsiveness, generalisability and interpretation?
5. Have clinically important difference criteria or cut-offs been established?

What Makes a Good Instrument?

The scientific and methodologically rigorous development of a PRO instrument involves careful item selection informed by a literature review and both expert and patient input [3, 67]. Important psychometric properties include *validity*, *reliability*, *sensitivity*, *responsiveness* and *interpretability*. To decide whether an instrument is "good", the (1) conceptual and measurement models; (2) validity; (3) reliability; (4) responsiveness to change; (5) interpretability; (6) respondent and administrative burden; (7) alternative forms; and (8) cultural and language adaptations should be considered. An instrument should fit for purpose, i.e. appropriate for the intended clinical context and population. Importantly, when choosing an instrument for a particular population and context, check whether its psychometric properties should be determined in that population and context, particularly if that differs from the population and context for which the instrument was initially developed. It must also be acceptable to patients and feasible for them to self-complete. In both clinical practice and research, instruments should only be used that have been previously demonstrated to display these important psychometric properties.

PRO Instruments for Ovarian Cancer Clinical Research: Core Cancer Instruments Versus Tumour Specific Modules

The two most widely used HRQL instruments in cancer clinical trials are the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30 [57]) and the Functional Assessment of Cancer Therapy-General (FACT-G [68]). Both instruments have ovarian cancer-specific modules that assess the HRQL of patients treated for ovarian cancer in clinical trials.

EORTC Instruments

The QLQ-C30 is the core instrument of the EORTC's modular approach to HRQL assessment. It includes HRQL domains relevant to a range of cancer sites and treatment types. The EORTC conceptualised HRQL as multidimensional with at least three basic domains: physical functioning, including symptom experience and functional status; emotional functioning; and social functioning. It has 30 items which are incorporated into nine multi-item subscales: five functional (physical, role, cognitive, emotional, and social functioning); three symptom (fatigue, pain, and nausea/vomiting); and a global health status/HRQL scale, as well as six single items that assess dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea, and perceived

financial impact of disease and treatment. Response options for each item range from 1 (not at all) to 4 (very much) during the past week. The QLQ-C30 is designed to be used across different cancer populations and takes about 11 minutes to complete [68]. It is available in 96 languages. The QLQ-C30 is complemented by modules specific to particular cancers, such as ovarian cancer (QLQ-OV28). The core module facilitates comparison of HRQL cross cancers, and the disease-specific modules provide sensitivity for particular trials.

The QLQ-OV28 is the EORTC module specific to ovarian cancer. It is a 28-item questionnaire developed to assess the HRQL of women with ovarian cancer treated in clinical trials [69]. It consists of seven multi-item scales: abdominal/gastrointestinal symptoms (7 items), peripheral neuropathy (3 items), other chemotherapy side effects (7 items), hormonal/menopausal symptoms (2 items), body image (2 items), attitude to disease and treatment (3 items) and sexual function (4 items.) Response options for each item range from 1 (not at all) to 4 (very much) during the past week/4 weeks. It has been translated into 40 languages.

FACIT Instruments

The FACT-G [68] is the core component within the Functional Assessment of Chronic Illness Therapy Measurement System (FACIT). The most recent version (version 4; 1997) includes 27 items intended for use with patients with any cancer type. The items cover four primary HRQL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. Apart from domain scores, the instrument also generates a total HRQL score. Each item is rated on a scale from 0 (not at all) to 4 (very much) with respect the past 7 days. The FACT-G is available in 65 languages. In addition to the FACT-G, the FACIT suite has cancer-specific (e.g. ovarian), treatment-specific (e.g. neurotoxicity from systemic chemotherapy), and symptom-specific (e.g. fatigue) instruments.

The FACIT approach differs slightly from the EORTC modular system, where stand-alone modules are used in conjunction with the QLQ-C30. In the FACIT system, each of these disease, treatment and symptom-specific instruments implicitly includes the FACT-G instrument. For example, the FACT-O instrument contains all 27 questions from the FACT-G plus an additional 12 questions that relate specifically to ovarian cancer. The additional 12 items cover stomach bloating, weight loss, bowel control, vomiting, hair loss, appetite, body image, mobility, femininity, stomach cramps, interest in sex and reproductive concerns. The FACT-O instrument can be self-completed or used in an interview format and takes about 8–10 minutes to complete [70]. The FACT-O items are rated from 0 (not at all) to 4 (very much) during the past 7 days. It is available in 44 languages.

The FOSI [71, 72] and NCCN-FACT FOSI-18 [73] were developed to measure high priority symptoms and HRQL concerns in patients with advanced ovarian cancer. They consist of 8 and 18 items, respectively, of the FACT-O. The FOSI has the same response options as the FACT-G, and provides a single score. The FOSI-18 has advantages over the FOSI by including more symptoms and separating them into three subscales: disease-related symptoms (10 items), treatment side effects (5 items) and general functioning/well-being (3 items). Another divergence from the FOSI is that its 18 items are rated on a scale from 0 (not at all) to 10 (very much) during the past 7 days. The FOSI-18 can be self-completed or interviewer administered and takes 4–5 minutes to complete. It has been translated into 27 languages.

In addition, the FACIT suite includes a number of chemotherapy-specific questionnaires that are relevant to ovarian cancer contexts. These include the Functional Assessment of Cancer Treatment (FACT) Gynecology Oncologic Group Neurotoxicity Questionnaire (FACT&GOG-Ntx) [74] and the FACT-Taxane [75], which assess the impact of neuropathy on patients HRQL and the HRQL of patients receiving taxane containing chemotherapy, respectively. The FACT&GOG-

Ntx consists of 13 items, which are summed to produce a total neurotoxicity score and the FACT-Taxane has 16 items which score into two domains: Neurotoxicity (11 items) and taxane-induced symptoms (5 items).

MOST: Measure of Ovarian Symptoms and Treatment concerns

While the EORTC-QLQ-C30 and QLQ-OV28 and the FACT-O and FOSI all assess ovarian cancer and treatment-related symptoms, their scoring algorithms either split the items into numerous scales (EORTC instruments) or generate scales by combining treatment side effects with other aspects of HRQL (FACIT instruments, except FOSI-18), which can dissipate effects [23]. Furthermore, the recall period for these PRO measures is a week, while the period between chemotherapy cycles is typically 3–4 weeks. The MOST [23] was developed to address these issues and provide a measure of overall symptom burden, as well as the benefits and adverse effects of chemotherapy that could be used as an endpoint in clinical trials of palliative chemotherapy for recurrent ovarian cancer.

There are two versions of the MOST. The original version (MOST-T35) contains 35 items, covering a mix of physical and psychological symptoms which may be caused by either disease and/or treatment side effects, other problems caused by treatment, and three aspects of well-being (physical, emotional, and overall) [76]. The MOST-T24 is a shorter symptom-focussed version containing 24 of the original 35 items [23]. These group into five psychometrically validated indexes for use as outcomes in clinical trials: abdominal symptoms (MOST-abdo, 2 items), chemotherapy-related symptoms (MOST-Chemo, 6 items), a group of 11 symptoms that may be caused by either ovarian cancer or its treatment (i.e. disease or treatment, MOST-DorT, 11 items), psychological symptoms (MOST-Psych, 2 items), and well-being (MOST-well-being, 3 items). In both versions, response options for each item range from 0 (no problem or best possible) to 10 (worst possible) during the past 3–4 weeks. The MOST is the newest ovarian cancer-specific instrument and has been translated into six languages so far.

The MOST change [76] is an alternate form of the MOST that asks patients to report on their perceived change since beginning chemotherapy by asking patients to "circle the number that best represents how you feel now, *compared to* how you felt before starting this chemotherapy treatment 6 to 8 weeks ago". The MOST change was developed to allow the estimation of the minimally important difference [66, 77]. It consists of 35 items corresponding to the 35 items in MOST-T35 (which include the 24 items in MOST-T24). Response options for each item range from 1 (much better) to 5 (much worse). The MOST change has also been translated into six languages.

On-Going Clinical Trials in Ovarian Cancer

Three clinical trials databases were searched (ClinicalTrials.gov, EU Clinical Trials Register, ANZCTR) to identify ongoing clinical trials in ovarian cancer. Internationally, there are currently 73 active ovarian cancer clinical trials collecting PROs from more than 28,200 women. Many of these studies are multi-national collaborations, with the majority coordinated in the UK, Italy, the USA and Australia. The treatments under investigation are predominately chemotherapy (18) and targeted therapies (46) for women with advanced ovarian cancer. PROs being assessed in these trials include overall HRQL; symptoms and treatment side effects; anxiety and depression; and functioning domains. Of the 47 trials that list the PRO instruments they include, 21 are using the EORTC QLQ-C30 (18 in combination with the QLQ-OV28), 13 are using the FACT-O, 4 include an ovarian cancer symptom index (NCCN-FACT FOSI-18), 3 use the MOST, and 12 include other measures not specific to ovarian cancer (e.g. the EQ-5D; NCI-PRO-CTCAE; HADS; SF-36). Nine trials are looking at PROs as a primary endpoint in interventions examining chemotherapy regimens (2),

counselling (2), exercise (1), mindfulness (1), nutrition (1), pain relief medication (1), and shared decision-making (1).

Conclusions and Recommendations

The main treatment modality for ovarian cancer is cytoreductive surgery and chemotherapy. Unfortunately, the majority of women are diagnosed at an already advanced stage and less than half of these women will survive beyond 5 years. Following first-line treatment, many women develop recurrence and may undergo repeated cycles of chemotherapy. The assessment of HRQL throughout each phase of treatment and survivorship is essential, not only to guide improvements in clinical practice, but also to inform treatment decision-making by providing information about the risks and benefits of treatments.

Given the aggressiveness of ovarian cancer and its treatments, it is imperative that patients' HRQL be considered in treatment decision-making at patient and policy levels and assessed in clinical trials and potentially in routine clinical care. Both physical and psychological symptoms as well as functioning impairments affect HRQL throughout the entire disease and treatment trajectory. The assessment of symptoms, functioning and HRQL is useful during patient consultations and survivorship phases to allow for the early detection and management of the issues that impact patients' HRQL as well as to identify and support their unmet needs. Clinicians should discuss the likely short- and long-term benefits and harms of treatments on HRQL with their patients. The provision of supportive care both during and after treatment may also help to manage symptoms and improve the HRQL of women with ovarian cancer. Consideration should also be given to the HRQL and unmet needs of the women's partners and/or caregivers.

HRQL research and the implementation of PROs in clinical practice is a growing field, which is evidenced by the 73 ongoing clinical trials in ovarian cancer that include PRO endpoints. Importantly, the inclusion of PRO endpoints in clinical trials requires careful consideration. However, reviews indicate that many past ovarian cancer trials lacked prespecified PRO hypotheses and guidance on PRO administration as well as shortcomings in the analyses and interpretation of PRO data [10, 78]. These issues can be addressed by complying with PRO guidance during trial protocol development, selecting appropriate PRO measures to match clinically motivated PRO hypotheses, minimising rates of avoidable missing PRO data during trial conduct, and transparently reporting PRO findings [79]. To facilitate international best practice standards of PRO inclusion in trial protocols, the SPIRIT-PRO was released in 2018 [80]. SPIRIT-PRO provides an international, consensus-based checklist that provides useful guidance on the minimum set of items that should be included in the PRO sections of clinical trial protocols.

In this chapter we provided a brief overview of the evidence for the impact of ovarian cancer and its treatment on HRQL to date, discussed issues to consider when using PROs in ovarian cancer research and clinical settings and summarised ongoing ovarian cancer clinical trials. Several PRO measures are available for use and the appropriate selection of PRO instruments should always be guided by the specific research question and patient/treatment context. Information about specific PRO instruments, including information about their psychometric properties, can be found on the Mapi Research Trust PROQOLID website. For further information and resources please visit the websites for the Sydney Quality of Life Office, University of Sydney, and The International Society of Quality of Life Research.

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