Origins and Pathology of Epithelial Ovarian Cancer: A Brief Overview

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Abstract

Since the emergence of data about the natural history of ovarian cancer (OC) approximately 150 years ago, tremendous advances have been made in the area of the molecular pathology of this aggressive cancer. However, OC remains one of the most lethal gynecological cancers worldwide, with no adequate screening and prevention program available yet to avoid diagnosis in advanced stages. Despite OC still being the silent killer, it has seen dynamic shifts in its classification, staging, and theories regarding its origins in the last years. In fact, the term OC has experienced a shift to include primary peritoneal and tubal cancer, as these tumors behave identically. The prognosis and treatment of OC are dependent on multiple factors, including tumor biology and extent of tumor spread, which has recently been reclassified in a new FIGO staging system. In the literature throughout the years, attempts to identify the origins of these heterogeneous tumor entities have better guided our diagnostic strategies and therapeutic arsenal. This chapter aims to give a general overview of the epidemiology, the natural history as well as the pathology of epithelial OC.

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1.1 Introduction

Epithelial ovarian cancer (OC) is a leading cause of morbidity, mortality, and disability for women worldwide (Sung et al. 2021). With the advances of clinical and molecular knowledge, OC has been dissected in a heterogeneous group of malignancies, characterized by reproducible specific prognostic and predictive features (Haunschild and Tewari 2021; Govindarajan et al. 2020; Lheureux et al. 2019a). To date, OC is viewed more as a spectrum of diseases, and not a single tumor entity, with different trajectories of ontogenesis, pathogenesis, and carcinogenesis (Shih et al. 2021; Wu et al. 2019). The identification of diversified drivers of the tumorigenesis in the different pathology subtypes of OC has enhanced the pathology-molecular biology continuum and facilitated the clinical implementation of therapeutic interventions per histology and molecular subtypes (Lheureux et al. 2019b). This chapter will briefly address ovarian carcinogenesis, portraying a pathology landscape with key elements of molecular pathogenesis. Useful elements in the clarification of the pathology-molecular biology continuum will be highlighted, and key points on the pathology diagnosis and staging will be presented to outline the essential knowledge on this aggressive women's cancer.

1.2 Epidemiology of Ovarian Cancer

OC is one of the most commonly diagnosed gynecological cancers, associated with the highest mortality rates among women (Bray et al. 2018). For instance, although it has a lower prevalence than breast cancer, it is three times more lethal (Bray et al. 2018; Yoneda et al. 2012; Momenimovahed et al. 2019). OC has been named "*The Silent Killer,*" for the indolent initial progression and the onset of non-specific symptoms only in advanced stages of the disease. Despite significant advances that have been made over the last decades in the diagnosis and treatment of OC, more than 75% of patients still presents in advanced stages (Bray et al. 2018; Bereck et al. 2015, 2018) due to lack of evidence-based and effective screening interventions, along with the delayed onset of symptoms and initial asymptomatic tumor growth (Ahmed et al. 2012; Wu et al. 2018). For the vague associated symptoms, initial OC can be misdiagnosed with other conditions, including gastro-intestinal and other pelvic disorders (Ahmed et al. 2012; Wu et al. 2018). OC is highly diverse in its epidemiological and geographical distribution. Approximately, one-third of OC cases are registered from European countries (Bray et al. 2018; Momenimovahed et al. 2019). Within Europe, OC has a North-to-South distribution gradient with the highest incidence rates in the Scandinavian Region (i.e., Denmark, Finland, and Sweden) and the lowest rates in southern Europe (i.e., Portugal, Greece,

Spain, Italy) (Sehouli and Fotopoulou 2006). This gradient in the incidence rates is also reflected in the worldwide distribution of OC, as it has a higher incidence in high-income countries and a lower incidence in low- and middle-income countries. According to the International Agency for the Research on Cancer (IARC) global cancer registry (GLOBOCAN), OC has an age-standardized incidence rate (ASR) of 8.5 per 100,000 women per year in countries with a very high Human development index (HDI) as compared to an ASR of almost half (4.7 per 100,000 women per year) in countries with a low HDI (Bray et al. 2018; Momenimovahed et al. 2019), based on 2018 estimates. The differences between high and low HDI countries have remained unchanged since 1973, as evaluated by Zhang et al. (2019a). In general, age-adjusted incidence rates for cancer has been increasing in the last decades, as a result of lifestyle changes and enhanced healthcare, with more longevous populations (Bray et al. 2018); however, still, the highest rates for OC are observed in high HDI countries, especially Central Europe, and Central and South America (Zhang et al. 2019a). These differences in the incidence are most likely attributable to the various risk factors associated with OC. It can be argued that factors such as obesity rates, smoking, use of the contraceptive pill, number of pregnancies, nutritional, and lifestyle factors do vary significantly between high HDI and low HDI countries and hence may influence the incidence rates of OC in these regions (Bray et al. 2018). Furthermore, in low HDI countries, quality registration of health conditions may be only partially implemented, and the lower incidence rates may mirror low population coverage of cancer registration and overall under diagnosis of cancer (Bray et al. 2018). Hence, this could be a confounding factor in representing the true incidence rates in these regions. In contrast to the above, the mortality rate for OC is inversely distributed to the incidence rates, with higher mortality rates in low HDI compared to high HDI countries. According to GLOBOCAN 2018 data, 184,799 deaths were registered due to OC in 2018, of which only one-third in countries at very-high HDI (Bray et al. 2018). This represents 4.4% of the mortality rate of all cancers in women (Bray et al. 2018; Momenimovahed et al. 2019). The highest mortality rates are seen in Asia (specifically in India) (Bray et al. 2018). The global disparities in cancer mortality can be attributed to the lack of resilient health systems and sufficient healthcare resources to deliver quality, timely, accessible, available, and affordable cancer care (Bray et al. 2018). For OC, the disparities in cancer mortality are mostly related to the delayed access to surgical treatments and to affordable chemotherapy (Bray et al. 2018). OC remains one of the deadly gynecological cancers worldwide until to date. Mortality varies greatly according to geographical distribution and mirrors the environmental, lifestyle, health system, socioeconomic, and reproductive risk factors around the world.

1.3 Origins of Ovarian Cancer

The exact origin of OC has remained controversial throughout the 150-year known natural history of the disease. The earliest theory was the development from the ovarian surface epithelium (OSE) (Desai et al. 2014). In the earliest study by Cheng

et al., mouse ovarian surface epithelial cells (MOSEC) with ectopic expression of *HOXA9*, *HOXA10* and *HOXA11* genes were injected into mice (Cheng et al. 2005). This resulted in the development of serous, endometrioid, and mucinous cancers, supporting the theory that OC can indeed originate from malignant transformation of OSE. Additionally, the OSE can also be vulnerable to malignant transformation due to repeated injury (such as the following ovulation or due to hormonal factors) (Eisen and Weber 1998). Ovarian inclusion can arise following ovulation and the invagination of the OSE into the ovarian stroma. The OSE was then postulated to undergo malignant transformation (Zheng and Fadare 2012). This is further supported by observational studies that suggest that factors suppressing ovulation (such as pregnancy, birth-control pill or breast-feeding) can reduce the occurrence of OC (Eisen and Weber 1998; Zheng and Fadare 2012; Purdie et al. 2003), whereas a higher number of lifetime ovulations increase the risk of OC (Zheng and Fadare 2012; Purdie et al. 2003; Risch 1998). However, the OSE theory was then reshaped in 1999 by Dubeau et al. (Dubeau 1999). The author argued that epithelial OCs do not resemble mesothelial tumors, though OSE cells are identical to the mesothelial cells lining the peritoneum. Moreover, the authors highlighted that precancerous lesions are most often not found in the OSE of ovarian inclusion cysts but in the adjacent organs. In 2001, Piek et al. then firstly proposed the fallopian tube as the origin from which epithelial OCs arise and implant on the peritoneum and the ovarian surface (Piek et al. 2001). Consequently, over the last decades, we have seen increasing evidence in the literature that, in fact, epithelial OCs are not a single entity and indeed develop from distinct binary pathways. These pathways result in type I tumors (low-grade serous cancers, low-grade endometrioid, clear cell, mucinous and Brenner tumors) and type II tumors (high-grade serous cancers) (Desai et al. 2014; Bowtell 2010). High-grade serous OC (HGSOC) typically shows *TP53* mutations and frequently occurs in the distal end of the fallopian tubes (Shih et al. 2021). This has been shown in prophylactic salpingectomy specimens obtained from patients with *BRCA1* or *BRCA2* mutation carriers (Shih et al. 2021). Studies have shown that serous tubal intraepithelial carcinomas (STICs) in the distal fimbriated end of the tube are the most likely precursors for the development of HGSOC. The STICs theory is further supported by the following findings:

- Fifty percent of pelvic HGSOCs show the presence of intraepithelial cancers in the fallopian fimbriae (Stanciu et al. 2019; Kindelberger et al. 2007).
- STICs have been found in 10–15% of fallopian tubes that have been prophylactically removed from women with *BRCA* mutations (Finch et al. 2006; Medeiros et al. 2006).
- Ninety-two percent of STICs have shown *TP53* mutations like those found in HGSOCs samples (Stanciu et al. 2019; Ahmed et al. 2010; Cancer Genome Atlas Research Network 2011).
- STICs-related oncogene products (e.g., cyclin E1, Rsf-1, and fatty acid synthase) are also overexpressed in HGSOCs (Stanciu et al. 2019).

Table 1.1 Clinical, histological, and molecular characteristics of type I and type II ovarian cancer

Type I tumors	Type II tumors
Mutated *RAS*	Wild-type *RAS*
Progress from LMP	De novo
Usually LGSC	Usually HGSC
Wild-type *BRCA*	*BRCA* mutations
Generally wild-type *TP53*	*TP53* mutations
Platinum resistant	Platinum sensitive

Abbreviations: *LMP* low malignant potential, *LGSC* low-grade serous cancer, *HGSC* high-grade serous cancer, *BRCA* breast cancer gene, *TP53* tumor protein 53

- STICs have also been found to be present in prophylactic salpingectomy samples without the presence of ovarian carcinomas, and hence, are unlikely it had been formed due to metastasis from an adjacent HGSOC (Desai et al. 2014).

The above observations support the theory that STICs are the origin of HGSOC in either women harboring or not a germline *BRCA* mutation. Compared with high-grade carcinomas, the low-grade serous OC (LGSOC) has a much lower expression of *TP53* mutations and higher expression of estrogen and progesterone receptors and PAX2 (Bowtell 2010). They typically display mutations related to specific signaling pathways which are not present in HGSOC, for example, *KRAS* and *BRAF*, and rarely *TP53* (Kyo et al. 2020). Cystadenomas and borderline tumors represent early stages in the carcinogenesis of LGSOCs (Ho et al. 2004). This is supported by several findings showing that both LGSOCs and borderline tumors express *KRAS* and *BRAF* mutations in about 30–35% of cases (Singer et al. 2003; Kyo et al. 2020). Interestingly, *KRAS* and *BRAF* mutations have even been detected in benign cystadenomas.

LGSOCs initiate their tumorigenesis from tubal epithelial cells invaginating into the ovarian surface epithelium and forming ovarian inclusion cysts or serous cystadenomas (Kyo et al. 2020; Bowtell 2010). These develop into borderline tumors and subsequently into carcinomas. In this process, molecular mutations in *KRAS*, *BRAF*, and *ERBB2* are increased. In contrast, HGSOCs are believed to develop from a different pathway. They start from the tubal epithelium, develop into latent pre-cancer (p53 signature), precancerous lesion (tubal dysplasia), early cancer (STICs) and ultimately into HGSOCs. In this process, the earliest change is the p53 mutation which is currently considered as a hallmark of OC initiation. Table 1.1 summarizes type I and type II pathways for the development of HGSOC and LGSOC (Kyo et al. 2020).

In summary, two distinct trajectories of ovarian carcinogenesis have been reported, associated with specific clinical conditions (e.g., hyperestrinism, endometriosis), pathology and molecular landscapes, resulting in a spectrum of ovarian epithelial malignancies with peculiar treatment-response patterns and prognosis. While the ontogenetic theories of OC seem to diverge substantially, it cannot be excluded that the different theories apply to different experimental and clinical scenarios and may be characteristic of specific OC types. To date, the better

definition of the ontogenesis of the high-grade tumors has resulted in a new perspective for cancer staging (i.e., 2014 FIGO system) and in the identification of precursor lesions in the fallopian fimbriae, and not exclusively in the ovaries—suggesting new options for the fertility-preserving risk-reducing surgical interventions for women carrying germline mutations at higher risk of OC (e.g., prophylactic fimbriectomy).

1.4 Ovarian Cancer Histotypes and Staging

1.4.1 Pathology of Epithelial Ovarian Cancer

OC encompasses a spectrum of diverse histology entities (Scully et al. 1998; Vargas 2014), with peculiar carcinogenesis, clinical and molecular patterns, and prognostic significance. Most of the OC arises from the malignant epithelial transformation, and only 10% origins from non-epithelial tissues, including germ cells, sex cord or stroma cells and mesenchymal tumors of the ovary. The majority of ovarian epithelial tumors present with a serous histology (around 80% of all) (Scully et al. 1998). However, a multitude of histology types has been reported, such as mucinous, endometrioid, clear cell, transitional and undifferentiated types, as shown in Table 1.2 (Vargas 2014; Scully et al. 1998). Two-thirds of the deaths from OC are related to high-grade serous adenocarcinomas that are associated with the poorest prognosis. Serous carcinomas are further classified into LGSOCs and HGSOCs. HGSOCs have a peculiar intrinsic biological aggressiveness, with local invasiveness and early peritoneal spread (Bell 2005). In fact, these tumors are more commonly diagnosed as bilateral or locally advanced with conspicuous spread into the peritoneum. HGSOC seems to originate from the coelomic Mullerian epithelium of the

Table 1.2 Overview of epithelial ovarian tumors

	Adenoma	Borderline	Carcinoma
Serous	Serous cystadenoma	Serous borderline tumor (BOT)	Serous ovarian carcinoma
Mucinous	Mucinous cystadenoma	Mucinous BOT of either intestinal type or endocervical type	Mucinous ovarian carcinoma
Endometrioid	Endometrioid cystadenoma	Endometrioid BOT	Endometrioid ovarian carcinoma
Clear cell	Clear cell cystadenoma	Clear cell BOT	Clear cell ovarian carcinoma
Transitional	Brenner tumor	Brenner BOT	Malignant Brenner tumor or transitional cell carcinoma
Undifferentiated	–	–	Undifferentiated ovarian carcinoma
Mixed	Cystadenoma	BOT	Carcinoma

ovarian surface, as well as from the tubo-ovarian fallopian fimbriae and the peritoneum (Zhang et al. 2019b). High-grade serous neoplasms are enriched in mutations of the breast cancer associated genes 1 and 2 (*BRCA1/2*), resulting in a deficiency in the DNA repair machinery and a high burden of DNA mutations, that is a key characteristic of serous tumors (i.e., higher tumor mutational burden) (Zweemer et al. 2000). Of note, the presence of these specific stigmata of the homologous recombination DNA repair mechanism is also associated with enhanced sensitivity to some DNA-targeting agents, including platinum compounds and targeted agents against Poly-ADP-ribose polymerase (PARP) (Alkema et al. 2016). Also, another distinguishing feature of HGSOCs is the presence of *TP53* mutations (with non-synonymous mutations more common than frameshift mutations or deletions) (Zhang et al. 2016; Singh et al. 2017; Ruba et al. 2020). The macroscopic aspects of HGSOCs are not specific; most patients present with advanced stages, with abdominopelvic extension, fallopian tubes are usually embedded in the tumor bulk (WHO 2020). HGSOCs are described at the gross pathology as variably-sized, exophytic tumors with solid or papillary growth patterns and solid areas with necrotic and hemorrhagic parts or bloody fluid-filled cysts (Kaku et al. 2003). Histologically, HGSOCs present with serous differentiation, high mitotic count (>5 mitoses/mm^2 equivalent to >12 mitosis/10 HPF of 0.55 mm in diameter and 0.24 mm^2 in the area) and marked cellular atypia associated sometimes with necrosis. The tumors may have a solid, cribriform papillary or glandular architecture with infiltrative borders (WHO 2020; Singh et al. 2017). At immunohistochemistry, HGSOCs particularly show abnormal p53 oncoprotein immunostaining, reflecting the *TP53* mutation (defined as diffuse and strong p53 nuclear expression ($\geq$80%) or complete absence of immunohistochemical staining with retained internal control staining); rarely, HGSOCs show aberrant cytoplasmic p53 expression (McCluggage 2012; Singh et al. 2017). Also, p16 is diffusely positive ("block-type" staining) in most cases of HGSOCs (McCluggage et al. 2015). Other non-distinctive immunohistochemical staining of HGSOCs (as well as other serous tumors) include the cancer-associated antigen Wilms tumor 1 (WT1) and the paired box 8 transcription factor (PAX8) positivity. Also, they can variously express estrogen and progesterone receptors; the pattern of cytokeratin (CK) staining is also quite peculiar, with CK7-positivity and CK20-negativity (Lee et al. 2002). The above-mentioned immunohistochemical features of HGSOCs may be particularly important in the differential diagnosis with other ovarian carcinomas or metastatic tumors to the ovaries.

LGSOC is a rarer entity of serous carcinomas, representing 1–3% of all epithelial OCs (Gadducci and Cosio 2020). These tumors present mostly in younger patients (i.e., 20–40 years), with an initial more indolent biological behavior. Though less sensitive to chemotherapy, their intrinsic, more indolent nature has been associated with better prognosis, especially in the earlier stages (Gershenson et al. 2006). Grossly, LGSOCs present as unilateral or bilateral solid-cystic tumors with ovarian surface involvement. Histologically, LGSOCs appear as cuboidal, columnar cells, with monotonous proliferation patterns, without high-grade cellular atypia and lower mitotic count ($\leq$12 mitoses/10 HPF), with usually papillary or micropapillary architecture, destructive stromal invasion and frequent calcifications (psamommas)

(WHO 2020). The key IHC finding of this serous variant is the low proliferation index, with Ki-67 staining usually less than 10%. LGSOCs often express estrogen and progesterone receptors, with a normal p53 pattern of immunoexpression (Slomovitz et al. 2020).Notably, the carcinogenesis of a half of low-grade serous proliferation can be peculiarly driven by molecular alterations of the mitogen-activated protein kinases (MAPKs), like *KRAS* and *BRAF*. Eventually, *BRCA* alterations are uncommon.

Mucinous OC (MOC) encompasses up to 5% of all epithelial OCs (Köbel et al. 2010). The clinical and pathology of mucinous malignancies in the ovaries is commonly challenging, as three-quarter of mucinous tumors in ovaries are secondary tumors (i.e., Krukenberg tumors, generally bilateral), and only one-third is a primitive MOC (generally unilateral) (McCluggage 2012). In addition, only a minority of MOC in the ovaries are primary malignant proliferation (i.e., pure MOC), as 90–95% can present in the context of benign or borderline proliferation (Rodríguez and Prat 2002). Younger women are mostly affected. MOC often appears as unilateral solid-cystic neoplasms with a smooth external surface filled with a large amount of gelatinous secretions. Two patterns of tissue invasion have been reported, expansive, and infiltrative (i.e., destructive stromal growth), respectively; the presence of an infiltrative pattern has been associated independently with an adverse prognosis, including in early-stage MOC (Lee and Scully 2000). The immunohistochemical feature of MOC includes positive staining with CK20, CK7, carcinoembryonic antigen (CEA), CA19-9 and CDX2 (McCluggage 2012). MOC stains negative to PAX8, WT1, and hormone receptors (estrogen and progesterone), in contrast with serous OC (McCluggage 2012). This immunostaining profile lacks unfortunately any specificity as many metastatic tumors to ovaries may have these immunohistochemical staining patterns, especially tumors from the digestive tract. Distinguishing primitive MOC from metastases is a challenging issue that requires histopathological, clinical, and imaging correlations (McCluggage 2012; Simons et al. 2019). For their intrinsic chemoresistance, MOC has a better prognosis when diagnosed early and dismal in advanced stages (Kelemen and Köbel 2011).

Endometrioid OC accounts for 10–25% of all epithelial OCs; in 10–15% of the cases, a diagnosis of endometrioid OC is contextual to pre-existing endometriosis, with or without synchronous endometrial hyperplasia or carcinoma (Oswald and Gourley 2015). Endometrioid OC presents mostly as unilateral and as solid hemorrhagic masses without papillae. Squamous metaplasia and adeno-fibroma components are reported in half of the specimens (Gilks and Prat 2009). Endometrioid OC is histologically, graded as its uterine counterpart according to the extent of glandular component and cellular atypia: $<5\%$ solid growth (grade 1); 5–50% solid growth (grade 2); $>50\%$ solid growth (grade 3) (WHO 2020; Fadare and Parkash 2019). At immunohistochemistry, typically, endometrioid OC stains positive with CK7, PAX8, hormone receptors, and stains negative with WT1, CK20, CDX2, with wild-type p53 staining (normal staining) (Fadare and Parkash 2019). Loss of *PTEN* is a hallmark of carcinogenesis in these tumors, described in 20–25%; also, in 10–20%, patients may have a Lynch syndrome, with a family history of

multiple tumors—therefore presenting a hyper-mutating DNA phenotype, recorded as microsatellite instability (MSI) (Pierson et al. 2020).

Clear cell OC are rarer variants, diagnosed in 5–10% of the patients; in women from Japan, this tumor type can encompass up to 25% of the epithelial OCs (Iida et al. 2020). Clear cell OC is associated with endometriosis in up to 70% of the cases (Iida et al. 2020). The prognosis of this tumor is stage-dependent: in the earlier setting, these tumors can have an excellent prognosis (Fujiwara et al. 2016). However, for their intrinsic platinum resistance, patients with advanced disease have a poor prognosis (Sugiyama et al. 2000). At the gross pathology, clear cell OC appears as unilateral cystic mass with solid components, mostly a single and marginated one (Sugiyama et al. 2000). Microscopically, this tumor exhibits tubule-cystic, papillary, or solid architecture, cells with clear to eosinophilic cytoplasm and dense eosinophilic intracytoplasmic secretions (Fadare and Parkash 2019). Cells with a hobnail appearance are typically found in tumors with tubule-cystic architecture. The typical immunohistochemical characteristics of clear cell OC are positive staining with Napsin A, HNF-1β (hepatocyte nuclear factor 1β), PAX8, CK7, and negative staining with hormone receptors (estrogen and progesterone), CK20, and WT1 (McCluggage et al. 2015; Fadare and Parkash 2019). An association with Lynch syndrome has been reported; however, the most characteristic genomic stigmata of these tumors are the presence of *ARID1A* alterations in a half of cases, resulting in a hyper-mutating DNA phenotype (Berns et al. 2018).

Other malignant ovarian epithelial tumors include malignant Brenner tumor, mixed ovarian carcinomas, and undifferentiated carcinomas. These are very rare cancers, and their molecular and histopathological features are not yet well established (WHO 2020; Bennett and Olivia 2020; Tafe et al. 2010). Malignant Brenner tumors resemble histologically invasive urothelial carcinoma but are associated with foci of benign or borderline Brenner tumors (Cuatrecasas et al. 2009). They are usually unilateral and express urothelial markers at immunohistochemistry (p63, GATA3 mainly) (Cuatrecasas et al. 2009). Mixed ovarian carcinomas show two or more histological differentiation (serous, mucinous, endometrioid, clear cell, etc.) (Mackenzie et al. 2015). These tumors seem to be monoclonal, suggesting a common precursor cell of all of the mixed histological components (WHO 2020). Undifferentiated carcinomas are defined as malignant carcinoma with no obvious morphological differentiation. Some are associated with foci of differentiated ovarian carcinomas (especially low-grade endometrioid carcinomas), suggesting progression or dedifferentiation from these tumors (WHO 2020; Tafe et al. 2010).

1.4.2 Staging of Ovarian Cancer

The surgical and pathological staging of epithelial OC is crucial and is a major determinant of the treatment choices and of the prognosis. A standardized international staging system aids in determining the following (Binder et al. 2015):

1. Extent of tumor spread
2. Individual prognosis
3. Treatment efficacy
4. Overall, disease-free and progression-free survival rates

There has been increasing molecular, histological, and genetic evidence in the literature that serous carcinomas of the ovary or peritoneum may have actually originated from the fimbrial end of the fallopian tube (Berek et al. 2018; Prat 2014; Callahan et al. 2007). The theory of the STICs as a precursor of HGSOC has been largely validated and accepted. Some epithelial OCs, in fact, present with extensive pelvic-peritoneal involvement, with no apparent origin in the ovaries (Berek et al. 2018; Callahan et al. 2007; Prat 2014). Therefore, STICs may originate in the fallopian fimbriae and rapidly grow on the ovarian surfaces and implant on the peritoneum, as commonly reported for HGSOC (Kurman and Shih 2010). Hence, the Gynecologic Oncology Committee of the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system in 2014 to incorporate ovarian, fallopian tube, and peritoneal cancer as a single entity (Prat 2014) (Fig. 1.1). The updated staging system enforces the efforts to retrieve the primitive tumor whenever possible; however, when the primary site cannot be successfully identified, the pathologist should label it as "undesigned," more than "unknown primary," as a peritoneal or fallopian origin can still be possible, namely a pelvic origin. In fact, international recommendations are now established for site assignment of the primary tumor in extra-uterine high-grade serous carcinomas of the ovary and distinguish them from fallopian tubes and peritoneal primaries (McCluggage et al. 2015; Singh et al. 2016). For this, the fallopian tubes, or at least their fimbrial ends, should be totally sampled in all the cases of high-grade serous carcinoma (Table 1.3 summarizes diagnostic criteria for assigning primary site in extra-uterine high-grade serous carcinoma according to the latest World Health Organization classification of female genital tumors).

The FIGO staging system includes four stages for OC, based on the peritoneal spread and metastatic pattern (Fig. 1.1). An important addition in the 2014 classification is the subdivision of Stage IC into three risk categories according to the spontaneous or iatrogenic rupture of the tumor capsule and the presence of malignant ascites (Berek et al. 2015). Stage III is now defined according to spread to the retroperitoneal lymph nodes, regardless of the intraperitoneal dissemination (i.e., stage IIIA1 and stage IIIA2, see Fig. 1.1) (Prat 2014). This is based on a study indicating that patients with positive retroperitoneal lymph nodes alone have significantly better survival than those who have intraperitoneal dissemination (Berek 2009). Stage IVB now also includes inguinal lymph nodes metastases (Prat 2014). The FIGO staging system must be considered as a surgical and pathological system. While imaging like computed tomography scan can detect the pelvic and abdominal involvement of epithelial OC, all tumors arising from ovaries, fallopian tubes and primary peritoneal malignancies require a precise surgical staging approach. The findings from operative surgical staging are critical to inform on the prognosis and the optimal treatment choices. In patients with no extra-pelvic symptoms, there is no

Primary tumor (T)		
TNM	**FIGO**	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor limited to the ovaries (one or both)
T1a	**IA**	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
T1b	**IB**	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
T1c	**IC**	Tumor limited to one or both ovaries with any of the subcategories below (IC1-3)
T1c1	**IC1**	Surgical spill
T1c2	**IC2**	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	**IC3**	Malignant cells in ascites or peritoneal washings
T2	**II**	Tumor involves one or both ovaries with pelvic extension below pelvic brim
T2a	**IIA**	Extension and/or implants on the uterus and/or tube(s)
T2b	**IIB**	Extension to and/or implants in other pelvic tissues
T3	**III**	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or retroperitoneal lymph node involvement
T3a	**IIIA2**	Microscopic peritoneal metastasis beyond the pelvis with or without positive retroperitoneal lymph nodes
T3b	**IIIB**	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension with or without positive retroperitoneal lymph nodes
T3c	**IIIC**	Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension including extension to liver capsule or spleen without parenchymal involvement of those organs and with or without positive retroperitoneal lymph nodes
Regional lymph nodes (N)		
TNM	**FIGO**	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) ≤0.2 mm
N1	**IIIA1**	Positive (histologically confirmed) retroperitoneal lymph nodes
N1a	**IIIAi**	Metastasis ≤10 mm in greatest dimension
N1b	**IIIAii**	Metastasis more than 10 mm in greatest dimension
Distant metastasis (M)		
TNM	**FIGO**	
M0		No distant metastasis
M1	**IV**	Distant metastasis including cytology-positive pleural effusion; liver or splenic parenchymal involvement; extra-abdominal organ involvement including inguinal lymph nodes; transmural intestinal involvement
M1a	**IVA**	Pleural effusion with positive cytology
M1b	**IVB**	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine

Fig. 1.1 The current FIGO classification

Table 1.3 Assigning tumor primary site in extra-uterine high-grade serous carcinomas

Primary site	Diagnostic criteria
Fallopian tube	– Presence of STIC, or – Presence of mucosal HGSC, or – Part or the entire length of the fallopian tube in separable from the tumor mass
Ovary	– Both fallopian tubes separate from ovarian mass, and – No STIC or mucosal HGSC in either tubes
Tubo-ovarian	– Fallopian tubes and ovaries not available for complete examination, and – Pathological findings consistent with extra-uterine HGSC
Peritoneal	– Both tubes and both ovaries fully examined, and – No gross or microscopic evidence of STIC or HGSC in tubes or ovaries

Abbreviations: *STIC* serous intraepithelial carcinoma, *HGSC* high-grade serous carcinoma

common need to provide a systemic staging, as the distant metastases are uncommon (Berek et al. 2018). In selected patients with advanced disease at presentation, in which the surgical staging is deemed not appropriate and/or unsafe, a diagnostic biopsy may be considered to provide histologically and molecularly appropriate treatments (Berek et al. 2018).

1.5 Conclusion

The carcinomas of ovarian, tubal, and peritoneal origin remain highly heterogeneous entities. Accumulating epidemiological and molecular evidence shows that the origin for serous high-grade carcinomas is indeed the fallopian tube secretory cells. Additionally, comprehensive molecular analyses have uncovered the key driver events for serous carcinogenesis. This has provided us with novel molecular targets and consequently vast opportunities for new therapies (for additional reading, see Box 1.1).

Box 1.1 Recommended reading of particular interest

Citation	DOI
Iida Y, et al. *Clear cell carcinoma of the ovary: a clinical and molecular perspective*. Int J Gynecol Cancer. 2020: ijgc-2020-001656.	https://doi.org/10.1136/ijgc-2020-001656
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Box 1.1 (continued)

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