

Ovarian Cancer

Recommendations from the society for diagnosis and therapy of
haematological and oncological diseases

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
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ICD-10: C56

Date of document: July 2023

Compliance rules:

- [Guideline](#)
- [Conflict of interests](#)

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1 Summary

Ovarian carcinoma comprises a heterogeneous group of epithelial tumors, both at the histological and molecular level, with different biological behavior and prognosis. The so-called high-grade carcinomas are the most common, and low-grade carcinomas are less common. Ovarian carcinoma has the highest mortality among gynecologic tumors, in part because it is often not diagnosed until an advanced stage due to the lack of characteristic early symptoms and appropriate screening. However, with the advancement of surgical therapy, molecular diagnostics, and systems therapy with the use of targeted therapies, the prognosis has improved significantly and chronic courses are observed more frequently.

In primary therapy, the combination of optimal surgical therapy with the goal of macroscopic tumor freedom is essential, followed by adjuvant platinum-containing chemotherapy depending on the stage. In the advanced stages, the combination of carboplatin and paclitaxel is standard; in high-grade carcinomas, response to platinum-containing combination chemotherapy is followed by maintenance therapy, depending on the HRD ("homologous recombination deficiency") status, with the angiogenesis inhibitor bevacizumab and / or a PARP ("poly adenosine diphosphate-ribose polymerase") inhibitor.

For relapse treatment, depending on the individual situation, re-operation, platinum-containing and platinum-free chemotherapy as well as bevacizumab and PARP inhibitors may be considered. Especially in advanced lines, palliative care and preservation of quality of life are the main focus. Due to the not insignificant number of long-term survivors, follow-up care and the development of survivorship programs are of particular importance.

2 Basics

2.1 Definition

Ovarian carcinoma comprises a heterogeneous group of epithelial tumors with different biological behavior and prognosis. Due to the similarity in tumorigenesis and the common tumor biological behavior, tubal carcinomas and peritoneal carcinomas are treated like ovarian carcinomas both surgically and systemically. In principle, therapy-oriented guidelines do not differentiate according to localization, but only according to histological, genetic and molecular parameters.

Epithelial ovarian cancer must be distinguished from germ cell tumors and the heterogeneous group of germ line stromal tumors, which are not addressed in this guideline.

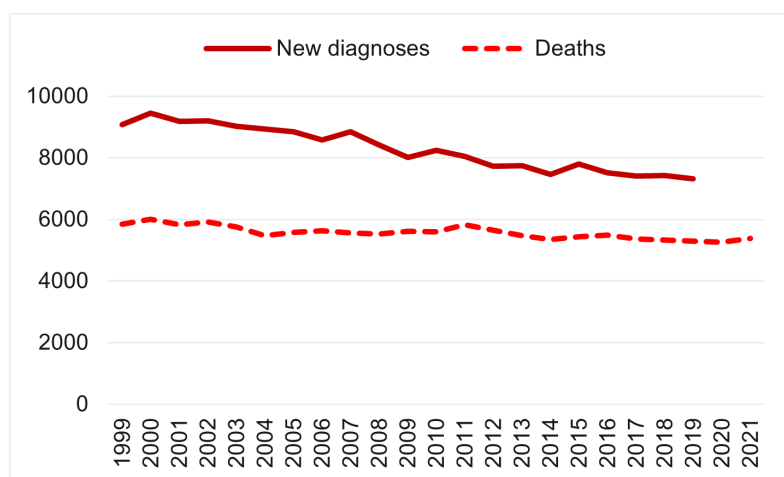
2.2 Epidemiology

Carcinomas of the ovary represent nearly one-third of all malignant neoplasms of the female genital tract and are the second most common fatal gynecologic cancer after breast cancer. Approximately one in 76 women will develop ovarian cancer during lifetime. Disease and mortality rates have been steadily decreasing in Germany since the turn of the millennium (Figure 1 and 2) [1]. Thus, approximately 7350 women developed ovarian cancer in Germany in 2018, and 5291 women died of ovarian cancer in Germany in 2019.

The median age at diagnosis is 69 years. Disease rates increase continuously until the age of 85 (Figure 3) [1].

Because the majority of ovarian cancers (approximately 75%) are diagnosed at an advanced stage (FIGO stage III/IV), the 5-year relative survival rate is only 42%. However, if the disease is detected early, the relative survival rates are 88% in stage I and 79% in stage II (Figure 4 and 5)[1].

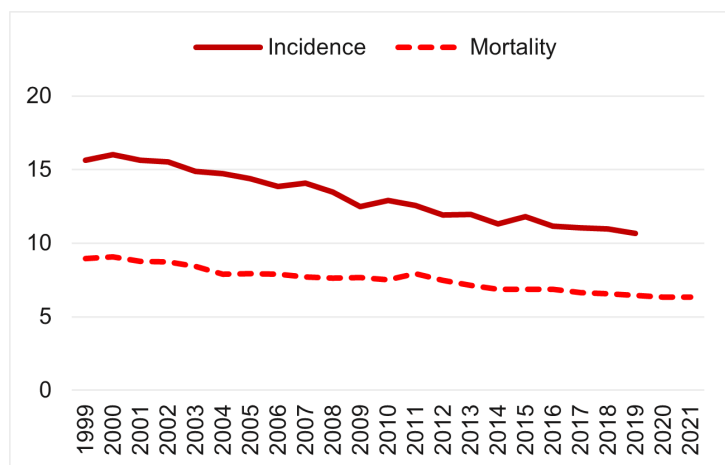
Figure 1: Age-standardized incidence and mortality of ovarian neoplasms in Germany



Legend:

Source: Center for Cancer Registry Data, Robert-Koch-Institute (RKI) as of 24 January 2023

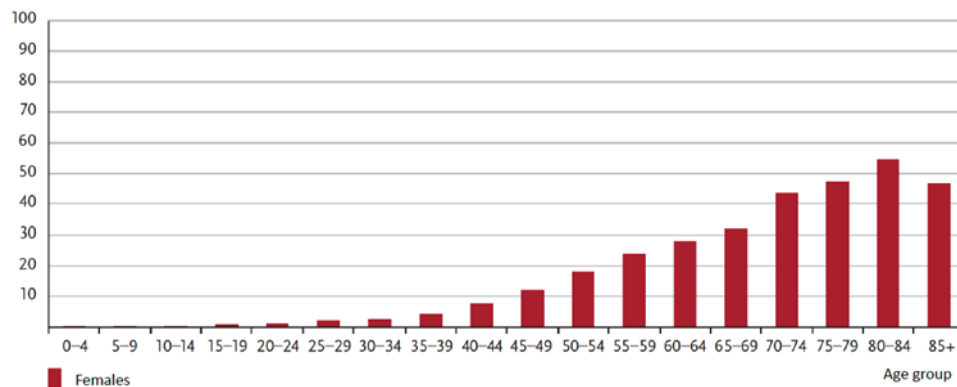
Figure 2: Absolute number of new cases and deaths of ovarian neoplasms in Germany



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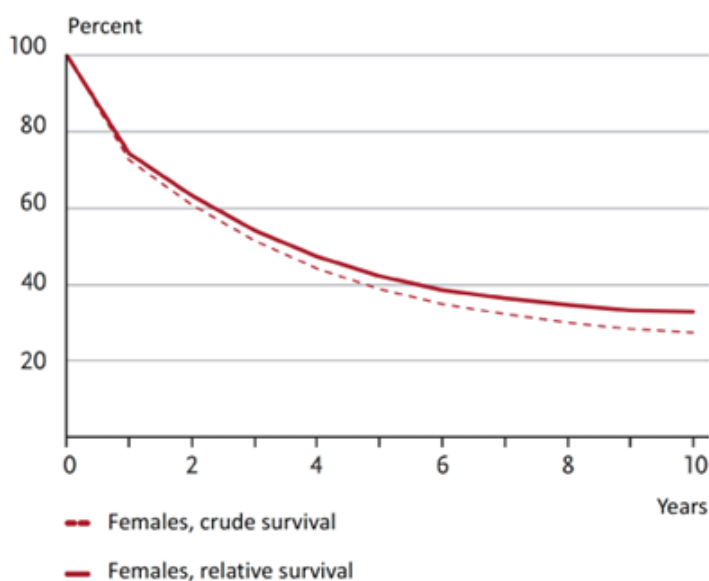
Source: Center for Cancer Registry Data RKI as of 24 January 2023

Figure 3: Age-specific new cases, Germany 2017-2018



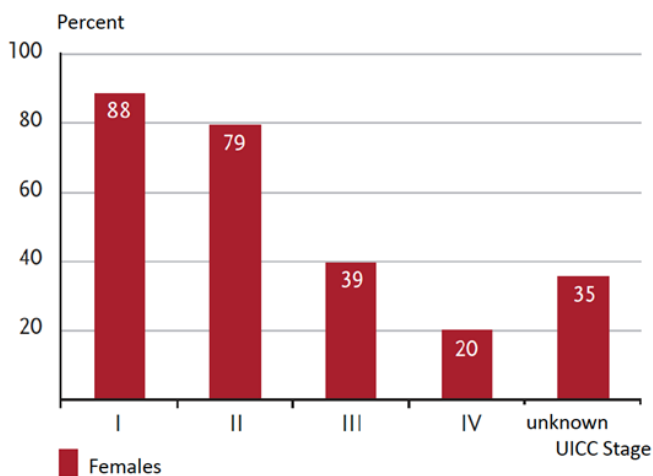
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Source: Center for Cancer Registry Data RKI as of 24 January 2023

Figure 4: Absolute and relative survival rates up to 10 years after initial diagnosis



Legend:
Source: Center for Cancer Registry Data RKI as of 24 January 2023

Figure 5: -year relative survival by UICC stage



Legend:
Source: Center for Cancer Registry Data RKI as of 24 January 2023

2.3 Risk factors

The risk of developing ovarian cancer increases with age. Furthermore, factors associated with relative hyperestrogenism increase the risk of developing the disease, such as nulliparity, infertility, hormone replacement therapy (especially estrogen monopreparations) and obesity. On the other hand, multiple gravidities, long breastfeeding periods, use of oral contraceptives, and sterilization by tubal occlusion reduce the risk.

In addition, there are genetic risk factors that can lead to the so-called hereditary breast and ovarian cancer syndromes (HBOC), in which there is an above-average incidence of breast cancer, ovarian cancer and other cancers in genetically related families. These include mutations in genes involved in homologous recombination (26% of cases), most notably mutations in the BRCA1 (15.5% of patients) or BRCA2 (5.5% of patients) genes [2]. BRCA1 mutation carriers have a cumulative risk of 39% for ovarian cancer and 46-65% for breast cancer by 69 years of age. BRCA2 mutation carriers have a risk of 11-22% for ovarian cancer and 45% for breast cancer. In addition, mutations in the BRCA1 and BRCA2 genes also lead to increased rates of other carcinomas such as pancreatic or prostate cancer [3]. Other relevant mutations are found in the ATM, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D and TP53 genes [4].

Furthermore, the hereditary non-polyposis colorectal carcinoma syndrome (HNPCC or Lynch syndrome) is of importance. It is associated with mutations in mismatch-repair genes (MLH1, MSH2, MLH3, MSH6, PMS2). Women up to the age of 40 years with an MSH2 or MLH1 mutation still have a low risk of ovarian cancer (at 1%), but this risk increases sharply to 24% (MSH2) or 20% (MLH1) by the age of 70 [5].

Patients diagnosed with ovarian cancer should be informed about the risk of hereditary disease (see Chapter 5.1).

Furthermore, asbestos exposure increases the risk of developing ovarian cancer. In case of occupational exposure to asbestos, suspected occupational disease should be reported [6].

3 Prevention and early detection

Approximately 75% of cases have been diagnosed at an advanced stage for decades. Prospective randomized studies have shown that screening by transvaginal ultrasound or testing for the biomarker CA-125 increases the rate of tumors diagnosed in early stages, but no reduction in mortality was achieved [7, 8]. In contrast, patients screened false-positive are exposed to a not insignificant risk of morbidity and mortality by subsequent surgical interventions.

This also applies to high-risk patients such as carriers of genetic mutations and relatives of women suffering from ovarian cancer in whom a disease-relevant pathogenic germline mutation has been detected [9]. However, they should be offered multidisciplinary counseling (gynecology and human genetics) and genetic testing (no fixed age limit) and, if necessary, informed about the possibility of prophylactic surgery.

Bilateral salpingo-oophorectomy (BSO) is the most effective method to reduce the risk of disease and mortality in hereditary ovarian cancer [10]. It is recommended in BRCA1 mutation carriers from the age of 35-40 years and in BRCA2 mutation carriers from the age of 40-45 years [11]. In principle, family history, especially the youngest age at diagnosis of a family member, as well as a potential desire to have children should be taken into account.

4 Clinical characteristics

In early stages, ovarian cancer causes no specific symptoms, so that approximately 70% of tumors are first diagnosed in advanced FIGO stages III to IV [12, 13]. As the disease progresses, nonspecific symptoms may emerge, including gastrointestinal symptoms such as bloating, flatulence, nausea, pain and constipation, frequent urge to urinate, decreased general performance and increasing waist circumference [14].

5 Diagnosis

5.1 Initial diagnostics

Any ovarian mass should be considered malignant until proven otherwise. The initial diagnostic procedures should include a bimanual gynecologic examination and transvaginal ultrasonography, after a detailed history [10].

In premenopause, reversible functional cysts or retention cysts frequently occur. In case of doubt, a wait-and-see approach for about 3-6 months with administration of ovulation inhibitors or progestogens, if necessary, is justified. In case of persistent findings, surgical exploration is required. In postmenopausal women, the risk of ovarian cancer is significantly higher, so that here a wait-and-see approach is justifiable only in exceptional cases (unilocular cyst < 4 cm and CA-125 < 35 U / ml) [10].

Further diagnostics should include cross-sectional imaging, usually computed tomography (CT) with contrast medium, alternatively a native thoracic CT scan and magnetic resonance imaging (MRI) with contrast medium of abdomen and pelvis, to assess the extent of the tumor in abdomen and thorax.

However, there is no diagnostic tool that can replace surgical staging in ovarian cancer and reliably assess operability. Skeletal scintigraphy should be performed only in symptomatic patients.

The tumor marker CA-125 can be determined as a supplement during diagnosis. However, it must be taken into account that an elevation of CA-125 is not specific for ovarian cancer and can also be elevated in benign diseases [10].

The definitive diagnosis is always made histologically, usually in the course of primary surgical treatment.

Recommendations for diagnosis and staging are summarized in Table 1.

Table 1: Diagnosis of suspected ovarian cancer and subsequent staging

Procedure	Note
Physical examination, gynecological examination	Bimanual gynecological examination
Transvaginal ultrasound	For evaluation of tumor size and structure, wall thickness, internal echo, septa, ascites
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation, TSH, with CA125 and CEA in mucinous subtype, if necessary
Computed tomography thorax, abdomen/ pelvis with contrast medium	Tumor spread in the abdomen, detection of distant metastases
Risk analysis of important organ functions	Clarification of operability
Operation	Staging and therapy, with multivisceral resection if indicated
Pathological examination	Histopathological findings, HRD diagnostics incl. BRCA 1/2 in stage FIGO III/IV
Genetic testing	Clarification of hereditary ovarian cancer

Patients diagnosed with ovarian cancer must be informed about the risk of hereditary disease. Since the presence of a mutation cannot be excluded based on age or family history alone, genetic testing for hereditary breast and ovarian cancer syndromes (HBOC) should be offered to all women under the age of 80 [2, 4]. Furthermore, it should be checked whether criteria for Lynch syndrome are present and testing should also be offered if indicated [5].

In addition, for any advanced high-grade ovarian cancer, the tumor should be evaluated not only for BRCA-1/2 mutations but also for HRD status using a validated assay to evaluate whether maintenance therapy with PARP inhibitors and/or bevacizumab should be considered in the primary therapy (see Treatment Protocols) [15].

In case of recurrence or progression, molecular tumor diagnostics for BRCA1/2, and, at least for the low-grade carcinomas, dMMR (deficient mismatch repair) or MSI^{high} (high-grade microsatellite instability) and BRAF should be performed at the latest. Furthermore, testing for NTRK can also be performed [16].

5.2 Monitoring during treatment

Assessment of response during chemotherapy should be primarily clinical [15, 17]. However, imaging techniques such as sonography or CT/MRI, PET-CT if indicated, and testing of tumor marker CA-125, if initially elevated, can be used to further evaluate response. An increase in CA-125 serum level, measured twice consecutively, should then trigger imaging.

During maintenance therapy, continuous therapy monitoring is performed by means of clinical evaluation, imaging procedures and testing of the tumor marker CA-125, if initially elevated [15, 17]. After completion of maintenance therapy, symptom-oriented follow-up is performed (see Chapter 8. Follow-up).

5.3 Diagnostics of suspected recurrence

In symptomatic patients, or if there is a suspicion of recurrence or progression based on clinical or gynecological examination including rectal examination and vaginal ultrasonography, further diagnostic imaging by CT or MRI is indicated (see also Chapter 8. Follow-up) [15, 17, 18].

PET or PET/CT may be used primarily when recurrence is still suspected despite negative CT or MRI, but it is unclear to date whether their use can reduce mortality and morbidity in patients [19].

Routine tumor marker testings in the absence of symptoms should not be performed because early diagnosis of recurrence in asymptomatic patients does not improve survival but does lead to earlier deterioration in quality of life [20].

5.4 Classification

5.4.1 Histology

Several histologic subtypes are distinguished, which differ significantly not only in terms of their clinical course (spread pattern and survival), but also in terms of their genesis, molecular pathology, and association with hereditary tumor syndromes (Table 2) [21].

Moderately to poorly differentiated serous adenocarcinomas (high-grade ovarian carcinomas), so-called type II carcinomas (70%), occur most frequently. They arise from serous tubal intraepithelial precursor lesions (STIC) or the surface epithelium of the ovary [22]. Because these are rapidly growing tumors, precursor lesions usually cannot be identified. Less frequently, so-called low-grade type I carcinomas occur. These are well-differentiated serous, mucinous, endometrioid, or clear cell carcinomas. Tumors are classified as a new subgroup of seromucinous carcinomas that have two or more types of Müllerian differentiation in at least 10% of the total epithelium. In addition, Brenner tumors and carcinosarcomas are also distinguished. Low-grade type I carcinomas arise from defined precursor lesions such as borderline tumors (BOT). Due to the slow growth of this tumor subgroup, the precursor lesions are more frequently detectable.

BOTs are atypical proliferative tumors (APT) of the ovary in which tissue architectural disruption and minor cellular atypia are present but no destructive invasive growth can yet be demonstrated. BOTs can spread peritoneally as so-called peritoneal implants but are not metastatic. In the context of a borderline tumor-carcinoma sequence, invasively growing low-grade carcinomas can arise from the primary ovarian BOT, but also from the peritoneal implants. In BOT, different histologic subtypes are distinguished in analogy to invasive carcinomas. Serous (50-55%) and mucinous (40-45%) BOT are most common, with endometrioid, clear cell, seromucinous, or Brenner BOT occurring less frequently. Ovarian cancers are typed primarily by typical histomorphologic growth patterns, supplemented by immunohistologic studies and molecular analyses (see Table 2).

Table 2: Ovarian cancer subgroups

Histology	Grading	Possible site of origin / precursor lesions	Typical immuno-histochemical changes	Typical molecular aberrations	Genetics	Frequency
Serious	High-grade	Tubal epithelium /STIL-> STIC	WT1 positive, p53 aberrant (negative or diffuse)	TP53, BRCA1/ 2, other HRD genes;	BRCA 1 / 2 other HRD genes	75%
Serious	Low-grade	Adenomas / BOT	p53 WT WT1, ER and PAX8 positive	BRAF/ KRAS Rare BRCA1/2	Rare: BRCA 1 / 2 Other HRD genes	≤5%
Mucinous	Low-grade	Tuboperitoneal junctions, ovarian/ transitional cell epithelium. → BOT, mature teratoma→ mucinous epithelium	WT1, Napsin A, PR, SATB2 negative p53 often aberrant (negative or diffuse) CK7+ and variable expression of CK20 as well as CDX2, in association with teratomas CK7 negative, CK20 and CDX2 positive	KRAS, HER2		≤5%
Seromucinous subtype of endometrioid carcinoma	Low-grade	Endometrium/ endometriosis → BOT	WT1, napsin A negative, PR positive, CK7, CDx2 positive, CK20 and p16 possibly weak positive	ARID1A		< 5%
Endometrioid	G1, G2, G3	Endometrium/ endometriosis → BOT	WT1, Napsin A negative PR positive Rarely p53 negative or diffuse (high-grade) If necessary dMMR	ARID1A PTEN MSI ^{high}	BRCA 1 / 2 Other HRD genes (HBOC) MRR genes (Lynch)	~10%
Clear cell	Always G3	Endometrium/ endometriosis → BOT	WT1 negative Napsin A positive PD1 positive, TILs Rarely high grade: p53 negative or diffuse	ARID1A HNF1β	Rare BRCA 1, BRCA 2 other HRD genes	~10%
Carcinosarcoma	High-grade	Tube (common precursor cell of the epithelium and mesenchyme) / STIC	Epithelial portion frequently HGSOE, mesenchymal portion: Müller's differentiation or rhabdomyo-/ chondro-/ osteo-/ liposarcoma	TP53	Rare: BRCA 1 / 2 other HRD genes	<5%
Undifferentiated	High-grade	Not known	Positivity for cytokeratins, possibly residual positivity for immunohistological ovarian cancer markers		BRCA 1 / 2 other HRD genes	
Malignant Brenner tumor		Tuboperitoneal junctions/transitional cell epithelium → BOT	p63, GATA3 positive ER, PR, WT1 weak positive p53 sometimes aberrant (negative or diffuse)	TP53 if applicable		<5%

Legend:

BOT, borderline tumor; dMMR, deficient mismatch repair; ER, estrogen receptor; HRD, homologous recombination deficiency; MSI-high, high-grade microsatellite instability; PR, progesterone receptor; STIC, serous tubular intraepithelial carcinoma; STIL, serous tubular intraepithelial lesion

5.4.2 Stages

Carcinomas of the tube and peritoneum have the same genesis and histomorphology as high-grade ovarian carcinomas. In addition, in many advanced tumors, the exact site of origin can no longer be determined with certainty. Therefore, according to WHO and FIGO (International Federation of Gynecology and Obstetrics), they are now classified and treated together. The T stage can be supplemented by the site of origin ([Table 3](#)). In bilateral disease without evidence of tumor or precursor lesions (STIC) in the tubes, the site of origin is most likely the ovary. For unilateral disease and evidence of tumor in the tube or a STIC, the site of origin is most likely the tubes. Primary peritoneal carcinomas are extremely rare [[15](#), [23](#)]. The current TNM and UICC classifications for ovarian cancer are summarized in [Tables 3](#) and [4](#), respectively.

Table 3: Identification of tumor origin

TNM	FIGO	Origin
Tov	OV	Ovary
Tft	FT	Tube
Tp	P	Peritoneum
Tx	X	Cannot be determined

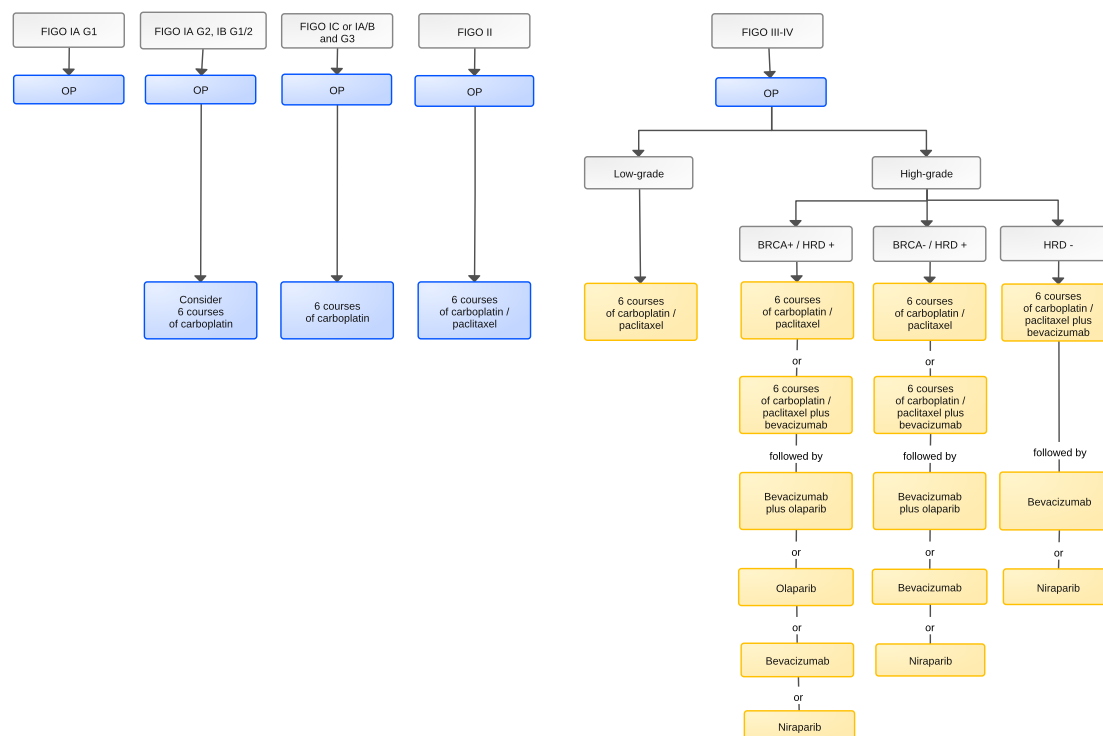
Table 4: TNM classification (8th edition) according to UICC and FIGO classification of ovarian cancer

TNM classification	FIGO stage	Features
T1	I	Tumor confined to one or both ovaries
T1	I	One ovary or tube affected
T1a	IA	One Ovary or tube affected, capsule or serosa intact, ovarian/tubal surface tumor-free, irrigation fluid tumor cell-free
T1b	IB	Both ovaries or tubes affected, capsule or serosa intact, ovarian/tubal surface tumor-free and irrigation fluid tumor cell-free
T1c	IC1	Same as IA or IB; surgically induced ovarian leakage.
	IC2	Like IA or IB; capsular rupture prior to surgery or tumor cells on ovarian/tubal surface.
	IC3	Same as IA or IB; malignant cells in ascites or peritoneal lavage.
T2	II	Involvement of one or both ovaries/tubes, cytologically or histologically proven spread to the lesser pelvis or primary peritoneal carcinoma
T2a	IIA	Spread to uterus and / or ovaries / tube(s)
T2b	IIB	Spread to other intraperitoneal structures in the area of the small pelvis
T2c	IIC	As IIA or IIB; additionally malignant cells in ascites or peritoneal lavage.
T3 and / or N1	III	as II but with spread outside the pelvis and / or metastases in the retroperitoneal lymph nodes (LN)
T3a	IIIA	Retroperitoneal LN affected and / or microscopic metastases outside the pelvis.
T3 N1a / N1b	IIIA1	IIIA1(i) Only pos. retroperitoneal LN \leq 10 mm IIIA1(ii) Only pos. retroperitoneal LN > 10 mm
T3a, each N	IIIA2	Microscopic extrapelvic peritoneal tumor involvement \pm pos. retroperitoneal LN
T3b, each N	IIIB	Macroscopic extrapelvic peritoneal metastases (\leq 2 cm) \pm pos. retroperitoneal LN and extension to liver / spleen capsule
T3c, each N	IIIC	Extrapelvic peritoneal metastases (> 2 cm) \pm pos. retroperitoneal LN and extension to liver / spleen capsule
N0	-	No infestation of regional LN
N1	-	Infestation of regional LN
M1	IV	Distant metastases other than peritoneal metastases
M1a	IVA	Pleural effusion with pos. cytology
M1b	IVB	Liver and / or spleen metastases; metastases outside the peritoneal space (incl. inguinal LN and LN outside the abdominal space)

6 Treatment

The therapeutic strategy at first diagnosis is multimodal and consists of primary staging/debulking surgery followed, if indicated, by adjuvant chemotherapy and maintenance therapy. The extent of tumor reduction is crucial for therapeutic success and survival. In early stages, patient desire for future pregnancies should be taken into account (see Chapter 6.5.1). An algorithm for first-line therapy is shown in Figure 6.

Figure 6: Algorithm for primary treatment of ovarian cancer



Legend:

therapy with curative intent; therapy with non-curative intent

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; BRCA, Breast Cancer gene.

6.1 Surgery

Surgery is a prerequisite for optimal staging and stage-appropriate therapy. It should only be performed in certified gynecological cancer centers. The surgical therapeutic goal is complete macroscopic tumor clearance with maximum tumor cell reduction. If possible, it is also performed in advanced stages FIGO III and IV. Patients with incomplete intraoperative staging have poor progression-free and overall survival (PFS and OS) [24]. Therefore, in cases of incomplete staging, a second surgery with adequate staging should be evaluated at a certified gynecologic cancer center.

Surgery includes longitudinal laparotomy, inspection and palpation of the entire abdominal cavity, peritoneal cytology, biopsies from all abnormal sites, peritoneal biopsies from inconspicuous regions, adnexal extirpation bilaterally, hysterectomy, omentectomy (at least infracolic), appendectomy (for mucinous/unclear tumor type), bilateral pelvic and para-aortic lymphonodectomy, and, if necessary, multivisceral resection in advanced disease. Pelvic and para-aortic lymphonodectomy can be omitted for mucinous G1 ovarian cancer and borderline tumors with invasive implants because of the extremely low rate of lymph node metastases, as well as if there is macroscopic tumor clearance and clinically unremarkable lymph nodes. Fertility-preserving surgery is possible for unilateral stage FIGO I tumor with adequate staging, and for uni-

lateral borderline tumor, but is associated with an increased risk of recurrence. Hyperthermic intraperitoneal chemotherapy (HIPEC) should not be performed outside of controlled trials.

6.2 Systemic therapy

6.2.1 Adjuvant chemotherapy - systemic therapy at first diagnosis

In stage IA, G1, after complete tumor debulking and adequate staging or STIC alone, adjuvant chemotherapy is not indicated because of a lack of significant benefit. Patients with borderline tumor should also not receive adjuvant therapy due to lack of evidence [15].

In stage IA G2, IB G1/2, platinum-containing adjuvant chemotherapy can be offered after complete tumor debulking and adequate staging, and should be given in stage IC or IA/B and G3. Six cycles of tri-weekly platinum-containing chemotherapy, preferably with carboplatin AUC5, should be administered; alternatively, paclitaxel 175 mg/m² with carboplatin AUC5, although the benefit of combination therapy over monotherapy with carboplatin has not yet been shown [25- 27].

In the more advanced stages (II-IV), tri-weekly chemotherapy with paclitaxel 175mg/m² and carboplatin AUC5 for 6 cycles is standard for both high-grade and low-grade carcinomas despite their lower chemosensitivity (response rate at less than 25%) [28- 30].

For patients with comorbidities or reduced general condition, the weekly combination regimen of paclitaxel 60 mg/m² and carboplatin AUC2 may also be considered (see [Treatment regimens](#) (german Version only)). Monotherapy with tri-weekly carboplatin should not be performed as it is associated with poorer overall survival [31].

In stages III and IV, chemotherapy is followed by maintenance therapy with bevacizumab and/or a PARP inhibitor (see chapter 6.2.3) [15].

6.2.2 Neoadjuvant chemotherapy

In patients with high perioperative risk and low probability of achieving cytoreduction < 1 cm residual tumor, neoadjuvant chemotherapy followed by maximal cytoreductive surgery may be considered. To date, there is no evidence that neoadjuvant chemotherapy improves overall survival [32, 33]. The results of the AGO-TRUST trial should be awaited.

6.2.3 Maintenance therapy after systemic therapy at initial diagnosis

Maintenance therapy in stage III and IV with partial or complete remission after chemotherapy is standard of care. In low-grade carcinomas, bevacizumab is used; in high-grade carcinomas, depending on the BRCA/HRD status and the question of the feasibility of bevacizumab therapy, the options available today are monotherapy with either bevacizumab or one of the the PARP ["poly adenosine diphosphate-ribose polymerase"] inhibitors olaparib or niraparib or the combination therapy with olaparib (PARP inhibitor) and bevacizumab.

Bevacizumab: Bevacizumab is given concurrently to chemotherapy with carboplatin and paclitaxel and subsequently as maintenance therapy for a maximum of 15 months in stages FIGO IIIA1 and IIIB-IV according to the current FIGO classification (corresponding to stages IIIB, IIIC and IV according to the 2009 FIGO classification). It leads to a prolongation of PFS. Prolongation of OS was only observed in cases of high tumor burden, residual tumor, stage IV or high-grade serous subtype [34- 36].

PARP inhibitors: The PARP inhibitor olaparib can be used in BRCA1/2 mutation (germline and/or somatic), according to the SOLO1 study, and the PARP inhibitor niraparib independent of BRCA1/2 status and HRD status (PRIMA study). A significant prolongation of PFS was observed for both agents, and a benefit in OS was also demonstrated for olaparib, although not statistically significant [37- 39].

The combination of olaparib and bevacizumab can be used after completion of first-line platinum-containing chemotherapy in responding patients whose tumor has a positive HRD status, defined by BRCA1/2 mutation and/or increased genomic instability. In the PAOLA-1 trial, the combination was shown to achieve a benefit in PFS [40] and PFS2 over placebo + bevacizumab [41]. Whether the combination of olaparib with bevacizumab actually provides a survival benefit over olaparib alone cannot be assessed based on current study data.

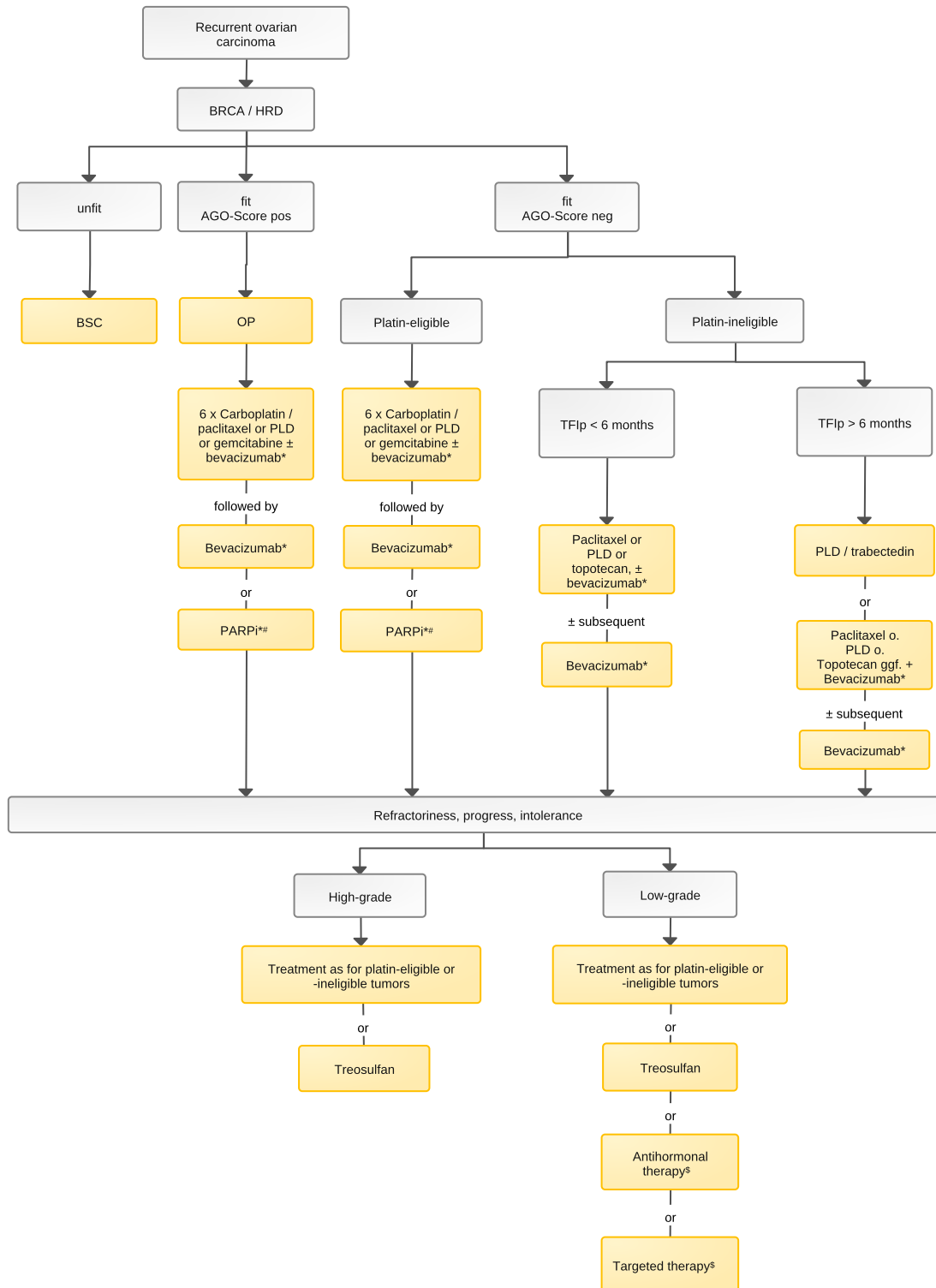
The value of endocrine maintenance therapy in the low-grade, hormone receptor-positive carcinomas has not been definitively evaluated (ongoing trials for anti-estrogenic therapy with aromatase inhibitors: MATAO/ENGOT-ov54/Swiss-GO2).

6.3 Treatment of relapse

Despite significantly improved results of primary treatment, the majority of patients with advanced ovarian cancer will relapse. Currently, there is no curative therapy for the treatment of recurrence. In addition to the achievement of remission, treatment is oriented in particular to the side effect profile and quality of life.

As the duration of the relapse-free interval increases, the probability of response to repeated platinum-based chemotherapy increases, although the rigid classification of relapses into platinum-sensitive (occurring > 6 months after the end of platinum-containing chemotherapy) and platinum-resistant (< 6 months after the end of platinum-containing chemotherapy) has been abandoned recently [42]. When deciding whether repeat platinum-containing therapy is an option, tumor biology and response to prior therapy, their number and tolerability, possible comorbidities, and patient preference should be considered in addition to the duration of the recurrence-free interval (platinum eligibility).

Figure 7: Therapy algorithm for recurrent ovarian cancer



Legend:

Therapy with non-curative intent

* note prior therapy and see [approval status](#) (German Version only)

Olaparib, niraparib, or rucaparib

\$ see [approval status](#) (German Version only)

TFlp, platinum-free interval; PARPi, PARP inhibitor

PLD, pegylated liposomal doxorubicin

6.3.1 Platinum-eligible recurrence

6.3.1.1 Surgery at relapse

In selected patients, secondary surgical cytoreduction may be considered in the first recurrence, before platinum-containing chemotherapy is repeated. With the help of the "AGO score", it can be estimated whether a new macroscopic complete resection can be achieved in the case of salvage surgery for platinum-eligible recurrence [43].

A positive AGO score is defined as the presence of all following three factors:

- Macroscopic complete resection during initial surgery
- Eastern Cooperative Oncology Group (ECOG) status = 0
- Ascites < 500ml.

The prospective randomized AGO-DESKTOP III trial demonstrated that median PFS and OS could be prolonged by secondary surgical cytoreduction in patients with a positive AGO score and a minimum of 6-month platinum-free interval. However, the OS survival benefit was observed only in the patients with complete resection, highlighting the importance of selecting the appropriate patients for salvage surgery and choosing an experienced center for such surgery [44].

6.3.1.2 Chemotherapy for platinum-eligible recurrence

In platinum-eligible patients, reinduction with platinum-containing combination therapy is usually performed (see [therapeutic regimens](#) (German Version only)) [42]. The combination of carboplatin and pegylated liposomal doxorubicin (PLD) is superior to the combination of carboplatin and gemcitabine in terms of PFS (therapy-free interval >6 months, AGO-OVAR-2.21 trial, see study results) [45].

By adding bevacizumab to chemotherapy followed by bevacizumab maintenance until progression, higher response rates and longer PFS can be achieved in the first relapse (OCEANS, GOG213) [46- 48]. An improvement in PFS was also observed when platinum-containing reinduction chemotherapy was also combined with bevacizumab in patients with platinum-sensitive relapse and bevacizumab pretreatment (MITO16B/MANGO-OV2b/ENGOT Ov-17, treatment beyond progression or rechallenge, see study results) [49]. However, no approval exists for this.

6.3.1.3 Maintenance therapy

If there is a response to platinum-containing relapse treatment, maintenance therapy with a PARP inhibitor should be started in high-grade ovarian cancer, if the patient is not receiving bevacizumab and has not previously been treated with a PARP inhibitor. In addition to a significant prolongation of the median PFS, disease control for many years may be achieved in a proportion of patients ("super-responders").

Olaparib (SOLO2 trial, study 19) [50, 51], niraparib (NOVA trial) [52], and rucaparib (ARIEL3) [53] are approved for maintenance therapy regardless of tumor BRCA status (see study results). Olaparib [54- 56] and niraparib [57] have now also been shown to achieve clinically relevant, although not statistically significant, OS prolongation (see Study Results). The greatest response was observed in the BRCA1/BRCA2 mutated cohorts (germline or somatic BRCA mutation).

However, the decision between PARP inhibitors should still take into account their specific side effect profile and patient preference.

There is currently no approval for re-treatment with PARP inhibitors after previous therapy with PARP inhibitors (rechallenge). So far, only preliminary data on olaparib from a prospective randomized phase III trial (OrEO-Trial/ENGOT-Ov38) are available. This had shown that particularly patients with a longer interval to the last PARP inhibitor therapy and adequate response to platinum-containing combination chemotherapy benefit from repeated maintenance therapy with olaparib, irrespective of the BRCA and HRD status of the tumor (see study results) [58].

6.3.2 Platinum-ineligible recurrence

6.3.2.1 Recurrence surgery

In contrast to platinum-eligible recurrence, no prospective data exist in this group showing prognostic improvement with repeat surgery.

6.3.2.2 Chemotherapy for platinum-ineligible recurrence

In refractory ovarian cancer, very short therapy-free interval, or contraindication to platinum-based recurrent therapy, monochemotherapy is the standard of care [42]. Combination therapies are not more effective. Excluded here are patients who cannot receive further platinum-based chemotherapy, but have a therapy-free interval >6 months. They can be offered a combination of PLD and trabectedin based on a subgroup analysis of the OVA-301 trial [59], showing an improved OS (22.4 months; 95% CI 19.4-25.1) compared to PLD alone (19.5 months; 95% CI 17.4-22.1).

Effective monotherapies are paclitaxel, topotecan, liposomal doxorubicin, or gemcitabine. In taxane-pretreated patients, topotecan and pegylated liposomal doxorubicin are equally effective. Treosulfan is inferior to topotecan or pegylated liposomal doxorubicin. Response rates range from 16.3% to 35% [42]. However, none of these agents has been compared with platinum in phase III trials.

Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin may prolong PFS and may be beneficial in cases of high remission pressure [60]. According to the approval, it can be used if no more than two chemotherapies and no therapy with a VEGF inhibitor or a VEGF receptor-targeting agent have been administered previously.

6.3.2.3 PARP inhibition

Monotherapy with the PARP inhibitors olaparib or rucaparib for patients with BRCA-mutated ovarian cancer is no longer recommended. The SOLO-3 trial demonstrated a statistically significant and clinically meaningful improvement in objective response rate (ORR) and progression-free survival (PFS) and PFS2 in platinum-naïve BRCA-mutated patients with a treatment-free interval greater than 6 months after two or more prior chemotherapies compared with chemotherapy, but no survival benefit [61, 62].

For rucaparib, the final analysis of overall survival within the ARIEL4 trial had shown that it was even less effective than chemotherapy in terms of overall survival (19.4 months with rucaparib compared with 25.4 months with chemotherapy) [17].

6.3.2.4 Endocrine therapy

60% of ovarian carcinomas express estrogen receptors, and 70% GnRH receptors. In patients who strictly decline chemotherapy or in whom this is no longer feasible due to toxicity, endocrine therapy can be considered despite - at least in the case of high-grade carcinomas - lower efficacy compared with monochemotherapy [63].

However, for the small group of low-grade ovarian cancers that are more resistant to standard platinum-based chemotherapy and have a recurrence rate of more than 70%, anti-hormonal therapy should be considered, although the data on this are insufficient to date.

Aromatase inhibitors are considered, followed by tamoxifen, although no substance has been approved for this indication. Objective response rates are in the range of 10% for all substances, with a further 20% of patients experiencing stabilization of the disease course [64]. GnRH analogues are currently not recommended in Germany. For the GnRH analogue leuprorelin, a phase III study is available that shows significant inferiority of leuprorelin compared to treosulfan in progression-free survival [65].

A retrospective study provides evidence that endocrine maintenance therapies in hormone receptor-positive low-grade carcinoma may have a beneficial effect on PFS [66].

Ongoing studies on the use of endocrine maintenance therapy must be awaited. Whether endocrine therapy in combination with a CDK4/6 inhibitor could be a future option in analogy to breast cancer also remains to be seen. Determination of estrogen receptor status prior to initiation of therapy is reasonable, as endocrine therapy is likely to be ineffective in receptor-negative tumors.

6.3.2.5 Targeted treatment options

Trametinib: A potential new option for relapsed low-grade serous ovarian cancer after at least one prior platinum-containing therapy is the MEK1/2 inhibitor trametinib. The phase II/ III GOG 281/LOGS trial showed that trametinib prolonged PFS in patients with relapsed LGSOC compared with standard therapy (13 months vs. 7.2 months) with an objective response rate of 26%. The benefit was independent of the presence of KRAS, BRAF, or NRAS mutations [67]. The value of trametinib, and when and in which combination trametinib should be administered, cannot be assessed at this time. Currently, the gain in PFS by using trametinib should be weighed against potential side effects, especially in patients with poor ECOG status. An approval for this indication does not exist.

Dabrafenib and trametinib: For BRAFV600E-mutated ovarian cancer, the selective BRAF inhibitor dabrafenib in combination with trametinib is an option (FDA approval June 2022 for unresectable or metastatic solid tumors with BRAFV600E mutation with progression after prior treatment and no alternative therapy) [68].

6.3.2.6 Checkpoint Inhibition

Tumors with a defect in DNA mismatch repair (dMMR or MSI^{high}) can be treated with the anti-PD1 antibody pembrolizumab starting in the second line, according to the Keynote-158 trial.

A dMMR can be attributed to germline variants in the Lynch syndrome-associated genes MLH1, MSH2, MSH6, and PMS2, a deletion of EPCAM, or MLH1 promoter methylation in the tumor, among others. The tumors are characterized by both increased tumor mutational burden (TMB) and high T-cell infiltration. The Keynote-158 study included a total of 351 patients, 25 of whom

had dMMR / MSI^{high} ovarian cancer. The overall response rate was 30.8% with a median response duration of 47.5 months, and the median overall survival was 20.1 months [69].

6.3.2.7 Radiotherapy for symptom control

Ovarian cancers are generally radiosensitive. In relapse, localized radiotherapy may not only improve symptom burden and quality of life, but may also lead to longer disease-free intervals [70- 72]. It should be noted that only data from smaller patient cohorts are available in this regard. Currently, radiation techniques such as intensity-modulated radiotherapy (IMRT) or stereotactic irradiation (STX) are used, which allow the required doses to be administered without higher-grade toxicity, even in radiation-sensitive regions. The indication is discussed individually for each patient on a multidisciplinary basis and is made after careful risk-benefit assessment. Whole-abdomen irradiation using IMRT should only be performed in the context of studies.

6.4 Systemic cancer treatment - substances*

*see [Treatment protocols](#) (German Version only)

6.4.1 Chemotherapeutics

- **Carboplatin:** Carboplatin is used for primary therapy and in platinum-eligible recurrence, primarily in combination with paclitaxel. Response rates in primary therapy depend on the subtype of ovarian cancer [28- 30]; in high-grade serous carcinoma, they are approximately 66% in combination with bevacizumab, and median PFS ranges from 15 to 20 months. Response rates for platinum-based relapse therapy range from 47% to 66%, with a median PFS around 10 months [42]. Common side effects include hematotoxicity, nausea, polyneuropathies, and nephrotoxicity. Allergic reactions are possible.
- **Gemcitabine:** Gemcitabine is primarily used in combination with carboplatin for relapsed ovarian cancer with a treatment-free interval of at least 6 months after first-line platinum-based therapy. Compared with carboplatin monotherapy, the combination with gemcitabine results in a significant improvement in PFS (median PFS 8.6 months in the combination arm, compared with 5.8 months in the carboplatin arm) with a response rate of 47% compared with 31% [73]. The combination showed comparable efficacy to the carboplatin/paclitaxel combination. Hematotoxicity is the primary side effect of gemcitabine.
- **Pegylated liposomal doxorubicin (PLD):** PLD can be used in combination with carboplatin in platinum-sensitive relapse and shows comparable efficacy to carboplatin/paclitaxel with a more favorable side effect profile (median PFS 11.3 months vs 9.4 months, median OS 30 vs 33 months) [74, 75]. Response rates of 20% are observed in platinum-naïve patients in relapse [76].
- **Paclitaxel:** Paclitaxel in combination with carboplatin is the standard of care in the primary treatment of ovarian cancer from FIGO stage IC. In relapse, it can also be used as monotherapy in a weekly regimen. Response rates with a platinum-free interval (TFIp) < 6 months range from 20.9% to 35%, and PFS is approximately 3.6 months [77, 78]. Polyneuropathy should be noted as a side effect that primarily affects quality of life.
- **Topotecan:** The topoisomerase I inhibitor topotecan is used as monotherapy for relapsed platinum-naïve ovarian cancer. The response rate is 17% and the median PFS is approximately 2 to 6 months. Standard of care is 5-day administration, every three weeks [79].
- **Trabectedin:** Trabectedin is a synthetic alkaloid that leads to p53-independent apoptosis via cell cycle disruption. It is used in combination with pegylated liposomal doxorubicin, due to synergistic effects, and is approved for platinum-sensitive ovarian cancer.

Response rates are around 28% and median PFS is approximately 8 months. The combination showed the best efficacy compared with trabectedin monotherapy in patients with a platinum-free interval > 6 months [59, 80]. However, the combination of PLD with trabectedin is not more effective than a combination of PLD with carboplatin with more overall higher-grade side effects [81]. However, the combination is an alternative for patients with a treatment-free interval > 6 months when platinum cannot be administered.

- **Treosulfan:** Treosulfan is an alkylating agent that can be used as monotherapy to treat relapsed ovarian cancer. The disease control rate is approximately 40%. According to a randomized phase III trial, intravenous administration is preferable to oral administration because of the lower rate of higher-grade leukopenia [82].

6.4.2 Targeted agents

- **Bevacizumab:** The VEGF antibody bevacizumab can be used in primary treatment as well as in relapse, in combination with chemotherapy and subsequently as maintenance therapy. While a significant benefit in prolongation of PFS has been observed in studies, a positive effect on overall survival in primary therapy seems to be restricted to high-risk groups (FIGO III and IV) [35, 36, 46, 47, 60, 83]. Since the patent period of the original antibody has expired, numerous generic products, so-called biosimilars, can now be used in analogy to the original antibody. Relevant side effects include intestinal perforation, fatigue, proteinuria, arterial hypertension, thromboembolism, and anaphylactic reactions.
- **Dabrafenib:** Dabrafenib is a selective BRAF inhibitor approved in combination with trametinib for BRAFV600E-mutated malignant melanoma. The FDA granted tumor-agnostic approval for pretreated BRAFV600E-mutated tumors in June 2022, based in part on the NCI-MATCH trial (subprotocol H). Dabrafenib in combination with trametinib resulted in a response rate of 38% and a PFS of 11.4 months in 29 patients with solid tumors, lymphoma, or multiple myeloma with progression after at least one standard therapy. Five of the six patients with ovarian cancer achieved partial remission, and one patient achieved disease stabilization [68]. The most common side effects include flu-like symptoms and gastrointestinal complaints, as well as headache, dizziness, hair loss, hyperglycemia, hypophosphatemia, and muscle and joint pain. In addition, benign (papillomas) and malignant tumors (basal cell carcinomas, squamous cell carcinomas) of the skin may occur, along with hyperkeratosis and exanthema.
- **PARP inhibitors:** PARP inhibitors inhibit poly(ADP-ribose)-polymerases (PARPs). They thereby block the repair of DNA single-strand breaks, which subsequently leads to an accumulation of double-strand breaks. These are usually repaired by homologous recombination. If homologous recombination deficiency is present, PARP inhibitors can lead to synthetic lethality in tumor cells due to the accumulation of DNA double-strand breaks. Homologous recombination deficiency occurs primarily in high-grade serous ovarian cancer (see chapter 5.3 Classification). PARP inhibitors are associated with a two- to threefold increased risk of acute myeloid leukemia and myelodysplastic syndrome, with an incidence of 0.73% (placebo group 0.47%) according to a meta-analysis [84].
 - **Olaparib:** Olaparib is approved in first-line therapy for BRCA1/2-positive ovarian cancer and in combination with bevacizumab for HRD-positive ovarian cancer. In recurrence, it can be used as maintenance therapy after response to repeat platinum therapy [50, 51]. For olaparib, the largest clinical and scientific experience is available to date in the field of PARP inhibitors. The most common grade 3/4 side effects of olaparib are anemia, neutropenia, fatigue, diarrhea, thrombocytopenia, and nausea.
 - **Niraparib:** Niraparib is approved for maintenance therapy in primary treatment [38, 39] and in relapse after a new response to platinum regardless of BRCA or HRD

status [52]. Toxicities observed with niraparib primarily include thrombocytopenia, anemia, neutropenia, and leukopenia, as well as hypertension and tachycardia. Early dose adjustment to 200 mg niraparib for patients with a baseline weight of ≤ 77 kg and/or a baseline platelet count of $\leq 150,000/\mu\text{L}$ should be considered to avoid significant hematologic toxicity, particularly thrombocytopenia [85]. Rarely, posterior reversible encephalopathy syndrome (PRES) may occur.

- **Rucaparib:** Rucaparib is approved for maintenance therapy in platinum-sensitive relapse after a new response to platinum regardless of BRCA or HRD status. The most common adverse reactions are fatigue/asthenia, nausea, abdominal discomfort, diarrhea, dysgeusia, elevated ALT and AST levels, anemia, thrombocytopenia, and elevated creatinine levels [53].
- **Trametinib:** Trametinib is an inhibitor of mitogen-activated extracellular signal-regulated kinases (MEK) 1 and 2 of the MAP kinase (mitogen-activated protein) pathway. Both enzymes are affected by activating mutations in low-grade serous carcinomas. Recently, trametinib has been shown to result in both improved objective response rate and PFS in low-grade serous carcinoma compared to standard chemotherapy or anti-hormonal therapy (see study results). The most common grade 3/4 adverse events with trametinib included rash (13%), anemia (13%), hypertension (12%), diarrhea (10%), nausea (9%), and fatigue (8%) [67]. Trametinib is not currently approved for the treatment of low-grade serous ovarian cancer.

6.4.3 Immunotherapy

Pembrolizumab: Pembrolizumab is one of the so-called checkpoint inhibitors and is a humanized monoclonal antibody that binds to the PD-1 (programmed cell death) receptor on active immune cells, especially T cells. This blocks an important immunological switch point (checkpoint), namely the interaction with its ligands PD-L1 (programmed cell death ligand) and PD-L2 on tumor cells and / or immune cells. As a result, the inhibition of immune cell activity that would otherwise occur is prevented, thus enhancing the immune response against the tumor. Pembrolizumab is already approved for numerous indications, including cross-entity in terms of a tumor-agnostic approach in dMMR / MSI^{high} tumors based on the Keynote-158 study [69]. In this specific regard, approval currently exists in Europe only for dMMR / MSI^{high} colorectal carcinomas, endometrial carcinomas, gastric/small bowel carcinomas and biliary carcinomas, but not for dMMR/MSI^{high} ovarian carcinomas. The most common immune-mediated side effects are pruritus, fatigue, and diarrhea.

6.4.4 Antihormonal therapy

- **Aromatase inhibitors:** Aromatase inhibitors such as letrozole, anastrozole, and exemestane are preferred in anti-hormonal therapy. They lower systemic estradiol levels in postmenopausal women by inhibiting the conversion of androgen precursors to estrogens in adipose tissue. A limited number of phase II studies have shown that they can lead to disease stabilization, and in some cases partial remission, in at least one-third of patients with endometrioid ovarian cancer without significant toxicities [86, 88].
- **Tamoxifen:** Tamoxifen acts via antagonism at the tumoral estrogen receptor. In principle, it is less effective than chemotherapy. It represents a treatment option for HR+ ovarian cancer with low chemosensitivity. The response rate in the different studies ranges from 0 to 56%. Stabilization of disease is observed in approximately one-third of patients [89, 90]. There is no approval for this indication. Tamoxifen is recommended after failure of aromatase inhibitors [16].

6.5 Special aspects

6.5.1 Treatment for childlessness

In stage IA G1 and stage IA G2 or IB (G1/ G2) and urgent desire to have children, the unaffected ovary can be left in place and chemotherapy for fertility preservation can be omitted [17].

6.5.2 Hormone replacement therapy after treatment of ovarian cancer

Women who have been treated for ovarian cancer may suffer from therapy-related estrogen deficiency with hot flashes, night sweats, urogenital atrophy, osteoporosis, and increased risk of cardiovascular disease, among other symptoms. Hormone replacement therapy (HRT) can relieve menopausal symptoms and also reduce the risk of osteoporosis and possibly cardiovascular risk. However, ovarian cancer is a hormone-dependent malignancy. The data on the use of HRT in premenopausal ovarian cancer survivors who have progressed to postmenopause due to therapy is very limited. At best, some studies provide evidence that HRT is oncologically safe [91]. Especially in women < 40 years of age and in patients with an early stage of the disease and a rather favorable prognosis, the therapy-related endocrine consequences must be carefully weighed against the potential risks of HRT.

7 Rehabilitation

Treatment of ovarian cancer by means of surgery and systemic therapy often leads to considerable side and late effects. The main focus here is on post-therapeutic fatigue, lymphedema and chemotherapy-induced peripheral polyneuropathy including impairment of deep sensitivity, which may not only impair physical activity and quality of life, but may also lead to inability to work and thus to financial losses and social isolation. As a result of these side effects and, of course, the oncological diagnosis itself, there is also a high psychological burden. Thus, not only somatic and occupational rehabilitation, but also psychosocial rehabilitation is of great importance. Targeted rehabilitation measures should be initiated as soon as possible after completion of primary therapy [17]. In addition to general measures such as exercise and occupational therapy as well as decongestive therapy, manual lymphatic drainage and skin care for the treatment of lymphedema, cognitive behavioral therapy, psycho-oncological co-treatment and psychosocial care should also be offered. Rehabilitation facilities should be able to continue ongoing maintenance therapy, if indicated. Patients who have not yet reached the statutory retirement age should be informed about services for participation in working life within the framework of medical-occupational rehabilitation (MBOR).

8 Follow-up

Although the value of structured follow-up for early relapse detection and improvement of prognosis has not yet been proven, a structured follow-up program follows the initial treatment (see Table 5) [17]. The aim is, on the one hand, to detect and treat therapy-associated long-term toxicities and thus contribute to an improvement in the quality of life, and on the other hand, to detect recurrence or progression of the disease. Clinical follow-up examinations is carried out quarterly during the first 3 years and semi-annually during the 4th to 5th year. Finally, after 5 years, examinations are performed semi-annually to annually as part of so-called survivorship programs for long-term survivors. They should be continued throughout life, as both somatic sequelae and psychological stress due to side effects or fear of recurrence play a major role in long-term survivors. Follow-up examinations include a medical history with questions about disease-specific symptoms and therapy-associated side effects such as polyneuropathy or symptoms due to hormone deficiency, as well as a gynecological examination, including rectal exam-

ination and vaginal sonography. Other imaging procedures are only indicated if there is a suspicion of progression or recurrence based on symptoms or findings. Similarly, routine tumor marker testing should not be performed in the absence of symptoms, as it has not been proven that initiation of relapse treatment prior to symptomatic recurrence/progress leads to improved survival.

Patients with genetically associated ovarian, tubal, or peritoneal carcinoma (BRCA1/2 mutation carriers, Lynch syndrome) should also participate in the appropriate screening programs for early detection of other genetic tumor diseases in parallel with follow-up.

Table 5: Follow-up schedule according to the AWMF S3 guideline ovarian cancer (2021) [17]

	Follow-up after completion of therapy		Follow-up after relapse therapy	"Survivorship program" after 5 years	Additionally: therapy monitoring for maintenance therapies
	1st to 3rd year	4th to 5th year			
Medical history	Every 3 months	Every 6 months	Every 3 months	Semiannual to annual	Every 3 months
General physical examination	Every 3 months	Every 6 months	Every 3 months	Semiannual to annual	Every 3 months
Gynecological examination	Every 3 months	Every 6 months	Every 3 months	Semiannual to annual	Every 3 months
Vaginal sonography	Every 3 months	Every 6 months	Every 3 months	Semiannual to annual	Every 3 months
Orienting abdominal sonography	Every 3 months	Every 6 months	Every 3 months and in the case of symptoms or suspected recurrence	Semiannual to annual	Every 3 months
CT/MRI, if required PET-CT or PET-MRI	Suspected recurrence		In case of suspected recurrence	In the event of symptoms or suspected recurrence	Every 3-6 months, in case of symptoms or if recurrence/progression is suspected
Tumor marker	No routine use		In case of symptoms	If clinically indicated	Every 3 months
Laboratory	For clinical indication		In case of symptoms	If clinically indicated	According to recommendations of the specific maintenance therapy
Breast diagnostics*	Biennial		Biennial	Biennial	Biennial

Legend:

**Breast diagnostics: In the case of breast carcinoma, according to the AGO guideline Breast carcinoma; in the case of genetic burden, according to the recommendations in the AGO guideline Breast carcinoma. In the absence of a risk burden, general recommendations for preventive care/screening with regard to breast diagnostics, an individual and critical risk-benefit assessment must be discussed with the patient.*

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16 Disclosures

according to the rules of the responsible Medical Societies.