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Recommendation of the Polish Society of Oncological Gynaecology on the diagnosis and treatment of epithelial ovarian cancer

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ABSTRACT

The Recommendations of the Polish Society of Oncological Gynaecology offers evidence-based advice on the care and treatment of women with ovarian cancer and low malignant potential/borderline tumour.

Key words: ovarian epithelial cancer, low malignant potential/borderline tumour, cytoreductive surgery, first-line chemotherapy, follow-up

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Aetiology [1]

Over 95% of malignant tumours of the ovary are of epithelial origin. The most important risk factors for the development of ovarian cancer include the following:

- carriage of mutation of *BRCA1* and *BRCA2* genes (concerns up to 13% of all ovarian cancer cases);
- syndromes of hereditary cancer of breast and ovary;
- familial occurrence of hereditary non-polyposis colon cancer (Lynch syndrome — early non-polyposis colorectal cancer, endometrial cancer, proximal digestive tract cancer, urothelial cancer of the urethra);

- childlessness, long-lasting stimulation of ovulation, ineffective attempts at in vitro fertilisation (IVF).

Hormonal contraceptive drugs, oviducts' occlusion, bilateral salpingo-oophorectomy, hysterectomy and breastfeeding decrease the risk of ovarian cancer development.

Screening [2]

Currently there are no unavailable screening tests detecting ovarian cancer, also in patients dur-

ing follow-up due to known mutation of *BRCA* genes [3]. Detection of an ovarian cancer at an early stage still occurs in a relatively small proportion of women (20–30%). In the remaining patients (nearly 70%), the disease is detected at higher clinical stages (III and IV).

Prevention

Due to considerable risk of development of ovarian cancer in carriers of mutation of *BRCA1* and *BRCA2* genes, bilateral adnexectomy after termination of procreative activity is currently recommended [4]. According to recently published reports suggesting that the majority of ovarian cancers derive from fimbriae of the oviduct, preventive oophorectomy should be also considered in women at low risk after meeting maternal goals and after menopause, who have undergone non-oncological surgical procedures [5, 6].

Diagnostic studies

While there are no clinical signs typical for ovarian cancer, most patients complain of non-specific dyspeptic ailments approximately one year prior to diagnosis of the tumour [7]. In early clinical stages (25–30% of cases) there may be a palpable adnexal tumour present. Patients with late stage disease (about 70% of the cases), apart from uni- or bilateral adnexal tumour, may present with ascites and/or hydrothorax and elevated CA-125 antigen levels. Some patients may have normal or only slightly enlarged ovaries in spite of cancer spread within the abdominal cavity.

In all cases of ovarian cancer we recommend calculating the risk of malignancy index (RMI) (Appendix 1) and the ROMA (Risk of Ovarian Malignancy Algorithm) test is indicated.

In case of RMI > 200 points or when the value of the ROMA test suggests that patients belong to a high-risk group it is recommended to refer the patients to a specialised centre with experience in ovarian cancer treatment [1, 8].

Diagnosis

Diagnosis of ovarian cancer relies on histological examination of tissue specimens obtained during the primary surgical procedure. In exceptional cases, diagnosis is possible based on analysis of peritoneal or pleural fluid obtained by biopsy, lymph nodes, or a metastasis to the liver.

In each case, the following should be determined:

- histological type;
- histological differentiation grade (G1, G2, or G3).

At present, subdividing the most common serous type of ovarian cancer into high grade and low grade seems to be justified [9].

Assessment of the incidence of gene mutations predisposing to higher risk of ovarian cancer

Due to their high importance both in the prevention and treatment of ovarian cancer, genetic consultation and assessment of the mutation carriage of *BRCA1* and *BRCA2* genes should be performed in all patients with this type of cancer. Detection of mutated status has a prognostic as well as predictive value and also indicates the high risk of breast cancer. It allows encompassing healthy female carriers in the patient's family in appropriate healthcare and activities decreasing the risk of breast cancer and ovarian cancer development [10].

Staging of the tumour

The clinical stage of a tumour of the ovary is determined in surgical-pathomorphological grades (it concerns epithelial and non-epithelial tumours). The current FIGO (*Fédération internationale de gynécologie et d'obstétrique*) classification of ovarian cancer was introduced in 2014 [11] (Appendix 2).

Treatment

The cornerstone of primary treatment of newly diagnosed ovarian cancer is combined management including surgical treatment and chemotherapy.

Surgical treatment

The aim of primary surgical treatment:

- confirmation of ovarian cancer diagnosis;
- determination of clinical stage;
- total, alternatively optimal, cytoreduction of the tumour.

The scope of primary cytoreductive procedure and adjuvant therapy depends mainly on the clinical stage of the tumour.

Cancer macroscopically limited to the genital tract

After inspection of the abdominal cavity excluding gross extrapelvic lesions, surgical treatment includes:

- obtaining fluid and lavage fluid for cytological study (before initiating of surgical procedures);
- bilateral salpingo-oophorectomy;
- radical hysterectomy;
- excision of the greater omentum;
- obtaining smears and random tissue samples from the peritoneum;

Table 1. Type of peritonectomy and the scope of resection during cytoreductive therapy of ovarian cancer

Type of peritonectomy	Scope of resection
Pelvic peritonectomy	Uterus, ovaries, sigmoid colon
Left upper quadrant peritonectomy	Greater omentum and spleen
Right upper quadrant peritonectomy	Tumour infiltrating Glisson's capsule of the liver
Anterior parietal peritonectomy	Old abdominal scars, umbilicus and epigastric fatty tissue
Omental bursectomy	Gall bladder, lesser omentum

- pelvic and aortal lymphadenectomy;
- appendectomy — mandatory in cases of mucous histology [12].

In young women who wish to preserve fertility, with cancer lesion limited to one ovary, without capsular infiltration or peritoneal adhesions, an acceptable option is to spare the uterus and contralateral ovary [13, 14].

Other cases of ovarian cancer

The primary aim of surgery is total cytoreduction, e.g. lack of gross residual tumour in the abdominal cavity. All visible lesions should be removed (Table 1). In case of a lack of the possibility to meet this goal, optimal cytoreduction should be achieved (with residual lesions of diameter < 1 cm). If such a solution is also not feasible, the scope of the operation should be limited to excision of the affected omentum, or big adnexal masses, in order to reduce perioperative complication and introduce chemotherapy as soon as possible. Suboptimal procedures significantly shorten the time to progression and overall survival time [15]. The patients with poor prognosis of at least optimal cytoreduction due to disease burden should be identified. They are candidates for neoadjuvant chemotherapy.

Excision of enlarged retroperitoneal lymph nodes is an additional part of the cytoreductive procedure.

The main reason that makes complete cytoreduction impossible is infiltration of the mesentery and lesions in the hepatic hilus. Mutilating procedures, e.g. total colectomy, should be avoided because they may reduce the patient's chances for further chemotherapy.

Validity of systemic pelvic and periaortic lymphadenectomy of normal-appearing lymph nodes in the case of residual tumour left in the abdominal cavity is currently questioned. On the other hand, the rationale for systemic pelvic and periaortic lymphadenectomy of normal-appearing lymph nodes in the case of lack of residual tumour in the abdominal cavity is currently a subject of the prospective clinical trial AGO – LION.

Conducting procedures determining the clinical stage (obtaining the fluid, biopsy of peritoneum, smears) during cytoreductive operations of advanced ovarian cancer is unfounded.

Delayed surgery

If complete cytoreduction is impossible, in some patients a delayed surgery (*interval debulking surgery*, IDS; *interval cytoreductive surgery*) should be considered after three cycles of chemotherapy, followed by continued chemotherapy (up to a total number of scheduled cycles). Such a protocol is recommended in the case of a favourable therapeutic response after chemotherapy [16].

Secondary cytoreductive surgery

Effectiveness of secondary cytoreductive surgery performed after completion of first-line chemotherapy in the case of cancer progression has not been confirmed in randomised clinical trials, and available data come from individual non-randomised studies [17].

Second-look operation

An operation performed to verify therapeutic response (second-look operation) does not affect prolongation of survival time and is currently not recommended in clinical practice.

Chemotherapy

Most patients with ovarian cancer are candidates for systemic chemotherapy. Desisting from postoperative chemotherapy is possible only in a small group of patients of stage IA or IB (according to FIGO) G1, G2 (good prognosis group) after complete surgical determination of the clinical stage (full scope of surgery with pelvic and periaortic lymphadenectomy). In other patients with stage I disease the cornerstone of first-line treatment is a combination of platinum (carboplatin or cisplatin) and taxoid (paclitaxel) administered intravenously in 21-day cycles. The whole treatment should consist of 3 to 6 cycles. Both mentioned chemotherapy schedules offer an identical efficacy. However, carboplatin is better tolerated and more convenient to use. Use of paclitaxel requires premedication with steroids, H2-receptor blockers, and antihistamines. In patients with late stage ovarian cancer (IIB–IV according to FIGO) standard postoperative chemotherapy usually consists of six cycles.

Table 2. Options of first-line chemotherapy in cancer of the ovary, depending on the clinical stage of the disease

FIGO stage	Chemotherapy protocol
I A/B G1	Follow-up*
I A/B G2 and G3/C	Paclitaxel at a dose of 175 mg/m ² IV (3-hours' infusion) on day 1 + carboplatin AUC 5–7 IV (1-hour' infusion) on day 1, every 21 days, 3–6 cycles [18, 24]
II–IV standard	Paclitaxel at a dose of 175 mg/m ² IV (3-hours' infusion) on day 1 + carboplatin AUC 5–7.5 IV (1-hour' infusion) on day 1, every 21 days, 6 cycles [18]
II–IV alternatives	Paclitaxel at a dose of 135 mg/m ² IV (24-hours' infusion) on day 1 + cisplatin at a dose of 75 mg/m ² IV on day 2 [19] or Paclitaxel at a dose of 80 mg/m ² IV (1-hour' infusion) on days 1, 8 and 15 + carboplatin AUC 6 IV (1-hour' infusion) on day 1, every 21 days, 6 cycles [21] or Paclitaxel at a dose of 60 mg/m ² IV (1-hour' infusion) + carboplatin AUC 2 IV (30-min' infusion) every 7 days, 18 cycles [22] or Docetaxel at a dose of 60–75 mg/m ² IV (1-hour' infusion) on day 1 + carboplatin IV AUC 5–6 (1-hour' infusion) on day 1, every 21 days, 6 cycles [23]
II–IV with residual tumour < 1 cm	Paclitaxel at a dose of 135 mg/m ² IV (24-hours' infusion) on day 1 + cisplatin at a dose of 75–100 mg/m ² IP on day 2 + paclitaxel at a dose of 60 mg/m ² IP on day 8, every 21 days, 6 cycles [20]
III–IV with residual tumour > 1 cm	Paclitaxel at a dose of 175 mg/m ² IV (3-hours' infusion) on day 1 + carboplatin AUC 5–7.5 IV (1-hour' infusion) on day 1, every 21 days + bevacizumab at a dose of 7.5 mg/kg body weight every 21 days starting on days 1 or 2 of chemotherapy (up to 18 applications)** [22]

*Possible only in cases of correctly performed surgical staging; clear-cell type is considered G3.

**Polish program of therapy with bevacizumab requires indicating the size of gross residual disease in the operation's protocol and performing computed tomography after the operation, in order to qualify the patients to the treatment.

Standard protocol includes paclitaxel at a dose of 175 mg/m² in a three-hour infusion and carboplatin at a dose according to AUC 6 (range 5–7) in a 30-minute infusion [18]. When using a cisplatin-based protocol, the treatment cycle is longer due to a 24-hours long administration of paclitaxel and necessary hydration before and after administration of cisplatin on the next day [19].

In the group of patients at stage II–IV with residual tumour with diameter of less than 1 cm after cytoreduction, the therapy of choice is intraperitoneal administration of chemotherapy combined with systemic treatment [20]. Paclitaxel-based chemotherapy administered every seven days at a dose of 80 mg/m² is an alternative to treatment every 21 days. During this schedule the risk of haematological toxicities is high and a significant percentage of patients (37%) require use of colony stimulating factors (CSFs) [21]. Based on the results of a phase III study MITO-7 it can be stated that a combination of paclitaxel (60 mg/m²) and carboplatin at a dose AUC 2 administered weekly showed lower toxicity with comparable effectiveness, and it seems to be worth considering in older patients or in those with poorer performance status [22].

In the group of patients at stage III with residual tumour of over 1 cm, in patients at stage IV, and not

operated the treatment with bevacizumab at a dose of 7.5 mg/kg combined with standard chemotherapy (paclitaxel 175 mg/m² and carboplatin AUC 5–7.5) with subsequent maintenance treatment (bevacizumab alone) up to a total of 18 applications significantly prolongs progression-free survival (PFS) and overall survival (OS). Currently in Poland this treatment is part of the therapeutic drug program (Table 2).

Development of hypersensitivity reactions to paclitaxel is an indication to consider its replacement with docetaxel [23].

Neoadjuvant chemotherapy

When primary cytoreduction in patients at FIGO stages III and IV is impossible, a reasonable option is to use an initial, neoadjuvant chemotherapy according to standard paclitaxel- and carboplatin-based protocol. Patients eligible for this treatment have histologically or cytologically confirmed ovarian cancer, adnexal tumour, and a CA-125/CEA ratio of 25:1 (20% of patients with clinical signs of ovarian cancer may harbour another tumour, e.g. gastrointestinal or breast cancer). The results obtained are similar to those seen in the group undergoing primary non-optimal cytoreduction, while perioperative mortality is significantly lower. After three

courses, performance of an IDC should be considered. Use of neoadjuvant chemotherapy in other clinical settings is hardly justified [25, 26].

Consolidation treatment

Systemic consolidation treatment in patients with complete remission after first-line chemotherapy, despite its proven efficacy [27], has not become everyday clinical practice.

Assessment of treatment outcome

Treatment outcomes should be evaluated four weeks after completion of first-line chemotherapy. For this purpose, the following studies should be done:

- medical history and physical examination;
- gynaecological vaginal and rectal examination, including vaginal specula;
- transvaginal and abdominal sonography;
- basic laboratory tests of blood and urine;
- assessment of serum level of antigens monitored during treatment;
- chest X-ray or CT-scan;
- pelvic and abdominal CT-scan.

Outcome assessment by imaging studies should be based on RECIST 1.1 criteria (Appendix 3).

Follow-up

Patients obtaining complete clinical remission should undergo systematic control. Follow-up exams should be performed every three months for two years after completion of treatment, then every six months for five years after completion of treatment, and then every 12 months. Follow-up examination should include medical history and clinical examination.

Routine assessment of CA-125 during follow-up should be discussed with the patient. Resumption of treatment solely based on clinical symptoms does not worsen final outcome in terms of overall survival [28]. Implementation of second-line chemotherapy based solely on elevated CA-125 is not justified; it does not improve survival but considerably compromises its quality.

Imaging studies are obtained only in the case of suspected recurrence.

Treatment of recurrence

Considering current state-of-the-art of surgery and chemotherapy, cancer of the ovary becomes a chronic disease for most patients. Time from diagnosis to recurrence is now shorter than time from recurrence to death.

For most ovarian cancer patients, the disease constitutes a continuum of alternating episodes of recurrence interspaced with increasingly short symptom-free periods, ending in a phase of lack of response to cytostatics.

Incurability of major cases of tumour recurrence results in a modification of treatment strategy. In such cases the treatment goals are as follows:

- alleviation of symptoms;
- improvement of quality of life;
- delay of symptomatic tumour progression;
- prolongation of survival.

Objective therapeutic response is not the primary goal. The main modality in the treatment of recurrence of ovarian cancer is palliative chemotherapy, but in selected cases a resective surgery should be considered, which may affect significantly the survival time in about 10% of patients [29].

Surgical treatment of recurrence

A significant impact on prolongation of survival is seen only in procedures resulting in total gross cytoreduction. Proper selection of patients is paramount. The results of many studies indicate that surgical treatment of recurrence is justified if primary surgery led to complete resection, recurrence occurred more than 12 months after completion of first-line chemotherapy, there is no ascites, and the recurrent lesion is potentially completely resectable, most often defined as isolated. There are three available recommendations for selection of patients (Appendix 4).

Use of AGO score [30] enables selection of patients where total cytoreduction will be obtained in 2 out of 3 cases. AGO score includes:

- good performance status (grade 0 in Eastern Cooperative Oncology Group scale);
- total resection during primary surgery;
- no fluid in abdominal cavity.

Chemotherapy of recurrence

Selection of second-line chemotherapy protocol is based on sensitivity to platinum derivatives, which defines prognosis. The effect of first-line treatment and time elapsing since completion of first-line treatment define the categories of patients [31]:

- platinum non-sensitive — tumour progression during first-line treatment (5.3% of patients);
- platinum resistant — recurrence within six months after completion of first-line treatment (17.2% of patients);
- partly platinum sensitive — recurrence within 6–12 months after completion of first-line treatment (22.7% patients);
- platinum sensitive — recurrence after more than 12 months since completion of first-line treatment (33.5% of patients) [32].

Table 3. Second-line chemotherapy depending on type of response to platinum

Response to platinum derivatives	Chemotherapy
Primary non-sensitive (refractory)	Inclusion in clinical trials or monotherapy:
Platinum-resistant (resistance)	liposomal doxorubicin [33]
	topotecan [34]
	gemcitabine [35, 36]
	paclitaxel every 7 days [37]
	liposomal doxorubicin or topotecan, or paclitaxel every 7 days + bevacizumab [38]
Partly platinum-sensitive	Paclitaxel + carboplatin/cisplatin [39]
Platinum-sensitive	Gemcitabine + carboplatin/cisplatin [40]
	Carboplatin + liposomal doxorubicin [41]
	Gemcitabine + carboplatin + bevacizumab [42]
	Carboplatin in monotherapy

In 3.7% of patients recurrence develops between 60 and 120 months after completion of first-line treatment.

The prognosis in patients resistant to platinum derivatives is poor. The rate of response to second-line chemotherapy usually does not exceed 10–15%, and the mean time to progression is about three months. In this group, no clinical benefit of multi-agent chemotherapy compare to single-agent regimens could be demonstrated (Table 3). A combination of cytostatics with bevacizumab significantly improved PFS (which is as twice as long as in the group not receiving bevacizumab). Treatment should be offered to selected patients only, in good performance status, without significant persistent complications, and motivated for treatment.

Treatment of platinum-sensitive recurrence, re-induction using platinum-based multi-agent protocols (selection of protocol should take into account expected toxicity of treatment) is more effective than platinum in monotherapy. Response rate increases proportionally to PFS and ranges from 29 to 70%.

Treatment of recurrence (both platinum-sensitive and platinum-resistant), addition of bevacizumab to chemotherapy, and subsequent administration of this agent in monotherapy until disease progression prolongs PFS. No prolongation of overall survival has been observed.

In the case of achieving an objective response (partial or complete) in patients with low-grade serous subtype of ovarian cancer with mutations of *BRCA1* and *BRCE2* genes (germinal and/or somatic) after treatment of platinum-sensitive recurrence with platinum derivatives using olaparib during maintenance therapy should be considered, which significantly prolongs time to progression. The effect of olaparib on overall survival is yet to be published [10, 43].

Response to second-line and subsequent lines of chemotherapy should be monitored using CA-125 biomarker and imaging studies. Lack of response to two

lines of treatment should result in interruption of chemotherapy.

Palliative procedures are performed most often in the setting of ileus. In some patients they result in transient alleviation of symptoms. The impact of such procedures on prolongation of survival is limited.

Radiotherapy

Use of radiotherapy is limited to the treatment of focal lesions (brain and bone metastases).

Borderline tumours

In 1971 (FIGO) and in 1973 (World Health Organisation, WHO) a group of cancers of the ovary were selected and defined as low malignant potential/borderline tumours. These tumours account for about 15% of epithelial cancers of the ovary and in 60–90% are unilateral only. Nearly two thirds of borderline ovarian tumours are of serous histology and the remaining are mucinous.

A characteristic feature of borderline tumours, particularly serous and mucinous of the cervical type, is the coexistence of implants in peritoneum and omentum, which may be noninvasive (90%) or invasive (10%).

Borderline tumours of the ovary usually develop in women of reproductive age; the mean age at diagnosis is 38–45 years.

Basic diagnostic criterion for borderline tumours is lack of destructive stromal invasion (according to the WHO) [44].

Clinical staging

This is done according the same FIGO classification criteria as those pertaining to ovarian cancer.

Treatment of borderline tumours

The cornerstone of treatment of borderline ovarian tumours is surgery.

Early clinical stages (I and II)

When the patient wants to preserve fertility (age under 40 years):

- at stage IA, scope of surgery includes: oophorectomy, detailed inspection of the pelvis and abdominal cavity, peritoneal lavage, and biopsy of the other ovary if grossly abnormal. Mucinous type requires appendectomy and excision of the entire ovary and not just enucleation of the tumour because this histology type is more frequently connected with recurrence. Intraoperative study may be unreliable (no entire tumour capsule is available for study). At stage IB, when tumours are present in both ovaries, unilateral enucleation of tumour is justified (considered as better delimited). Some authors accept enucleation of both tumours [45, 46].

When the patient does not want to preserve fertility:

- stages I and II: recommended total hysterectomy with oophorosalingectomy, omentectomy, and staging of the disease. Only enlarged lymph nodes should be excised. There is no proven improvement after systemic lymphadenectomy;
- stages III and IV: surgical treatment is recommended, aiming at total cytoreduction.

Chemotherapy of borderline tumours

Adjuvant platinum-based chemotherapy is not currently recommended in patients after operation of borderline tumours with detected invasive implants, because the results of reports published to date show no significant decrease in the recurrence risk or mortality after such a treatment [47].

Postoperative chemotherapy does not prolong survival and is not recommended [48].

Follow-up

Similarly to invasive cancers, patients should be monitored. This is particularly important in patients undergoing sparing surgery. There are no data justifying excision of spared ovary and uterus after giving birth to a planned number of children.

Recurrences of borderline tumours

They are a rare phenomenon and occur in about 7.8% of the patients. In approximately 30% of patients recurrent borderline tumours transform into ovarian

cancer. The recurrences are significantly more frequent in the following cases:

- presence of residual tumour after primary surgery;
- presence of invasive implants;
- sparing procedure;
- inadequate determination of clinical stage [47].

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APPENDIX 1
RMI (risk of malignancy index)

$$\text{RMI} = \text{U} \times \text{M} \times \text{CA-125}$$

Feature	Description	Score of the feature
CA-125 level	Serum concentration	Value in U/ml
USG index	Receives 1 point for each of the feature of ovarian tumour: — multilocular cyst — solid components — presence of implants/metastases — pelvis fluid — bilateral ovarian lesions	U = 0 (when score value of USG index is 0) U = 1 (when score value of USG index is 1) U = 3 (for all higher values, e.g. 2–5)
Menopausal state	Definition of menopause: amenorrhea since ≥ 1 year or patients after hysterectomy and at the age of more than 50 years	M = 1 point, if patient is before menopause, or M = 3 points, if patient is after menopause

Ultrasonography index "U" is calculated adding points for features (1 point for each).

Parameter "U" could have the value:

U = 0 (number of points: 0);

U = 1 (number of points: 1);

or U = 3 (number of points: 2–5)

Patients are considered to be after menopause if they had no menorrhoea for more than 1 year or are women who are more than 50 years old and have undergone hysterectomy.

APPENDIX 2
Cancer of ovary, fallopian tube and peritoneum: current staging according to FIGO classification (version 2014); stage I

FIGO classification, version 1988	FIGO classification, version 2014 (*)
Stage I: Tumour limited to ovary	Stage I: Tumour limited to ovary or fallopian tube
IA Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings/ascites	IA Tumour limited to 1 ovary or fallopian tube, capsule intact, no tumour on surface of ovary or fallopian tube, negative washings/ascites
IB Tumour involves both ovaries, capsule intact, no tumour on surface, negative washings/ascites	IB Tumour involves both ovaries or fallopian tubes, capsule intact, no tumour on surface of ovary or fallopian tube, negative washings/ascites
IC Tumour involves 1 or both ovaries with any of the following: capsule rupture, tumour on surface, positive washings/ascites	IC Tumour limited to 1 or both ovaries or both fallopian tubes with: <i>IC1 Surgical spill</i> <i>IC2 Capsule rupture before surgery or tumour on ovarian or fallopian tube surface</i> <i>IC3 Malignant cells in the ascites or peritoneal washings</i>

*Changes marked with italics

Cancer of ovary, fallopian tube, and peritoneum: current staging according to FIGO classification (version 2014); stage II

FIGO classification, version 1988		FIGO classification, version 2014 (*)	
Stage II: Tumour involves 1 or both ovaries with pelvic extension		Stage II: Tumour involves 1 or both ovaries <i>or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer</i>	
IIA	Extension and/or implant on uterus and/or fallopian tube/tubes, negative washings/ascites	IIA	Extension and/or implant on uterus and/or fallopian tube/tubes
IIB	Extension to other pelvic intraperitoneal tissues, negative washings/ascites	IIB	Extension to other pelvic intraperitoneal tissues
IIC	Extension to other pelvic intraperitoneal tissues (IIA or IIB) with positive washings/ascites		

*Changes marked with italics

Cancer of ovary, fallopian tube, and peritoneum: current staging according to FIGO classification (version 2014); stage III

FIGO classification, version 1988		FIGO classification, version 2014 (*)	
Stage III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the regional lymph nodes		Stage III: Tumour involves 1 or both ovaries <i>or fallopian tube/tubes, or primary peritoneal cancer with spread to the peritoneum outside the pelvis and/or metastasis to the regional retroperitoneal lymph nodes</i>	
IIIA	Microscopic metastasis to the peritoneum beyond the pelvis	IIIA1	<i>Cancer metastases only to the retroperitoneal lymph nodes (cytologically or histologically confirmed)</i>
		IIIA1(i)	<i>Metastases with the greatest size ≤ 10 mm</i>
		IIIA1(ii)	<i>Metastases with the greatest size > 10 mm</i>
		IIIA2	<i>Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes</i>
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in greatest dimension	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± <i>positive retroperitoneal lymph nodes</i> , including extension to capsule of liver/spleen (with no lesions in parenchyma)
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis	IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± <i>positive retroperitoneal lymph nodes</i> , including extension to capsule of liver/spleen (with no lesions in parenchyma)

*Changes marked with italics

Cancer of ovary, fallopian tube, and peritoneum: current staging according to FIGO classification (version 2014); stage IV

FIGO classification, version 1988		FIGO classification, version 2014 (*)	
Stage IV: Distant metastasis (excluding peritoneal metastasis)		Stage IV: Distant metastasis (excluding peritoneal metastasis)	
IV	Distant metastasis (excluding peritoneal metastasis)	IVA	<i>Pleural effusion with positive cytology</i>
		IVB	<i>Hepatic and/or splenic parenchymal metastases, metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)</i>

*Changes marked with italics

APPENDIX 3**RECIST criteria 1.1**

Patients' status is qualified as:

- Complete Response (CR): disappearance of all target lesions. Shrinkage of any pathological lymph nodes (whether target or non-target) in short axis to < 10 mm (RECIST 1.1). Parallel biochemical normalization
- Partial Response (PR): shrinkage of at least a 30% of tumour or the sum of diameters of target lesion, taking as reference the baseline sum diameters
- Stable Disease (SD): neither shrinkage of less than 30% of tumour or the sum of diameters of target lesions or increase of less than 20% of tumour or the sum of diameters of target lesion
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study (absolute increase of at least 5 mm) and/or appearance of one or more new lesions

APPENDIX 4**Recommendations concerning second-line cytoreduction surgery****A. Recommendations of Norwegian Radium Hospital [29]**

Disease-free survival (months)	Localised disease	Disseminated disease
0–5	Consider	Do not perform
6–11	Suggest	Do not perform
12–23	Suggest	Do not perform
> 24	Suggest	Consider

B. Memorial Sloan-Kettering Cancer Centre [48]

Disease-free survival (months)	Localised disease	Disseminated disease	Peritoneal cancer spread
6–12	Suggest	Consider	Do not perform
12–30	Suggest	Suggest	Consider
> 30	Suggest	Suggest	Suggest

C. Onda [48]

Patient should fulfil at least 3 out of 4 criteria:

- disease-free survival > 12 months
- no metastases to the liver
- isolated lesion
- tumour size < 6 cm