Chapter 22
Ovarian Cancer

Renata Félix da Justa and Ramon Andrade De Mello

Abstract Ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death in them. The overall 5-year relative survival currently is between 30% and 40% across the globe. However, the disease typically presents at late stage when this rate is only 29%. Despite the public health significance, the etiology of this lethal disease is not completely understood but many associated risk factors have been identified. Ovarian tumors benign or malignant originate from one of three cell types: epithelial cells, stromal cells or germ cells. More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors. Staging of ovarian cancer is surgical and the International Federation of Gynecology and Obstetrics staging remains the most powerful indicator of prognosis. Primary treatment for presumed ovarian cancer consists of appropriate surgical stagin and debulking, followed in most patients by systemic chemotherapy with or without Targeted Therapies. In the relapse setting, treatment considerations include the disease-free interval, existing toxicities from first-line treatment and volume of disease at the time of relapse.

Keywords Ovarian carcinoma · Review · Management · Epidemiology

R. F. da Justa
Division of Surgical Oncology, Haroldo Juaçaba Hospital, Ceará Cancer Institute, Fortaleza, CE, Brazil

R. A. De Mello (✉)
Division of Medical Oncology, Federal University of São Paulo (UNIFESP) & Hospital Israelita Albert Einstein, São Paulo, Brazil

Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
e-mail: ramello@ualg.pt; ramondemello@doctors.org.uk

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22.1 Introduction and Epidemiology

Ovarian cancer (OC) is the fifth most common type of cancer in women and the fourth most common cause of cancer death in them [59]. The estimated number of new OC cases is 239,000 worldwide annually, and 152,000 deaths from this cancer. The highest rates are seen in Eastern and Central Europe, 11.4 per 100,000 and 6.0 per 100,000, respectively [1].

The risk of a woman developing OC is 1 in 75, and her chance of dying of the disease is 1 in 100 [2]. The overall 5-year relative survival rate has seen only very modest increases (2–4%) since 1995 [3]. Currently this rate is between 30–40% across the globe. However, the disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92% [2].

Despite the public health significance, the etiology of this lethal disease is not completely understood but many associated risk factors have been identified. This disease is predominantly in older, postmenopausal women (> 80% over 50 years). In relation to reproductive history, women who have had multiple pregnancies have a lower risk than those with fewer pregnancies, who in turn have a lower risk than nulliparous women. Early menarche and late menopause also seem to contribute to a greater risk. Use of the oral contraceptive pill, tubal ligation, breastfeeding and suppression of ovulation offer protection against OC.

In relation to family history women with a first-degree relative have more than a twofold increase in risk of ovarian cancer compared with women with no family history. However, only 10% of ovarian cancer cases have an identifiable genetic mutation. An inherited BRCA 1 mutated gene confers a 15–45% lifetime risk of developing OC and BRCA 2 mutatated gene increases to 10–20%. Women with hereditary OC tend to develop the disease approximately10 years earlier than women with non-hereditary OC [14, 59].

22.2 Pathology

Ovarian tumors benign or malignant originate from one of three cell types: epithelial cells, stromal cells or germ cells. More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors [4, 7]. (Table 22.1).

High-grade serous carcinoma is the most common histological type (70–80%), followed by endometrioid (10%), clear cell (5–10%), mucinous (3%), and low-grade serous (<5%) [8, 9]. Subtype and grade have prognostic importance [5]. Grade is a number of grading systems [1–3] which are defined according to tumour characteristics: architectural features, mitotic counts and nuclear atypia [6].

Low-grade serous tumours tend to present at a younger age and to do not respond to traditional chemotherapy regimens, but have a longer survival compared with

Table 22.1 Histological subtypes of ovarian tumors

Epithelial Ovarian tumours	Sex cord-stromal tumors	Germ cell tumors
Serous	Granulosa Cell Tumors	Teratomas
Endometrioid	Thecomas	Dysgerminomas
Clear Cell	Fibroma	Embryonal carcinoma
Mucinous	Leydig cell tumor	Non-gestational choriocarcinoma
Brenner (Transitional Cell)	Seroli Cell tumor	Struma Ovarii
Mixed Epithelial Tumours		Endodermal sinus tumor
Undifferentiated		
Unclassified		

women with high-grade tumours [10, 11]. In recent years, accumulating evidence has shown that the majority of high-grade serous ovarian and peritoneal tumours originate in the fimbria of the fallopian tube (serous tubal intraepithelial carcinoma). These malignant cells then metastasise to the ovaries and the peritoneal cavity [15, 16].

Endometrioid ovarian cancers are usually early stage (stage 1) and low grade.

Endometriotic cysts are possibly precursor lesions to endometrioid ovarian cancer. The presence of ARID1A mutations in endometriotic cysts and in endometrioid ovarian cancer suggests this cause relationship [12].

Clear-cell cancers incidence varies worldwide. It is more common among Japanese women. The prognosis for its stage 1 is relatively good. However, advanced stage clear-cell cancers have a worse prognosis than serous OC and the first tend to be resistant to the standard chemotherapeutic agents used. Clear-cell cancers are also strongly associated with endometriosis because a significant proportion carry ARID1A mutations [12].

Mucinous carcinoma usually present as large pelvic abdominoidal cystic masses suggesting mucinous histology. These tumors usually occurs in young adult women and are diagnosed in recent stages, having a good prognosis (5 years OS 80–90%) [85].

Malignant Brenner tumor (MBT) is extremely rare [43, 44]. Histologically MBTs demonstrate transitional- type differentiation as is seen in bladder and ureters with clear stromal invasion. But these tumors do not originate in the urothelial tract. It derive from sites of transitional cell metaplasia from ovarian surface epithelium. [45–47].

When more than one histological type are present in the histological analysis of an ovarian tumor and the minor component forms >10% this tumor is classified as mixed carcinoma. Undifferentiated carcinoma is rare and is likely to represent one end of the high-grade serous spectrum [13].

Malignant germ cell tumors (MGCT) (less than 5%), and sex cord-stromal tumors (SCST) (5–8%) are classified as non-epithelial ovarian cancer (NEOC), which mostly affect the adolescent, median 16–20 years, and present in early stages (85% stage 1). Germ cell tumor are the most common ovarian tumors in this age group. Fertility-sparing surgery is possible for both. The 5-year overall survival of MGCT and SCST can reach 75–100% and 97.2%, respectively [48].

Borderline tumours have low malignant potential. They comprise about 10–15% of ovarian tumours and do not fit into the category of benign or malignant. As most ovarian tumours are serous in origin. They are managed primarily by surgery and respond poorly to chemotherapy [59].

22.3 Diagnosis and Staging

A full clinical assessment is the first step to begin the diagnostic propaedeutics of the patient with suspected OC. HOwever, women with early OC have few or no symptoms, making clinical diagnosis more difficult. Symptoms are most commonly seen with advanced disease. Abdominal or pelvic pain, nausea, anorexia, dyspepsia, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension, fatigue, bloating, ascites and abdominal masses are the symptom referred by patients with OC [49, 51, 52].

Following imaging investigation and appropriate laboratory studies are recommended. Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis. Others tumor markers can be measured if clinically indicated to assess NEOC. For example, alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55]. Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are measured when it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumour. In these situations, colonoscopy and/or gastroscopy are considered, particularly when CA 125/CEA ratio is ≤ 25 [17, 50, 52].

In image exams the presence of a large lesion, multi-locular cysts, solid papillary projections, irregular internal septations and ascites are highly suggestive of ovarian cancer. A 'risk of malignancy' índex can be calculated from clinical factors, ultrasound and CA 125. Computed tomography (CT) scans are routinely used to determine the extent of disease and to aid in surgical planning. Imaging of the chest with CT or chest X-ray should be done if respiratory symptoms are present. Magnetic resonance imaging (MRI) scans do not form part of routine investigations, but for lesions indeterminate on ultrasound, MRI increases the specificity of imaging evaluation, thus decreasing benign resections. Although 18F-FDG-avid ovarian lesions in postmenopausal women are considered suspicious for malignancy, PET/CT is not recommended for primary cancer detection because of high false-positive rates [53, 56, 59].

The diagnosis of OC is confirmed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively or postoperatively. Primary surgery remains the most common and preferred approach, but where this is deemed not feasible, an imageguided or laparoscopic biopsy should be carried out. Preoperative assessment with cross-sectional imaging (CT) is essential as it guides surgery and the pathway of intervention [59]. After confirming the diagnosis, genetic testing is recommend for all women with OC [39, 61].

Table 22.2 FIGO staging

Stage I	Tumor limited to the ovaries
IA	Tumor limited to one ovary; no ascites or peritoneal washings containing malignant cells. No tumour on the external surface; capsule intact
IB	Tumor limited to both ovaries; no ascites or peritoneal washings containing malignant cells. No tumour on the external surface; capsule intact
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites
	IC1 Surgical spill
	IC2 Capsule rupture before surgery or tumor on ovarian surface
	IC3 Malignant cells in the ascites or peritoneal washings
Stage II	Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim)
IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic tissues
Stage III	Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)
	IIIA1 Positive retroperitoneal lymph nodes only
	IIIA1(i) Metastasis $\leq$ 10 mm
	IIIA1(ii) Metastasis > 10 mm
	IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis $\leq$ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
Stage IV	Distant metastasis excluding peritoneal metastasis
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Staging of ovarian cancer is surgical and the International Federation of Gynecology and Obstetrics (FIGO) staging (Table 22.2) remains the most powerful indicator of prognosis.

22.4 Treatment Plan

Primary treatment for presumed OC consists of surgery with an availability of a frozen section to identify a malignant specimen and appropriate surgical stagin and debulking surgery, followed in most patients by systemic chemotherapy [57–60].

22.4.1 Surgical Management of Early Primary Disease

The aim of surgery for early OC is to resect the tumour and to undertake adequate staging. This initial non-fertility-sparing surgery should include aspiration of ascites or peritoneal lavage taken before manipulation of the tumour for peritoneal cytologic examinations, a total abdominal histerectomy (TAH), bilateral salpingo-oophorectomy (BSO) with every effort to keep an encapsulated mass intact during removal, omentectomy, multiple peritoneal biopsies of all abdominal fields and pelvic and para-aortic lymph node dissection up to the renal veins [59, 67]. If suspected or confirmed mucinous histology, appendectomy also should always be performed [85].

When young women are affected, fertility-sparing surgery (unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC) and favourable histology (grade 1 or 2 boderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging, thoroughly informing the patient about the potential risks and about completion surgery shoud be considered after finishing childbearing [22]. In some cases of pediatric/adolescent patients with clinically apparent early stage MGCT surgical staging may be omitted [84].

Although there is a trend for improved progression-free survival (PFS) and overall survival (OS) in the lymphadenectomy group when compared with the control group, the studies lacked the statistical power to be conclusive in this respect [21]. Depending on the histological grade and subtype, 15–30% of the patients with apparently early epithelial ovarian câncer (EOC) will be upstaged after comprehensive surgical staging [18–20]. Therefore, accurate surgical staging is important as it may unmask occult advanced disease.

22.4.2 Surgical Management of Primary Advanced Ovarian câncer

Debulking surgery is the initial treatment for patients with EOC clinical stages II, III, or IV and also to many of the malignant NEOT [23, 57, 59, 68, 69]. The aim is complete cytoreduction of all macroscopic visible disease or to less than 1-cm residual disease (optimal cytoreduction). To achieve this, for patients who can tolerate a large surgery, maximal surgical effort is required, including, if necessary, appendectomy, intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky pelvic and para-aortic lymph nodes, splenectomy, cholecystectomy, partial, hepatectomy, partial gastrectomy, partial cystectomy and/or distal pancreatectomy [59, 70, 71]. This has been shown to be associated with a significantly increased OS and PFS [23–25]. Residual tumour is a more powerful prognostic determinant than FIGO stage; patients with suboptimally debulked stage IIB–IIIB tumours had a

worse outcome that those with completely debulked stage IIIC tumours [23]. Debulking surgery is most widely performed via laparotomy, but, in select patients, minimally invasive procedures may be used to assess wether optimal cytoreduction is feaseble reducing the number of futile laparotomies [67, 72–74].

The value of systematic pelvic and para-aortic lymphadenectomy in advanced disease has been widely discussed in recente years. A retrospective analysis of more than 1900 patients found that lymphadenectomy was associated with a prolonged survival in patients with no gross residual disease [27]. However, a prospective randomised trial of lymphadenectomy versus removal of bulky nodes in patients with <2 cm residual tumour showed an improvement in PFS but not OS for the lymphadenectomy group [28]. A large multi-centre, prospectively randomised trial including patients with newly diagnosed advenced OC (AOC) FIGO IIB-IV with macroscopic complete resection and pre- and intra-operatively clinical negative lymph nodes were randomized intra-operatively to systematic pelvic and para-aortic lymphadenectomy versus no systematic lymphadenectomy. Systematic pelvic and para-aortic lymphadenectomy (LNE) neither improve overall nor progression-free survival despite detecting and removing sub-clinical retroperitoneal lymph node (LN) metastases in 56% of the patients. Therefore, this trial indicated that systematic LNE of clinical negative LN in patients with AOC and complete resection should be omitted to reduce post-operative morbidity and mortality, just the removal of bulky lymph nodes is carried out as part of an attempt to achieve maximum cytoreduction [26].

In the therapeutic management of AOC, the best outcomes are consistently seen with complete resection of all visible disease (resection R0) and subsequently intraperitoneal [78] or intravenous therapy, but a large prospective trial showed that in OC bulky stage IIIC or IV disease, three cycles of platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy [25, 54, 64, 65]. As a result of these data, the use of primary chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status at presentation and in those an optimal cytoreduction will not be achieved [25, 75–77].

A prospective, non-randomized, multicenter trial of patients who underwent primary debulking for stage III–IV epithelial OC was realize with objective to assess preoperative predictive criteria of gross residual diasease (RD) at primary cytoreduction in AOC. Three clinical and 8 radiologic criteria were significantly associated with the presence of any RD: age ≥ 60 years; CA-125 ≥ 600 U/mL; ASA 3–4; lesions in the root of the superior mesenteric artery, splenic hilum/ligaments, lesser sac N1 cm, gastrohepatic ligament/porta hepatis, gallbladder fossa/intersegmental; suprarenal retroperitoneal lymph nodes; small bowel adhesions/thickening; and moderate-severe ascites. A ‘predictive score’ was assigned to each criterion and the rate of having any RD for patients who had a total score of 0–2, 3–5, 6–8, and ≥ 9 was 45%, 68%, 87%, and 96%, respectively. This model may be helpful in treatment planning [79].

22.4.3 Systemic Therapy

22.4.3.1 Adjuvant Chemotherapy for Early-Stage Disease

In those patients with early-stage OC, but with high risk of recurrence (stage 1B/C grade 2/3, any grade 3 or clear-cell histology) the meta-analyses showed that chemotherapy is more beneficial than observation. Patients who received platinum-based adjuvant chemotherapy had better OS than patients who did not receive adjuvant treatment [33, 34]. The optimal duration of single-agent carboplatin or addition of paclitaxel for patients with early-stage disease remains controversial. There is a randomised trial (GOG 157) which showed that six cycles of carboplatin and paclitaxel were not associated with longer PFS or OS, but with a significantly greater toxicity than with three cycles [35] and there are no data to demonstrate that the addition of paclitaxel to carboplatin is superior. Therefore, it is reasonable to consider single-agent carboplatin to all women with intermediate and high-risk stage I disease for 3–6 cycles [59].

Surgical treatment alone and observation after is recommended just for patients with surgically staged IA or IB, grade 1 endometrioid carcinomas and other histologies, beacuse in these cases the survival is greater than 90% [33, 82, 83].

22.4.3.2 Neoadjuvant Chemotherapy

When indicated, before neoadjuvant chemotherapy, histologic confirmation of OC should be obtained. Minimally invasive techniques maybe used to realize the biopsy. Intravenous taxane/carboplatin and liposoml doxorubicina/carboplatin are the regimens recommended for neoadjuvant and adjuvant therapy after interval debulkin surgery. In adition, further studies have shown promising data with the use of bevacizumab in addition to standard neoadjuvant chemotherapy and the use of intraperitoneal chemotherapy as adjuvant treatment option for interval surgery [80, 81].

In general, 3 cycles of neoadjuvant chemotherapy are recommended before interval debulkin surgery and 3 cycles after completing a minimun of 6 cycles of treatment. However, the patients should be evaluated for potential interval debulkin surgery. This surgical procedure should be similar to those recommended for a primary debulking procedure. For patients with disease considered unresectable in evaluation for interval debulkin surgery, this procedure may be performed after 4–6 cycles based on the clinical judgement.

22.4.3.3 Chemotherapy for OC FIGO Stage II–IV

Due to the risk of recurrence, for FIGO stage II–IV disease chemotherapy is recommended for all these patients post surgery. A combination of paclitaxel 175 mg/m2 and carboplatin dosed at an area under the curve (AUC) of 5–6, both administered

intravenously on day 1 every 3 weeks usually for six cycles is the regimem more accepted by a consensus for EOC and some NEOC [36–38]. This regimen is associated with sensory peripheral neuropathy. There is no evidence to suggest that more than six cycles results in a better outcome.

The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. For those patients who do not tolerate paclitaxel, docetaxel plus carboplatin or pegylated liposomal doxorubicin (PLD) plus carboplatin can be considered an alternative, based on two randomised clinical trials that showed similar efficacy [40, 41]. Docetaxel/carboplatin regimen is associated with increased risk for neutropenia and PLD/carboplatin, with more hematologic adverse events.

An alternative scheme with intraperitoneal (IP) and intravenous (IV) chemotherapy has been increasingly studied. Intraperitoneal chemotherapy has a solid pharmacokinetic background and consists of administration of part of the chemotherapy, usually the platinum agent, directly into the peritoneal cavity through a catheter. One randomised clinical trial with stage III OC with no residual mass greater than 1.0 cm demonstrated a benefit in PFS and OS for a regimen that included not only intraperitoneal cisplatin on day 2 and intravenous paclitaxel on day 1, but also intraperitoneal paclitaxel on day 8 every 3 weeks for six cycles. Grade 3 and 4 pain, fatigue, and hematologic, gastrointestinal, metabolic, and neurologic toxic effects were more common in the intraperitoneal-therapy group than in the intravenous-therapy group and only 42% of the patients in the intraperitoneal-therapy group completed six cycles of the assigned therapy. Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to 6 weeks after treatment but not 1 year after treatment [42]. Other studies, including a meta-analysis of five clinical trials confirmed a benefit for IP chemotherapy in OS [43, 63].

Intraperitoneal therapy has been seen more consistently considered in patients with FIGO stage III disease, with small volume (<1 cm) or no residual disease after surgery and with a apropriated performance status [39]. However, this treatment has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and difficulty in delivering all of the planned treatment. This has further influenced many clinicians still regard IP therapy as experimental [59].

For MGCT the most recommended chemotherapy regimen is different. It is based on bleomicin/etoposide/cisplatin (BEP) for 3–4 cycles postoperative for any stage embryonal tumors or endodermal sinus tumors, stages II to IV dysgerminoma and stage I, grade 2 or 3, or stage II to IV immature teratoma [39].

22.4.3.4 Targeted Therapies

Angiogenesis has been a promising target in advanced EOC. The addition of the antiangiogenesis agent bevacizumab to front-line treatment (carboplatin and paclitaxel) showed a increased in PFS when compared with chemotherapy alone in two trials, GOG 218 and ICON-7 trials [62, 66]. The addition of bevacizumab to upfront chemotherapy has been approved in Europe but remains controversial in the United States [39, 61].

Olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, was approved for patients with germline BRCA-mutated advanced ovarian cancer after three or more lines of chemotherapy based on overall response rate of 34% [39, 61].

22.5 Follow-Up

After the primary treatment, patients with EOC and some NEOC who have had a complete response should be seen every 3–6 months for 5 years and physically examined, mainly pelvic exam. They should perform imaging exams when clinically indicated. CA-125 and other tumor markers should be dosed if initially elevated [39].

22.6 Surgical Management of Relapsed Ovarian Cancer

Improved survival following secondary surgery is controversial [24, 29]. A secundary cytoreduction appears to be associated with a survival benefit only when a complete tumour resection can be obtained [30, 31]. This procedure can be considered when the recurrence occurs after 6–12 months after completion of inicial chemotherapy, a complete resection was possible at first surgery, there is good performance status, there is not ascites and when a disesase is localizated and a complete tumour resection can be obtained [39, 59].

The value of a third cytoreduction surgery at later relapse is less clear. The largest multi-centre retrospective analysis showed that residual tumours retain a positive effect on survival even in the tertiary setting of epithelial ovarian cancer, attenuating the impact of other well-established negative prognostic predictors of survival such as ascites, advanced FIGO stage and peritoneal carcinomatosis [32].

22.7 Recurrent Disease

In the relapse setting, treatment considerations include the disease-free interval, existing toxicities from first-line treatment and volume of disease at the time of relapse. For patients whose disease recurs in less than 6 months, it is considered platinum-resistant and has a poor prognosis. For these patients, a nonplatinum agent (example: docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin), with or without bevacizumab, is indicated, but sequential single agent is most commonly used. For those with platinum-sensitive (recurrence beyond 6 months), a combination platinum-based chemotherapy, with or without bevacizumab, is indicated [39, 61].

Questions

1. Where does the most common ovarian cancer occur?

   A. On tissue within the ovary
   B. On the surface of the ovarian tissue
   C. In egg-forming germ cells within the ovary
   D. Any of above

Answer: B – Introduction and Epidemiology: "More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors [7]."

2. Which of the following affirmative is correct about ovarian cancer?

   A. The majority of ovarian cancers are diagnosed late.
   B. Ovarian cancer is the third most common type of cancer in women.
   C. The overall 5-year relative survival rate has seen an important increase due the news chemotherapy drugs.
   D. The overall 5-year relative survival rate is more than 50%.

Answer: A – Introduction and Epidemiology: "Ovarian cancer (OC) is the fifth most common type of cancer in women…"
"The overall 5-year relative survival rate has seen only very modest increases (2–4%) since 1995 [3]. Currently this rate is between 30–40% across the globe. However, the disease typically presents at late stage when the 5-year relative survival rate is only 29%."

3. Who is most at risk for developing ovarian cancer?

   A. A woman who has had multiple children
   B. A woman who use contraceptive pill
   C. A woman over the age of 60
   D. A woman of childbearing age

Answer: C – Introduction and Epidemiology: "This disease is predominantly in older, postmenopausal women (> 80% over 50 years)."
"In relation to reproductive history, women who have had multiple pregnancies have a lower risk than those with fewer pregnancies, who in turn have a lower risk than nulliparous women."
"Use of the oral contraceptive pill, tubal ligation, breastfeeding and suppression of ovulation offer protection against OC."

4. Which of the following affirmative is wrong about ovarian cancer?

   A. Ovarian cancer can occur at any age, even in childhood.
   B. Ovarian cancer is most common after menopause.
   C. Ovarian cancer affecting both ovaries is classified in stage 1
   D. Ovarian cancer with malignant cells in the ascites is classified in stage 3

Answer: D – "Table 22.2 -FIGO staging".

5. Usually, the first treatment for ovarian cancer is…

   A. Surgery
   B. Chemotherapy
   C. Radiation
   D. Any of the above

Answer: A – Treatment Plan. "Primary treatment for presumed OC consists of surgery with an availability of a frozen section to identify a malignant specimen and appropriate surgical stagin and debulking surgery, followed in most patients by systemic chemotherapy."

6. Which of the following affirmative is wrong about ovarian cancer?

   A. Ovarian cancer can be prevented.
   B. Ovarian cancer can cause vaginal bleeding.
   C. Ovarian cancer can affect both ovaries.
   D. Ovarian cancer with malignant cells in the ascites is classified in stage 1C.

Answer: A – Diagnosis and Staging "… vaginal bleeding, abdominal distension, fatigue, bloating, ascites and abdominal masses are the symptom referred by patients with OC."
"Table 22.2 -FIGO staging"

7. What is the most used tumor marker in the propaedeutics of ovarian cancer?

   A. Alpha-fetoprotein
   B. CEA
   C. CA 19-9
   D. CA-125

Answer: D – Diagnosis and Staging **"**Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis."

8. Woman of 65 years with pelvic mass on physical examination. What tests should be required for this patient to evaluate ovarian cancer?

   A. Magnetic resonance imaging and CA-125
   B. Computed tomography, CA-125, CEA, AFP
   C. PET-CT, CA-125, CEA
   D. Abdominal/pelvic ultrasound, CA-125

Answer: D – Diagnosis and Staging **"**Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis. … alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55]. Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are measured when it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumour. … Magnetic resonance imaging (MRI) scans do not form part of routine investigations… Although 18F-FDG-avid ovarian lesions in postmenopausal women

are considered suspicious for malignancy, PET/CT is not recommended for primary cancer detection because of high false-positive rates".

9. Woman with pelvic mass on physical examination. When should we think about germ cell tumor?

   A. women younger than 35 years with increased AFP
   B. women over 45 years with increased AFP
   C. women younger than 35 years with increased CA-125
   D. women over 45 years with increased CA-125

Answer: A – Diagnosis and Staging **"…**alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55]."

10. Staging of ovarian cancer is done by means of…

    A. Surgery
    B. Abdominal/pelvic Computed tomography, chest X-ray and CA-125
    C. Abdominal/pelvic magnetic resonance imaging and CA-125
    D. Abdominal/pelvic ultrasound, PET-CT, CA-125

Answer: A – Diagnosis and Staging **"**Staging of ovarian cancer is surgical…"

11. An 62-year-old female was diagnosed with ovarian cancer. Following gynecological surgery, pathological evaluation showed stage IIIC epithelial ovarian cancer. What is the most appropriate adjuvant therapy?

    A. Adjuvant therapy is not necessary
    B. Six cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
    C. Three cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
    D. Chemotherapy combined with Radiotherapy

Answer: B – Chemotherapy for OC FIGO stage II–IV: "Due to the risk of recurrence, for FIGO stage II–IV disease chemotherapy is recommended for all these patients post surgery. A combination of paclitaxel 175 mg/m2 and carboplatin … both administered intravenously … for six cycles is the regimem more accepted by a consensus for EOC."

12. An 73-year-old female was diagnosed with pelvic mass on physical examination. Following gynecological surgery, pathological evaluation showed stage IA clear cell ovarian cancer. What is the most appropriate adjuvant therapy?

    A. Adjuvant therapy is not necessary
    B. Six cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
    C. Three cycles of chemotherapy combined with intravenous paclitaxel and carboplatin

D. Chemotherapy combined with Radiotherapy

Answer: A – Adjuvant chemotherapy for early-stage disease: **"**Surgical treatment alone and observation after is recommended just for patients with surgically staged IA or IB, grade 1 endometrioid carcinomas and other histologies, beacuse in these cases the survival is greater than 90%."

13. An 30-year-old female was diagnosed with pelvic mass on physical examination. The patient does not have children and wishes to preserve fertility. In what situations can not a fertility-sparing surgery be proposed for this patient?

    A. stage IA clear cell, grade 1 ovarian cancer
    B. stage IC mucinous ovarian cancer
    C. stage IA germ cell grade 2 ovarian cancer
    D. stage IC sex cord-stromal grade 2 tumours ovarian câncer

Answer: A – Surgical management of early primary disease: "When young women are affected, fertility-sparing surgery (unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC) and favourable histology (grade 1 or 2 boderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging."

14. A 40-year-old female patient who was unable to have children made the choice to undergo in-vitro fertilization (IVF). The patient's ovaries were super stimulated by chemicals to help ovulation occur. After each cycle an ultrasound was performed. After the third cycle of IVF the patient developed a right complex ovarian cyst with irregular mural projections and internal vascularity. The patient wished to continue with IVF treatments, therefore a conservative surgery was proposed. A right laparoscopy salpingo-oophorectomy was performed and a invasive endometrioid adenocarcinoma restricted to ovary was identified by frozen section. What is the most appropriate surgery in this case?

    A. A total abdominal histerectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection and appendectomy
    B. A total abdominal histerectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection without appendectomy
    C. A unilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection without appendectomy
    D. A unilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields and appendectomy

Answer: C – Surgical management of early primary disease: "When young women are affected, fertility-sparing surgery (unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC)

and favourable histology (grade 1 or 2 boderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging."

15. A 16 year old girl with pelvic pain was diagnosed with pelvic mass on physical examination. A 7cm ovarian tumor was visualized on abdominal/pelvic ultrasonography. What is the most suitable histological type?

    A. Serous
    B. Mucinous
    C. Clear Cell
    D. Dysgerminoma

Answer: D – Pathology: "Malignant germ cell tumors (MGCT) (less than 5%), and sex cord-stromal tumors (SCST) (5–8%) are classified as non-epithelial ovarian cancer (NEOC), which mostly affect the adolescent, median 16–20 years".

Fictitious Clinical Case

Ms. Catarina Brasil, 52 years old, natural from Porto, Portugal presented with increased abdominal volume 2 months ago, dyspepsia, flank pain and weight loss performed ultrasonography that showed ascites and abdominal mass. At medical consultation was requested CA-125: 325 U/ml and abdominal/pelvic CT that showed: ascites, expansive solid-cystic formation of 15 cm in the central region of the abdomen and pelvis on the right, 3 expansive formations in the pelvis measuring 6.5 cm, 8 cm and 4.5 cm each. Patient without comorbidities. Faced with the suspicion of ovarian cancer, the gynecological oncology surgeon decided to exploratory laparotomy with optimal cytoreduction surgery intensity. During the procedure was detected large amount of ascites, 5 cm right ovary mass, 5 cm retrouterine mass, 15 cm tumor mass in omento, right subdiaphragmatic implant of 3 cm and lesions suggestive of metastatic implantation affecting 3 points of the intestine, vesical peritoneum, hepatic round ligament, right and left flank peritoneum. Abdominal total hysterectomy, bilateral salpigo-oophorectomy, omentectomy, resection of retrouterine and peritoneal masses, intestinal implants and of bulky nodes were performed. All evidence of macroscopic disease was removed. Pathological assessment showed serous high grade ovarian cancer. Following surgery, the patient's CA-125 levels declined to 81 U/ml. After 1 month the patient received six cycles of conventional treatment. During chemotherapy, the patient presented neutropenia grade 2 and distal paraesthesia grade 1.Following chemotherapy, CA-125 levels declined to 7.3 U/ml and abdominal/pelvic CT showed no disease.

(a) Which classification should be used for patient staging above?

The International Federation of Gynecology and Obstetrics (FIGO) staging. Stage IIIC – Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pélvis and/or metastasis to the retroperitoneal lymph nodes. Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

(b) Which chemotherapy regimen is most commonly accepted for this patient?

A combination of paclitaxel 175 mg/m2 and carboplatin dosed at an area under the curve of 5–6, both administered intravenously on day 1 every 3 weeks usually for six cycles.

(c) If in less than 6 months the patient has increased Ca-125 and ascites what should be the conduct?

Due to early relapse (less than 6 months), this disease is considered platinum-resistant and has a poor prognosis. For these patients, a nonplatinum agent (example: docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin), with or without bevacizumab, is indicated.

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