28

Ovarian Cancer

Nomonde Mbatani

INTRODUCTION

Incidence

Ovarian cancer accounts for 4% of all cancers in women and around 31% of cancers of the genital tract in developed countries (the most common cancer of the female gynecological tract worldwide is cervical cancer); however, ovarian cancer has the highest incidence to mortality ratio of all the gynecological malignancies, in both well- and under-resourced parts of the world (Figure 1[1]).

The majority of women are diagnosed at an advanced stage of disease due to the relative absence of symptoms and signs during early stages of the disease. In addition, there are currently no cost-effective screening tests with sufficient sensitivity or specificity for use in population screening to detect early disease.

In most underdeveloped countries, the most common causes of death in women are caused by communicable diseases such as HIV, tuberculosis, malaria and maternal mortality. Cancer is a less common cause of death but the incidence of cancer in developed as well as developing countries is increasing and, by 2020, according to the world cancer report, it is estimated that >50% of global cancers will be diagnosed in low- and middle-income countries[2].

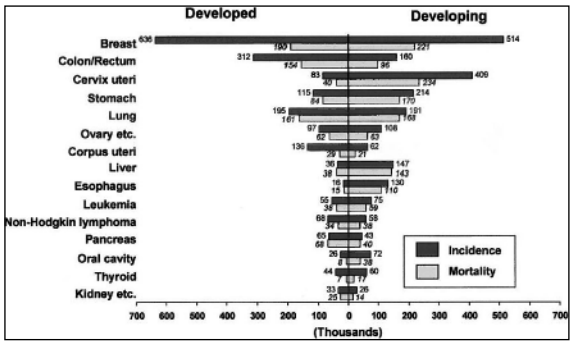

Figure 1 Incidence of malignancies in women.
Source: Global Cancer Statistics, 2002[2]

The true incidence of ovarian cancer, along with other cancers is unknown in less-developed countries, as there are few developing countries with cancer registries. The cancer registry in South Africa stopped collecting data in 1999 but the Department of Health has recently started moves to recreate the South African Cancer Registry. In the USA, there are approximately 21,550 new cases of ovarian cancer diagnosed per year, and more than 14,600 women will die of the disease. It is the fifth most common cancer in women in the USA after lung, breast, colon and uterus. A woman's risk of developing ovarian cancer in her lifetime is 1.5%.

The difference in incidence between developed countries and less-developed countries, could be attributed to women having a shorter life expectancy in undeveloped countries [on average 45 years compared to 82 years (median age of patients with ovarian cancer is 56 years)]. In addition, women in poorer countries have some protection from lifestyle factors such as:

- Late menarche
- High parity.

Survival

Survival rates can be as high as 90% in early stages and decline in the late stages. Determinants of survival according to the SEER (Surveillance, Epidemiology and End Results) database include race, stage, histological type, grade and age at diagnosis. Survival declines with age with 5-year survival rates

of 77% in women aged <50 years compared with rates of 50% in women aged 50–69, and a reported 32% in women aged >70 years. Being non-Caucasian is associated with a poor prognosis. Borderline ovarian tumors as well as germ cell tumors are associated with a much better prognosis while serous papillary cancers are associated with poorer survival[3,4].

Varying inequalities in survival could exist between and within developing countries due to the wide range of cancer health services available.

Risk factors

Genetic abnormalities: BRCA1 and BRCA2 and Lynch syndrome

About 10–14% of women with epithelial ovarian cancer have a germ-line mutation in the *BRCA1* or *BRCA2* genes. *BRCA1* is located on chromosome 17 and most genetic inherited ovarian cancers are associated with this mutation (a small proportion are associated with *BRCA2* which is located on chromosome 13). The lifetime risk of developing ovarian cancer for women with *BRCA1* mutation may be as high as 28–44% and for women with the *BRCA2* mutation around 27%. Of note, women with BRCA mutations tend to develop ovarian cancer about 10 years earlier than non-hereditary tumors.

There is also a higher risk of ovarian and endometrial cancer in women with the Lynch II syndrome, which is also known as the hereditary non-polyposis colorectal cancer (HNPCC) syndrome. The mutations are autosomal dominant and thus a complete family history is important to document.

General risk factors

General risk factors for ovarian cancer include low parity, infertility and endometriosis.

Protection against ovarian cancer

The use of combined oral contraceptives (COC), breastfeeding, tubal ligation and hysterectomy are protective[5,6].

Staging

Staging for ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) is shown in Table 1.

Table 1 Ovarian cancer staging by FIGO, 2009

Stage I Cancer limited to the ovaries	
IA	Growth limited to one ovary, no ascites. No tumor on the external surfaces, capsule intact
IB	Growth limited to both ovaries, no ascites. No tumor on external surfaces, capsule intact
IC	Tumor either stage 1A or 1B, but with tumor on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells or with positive peritoneal washings
Stage II Growth involving one or both ovaries with pelvic extension	
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissue
Stage III Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal node	
IIIA	Tumor limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative
IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant metastasis. If pleural effusion present, there must be positive cytological test results to allot a case to stage IV. Parenchymal liver metastases equals stage IV

Classification/histological types

Three main types of primary ovarian cancers exist. Epithelial cancers are the most common and account for 80% of the cancers and are believed to arise from the single layer of cells that cover the ovary or from those that line celomic epithelium. The remainder (20%) are germ cell tumors, sex cord stromal tumors and cancers metastatic to the ovaries.

- *Epithelial*: derived from the ovarian celomic epithelium, more frequently found in the older woman. The most common is the serous papillary type (75%). Other types are endometrioid, mucinous, clear cell, undifferentiated, Brenner, transitional cell and mixed histological types. Borderline epithelial tumors or tumors of low malignant potential tend to remain confined to the ovary for long periods of time, occur in younger women than invasive epithelial tumors and are associated with a much better prognosis. Another entity that is recognized is primary peritoneal carcinoma which simulates ovarian cancer clinically, although there is usually extensive intra-abdominal disease associated with normal sized ovaries or with tumor only on the ovary surface. CA-125 is the most common tumor marker of epithelial ovarian cancers. Carcinoembryonic antigen (CEA) is a marker for mucinous ovarian carcinomas.
- *Germ cell tumors*: common in children and young adults aged <40 years. Subclasses: dysgerminomas, yolk sac tumors, non-gestational choriocarcinoma, endodermal sinus tumors, immature teratomas, polyembryomas. Tumor markers include: β-human chorionic gonadotropin (β-hCG), α-fetoprotein (αFP), lactase dehydrogenase (LDH).
- *Sex cord stromal tumors*: include Sertoli/Leydig cell tumors, granulosa and theca-cell tumors. Tumor markers in granulosa cell tumors are inhibin and estradiol (granulosa cell tumors often produce estradiol and cause endometrium hyperplasia and bleeding).

PREVENTION AND SCREENING

Primary prevention would save many lives. Currently, no ideal screening strategy has been developed. Overall survival remains low in advanced stages. The predictive value of the combination of CA-125 with ultrasound examination is disappointing even in high-risk groups (BRCA mutations). CA-125 is not diagnostic in premenopausal women especially if the levels are low. High levels of CA-125 tend to correlate with advanced stages. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was a randomized controlled trial designed to assess the effect of screening on mortality, comparing ultrasound to a combination of CA-125 and ultrasound as screening strategies in just over 98,000 postmenopausal women[7]. The difference in sensitivity between the two strategies was not significant. Specificity was higher in the multimodal screening group resulting in fewer repeat tests and unnecessary surgical interventions. It must be said, that the ultrasound screening was performed by experienced sonographers, and similar results may not be reproducible in less-developed countries.

SIGNS AND SYMPTOMS

Many patients with early-stage ovarian cancer do not have signs or symptoms and the abdominal mass is diagnosed by coincidence. Patients with advanced disease often present with vague gastrointestinal complaints, weight loss, micturition and defecation changes, abdominal distention, progressive ascites, an abdominal mass and/or bowel obstruction. Inguinal and supraclavicular lymph nodes might be enlarged.

ULTRASOUND FEATURES OF OVARIAN MALIGNANCY

A uni- or multilocular mass with papillary structures and solid masses in the cysts and thick septa is very suspicious for epithelial ovarian tumors while more solid masses are seen in granulosa cell and other sex cord stromal tumors. On ultrasound, ascites may be seen as well as peritoneal implants in Douglas' cavity[8]. In Chapters 1 and 11 you can find more details of examination and ultrasound in ovarian masses.

DIAGNOSIS

Good history taking, a thorough physical examination and a high index of suspicion cannot be overemphasized. Pelvic examination should include a recto-vaginal examination to exclude an ovarian mass in the pouch of Douglas. Attempts should

be made to rule out the possibility of non-gynecological causes of pelvic masses. Very few low-income countries have access to highly technological diagnostic apparatus such as computerized tomography (CT) scans and magnetic resonance imaging (MRI). Their use should, even when available, serve as adjuncts to diagnosis. A definitive preoperative diagnosis is usually not possible, therefore, a presumptive diagnosis of ovarian cancer is made based on the presence of a pelvic mass, with or without ascites, and an elevated CA-125. Development of other biomarkers of diagnose ovarian cancer at earlier stages is awaited.

MANAGEMENT OF EPITHELIAL OVARIAN CANCER

Patients with early-stage ovarian cancer (stage I–IIA) need a staging procedure, while patients with advanced disease need a debulking procedure. Both procedures are described below.

Staging procedure

In developing countries doctors are often confronted with abnormal pelvic masses in young women. Therefore at diagnostic surgery of the ovary/tube, abnormal tissue should be sent for a pathology examination. When it turns out that the mass is malignant, the patients should have an optimal surgical staging procedure to rule out spread of the disease. Where facilities are available, the laparoscopic approach is an alternative for diagnosis and staging.

In early ovarian cancer (FIGO stage I–IIA) an optimal staging procedure (see Appendix 1 for a systematic approach) must be performed, consisting of: a midline incision in order to assess the pelvis as well as the upper abdomen; removal of the affected ovary, the contralateral ovary and the uterus; careful inspection and palpation of all peritoneal surfaces; peritoneal washing for cytology analysis; biopsy sampling of any suspicious areas, such as adhesions adjacent to the primary tumor; infracolic omentectomy; peritoneal biopsy sampling of the right hemidiaphragm, the right and left paracolic gutters, the pouch of Douglas, the bladder peritoneum; the pelvic side walls; and sampling of at least ten para-aortic and pelvic lymph nodes at five different locations. The aim of the staging procedure is to make sure that the disease is indeed limited to the ovaries, tubes and uterus (in that case no adjuvant chemotherapy is indicated) or whether the disease is in advanced stage and needs to be treated with systemic chemotherapy. In young patients with early FIGO stage IA tumor who want to remain fertile, the contralateral ovary and uterus can be left *in situ* but an infracolic omentectomy and optimal staging procedure should always be performed in cases of epithelial ovarian cancer.

Debulking procedure

In advanced-stage ovarian cancer (FIGO stage IIB–IV), primary debulking surgery or debulking surgery after neoadjuvant chemotherapy should be considered[10]. Survival outcomes are related to the success of the cytoreductive surgery:

- *Complete debulking*: a complete resection of all macroscopic tumor lesions improves the disease-free and overall survival and is the goal of cytoreductive surgery.
- *Adequate debulking*: removal of all macroscopic disease to <1 cm^3 is defined as an adequate debulking surgery by the gynecologic oncology group (GOG)[11].
- *Incomplete debulking*: macroscopic lesions of >1 cm^3 are left behind after surgery.

Debulking surgery even in advanced-stage disease is suggested to improve efficacy of systemic chemotherapy[12]. The best results are achieved when surgery is performed by a gynecologic oncologist experienced in ovarian cancer surgery, usually those who perform more than 10 ovarian cancer debulking operations per year[9]. The procedure for debulking surgery is: open the abdomen with a midline incision and carefully systematically assess the pelvis as well as the upper abdomen. Both ovaries, tubes, the uterus and the omentum are resected and all other macroscopic tumor lesions are removed if feasible. This can include bowel surgery, splenectomy or diaphragm stripping. Blood loss and morbidity of debulking surgery may be major and for this reason these procedures should be done by an experienced gynecologic oncologist.

Challenges of surgery in low-resource countries

Most surgeons in developing countries do not have formal training in cytoreductive surgery. When ovarian cancer surgery is performed by inexperienced hands, the chance is great that bulky residual tumor would be left behind which in experienced

hands could have been resected. If it is clear before surgery that in patients with FIGO stage IIIC or IV an adequate resection of lesions of <1 cm seems not to be feasible, or when patient-associated co-morbidities, malnutrition or, as in most low-resourced areas, the limited or non-existent intensive care facilities to monitor these patients postoperatively, makes an adequate debulking surgery unachievable, patients can start with three cycles of neoadjuvant chemotherapy followed by interval debulking surgery followed by three additional chemotherapy cycles (see Box 4). Histological proof of ovarian malignancy prior to the start of chemotherapy, is however mandatory. Please note that histological diagnosis must be achieved through open biopsy and not through tapping of a suspicious cystic tumor through the vagina or abdominal wall. This can lead to rupture of the tumor and spread of disease and is associated with a worsened prognosis.

Quality of life should be weighed against treatment toxicity when making treatment decisions. Patients' performance status, stage and tumor burden should be carefully assessed before taking the decision to operate. Concurrent infections and malnutrition should be aggressively managed in order to improve surgical outcome.

Unfortunately, no test or imaging modality, even when available, can reliably predict complete or optimal cytoreduction preoperatively. Neoadjuvant chemotherapy with three cycles of platinum-containing chemotherapy may be considered in patients with advanced-stage ovarian cancer (FIGO stage IIIC and IV) and patients in too poor a condition for surgery and awaiting improvement in general health[10].

Adjuvant treatment in early-stage epithelial ovarian cancer

For FIGO stage IA–IIA ovarian cancer patients, optimal surgical staging is the standard of care. The 10-year survival in patients with FIGO stage IA–IIA is around 90% after an optimal surgical staging alone. No additional benefit in progression-free nor overall survival was observed with adjuvant chemotherapy in *optimally* staged early-stage ovarian cancer, in contrast to patients with a non-optimal staging surgery where the progression-free as well as the overall survival were significantly increased by adjuvant chemotherapy (Box 1).

Box 1 Landmark studies for chemotherapy in early-stage ovarian cancer

The ACTION study (EORTC 55904) investigated the role of adjuvant chemotherapy in early-stage ovarian cancer (FIGO stage I and IIA) comparing adjuvant chemotherapy with no further treatment after surgery. In the original analysis adjuvant chemotherapy improved recurrence-free survival but not overall survival[13].

A similar trial carried out by the MRC, *the ICON-1 Study*, demonstrated that women with early-stage epithelial ovarian cancer who received adjuvant chemotherapy had better recurrence-free and overall survival than women who did not[14]. In the pre-planned combined analysis of these two parallel randomized clinical trials (ACTION and ICON-1) the improvement in recurrence-free and overall survival after adjuvant chemotherapy was confirmed[15].

In the ACTION study, subgroup analysis showed that the completeness of surgical staging was an independent prognostic factor and that the benefit of adjuvant chemotherapy was mainly limited to patients who underwent incomplete (non-optimal) surgical staging. The long-term analysis with a median follow-up of 10.1 years confirmed the main conclusions of the original analysis[16]. A recurrence-free survival benefit but no cancer-specific survival benefit of adjuvant chemotherapy was seen for the whole ACTION study group. Completeness of surgical staging was found to be statistically significantly associated with a better outcome in the control group as well as in the chemotherapy group.

The benefit from adjuvant chemotherapy in terms of overall and recurrence-free survival appeared to be most evident in patients with non-optimal surgical staging[15]. There remains a discussion about whether chemotherapy can be omitted in patients with optimally staged early-stage ovarian cancer. The benefit from adjuvant chemotherapy appeared to be predominantly effective in patients with non-optimal surgical staging, presumably because these patients have more risk of harboring unappreciated residual disease, this subgroup analysis must be interpreted with caution.

Chemotherapy in advanced-stage ovarian cancer (FIGO stage IIB–IV)

Despite optimal surgical tumor resection the majority of the patients will experience a recurrence eventually, even patients with a macroscopic radical resection of all tumor lesions. Combination therapy with cisplatin and alkylating agents in the 1980s, and since the 1990s, the adoption of paclitaxel with either cisplatin or carboplatin are considered first-line treatment for advanced ovarian cancer; however, myelosuppression, neurotoxicity, ototoxicity and gastrointestinal side-effects still remain a challenge with the recommended agents. Six cycles of 3-weekly carboplatin (or cisplatin) with paclitaxel are recommended.

Chemotherapy in low-resource settings

Low-resource countries may lack personnel skilled in dispensing cytotoxic drugs, there are few laboratory facilities to monitor toxicities, or effective drugs that would prevent or treat the drug toxicities. The costs and availability of anticancer drugs differ from developing country to developing country.

The knowledge of, and attitude to the disease and treatment should be taken into consideration when management decisions are taken. Long distances travelling to access health facilities and the differences in the process of care between the health facilities could limit compliance[17].

Single-agent regimens are cheaper, easier to administer and to monitor, and have fewer side-effects, and are therefore more appealing in low-resourced settings. Cisplatin was the first single agent to demonstrate longer survival and response compared to cyclophosphamide, the traditional alkylating agent used in the 1970s[18]. Combination treatments are associated with higher response rates, increased progression-free and overall survival but also with more side-effects[13,19] (Box 2). Combination regimens could be quite cumbersome and expensive to administer in low-resourced settings.

The combination of paclitaxel with carboplatin is considered to be the standard first-line therapy (Table 2, Appendices 2 and 3). Single-agent carboplatin may be a reasonable alternative for first-line in patients with ovarian cancer because of its relative safety, tolerability, ease of administration and fewer side-effects[20]. The myelotoxicity of the carboplatin monotherapy is of concern, and treatment delays may affect treatment efficacy.

Box 2 Landmark studies in chemotherapy for advanced ovarian cancer

The *International Collaborative Ovarian Neoplasm Group (ICON 3)* randomized trial compared paclitaxel/carboplatin against a non-taxane-containing platinum-based control drug combination of cyclophosphamide, doxorubicin and cisplatin (CAP) or single-agent carboplatin in women with advanced ovarian cancer. The results showed that single-agent carboplatin or CAP as a triple regimen were as effective as paclitaxel/carboplatin as first-line treatment for women with advanced ovarian cancer. There was no statistical difference in both progression-free survival or in overall survival when paclitaxel/carboplatin was compared to the two control groups[18]. In contrast, the *GOG 111 Study* and the *European–Canadian Intergroup Trial* in the first-line setting where cisplatin/paclitaxel was compared to cisplatin/cyclophosphamide, a significant improvement for the paclitaxel/cisplatin regimen was shown in progression-free survival and overall survival. In addition, the survival superiority of the paclitaxel/carboplatin regimen was confirmed in the long-term follow-up results[19,21].

Intraperitoneal chemotherapy

Intraperitoneal chemotherapy (IP) involves direct administration of chemotherapeutic agents directly into the body cavity. IP chemotherapy theoretically directly exposes the tumor to higher doses of chemotherapy and avoids systemic drug dose side-effects. Little is known about correct indications for IP chemotherapy, the appropriate drugs, correct dose and the appropriate scheduling of treatment. Toxicity concerns have been raised. Use of IP chemotherapy is currently discouraged in low-resource settings[22].

Table 2 Chemotherapy in advanced ovarian cancer

3-weekly paclitaxel/carboplatin	*3-weekly carboplatin*
Paclitaxel 175 mg/m^2 Carboplatin AUC 6 *repeat day* 22	Carboplatin AUC 6 *repeat day* 22

AUC, area under the curve

Interval cytoreductive surgery in advanced epithelial ovarian cancer

Interval debulking (IDS) is a repeat surgical attempt after induction chemotherapy in a patient who could not be optimally debulked at primary surgery. The main aim is to achieve complete cytoreduction of residual tumor. In patients who did not have a maximal effort for cytoreduction by an experienced surgeon at initial surgery, IDS is beneficial (Box 3).

Box 3 Landmark studies on interval debulking surgery

The *EORTC 55865* trial performed a randomized study in FIGO stage IIB–IV patients in which patients with residual disease after primary debulking surgery were randomized to either ≥6 cycles of chemotherapy without additional surgery or 3 cycles of chemotherapy followed by interval debulking surgery and additional ≥3 cycles of chemotherapy. This study showed, and continues to show with over 10 years of follow-up, that there is a significant survival advantage to the patients who underwent IDS[23]. *The GOG 158* study showed no benefit of interval debulking surgery. However, there were some significant differences in the entry criteria and also the specialization of the surgeon. In the GOG study all patients were operated on by gynecological oncologists but in the EORTC there was a mixture of general gynecologists and gynecological oncologists. In addition in the GOG 158 a maximal surgical effort at primary surgery was required for inclusion, which was not needed for inclusion in the EORTC study. Many oncologists have interpreted these results as showing that when an initial surgery has been performed by a gynecological oncologist then IDS probably has a minimal role to play, in all other cases IDS is of benefit.

Neoadjuvant chemotherapy in epithelial ovarian cancer

Neoadjuvant chemotherapy refers to initial use of chemotherapy in patients with advanced-stage epithelial ovarian cancer in order to reduce the tumor volume prior to surgical intervention (Box 4).

Box 4 Landmark studies in neoadjuvant chemotherapy

In the *EORTC/NCIC-CTG* trial the primary debulking surgery followed by chemotherapy with or without interval debulking was compared with neoadjuvant chemotherapy and delayed primary surgery in stage IIIC and stage IV ovarian cancer[9]. The progression-free and overall survival rate was not significantly different, while the morbidity and mortality was significant in favor of the neoadjuvant regimen. The advantages of neoadjuvant chemotherapy include an increased rate of optimal surgery, reduced blood loss, lower morbidity, shortened hospital stay, improved quality of life, and acting as a mechanism to select out patients with platinum resistance. In the multivariate analyses, complete resection of all macroscopic lesions was the strongest independent prognostic factor for overall survival. The results of the trial are not applicable to patients with lower stage disease (IIB–IIIB). Recently many institutions have switched to using neoadjuvant chemotherapy in selected patients with advanced ovarian cancer (without primary attempt of debulking), followed by an IDS (usually after three courses of chemotherapy).

The lack of specialized care facilities and experienced gynecology oncologists in low-resourced countries makes neoadjuvant chemotherapy an appealing option. Another advantage of neoadjuvant therapy is that it would allow the patient's general condition to improve and would reduce the bulk of the tumor, thereby rendering the surgery easier with fewer surgical complications. The decision to offer neoadjuvant chemotherapy should be made when the diagnosis of primary ovarian cancer is most certain. This diagnosis is preferably based on a histologically obtained sample of the tumor or metastases. An alternative way (although less precise) is the presence of the following three features:

1. A cytological diagnosis of adenocarcinoma, achieved through fluid aspiration of the ascites or pleural fluid.
2. A typical clinical picture with a mass arising from the pelvis associated with macroscopic tumor >2 cm in abdomen or extraperitoneal tumor: clinically felt and radiologically confirmed.

3. Ratio of CA-125/CEA >25; in cases of a lower ratio, additional examinations (digestive tract endoscopy and mammography) should be performed to exclude intestinal and breast cancer.

Response to chemotherapy should be assessed after three chemotherapy cycles, taking note of any reduction in the size of the mass or volume of ascites, a drop (ideally logarithmic) in the tumor marker level and improvement in the patient's general condition. Delayed primary surgery is considered in patients with a response or stable disease after completion of three chemotherapy cycles. Debulking surgery should be performed after the third or at the latest after the fourth chemotherapy cycle. Further delays in surgery affect survival negatively. Progression whilst on chemotherapy signifies poor surgical outcome, therefore patients who show progression during neoadjuvant chemotherapy should not be considered for interval or delayed primary surgery.

Follow-up of advanced ovarian cancer after first-line therapy

In resource-rich countries 3-monthly follow-ups for high-risk ovarian cancer are performed. In cases of symptomatic relapse a course of chemotherapy is considered. Serum CA-125 often rises several months before women with ovarian cancer have clinical/symptomatic relapse, but there is no survival benefit in starting chemotherapy before start of clinical symptoms (Box 5).

Box 5 Landmark study for early start of chemotherapy

The *MRC 0VO5/EORTC 55955* investigated in a randomized trial in relapsed ovarian cancer after first-line chemotherapy whether there were benefits from early treatment based on confirmed elevation of CA-125 versus delaying treatment until clinically indicated[24]. In the early arm second-line and third-line chemotherapy were started a median of 4.8 months and 4.6 months earlier compared with the delayed arm. After a median follow-up of 56.9 months there was no evidence of a survival benefit or better quality of life with early treatment of a relapse based on a raised CA-125 level alone, and therefore no value in the routine measurement of CA-125 in the follow-up of ovarian cancer patients.

MANAGEMENT OF GRANULOSA CELL CANCER

Granulosa cell cancer of the ovaries occurs at all ages. Many granulosa cell tumors produce estrogens and cause abnormal uterine bleeding. The cornerstone of granulosa cell tumor therapy is surgery. When surgery is incomplete, radiotherapy may be considered. Inoperable granulosa cell tumors may be treated with (B)EP (bleomycin, etoposide and cisplatin) chemotherapy (see Appendix 4). Recurrence can happen after many years and in that case surgery is the first option for treatment.

MANAGEMENT IN GERM CELL OVARIAN CANCER

In young patients with ovarian cancer limited to one ovary and who want to preserve their fertility, tumor resection can be limited to one ovary plus omentectomy and optimal surgical staging.

Germ cell tumors have the highest incidence in the group of women aged between 20 and 35 years. Most germ cell tumors are rapidly growing and should be diagnosed and treated without delay. Around 15–20% of the tumors are bilateral. Tumor markers are αFP, LDH and hCG (pregnancy test!). Patients with low tumor markers have a better prognosis. Tumors are staged according to the FIGO classification described in Table 1. Therapy for germ cell tumors is:

- *Stage I* Surgery: remove the affected ovary but leave uterus and other ovary (if normal) intact. Do staging procedure as described for epithelial ovarian cancer: take biopsies and do lymph node sampling. FIGO stage IA dysgerminoma and FIGO stage IA immature teratoma grade 1: follow-up with tumor markers. All other tumor types FIGO stage I administer three cycles of adjuvant therapy, (B)EP3 – bleomycin, etoposide and cisplatin (see Appendix 4).
- *Stages II–IV* Debulking surgery if radical resection is feasible followed by three courses of (B)EP3 in low-risk patients and four courses BEP5 in intermediate- and high-risk patients (Table 3 and Appendix 4).

CONCLUSIONS

Timely diagnosis and treatment of ovarian cancer is a huge challenge worldwide. There is no useful screening test for the general population and it is

Table 3 Germ cell tumors: classification in risk categories

	Low risk	*Intermediate risk*	*High risk*
Dysgerminoma	No extrapulmonary metastases Normal αFP hCG and/or LDH*	Extrapulmonal visceral metastases Normal αFP* hCG** and/or LDH*	• αFP >10,000 μg/l* • hCG > 50,000 IU/l* • LDH >10 × the upper limit of normal* • Visceral metastases (liver, bone or brain) • Mediastinal localization
Non-dysgerminoma	• αFP <1000 μg/L* • hCG <5000 IU/L* • LDH <1.5 × the upper limit of normal* No extrapulmonary or visceral metastases	• αFP 1000–10,000 μg/l* • hCG 5000–50,000 IU/l* • LDH 1.5–10 × the upper limit of normal* No extrapulmonary or visceral metastases	

*Serum marker should be measured before the start of the chemotherapy. **If hCG >500 IU/l consider as a non-dysgerminoma and treat as a non-dysgerminoma

difficult to make a preoperative diagnosis. The gold standard of treatment is complete debulking surgery either at primary surgery or after neoadjuvant chemotherapy followed by platinum-based combination chemotherapy. The challenges in developing countries include inadequate imaging, inadequate surgical training, lack of availability of chemotherapy and difficult access to healthcare for treatment and follow-up. The costs of the drugs available for the management of cancers make it very difficult for low-resourced settings to develop appropriate management protocols. Newer, affordable drugs focusing on maximal clinical benefit with minimal toxicity need to be developed.

It may also be possible that the outcomes from use of chemotherapeutic agents researched in clinical trials in affluent societies may differ significantly in less-developed countries due to differences in genetic, environmental, lifestyle and nutritional factors and health service infrastructure in the different resource settings. Quality of life studies assessing treatment effects in low-resourced communities would need to be done. Prolonged hospital stay, treatment side-effects, lack of post-treatment support, for a disease with limited survival may be unacceptable in less-developed communities.

ACKNOWLEDGEMENT

Dr MEL van der Burg, PhD, medical oncologist, critically reviewed the manuscript.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. *CA Cancer J Clin* 2005;55;74–108
2. WHO. Burden: mortality, morbidity and risk factors. Chapter 1. In: *Global status report on noncommunicable diseases*. Geneva: WHO, 2010. Available at: http://www.who.int/nmh/publications/ncd_report2010/en/
3. Clark TG, Stewart ME, Altman DG, *et al*. A prognostic model for ovarian cancer. *Br J Cancer* 2001;85:944–52
4. Kosary CL. Cancer of the ovary. National Cancer Institute. *SEER Survival Monograph* 1988–2001;133–44
5. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol* 2000;19:3–10
6. Gershenson DM, Ramirez PT. Ovarian cancer. In: *The Merck Manual of Diagnosis and Therapy*, 2008
7. Menon U, Gentry-Maharaj A, Hallet R, *et al*. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOKS). *Lancet Oncol* 2009;10:327–40
8. Valentin L, Ameye L, Testa A, *et al*. Ultrasound characteristics of different types of adnexal malignancies. *Gynecol Oncol* 2006;102:41–8
9. du Bois A, Quinn M, Thigpen T, *et al*. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;16 (Suppl. 8): viii7-viii12
10. Vergote I, Amant F, Ehlen T, *et al*. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943–53
11. Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free

interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 1992;47:159–66
12. Münstedt K, Franke FE. Role of primary surgery in advanced ovarian cancer. *World J Surg Oncol* 2004;2:32
13. Trimbos JB, Vergote I, Bolis G, *et al*. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst* 2003; 95:113–25
14. Colombo N, Guthrie D, Chiari S, *et al*. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst* 2003;95:125–32
15. Trimbos JB, Parmar M, Vergote I, *et al*. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105–12
16. Trimbos B, Timmers P, Pecorelli S, *et al*. Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. *J Natl Cancer Inst* 2010; 102:982–7
17. Sterling L, Lonkhuijzen L, Nyangena J, *et al*. Protocol development for ovarian cancer treatment in Kenya: a brief report. *Int J Gynecol Cancer* 2011;21:424–7
18. Lambert HE, Berry RJ. High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer (FIGO stages III and IV): report from the North Thames Cooperative Group. *BMJ* 1985;290:889–93
19. Piccart MJ, Bertelsen K, James K, *et al*. Randomized intergroup trial of cisplatin–paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708
20. The International Collaborative Ovarian Neoplasm Group (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002;360:505–15
21. Piccart MJ, Bertelsen K, Stuart G, *et al*. Long-term follow-up confirms a survival advantage of the paclitaxel–cisplatin regimen over the cyclophosphamide–cisplatin combination in advanced ovarian cancer. *Int J Gynecol Cancer* 2003;13 (Suppl. 2):144–8
22. Vergote I, Amant F, Leunen K, *et al*. Intraperitoneal chemotherapy in patients with advanced ovarian cancer: the con view. *The Oncologist* 2008;13:410–14
23. van der Burg ME, van Lent M, Buyse M, *et al*. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629–34
24. Rustin GJ, van der Burg ME, Griffin CL, *et al*. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet* 2010;376:1155–63

APPENDIX 1

Guideline for staging surgery early-stage ovarian cancer stage FIGO IA–IIA

- Inspection, palpation and resection
  - Median abdominal laparotomy
  - Cytologic whashing of ascites
  - Inspection and palpation of abdomen and pelvis
  - Uterus and adnexal extirpation
  - Omentectomy
  - (Appendectomy at mucinous adenocarcinoma)
- Staging biopsies
  - Biopsy of all sites where the ovary was adhesive
  - Biopsy every lesion suspicious for tumor
  - 'Blind' biopsy of the peritoneum from:
    - Bladder
    - Pouch of Douglas
    - Lateral pelvic sidewalls (fossa ovarica)
    - Left and right paracolic grooves
    - Right diaphragmatic site
- Lymph node dissection, or sampling of at least 2 lymph nodes from the following sites:
  - Para-aortic lymph nodes
  - Lymph nodes at the common iliac vessels
  - Lymph nodes at the internal iliac vessels
  - Lymph nodes at the external iliac vessels
  - Lymph nodes at the obturator fossa

NOTE: In young patients with ovarian cancer limited to one ovary and who want to preserve their fertility, tumor resection can be limited to one ovary + omentectomy and optimal surgical staging.

APPENDIX 2

Antiemetics in patients with chemotherapy for ovarian cancer

Medicine	*Day 1 of the chemotherapy*	*Day 2*	*Day 3*	*Day 4 and if necessary the following days*
Dexamethasone (1.5 mg)		2 × 1.5 mg	2 × 1.5 mg	1 × 1.5 mg
Ondansetron (4 mg) (Zofran®)		2 × 4 mg	2 × 4 mg	–
Domperidone (Motilium®)	2 × 2 tablet or 2 × 1 suppository	4 × 2 tablet or 4 × 1 suppository	4 × 2 tablet or 4 × 1 suppository	If necessary continue with domperidone

Take care of a daily urine output of 2 liters and a daily defecation. Daily 1 × 150 mg ranitidine; 3 times daily 1 or 2 tablets magnesium oxide to prevent constipation.

APPENDIX 3

Three-weekly carbotaxol/paclitaxel for epithelial ovarian cancer

Hour	*Time*	*Infusion fluid + medication*	*Initial*	*Control initial*
	T = –0 h 30 min	50 ml NaCl 0.9% + 10 mg dexamethasone + 50 mg ranitidine		
	T = –0 h 15 min	50 ml NaCl 0.9% + 2 mg clemastine		
	T = 0 h	500 ml NaCl 0.9% + paclitaxel 175 mg/m^2 in 3 h		
	T = 3 h	100 ml NaCl 0.9%		
	T = 3 h 30 min	50 ml NaCl 0.9% + 1 mg granisetron		
	T = 4 h	500 ml NaCl 0.9% + carboplatin (AUC 6) in 1¾ h		
	T = 1 h	End of infusion		

APPENDIX 4

BEP chemotherapy for germ cell tumors: chemotherapy regimens for patients in the different risk groups

Group	*Regimen*	*Day of administration*	*Interval*	*Number of cycles*
Good prognosis	BEP5			
	Bleomycin 30 mg	Day 2, 8 and 15	21 days	3
	Etoposide 100 mg/m^2	Day 1–5		
	Cisplatin 20 mg/m^2	Day 1–5		
	BEP3			
	Bleomycin 30 mg	Day 2, 8 and 15	21 days	3
	Etoposide 165 mg/m^2	Day 1–3		
	Cisplatin 50 mg/m^2	Day 1 and 2		
	EP			
	Etoposide 100 mg/m^2	Day 1–5	21 days	4
	Cisplatin 20 mg/m^2	Day 1–5		
Intermediate risk or poor prognosis	BEP5			
	Bleomycin 30 mg	Day 2, 8 and 15	21 days	4
	Etoposide 100 mg/m^2	Day 1–5		
	Cisplatin 20 mg/m^2	Day 1–5		
	VIP			
	Etoposide 75 mg/m^2	Day 1–5	21 days	4
	Ifosfamide 1.2 g/m^2	Day 1–5		
	Cisplatin 20 mg/m^2	Day 1–5		