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CONSENSUS DOCUMENT FOR MANAGEMENT OF EPITHELIAL OVARIAN CANCER

Prepared as an outcome of ICMR Subcommittee on Epithelial Ovarian Cancer

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Coordinated by:

Division of Non Communicable Diseases

Indian Council of Medical Research

Ansari Nagar, New Delhi – 110029

2019

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Prof. Balram Bhargava
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus document for Management of Epithelial Ovarian Cancer. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in formulating site-specific guidelines. The purpose of consensus document is to provide clear, consistent, succinct, evidence-based guidance for management of various cancers. I appreciate and acknowledge support extended by each member of the subcommittees for their contribution towards drafting of the document.

Epithelial Ovarian Cancer requires specialized multi-disciplinary care and treatment for better outcome. This document consolidates the modalities of treatment including the diagnosis, risk stratification and treatment. Hope that it would provide guidance to practicing doctors and researchers for the management of patients suffering from Epithelial Ovarian Cancer and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on the subject based on available evidence. Mention of drugs and clinical test for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinician in complex decision making. We are confident that this Consensus Document for Management of Epithelial Ovarian Cancer would serve desired purpose.

(Dr. Balram Bhargava)
Secretary, Department of Health Research
and Director-General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.

The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome, Pediatric Lymphoma, Pancreatic Cancer, Hepatocellular Carcinoma, Neuroendocrine Tumours and Ovarian Cancer. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till October 2015 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Ovarian cancer is the second most common gynaecological cancer in India. It is undoubtedly the most aggressive and lethal gynaecological cancer encountered by the Oncologists and Gynaecologists in their clinical practice, being associated with a high disease related mortality rate. This is partly due to the fact that most of the patients with ovarian cancer are diagnosed in advanced stages consequent upon its asymptomatic nature in early stages of the disease, and partly because many patients do not get optimum treatment of their disease, leading to dismal outcomes.

The management of ovarian cancer has changed dramatically in the last two decades. It is now well understood that in order to achieve optimal outcomes, it is mandatory to treat these patients with a combination of aggressive cytoreductive surgery and intensive chemotherapy. Apart from newer chemotherapeutic agents, there are novel drugs and novel drug delivery approaches, which have also made a significant impact. It is hence not surprising that there is evidence that these patients achieve a better outcome if treated by a trained Gynaecologic Oncologist, who is more likely to follow the standard management guidelines.

A panel of multidisciplinary experts from different parts of the country has reviewed, extensively deliberated and debated about all the present evidence pertaining to all aspects ovarian cancer including prevention & early detection to palliation, and have formulated these guidelines. These are implementable in day to day clinical practice and will help the clinicians offer the "state of the art" management to all patients with ovarian cancer, bring uniformity in patterns of care and will ultimately translate into better disease related outcomes in the whole country. However, as new evidence emerges in future, we will need to update these guidelines from time to time.

I wish to acknowledge the immense commitment, contribution and inputs of all the members of this subcommittee, who took out time from their busy schedules to bring out this document. I would also like to thank Dr. G. K. Rath and Dr. Tanvir Kaur for their unstinted support and guidance at all times and the ICMR for its excellent initiative to compile the guidelines for all important cancers in the country, which should serve as a useful reference resource for the practicing oncologists in India.

(Dr. Hemant Tongaonkar)
Chairperson
Sub-Communicate on Epithelial Ovarian Cancer

Preface

Cancer is a leading cause of death worldwide. Globally cancer of various types affect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

Consensus Document on Management of Epithelial Ovarian Cancer is a concerted outcome of efforts made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, ovary, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee Dr. Hemant Tongaonkar, is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Balram Bhargava, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to benefits the cancer patients.

I would like to thank Dr. R.S. Dhaliwal, head, Division of Non-Communicable Diseases for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

Tanvir Kaur

(Dr.Tanvir Kaur)
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CHAPTER

1 EPIDEMIOLOGY, RISK FACTORS, PREVENTION, SCREENING & EARLY DETECTION:

Epidemiology:

Ovarian cancer was estimated to be the third most common cancer among Indian women and eighth overall as per the Globocan 2018 Fact sheet, constituting 3.44% (36170) of all cancer cases [1]. It is also a leading cause of death from cancer in Indian women, with 3.34% (24015) of all cancer deaths in India in the same year. While 5-year survival from ovarian cancer is 94% when diagnosed in Stage I, only 15% of cases are diagnosed at this stage. Most (62%) of cases are diagnosed in Stages III and IV, when 5-year survival is only 28% [2]. Advanced stage ovarian cancer has a dismal prognosis, with the highest case-fatality ratio amongst all gynaecological cancers globally.

The estimated age-adjusted incidence varies from 0.9 – 8.4 per 100,000 women in various population-based cancer registries in India [3]. The incidence of ovarian cancer increases with age. The age specific incidence rate (ASIR) increases from age 35 years and peaks between the ages of 55-64 years. Most population-based cancer registries have documented a gradual increase in the incidence of ovarian cancer over the years. Since the population prevalence is low, the specificity of any screening strategy must therefore be high in order to achieve an acceptable positive predictive value (PPV), particularly since the follow-up testing associated with screen positive results is quite invasive.

Many western countries have reported a trend towards reduced incidence and mortality, which may be attributed to preventive measures like wider utilization of oral contraceptives, reduced use of post-menopausal hormone replacement therapy and increase in the risk-reduction surgeries.

Many studies report ovarian cancer, fallopian tube cancer and primary peritoneal cancer as one group, though some will also identify independent sub-groups, with the latter two comprising 15-20% of cases [4].

Risk Factors

According to IARC, there is sufficient evidence that epithelial ovarian cancer is caused by oestrogen hormone replacement therapy (HRT), tobacco smoking and exposure to asbestos. There is limited evidence regarding perineal use of talc-based body powder and exposure to X-radiation and gamma-radiation [5]. A long oestrogen window (early menarche and late menopause) also correlates strongly with risk of ovarian cancer. Nulliparity and older age at first childbirth (more than 35 years) confers an increased risk of developing ovarian cancer

There is a strong genetic predisposition for ovarian cancer. A family history of ovarian cancer in 2 or more first-degree relatives increases risk and is also associated with an early onset disease. A personal history of breast cancer prior to 40 years of age, or a personal history of breast cancer prior to 50 years of age with a family history of breast or ovarian cancer also increase the risk. Women of Eastern European (Ashkenazi) Jew descent are a special category at high risk. Women with an inherited gene

mutation have the highest risk, i.e. presence of BRCA1/BRCA2 gene mutations (associated with breast-ovarian cancer syndrome) or presence of a mismatch repair gene mutation associated with hereditary non-polyposis colorectal cancer (HNPCC)/ Lynch syndrome [6]. The estimated lifetime risk of developing ovarian cancer is 26-54% in carriers of BRCA1 mutation and 10-23% in carriers of BRCA2 mutation. However, these factors are present in only about 15% patients of ovarian cancer.

Studies on other potential risk factors, such as obesity, infertility, endometriosis, sedentary lifestyle, smoking and alcohol consumption have conflicting results [5,7]. Obesity is generally believed to be associated with the less aggressive types of ovarian cancer. Post-menopausal hormone therapy may actually increase the risk of ovarian cancer [8]. Certain fertility drugs have also been implicated in the aetiology of ovarian cancer. Risk of low malignant potential ovarian cancer may be increased after ovarian stimulation for in-vitro fertilization [9-10]. Recent data suggests that pelvic inflammatory disease may increase the risk of ovarian cancer [11]. A recent meta-analysis of published studies of tubal ligation reported 60% risk reduction in the risk of high-grade serous carcinoma including the high-risk population (BRCA 1 & 2 mutation carriers) (12,13)

Factors found to be protective against ovarian cancer include younger age (less than 25 years) at pregnancy and first childbirth (30-60% decreased risk of cancer), high parity, use of combined oral contraceptives for more than 5 years, and, possibly, breast feeding, hysterectomy and tubal ligation [14,15]. The odds ratio for cancer of the ovary among women who use oral contraceptives for more than 5 years is 0.44-0.54. Conversely, nulliparity or older age at first pregnancy confers an increased risk of ovarian cancer. Tubal ligation reduces the risk of developing ovarian cancer by 29% overall, with the greatest risk reduction in endometrioid and clear cell histology. This risk reduction by tubal ligation has been observed in high-risk populations of BRCA1 & 2 mutation carriers.

Prevention

Risk reducing surgery is the most effective risk reducing strategy presently. Prophylactic salpingo-oophorectomy after the completion of childbearing in high risk women, i.e., carriers of BRCA1/BRCA2 gene mutations or carriers of mismatch repair gene mutations in HNPCC syndrome group can prevent up to 90% of ovarian, fallopian tube and primary peritoneal cancers in this group [16-19], and lead to reduction in the all-cause mortality [18,20] as well as improvement in the physical and psychological well-being of the women. However, a residual risk of developing primary peritoneal cancer in women at high risk of cancer still remains. Women with these conditions should be referred for formal genetic counseling to better assess their cancer risk, including risk of ovarian cancer. ACOG recommends that prophylactic surgery be done by age 40 years in these high-risk groups [21]. Occult cancer may sometimes be found after prophylactic risk reducing surgery and this mandates a careful pathology review of the specimen. It is recommended that the fallopian tubes should be processed by sectioning and extensively examining the fimbrial end to determine whether any evidence of cancer is present, since it has recently been suggested that fallopian tube may the origin of serous ovarian and primary peritoneal cancers [22-24]. The ovaries should also be similarly assessed by carefully sectioning them [24]. Risk reducing surgery may be done by the laparoscopic route. Risk reducing BSO is not recommended in general or low-risk population because of the increased incidence of coronary heart disease, stroke, osteoporosis and increased mortality etc after ovarian removal [25-28].

It has been suggested that serous carcinomas of the ovary, fallopian tube or peritoneum (including serous tubal intraepithelial carcinoma – STIC) may originate in the fallopian tube (29). Consequently, opportunistic salpingectomy (from fimbria to insertion of tube into uterus) should be considered in women undergoing intra-peritoneal gynaecological procedures, at hysterectomy or during sterilization procedures, with a

42-65% reduction in the risk for ovarian cancer [27,28]. However, the impact of salpingectomy alone on cancer prevention is not yet proven. This is essentially indicated in general/low-risk women, while in high-risk women, salpingo-oophorectomy is the standard of care. It is important for the pathologist to do a systematic and complete examination of the fallopian tubes in all women undergoing salpingectomy or salpingo-oophorectomy for benign conditions (30).

In BRCA and BRCA2 carriers, a premenopausal prophylactic BSO will also reduce the risk of breast cancer by 50%. Occult ovarian or fallopian tube tumours have been found in 4.4% of these women.

Recently, implementation of universal germ-line screening for all women with epithelial ovarian cancer has been recommended. All women with newly diagnosed ovarian cancer should consider germ-line screening for BRCA1/2 and other genetic mutations associated with an increased risk, regardless of family history. Screening and identification of high-risk family members is also recommended.

In high-risk women, use of oral contraceptives, dietary changes and lifestyle modifications have been recommended.

Screening & Early Detection

Randomized controlled trials do not support routine screening for ovarian cancer in general population. Screening asymptomatic women for ovarian cancer using ultrasonography, serum tumor markers or pelvic examination is not recommended [2, 31-38]. [Level A recommendation]

Screening by serum CA-125 testing or transvaginal ultrasonography (TVS) or both can result in detection of ovarian cancer at an earlier stage, but also there is fair evidence that impact on mortality is small and potential harms, e.g., invasive diagnostic testing and unnecessary surgery, can outweigh potential benefits. In general, most tumours in the below-cited major randomized clinical trials were not detected in earlier stages.

In 2011, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a randomized controlled trial in 78000 women, found that annual screening of women at average risk for ovarian cancer with serum CA-125 and TVS did not reduce cancer-specific or overall mortality compared with usual care [4]. It also confirmed the risk of potential harms associated with false-positive screening test results, including a higher frequency of surgery and surgical complications in such cases. It however showed that significantly fewer patients were diagnosed with advanced stage disease in the screening arm; and survival was significantly improved, without significant reduction in mortality.

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS), both randomized controlled trials, have presented potential harms due to associated complications, but did not publish results on mortality [39,40]. In UKCTOCS women were randomized to receive annual screening with CA-125 testing with abnormal tests followed up with TVS, annual screening with TVS alone, or no treatment. In SCSOCS, annual screening was done by serum CA-125 and TVS. If TVS was abnormal, they were referred for further evaluation, including a repeat scan prior to surgery. If CA-125 was abnormal, women were rescreened after 6 months with both tests. Both these studies showed that multimodal screening was more effective (higher specificity) than TVS alone for early detection of ovarian cancer. In spite of this, it is not routinely recommended since its impact on mortality reduction has not been demonstrated.

The recently published final results of the UKCTOCS trial (2015) with median 11 years of follow up, reported encouraging results using ROCA –driven multimodal screening, with a high sensitivity of 84-85.9%, specificity of 99.8%, an acceptable rate of 2.7 operations per cancer case detected and a 3%

complication rate [41,42]. Although the Cox model showed a non-significant 15% mortality benefit, post-hoc analysis showed a statistically significant delayed effect on mortality only after more than 7 years after randomization. The authors also showed a statistically significant down-staging to stage III A or less (26% vs. 40%), which may have resulted in more number of patients achieving complete (R0) cytoreduction and may have translated into better survival. The impact of MMS on ovarian cancer mortality based on the results of this trial is not established and is, at best, modest. It is possible that additional follow up may show a significant mortality benefit but till such time, screening for ovarian cancer cannot be considered for introduction into routine practice or a national programme.

A trial comparing Ca-125 alone, ultrasound alone and ultrasound plus Ca-125 showed no additional benefit of adding Ca-125 to ultrasound and that ultrasound was superior to Ca-125 alone [43].

A recent screening trial (Risk of Ovarian Cancer algorithm- ROCA) used an algorithm that used age and longitudinal changes in Ca-125 levels to determine whether women at average risk would develop ovarian cancer and to triage at-risk women for transvaginal sonography [44]. However, this algorithm based screening is presently not recommended due to lack of sufficient evidence supporting the same.

Several biomarker--based screening tools are available in the western countries (e.g. OVA 1, OvaSure). However, their routine use is not recommended due to lack of conclusive evidence regarding their efficacy for early detection or mortality reduction.

Recommendations: Women with no increased risk should not be recommended screening, women with increased risk may be advised screening only in the framework of research studies, and women with inherited risk may undergo screening beginning between the age of 30 and 35 years in the case of BRCA1 and mismatch repair gene mutations, and between 35 and 40 years in the case of BRCA2 mutations, but the more effective strategy is risk reducing surgery at the completion of childbearing.

Because of the location of the ovaries and the asymptomatic nature of early ovarian cancer, it is extremely difficult to diagnose ovarian cancer early, when the cure rates are high. Early detection requires the education of both the patient and her physician regarding symptoms commonly associated with ovarian cancer, in order to have a high index of suspicion of the diagnosis in symptomatic women. Based on the findings of the clinical research study funded by the Canadian Institute of Health Research, it is recommended that tests be carried out especially in women aged 50 years or greater if they report the following symptoms to be persistent and progressive, particularly more than 12 days per month: Increase in bloating or distension of abdomen, pelvic or abdominal pain, difficulty in eating or early satiety, nausea, vomiting, heartburn, gas; increased urinary urgency and/or frequency; symptoms suggesting irritable bowel syndrome (IBS), vaginal discharge or unexplained weight loss for the first time after 50 years of age.

In evaluating these symptoms, a physical examination including a bimanual pelvic examination and rectovaginal examination should be performed. Serum CA-125 levels should be tested and especially in those with elevated levels, imaging studies, especially TVS, should be advised to recognize increased ovarian size of morphologic changes associated with ovarian cancer. The DOVE (Detecting Ovarian Cancer Early) study using these symptoms to triage patients for early investigations for detection of possible ovarian cancer, however, did not result in a higher detection of ovarian cancers or improved survival from ovarian cancer.

When a patient with a suspicious or persistent complex adnexal mass requires surgical evaluation, it should be carried out by a Gynaecologic Oncologist who is trained to optimally stage and adequately treat these patients if the mass turns out to be malignant [45,46].

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CHAPTER

2 PATHOLOGY:

Cancer of the ovary represents about 30% of all cancers of the female genital organs; and surface epithelial-stromal tumors are the most common neoplasms of the ovary (1). Malignant ovarian tumours encompass different histologic types (surface epithelial-stromal tumors, sex cord stromal tumors, germ cell tumors and others including secondary tumours).

Surface epithelial tumors comprise nearly 90% of all epithelial tumours. These are subclassified into serous, mucinous, endometrioid, clear cell, transitional cell and squamous (WHO classification). Each of them represents distinct entities, with distinct pathogenesis and distinct biological behaviour. They may be benign or malignant. A separate entity with a distinct natural history, called tumours of low malignant potential (borderline malignancy) has been described. Borderline tumours or tumours of low malignant potential are characterized by cytological characteristics of malignancy but without frank invasion.

The major types of malignant epithelial ovarian tumors are- serous adenocarcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, clear cell carcinoma, transitional carcinoma, squamous carcinoma, undifferentiated carcinoma and mixed carcinoma. Morphology remains the mainstay in diagnosis; but immunohistochemistry is of value in supplementing the diagnosis. Each of these tumour subtypes is associated with distinct clinical and molecular features and has specific molecular targets for planning therapy.

It is recently proposed that there are two distinct types of ovarian serous carcinomas- low grade (type I) and high grade (type II). It is to be clarified that they are not two grades of the same neoplasm; but represent two different entities with differing pathogenesis, molecular events, natural history, biological behavior, response to therapy and prognosis. High grade OSC are more common than the low grade OSC. Low grade OSC is thought to arise from cystadenoma, through to borderline serous tumour, borderline serous tumour with micropapillary pattern and then invasive low grade OSC (similar to a well defined adenoma-carcinoma sequence), although they may also arise de-novo. However, it may be rare to see all the features in a given tumour. In contrast, high grade OSC arises from ovarian surface epithelium or the epithelium of the cortical inclusion cysts._Low grade and high grade OSC are both high stage disease; but low grade is more indolent, slow growing and shows poor response to platinum based therapy. Although it usually results in death of the patient, it is compatible with prolonged survival._High grade OSC are aggressive, show initial response to platinum based therapy but shows recurrence and are eventually fatal.

Low grade OSC/ Type I tumors	High grade OSC/ Type II tumors
- K-RAS or B-RAF mutations	-No K –RAS or B-RAF mutations
-Lower expression of mib-1, bcl2, her2 neu, p16, Ki-67, c-KIT & MMP-9.	-Higher expression of p53,bcl2,mib-1,p16 her-2neu
- Weak or negative expression for p53	-p53 mutation, high chromosomal instability

- Express WT1	-Express WT1
- Express ER, PR (Possible therapeutic role?)	-Do not express ER, PR
- Younger age group	-Older age group

Endometrioid adenocarcinomas of ovary are associated with endometriosis. Low-grade endometrioid carcinomas are known to arise from endometriosis and are classified as type 1 carcinomas akin to low-grade serous carcinomas. Considering morphological overlap between high-grade serous and high-grade endometrioid carcinomas, the latter have been similarly classified as type II ovarian carcinomas. These tumors are genetically characterized by inactivating mutations of the tumor suppresser gene PTEN in 14-21% ovarian endometrioid carcinomas (2).

Clear cell adenocarcinoma occurs primarily in 5th decade and about 50-70% cases are associated with endometriosis. They are usually unilateral and have a lower incidence of lymph node involvement than high-grade serous cancers. It characteristically associated with poor response to chemotherapy (including intraperitoneal chemotherapy) and the poorest prognosis in epithelial tumors. Immunophenotypically, they express hepatocyte nuclear factor 1- beta (HNF-1Beta), lack of WT1 and ER, and lack of p53 overexpression. About 1/3rd of clear cell carcinomas have PIK3CA mutation. Recently, mutation in ARID1A gene which encodes BAF250 protein, in high percentage of endometriosis associated ovarian carcinomas (clear cell type and endometrioid type) has been detected (3,4). Stage I clear cell carcinomas are treated as per the recommendations for stage I grade III tumours.

While reporting on the biopsy or histopathology of the surgical specimen, the WHO classification of primary epithelial tumours (5) given below should be followed.

WHO classification of primary ovarian epithelial tumours

Serous tumours

Borderline

Serous borderline tumour / atypical proliferative serous tumour

Serous borderline tumour – micropapillary variant / non-invasive low grade serous carcinoma

Malignant

Low grade serous carcinoma

High grade serous carcinoma

Mucinous tumours

Borderline

Mucinous borderline tumour / atypical proliferative mucinous tumour

Malignant

Mucinous carcinoma

Endometrioid tumours

Borderline

Endometrioid borderline tumour / atypical proliferative endometrioid tumour

Malignant

Endometrioid carcinoma

Clear cell tumours

Borderline

Clear cell borderline tumour / atypical proliferative clear cell tumour

Malignant

Clear cell carcinoma

Brenner tumours

Borderline

Brenner borderline tumour / atypical proliferative Brenner tumour

Malignant

Malignant Brenner tumour

Seromucinous tumours

Borderline

Seromucinous borderline tumour / atypical proliferative seromucinous tumour

Malignant

Seromucinous carcinoma

Undifferentiated sarcoma

Mixed epithelial and mesenchymal tumours

Carcinosarcoma

Comprehensive reporting of the histopathology specimen of surgery for ovarian cancer:

Histopathology reporting:

Gross examination: A diligent gross examination and sampling is crucial. The specimen should be sent to the laboratory as quickly as possible. Proper fixation will prevent the tissue degeneration or the autolysis, especially if the specimen is to be sent to a higher centre / referral centre. The practice of slicing the specimen in the operating theatres should be resisted, or at least this should be done with the presence / help of the pathologist. This will ensure proper documentation of the gross findings.

Along with the dimensions and weight, comment about the capsular breach or intactness is important. Sometimes, the ovarian cysts are ruptured during surgery and the pathologist may not have immediate access to the surgical notes. Hence, status of the capsule, at receipt, should be mentioned. If any carcinomatous cyst or a tumour has had a rupture before or during surgery, then the stage of the disease is at least – stage I C.

Generally, a rule of one section per cm of diameter in ovarian tumors is observed. This should be particularly followed in mucinous ovarian tumors. Discretion can be used in cases of large unilocular simple cysts or large solid obvious malignant tumors.

Datasets and reporting systems: Various datasets and reporting systems (6) have been used for

reporting of the histopathology and cytology specimens obtained at surgery. Some commonly used ones are Royal College of Pathologists system (RC-Path), College of American Pathologists (CAP) system and the International Collaboration on Cancer Reporting (ICCR) dataset. Although it is recommended that such comprehensive reporting should be carried out at tertiary care centres, this may not be practical in many parts of our country and hence each Institute or Pathologist should develop an independent dataset which can give the minimum requirement for optimum staging, prognostication and planning therapy.

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CHAPTER

3 HISTORY & CLINICAL PRESENTATION & INVESTIGATIONS:

The symptoms of ovarian cancer in the early stages may be minor, transient and may be ignored by the patient and the physician. However, the following symptoms if persistent should raise the suspicion of ovarian cancer and warrant further evaluation and investigations (1,2):

- Symptoms of bloating, dyspepsia, nausea, changes in bowel habits (constipation or diarrhoea), early satiety, distension, abdominal or pelvic pain or discomfort, urinary frequency or urgency, constipation, dyspareunia
- In premenopausal women, changes in the menstrual cycle pattern
- Palpable pelvic or abdominal mass
- Symptoms of intestinal obstruction
- Ascites / pleural effusion causing cough, breathlessness etc.

Past history of breast or endometrial cancer in the patient or a family history of breast, ovarian, endometrial or colonic cancers need to be elucidated in all patients. Clinical examination should include a thorough abdominal and pelvic (per vaginal and per rectal examination), breast examination as well as examination of the lymph nodes in the cervical (especially supraclavicular), inguinal and axillary regions.

Investigations

The aim of investigations is to accurately differentiate between benign and malignant masses, determine the extent of disease and to assess the operability.

- Haematological and biochemical investigations
- Serum tumor markers: CA-125, CEA, CA 19.9. Serum Ca-125 estimation is especially useful in postmenopausal women in whom its specificity is higher than in premenopausal women. However, it does not have sufficient sensitivity or specificity for it to accurately diagnose ovarian cancer consistently. Recent analysis of 5 studies comparing Ca-125 with HE4 in women with pelvic masses consistently demonstrated that HE4 is more sensitive and more specific than Ca-125 for diagnosis of ovarian cancer. Combination of Ca-125 and HE4 was found to be more specific but less sensitive than either of the markers in isolation. Their use to diagnose an ovarian cancer and also to distinguish benign from malignant masses is limited. Serum alpha-fetoprotein, serum beta-hCG should be done in women less than 35 years of age with an ovarian mass, when germ cell tumour is suspected. Serum inhibin may be done when sex cord stromal tumour of the ovary is suspected or diagnosed.
- Imaging studies. Ultrasonography of abdomen and pelvis (transabdominal and transvaginal) is the usual first investigation for assessment of an undiagnosed adnexal mass and/or ascites or of symptom complex suggestive of ovarian mass. The presence of a complex solid and cystic mass

with presence of internal septae (especially if vascular), solid areas, internal echoes or papillary projections may indicate presence of malignancy. Colour Doppler has not been shown to improve the sensitivity or specificity of ultrasonography significantly. CT scan of the abdomen & pelvis and CT scan of the chest (with oral & intravenous contrast unless contraindicated) is recommended as the modality of choice for optimum evaluation of extra-ovarian spread. Diffusion weighted MRI (with contrast unless contraindicated) or PET scan may provide additional information but are not routinely recommended in the primary work up for a suspected ovarian or cancer. They may be used for characterization of indeterminate adnexal/ovarian lesions.

Accuracy of good quality ultrasonography with colour Doppler, CT scan and MRI are similar (sensitivity about 90% and specificity 85%) for differentiating benign from malignant ovarian masses (evidence from systematic reviews & meta-analysis)(3-7). In patients with suspicious ovarian masses (where simple cysts have been excluded), MRI probably has a better positive predictive value (8-9). For staging and for predicting optimal cytoreduction, CT and MRI are probably equivalent and both are superior to ultrasonography (10). However, as a predictor of optimal cytoreduction, both CT and MRI have significant limitations. PET-CT may be used for indeterminate lesions and for mapping the disease extent if primary surgery is not contemplated (11-14).

- X-ray chest or CT scan of the chest
- Upper and Lower GI evaluation including endoscopy only if clinically indicated (for mucinous tumours or in presence of GI symptoms, raised serum CEA levels or a family history of colorectal cancer) to rule out gastric, colorectal or appendicular primary cancers but their routine use is not recommended. Other cancers that need to be ruled out are gall bladder, pancreas and breast cancers.
- Ascitic fluid/ pleural fluid cytology (if ascitic or pleural fluid present).
- Fine needle aspiration cytology (FNAC)/ biopsy of the mass should be done only if primary surgery is not indicated, prior to starting neoadjuvant chemotherapy. Pre-operative FNAC of the mass should be avoided in patients with presumed early stage disease to prevent rupturing the cyst & spilling of the malignant cells into the peritoneal cavity. Pre- or intra-operative spillage has been found to be an independent prognostic variable impacting survival (15). Histological or cytological diagnosis may be necessary in patients with advanced clinical stage III / IV where primary surgery is not contemplated in view of unresectable disease or in patients with low performance status who are not candidates for primary surgery, prior to starting neoadjuvant chemotherapy. Histological evaluation from tissue biopsy is more accurate than cytological examination of ascitic or pleural fluid but is also associated with greater risk. Tissue for biopsy may be obtained by percutaneous image guided biopsy or if this is not possible or inadequate, then by the laparoscopic route.
- Risk of malignancy indices (RMI) or Risk of malignancy algorithms (ROMA): Several parameters useful for differentiating benign from malignant tumours e.g. age, menopausal status, ultrasound findings, serum tumour marker Ca-125 levels etc. may be combined to provide risk of malignancy indices which help to predict the probability of malignancy in a particular patient. Presently, none of these parameters either individually or in combination as predictive indices have adequate accuracy to accurately predict malignancy in an adnexal mass. An analysis of validated risk of malignancy indices (16) showed that the RMI I proposed by Jacobs in 1990 (17) was superior to

other RMIs in terms of sensitivity and specificity (with a cut off level of 200, sensitivity 78% and specificity 87%; and with a cut off of 50, sensitivity 91% and specificity 74%). This RMI score considers ultrasonography features, menopausal status and CA 125 levels for evaluating the mass. There are two scoring systems RMI 1 and RMI 2.

RMI score = Ultrasound score x menopausal score x CA125 level.
Cut off Level: More than 200.
RMI score 2 was found to be more sensitive (74-80%), with a specificity of 89-92% and a positive predictive value of 80%.

Feature	RMI 1 score	RMI 2 score
Ultrasonography	0= None	0= None
Multilocular cyst	1= one abnormality	1 = one abnormality
Solid areas	3= two or more abnormalities	4 = two or more abnormalities
Bilateral masses		
Ascitis		
Intra-abdominal metastases		
Premenopausal	1	1
Postmenopausal	3	4
CA 125 levels U/ml		

It is recommended that all women with RMI 1 score of >250 should ideally be referred to a specialist Gynaecologic Oncologist for further management. However, the optimum RMI 1 threshold to be applied in practice to guide management of women with suspected ovarian cancer is still uncertain and is a matter of research.

Specific biomarkers such as serum HE4 and Ca 125 along with the Risk of Ovarian Malignancy algorithm may be useful in differentiating benign from malignant masses but its routine use in patients with undiagnosed pelvic mass is not recommended. (18)

Referral criteria for referral to a tertiary centre or a Gynecologic Oncologist:

- Any complex adnexal / ovarian mass diagnosed in either pre / postmenopausal woman should be referred without doing FNAC.
- Risk of malignancy index (RMI 1) score >250
- Suspected ovarian cancer advanced stage.
- Suspected ovarian cancer with a diagnostic dilemma.
- Suspected recurrent ovarian cancer.

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CHAPTER

4 PRIMARY SURGICAL TREATMENT OF EARLY STAGE DISEASE AND SURGICAL STAGING

Ovarian cancer is staged surgico-pathologically. Optimal surgery is of importance for determining the extent of disease, to stage the disease, to plan optimal treatment and for prognostication. Comprehensive surgical staging to rule out occult higher stage disease should be performed and has been shown to be an independent prognostic factors impacting survival in multivariate analysis since approximately 22-31% of apparently early stage disease are upstaged after a comprehensive surgical staging (1). It is recommended that the surgery is carried out by a specialist Gynaecologic Oncologist trained and experienced in the management of ovarian cancer, based on the published improved outcome results (category 1 recommendation) (2-4).

A midline vertical incision laparotomy with adequate exposure for thorough examination of the entire abdomen and pelvis should be used whenever a staging procedure or primary/interval/secondary cytoreductive surgery is contemplated for a suspected or proven ovarian or tubal or primary peritoneal cancer.

Surgical staging and management of a patient with ovarian cancer apparently confined to ovary / pelvis:

1. Aspiration of ascites when present or peritoneal washings (lavage) for cytological examination. The specimen should reach the laboratory as early as possible.
2. All peritoneal surfaces should be visualized and any abnormal peritoneal surface or adhesions excised and biopsied. In case of normal peritoneal surfaces, random peritoneal biopsies should be taken from pelvis, utero-vesical peritoneal fold, recto-uterine pouch, bilateral paracolic gutters, undersurface of the diaphragm etc.
3. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, excising the mass intact as far as possible using an extraperitoneal approach to prevent intra-operative spillage (5-7)
4. In case of the rupture of the capsule, it is important to differentiate between pre-operative spontaneous tumour rupture and intra-operative rupture caused by the surgeon and document the same.
5. Total omentectomy
6. Pelvic and para-aortic lymph node assessment (8, 9): Complete pelvic and retroperitoneal lymphadenectomy should be performed in all cases. The upper extent of lymphadenectomy may vary according to the risk of nodal metastases in an individual patient. The upper limit of lymphadenectomy should be at the level of the renal vessels in high-risk patients and should at least be to the level of inferior mesenteric artery in lower risk patients (level of evidence 3). Present evidence does not allow recommendation of a formal systematic lymphadenectomy in patients where the disease is low grade and is confined to the ovaries.
7. Appendicectomy (in mucinous tumours)

8. Staging for borderline (low malignant potential) tumours is similar to that in invasive cancers. The retroperitoneal lymph node dissection may be omitted

9. In selected young patients desirous of fertility preservation, with stage stage I A low risk (low grade or low malignant potential) tumours, unilateral salpingo-oophorectomy may be done along with comprehensive staging. Proper counseling of the patients regarding the need for a regular follow-up and the risk of recurrence in the other ovary and peritoneum is essential prior to fertility sparing surgical approach (10-15). For those with stage IB tumours who wish to preserve fertility, BSO with preservation of uterus may be considered. Role of completion surgery after completion of family is not well defined, although most women are encouraged to undergo completion surgery after they finish childbearing (category II B recommendation). Women who do not desire fertility-sparing surgery should undergo a standard cytoreductive surgery, although the accrued benefit with lymphadenectomy and omentectomy is doubtful (16,17). The role of conservative surgery in patients with stage IC and/or grade II/III (high grade) patients is controversial at present. It may be offered to these patients on an individual basis after thorough counseling regarding increased risk of relapse and should be followed by adjuvant chemotherapy. These patients should be encouraged to have completion surgery after her childbearing has been completed.

10. In the operative report, the surgeon should carefully document a. the extent of initial disease, b. amount, extent & location of the residual disease, and c. whether complete or incomplete resection has been performed (18)

11. Presently, there is no evidence to suggest that laparoscopic or robotic staging of early epithelial ovarian cancer is equivalent or superior to staging by laparotomy. However, in select patients, minimally invasive procedures may be used for surgical staging (19-22) and to achieve surgical goals (23,24) if surgery is performed by an experienced Gynaecologic Oncologist trained in advanced minimal access surgery.

12. Role of frozen section: Whenever exploration is being done for a suspicious adnexal mass, frozen section facility is required as it can have a significant impact on extent of surgery and the outcomes. The reported accuracy of frozen section is about 95-97%.

13. Patients referred after an incomplete surgery should have comprehensive surgical staging if feasible after appropriate investigations mentioned above (see Investigations for undiagnosed pelvic mass)

FIGO has recently recommended a modified staging system which will help in better prognostication by subdividing certain sub-stages to stratify patients according to risk of relapse.

Staging: Ovarian Cancer (FIGO staging system 2014) (25-26)

Stage	
I	Tumour limited to ovaries (one or both)
I A	Tumour limited to one ovary; capsule intact, no tumour on ovarian surface. No malignant cells in ascitis or peritoneal washings.
IB	Tumour limited to both ovaries; capsules intact, no tumour on ovarian surface. No malignant cells in ascitis or peritoneal washings.
IC IC1 IC2 IC3	Tumour limited to one or both ovaries Surgical spill Capsule ruptured before surgery or tumour on ovarian surface Malignant cells in ascitis or peritoneal washings
II	Tumour invades one or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

II A	Extension and/or implants on uterus and/or tubes.
IIB	Extension to and/or implants on other pelvic intraperitoneal tissues.
III	Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.
IIIA IIIA1 IIIA1(i) IIIA1(ii) IIIA2	Positive retroperitoneal lymph nodes and/or microscopic peritoneal metastases beyond pelvis. Positive retroperitoneal lymph nodes only Metastasis <10 mm Metastasis >10 mm Microscopic extrapelvic (above the brim) peritoneal involvement +/- positive retroperitoneal lymph nodes
IIIB	Macroscopic extrapelvic peritoneal metastases beyond pelvis 2 cm or less in greatest dimension +/- positive retroperitoneal lymph nodes, includes extension to capsule of liver/spleen
IIIC	Peritoneal metastases beyond pelvis more than 2 cm in greatest dimension +/- positive retroperitoneal lymph nodes, includes extension to capsule of liver/spleen
IV IVA IVB	Distant metastasis (excluding peritoneal metastasis) Pleural effusion with positive cytology Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

Other major recommendations for staging were as follows:

1. Histologic type including grading should be designated at staging
2. Primary site (ovary, fallopian tube, peritoneum) should be designated where possible.
3. Tumours that may otherwise quality for stage I but involved with dense adhesions justify upgrading to stage II if tumour cells are histologically proven to be present in the adhesions.

In the event the patient receives chemotherapy prior to surgery, clinical staging is followed. However, it is recommended that an effort must be made to stage the disease as accurately as possible by imaging studies or laparoscopic evaluation prior to initiation of chemotherapy. Incompletely staged patients after initial surgery should be counseled regarding the need for comprehensive surgical staging for planning optimum treatment and for achieving optimum outcomes. They should undergo a restaging laparotomy as described earlier.

Prognostic factors and risk grouping:

Numerous prognostic factors have been identified by multivariate analysis in patients with early stage epithelial ovarian cancer, such as, tumour differentiation or grade, histology, stage, pre-op or intra-operative tumour rupture and age of the patient. Based on these independent prognostic variables, the comprehensively staged patients are stratified into different risk groups according to the risk of relapse viz.

a. Low risk (Low malignant potential or Grade I/II, stage 1A/B tumours with non-clear cell histology and adequately staged)

No adjuvant therapy recommended

b. High risk (Grade III and/or stage IC tumours or high-risk histology e.g. clear cell, transitional cell etc. Also include suboptimally staged patients)

Adjuvant therapy recommended. Platinum based adjuvant chemotherapy improves 5 years overall survival and recurrence free survival in patients with early stage ovarian cancer (ICON-1/ACTION).

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CHAPTER

5 ADJUVANT CHEMOTHERAPY FOR EARLY STAGE OVARIAN CANCER:

Recommendations:

1. Patients with epithelial ovarian cancer of FIGO stage I are considered to have early stage disease. Patients with FIGO stage II disease are variably considered to have early or advanced stage disease.
2. Patients with stage IA and IB, grade 1 tumors are candidates for observation without adjuvant systemic therapy, because survival is more than 90% with surgical treatment alone.
3. Patients with stages IA and IB tumors grade 2 tumors can be either observed or offered 3-6 cycles of adjuvant chemotherapy. However, a thorough comprehensive surgical staging is recommended in all these patients.
4. Patients with stages IA and IB with grade 3 tumors and those with stage IC tumor of any grade should be offered 3-6 cycles of adjuvant chemotherapy.
5. Patients with stage II disease of any grade should be offered 6 cycles of adjuvant chemotherapy.
6. The stage wise recommendations for adjuvant chemotherapy are applicable to patients who have been meticulously surgically staged and found to have early stage disease. Patients with potential early stage disease who have been inadequately surgically staged should preferably undergo complete surgical staging prior to adjuvant decision-making. If this is not possible for any reason, such `early stage' patients should be offered adjuvant chemotherapy as outlined above.
7. The standard chemotherapy regimen is a platinum and taxane combination in the same doses and schedules as for advanced stage disease. Single agent platinum therapy (carboplatin or cisplatin) is an acceptable alternative. The use of alternative combinations is governed by the same principles as for advanced stage disease.
8. Dose dense schedules, intraperitoneal administration, maintenance strategies and targeted therapies are not recommended in early stage patients.
9. The use of whole abdominal radiation and intraperitoneal administration of radioactive compounds as adjuvant therapy is not recommended.
10. There is no proven benefit of adjuvant chemotherapy in patients with low malignant potential ovarian cancer.

Background:

The current standard of care is to categorize patients as having early stage disease after a meticulous surgical staging procedure. In patients with inadequately staged `early stage' disease, a considerable fraction has occult stage III dissemination (1). Adjuvant decision-making is complicated in the latter patients.

Evidence:

a. Observation without adjuvant systemic therapy in stages IA/IB, grade 1-2 tumours. Multivariate analysis in a large retrospective study of more than 1500 FIGO stage 1 patients indicated that degree of differentiation was the most powerful prognostic factor followed by preoperative and intraoperative tumour rupture (2). Another combined analysis of two randomized trials in patients with stage 1 and 2 ovarian cancer suggested that well to moderately differentiated tumours confined to the ovaries (stages 1A and 1B) derived no significant benefit from adjuvant therapy (3). Based on these and other analyses, there is general consensus that patients with stages 1A and 1B disease (based on an optimal surgical staging procedure) of good to moderate differentiation can be observed without adjuvant chemotherapy.

b. Benefit of adjuvant chemotherapy in early stage disease. Two randomized trials of platinum based chemotherapy in early stage ovarian cancer (1,4) and their combined analysis (5) form the most definitive body of evidence for the use of adjuvant chemotherapy in this disease. In aggregate they suggest that there is a statistically significant benefit of adjuvant platinum based chemotherapy in terms of both overall survival (absolute improvement at 5 years of 8%, from 74 to 82%) and recurrence free survival (absolute benefit of 11% at 5 years, from 64 to 76%). Importantly, patients received a variety of adjuvant platinum regimens in these trials including single agent platinum and combinations. A recent Cochrane systematic review has essentially reached the same conclusions (6).

c. Inadequately surgically staged `early stage' patients. At least one well-conducted large randomized phase III trial has shown that the benefit of adjuvant platinum based chemotherapy in early stage ovarian cancer is essentially limited to suboptimally staged patients indicating the presence of `occult' higher stage patients within this group (1). Therefore an optimal staging procedure is recommended for all apparently early stage patients. If, for any reason (such as patient refusal to undergo a second surgery after an initial suboptimal one), this is not possible, such patients are candidates for adjuvant chemotherapy.

d. Use of combination chemotherapy versus single agent platinum in early stage disease. The majority of patients (>90%) in ICON 1 trial (4) received single agent platinum therapy whereas only a minority of patients (33%) received this in the ACTION trial (1). Other studies that have used the standard paclitaxel and platinum combination (7) have also achieved excellent outcome in early stage disease. Based on these and other studies, combination paclitaxel and carboplatin is considered standard adjuvant treatment in early ovarian cancer. Single agent platinum is an acceptable alternative.

e. Number of cycles of adjuvant chemotherapy. One recent study (7) compared the use of three versus six cycles of adjuvant paclitaxel-platinum regimen in early stage ovarian cancer. The overall results failed to prove the superiority of 6 over 3 cycles with respect to both disease-free and overall survival. However subgroup analysis by histology suggested a benefit in serous tumours (8). Six cycles are considered standard in early stage disease with three cycles being an acceptable alternative.

f. Use of whole abdominal radiation and radioactive phosphorus. Epithelial ovarian cancer is a radiosensitive tumour. Studies have shown that radioactive phosphorus (9) or whole abdominal radiation (10) have reasonable efficacy in the adjuvant setting. However, because of the higher risk of late complications, especially involving the bowel, these treatments are no longer recommended in the adjuvant setting.

g. Early stage clear cell carcinoma. The bulk of tumors in randomized trials have been serous carcinomas because of the rarity of other subtypes.There is emerging evidence that the uncommon subtypes

(mucinous and clear cell) have different biological characteristics, chemosensitivity and outcome (poorer outcome in advanced stages) compared to the serous subtype (11). High quality evidence, on which to base treatment recommendations, is lacking. They are generally treated in a manner similar to serous tumours.

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CHAPTER

6 TREATMENT OF ADVANCED OVARIAN CANCER: CYTOREDUCTIVE SURGERY

Definitions:

Cytoreductive (debulking) surgery refers to debulking surgery where gross tumour is resected.

Primary cytoreduction is when debulking surgery is the first modality of treatment

Interval cytoreduction is when debulking is done in between courses of chemotherapy

Complete debulking is defined as no visible or palpable macroscopic residual disease.

Optimal debulking is defined as no macroscopic residual deposits over 1 cm in diameter.

Sub-optimal debulking is residual deposits over 1 cm in diameter.

Recommendations:

1. All women with suspected stage III/IV invasive epithelial ovarian cancer should be evaluated by a Gynaecologic Oncologist in a multidisciplinary setting prior to initiation of therapy to determine the optimum primary treatment for that particular patient. There is evidence to suggest that patients treated by a Gynaecologic Oncologist are more likely to undergo proper staging, optimal cytoreduction, receive chemotherapy and have better survivals than those treated by General Gynaecologists or surgeons (1-5)
2. Radical surgical cytoreduction followed by adjuvant chemotherapy is the standard of care for advanced epithelial ovarian cancer (6,7). Although this is considered the standard of care, it is based on consistent retrospective data and hence not a category I recommendation (8).
3. For patients with a high likelihood of achieving optimum or complete cytoreduction with acceptable morbidity, primary cytoreductive surgery is preferred over neoadjuvant chemotherapy.
4. Patients who are fit for primary cytoreductive surgery but have a low likelihood of achieving optimum or complete cytoreduction should be offered neoadjuvant chemotherapy.
5. Patients with high peri-operative risk features (advanced age, multiple co-morbidities, poor performance status, presence of thromboembolism) or poor nutritional status with low serum albumin or those with a low likelihood of achieving optimum or complete cytoreduction irrespective of performance status) should be advised neoadjuvant chemotherapy. Neoadjuvant chemotherapy is associated with less peri-operative morbidity & mortality at interval cytoreductive surgery.
6. More data is needed before recommending the approach of neoadjuvant chemotherapy in medically fit patients with potentially resectable ovarian cancer and primary cytoreductive surgery remains the treatment of choice (9-10)
7. The decision whether to offer primary cytoreductive surgery or neoadjuvant chemotherapy should be a shared one between the Gynaecologic Oncologist (Gynecologic Oncology multidisciplinary

team including Critical Care specialist) and the patient. The Clinician should explain the disease extent, discuss options of treatment with their comparative efficacies, risks, benefits, morbidity & cost and should take into consideration the personal choice and priorities of the patient before making an informed decision about the sequence of treatment. Minimally invasive procedures like laparoscopy or mini-laparotomy may be used to assess whether optimal cytoreductive surgery is feasible and safe in an individual patient.

8. The goal of cytoreductive surgery is to achieve complete cytoreduction (no visible or palpable disease), leaving no more than microscopic residual disease or if this is not possible, then to achieve optimal cytoreduction (residual disease <1cm & preferably <0.5 cm in maximum diameter or thickness). Although there is no level I evidence through randomized clinical trials regarding the survival benefit of cytoreductive surgery, patients with optimal cytoreduction consistently achieve better survival rates as compared to those with suboptimal cytoreductive effort (11). Hence, a maximal effort should be made to remove all gross disease, since more complete debulking is associated with better outcomes (12,13)

9. The cytoreductive surgery should include excision of ovarian mass(es) & fallopian tubes preferably by the extraperitoneal route, total abdominal hysterectomy, total omentectomy, pelvic and retroperitoneal lymphadenectomy, peritoneal cytology (aspiration of ascites or peritoneal lavage) and removal of any other metastatic deposits within the abdomen & pelvis. Lymph node involvement is common in advanced stage ovarian cancer (50-70%) and hence lymph nodes need to be addressed during cytoreductive surgery (14). In patients with advanced ovarian cancer who are optimally cytoreduced, systematic lymphadenectomy has been shown to increase overall survival (15). A randomized clinical trial assessed the impact of systematic aortic and pelvic lymphadenectomy versus resection of the bulky nodes in optimally debulked advanced ovarian cancer. Systematic lymphadenectomy improved progression-free but not overall survival in women with optimally debulked advanced ovarian carcinoma (16).

10. Numerous authors have shown a significantly improved survival in patients who underwent complete cytoreduction compared to that in patients with <1 cm residual disease at the end of surgery (11, 17-19). To achieve this goal, extensive resection, mainly of upper abdominal metastatic disease has been recommended for patients who can tolerate this surgery (20-23). The common procedures performed are peritonectomy, bowel resections, diaphragmatic stripping or excision, splenectomy, distal pancreatectomy, partial hepatectomy, cholecystectomy, appendicectomy, porta hepatic nodal excision, urinary tract excisions (partial cystectomy or ureteric resection with suitable reconstruction) and may be performed if complete cytoreduction can be achieved at the end of the procedure, with no significantly increased morbidity. Although this recommendation is based largely on retrospective studies with an inherent selection bias, numerous recent publications have shown that the survival of patients with high volume upper abdominal disease cytoreduced to nil macroscopic level using aggressive surgical approach was not inferior to that of those patients who could be cytoreduced to nil macroscopic status without the use of aggressive surgery. This indicates that aggressive surgery can overcome the negative impact of high volume upper abdominal disease and other adverse clinical factors in all risk groups. Since there are no randomized trials, the selection of patients for an aggressive cytoreductive surgery needs to be balanced by an individualized assessment of perioperative risks, likelihood of resecting all macroscopic disease, local infrastructure and facilities to support the surgery and anticipated clinical benefit.

11. Primary cytoreductive surgery in patients with stage IV disease should be offered to only select

patients. Those with pleural effusion only or supraclavicular node metastasis can be treated on the lines of stage Ill disease. Primary debulking is not recommended in patients with parenchymal liver or lung metastases, who should preferably be treated with neoadjuvant chemotherapy.

12. Patients diagnosed with ovarian cancer after incomplete surgery or staging should be individually evaluated in the same manner as described before by a Gynaecologic Oncologist. They should be offered surgical restaging with completion surgery followed by adjuvant chemotherapy if the residual disease is considered optimally resectable. In those with disease deemed not optimally resectable, neoadjuvant chemotherapy, with evaluation for interval cytoreductive surgery after 3 cycles (may also be done after 4-6 cycles based on the clinical judgment of treating Gynaecologic Oncologist) of chemotherapy is recommended.

13. It should be emphasized that the surgical approach for cytoreductive surgery for ovarian cancer should be open laparotomy and not by minimal access route.

14. At the end of the operation, it is important to document the initial extent of disease, whether a complete, optimal or suboptimal cytoreduction has been achieved and the site(s) and volume of residual disease. (23)

15. Predictors of cytoreduction: To date, there are no prospectively validated non-surgical approaches or universally accepted criteria to predict the likelihood of optimal or complete primary cytoreduction. Laparoscopy has been investigated as a tool to assess operability and remains the best approach at present before proceeding to laparotomy. Recent studies have demonstrated that staging laparoscopy is feasible, safe and can reliably assess the extent of disease (24), as well as to predict the result of cytoreductive surgery and to prevent futile laparotomies (25,26). Some commonly described contraindications to primary surgery include the presence of many of the following: parenchymal liver metastases, large pleural effusion, bulky mesenteric root involvement or retraction, extensive peritoneal plaques including on the undersurface of diaphragm, extensive peritoneal or bowel serosal carcinomatosis, large volume ascites, suprarenal retroperitoneal lymph node involvement, bulky unresectable retroperitoneal or periportal nodal involvement etc. However, it is recommended that each treating Gynaecologic Oncologist should develop his/her own criteria of resectability with the radiologist and clinical oncologist.

16. Patients planned to receive neoadjuvant chemotherapy should have a histological confirmation of invasive malignancy by core biopsy. When it is not possible to safely do a biopsy, cytological confirmation of ascitic or pleural fluid (preferably in addition to a Ca-125:CEA ratio of 25 or more to rule out non-ovarian or non-primary peritoneal origin) may be acceptable to start therapy. If the Ca-125:CEA ratio is less than 25, gastrointestinal malignancy needs to be excluded by appropriate investigations including gastroscopy & colonoscopy. Only cytological evaluation may be inadequate to differentiate between borderline and invasive carcinoma.

17. Patients undergoing neoadjuvant chemotherapy who have demonstrated response or with resectable stable disease to after 3 cycles of chemotherapy may be offered interval cytoreductive surgery. (27-32) The timing of cytoreductive surgery has not been prospectively evaluated in a randomized controlled study and may be tailored to the patient's response and performance status. The principles of interval cytoreductive surgery remain essentially the same as those of primary cytoreductive surgery and every effort should be made to achieve a maximal cytoreduction during interval cytoreductive surgery. Patients with bulky and stage IV disease are likely to have better survival with neoadjuvant chemotherapy while those with III C disease and less bulky tumours are

more likely to have a favourable outcome with primary surgery (33). At least 3 cycles of adjuvant chemotherapy are recommended after interval cytoreductive surgery.

18. Patients with progressive disease on neoadjuvant chemotherapy have a poor prognosis. The options of treatment in these patients include alternative chemotherapy regimens, enrolment in clinical trials or best supportive care. The role of surgery in such cases is purely palliative to relieve symptoms and may be offered after a thorough discussion of benefits and risk of surgery with the patient.

19. Molecular profiling: Germline mutations in BRCA1/2 and other genes should ideally be determined at diagnosis and genomic analysis of tumour specimens for somatic mutations is recommended since these mutations can have an impact on prognosis, can predict benefit from specific therapeutic interventions such as PARP-inhibitors in the setting of recurrent disease and can determine personal and family risk for planning preventive intervention (34). All patients with epithelial ovarian cancer should be referred for genetic risk evaluation.

20. The post-operative menopausal symptoms in young patients should be alleviated using appropriate measures. Hormone replacement therapy is not recommended (35).

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CHAPTER

7 TREATMENT OF ADVANCED OVARIAN CANCER: ADJUVANT SYSTEMIC THERAPY

Recommendations:

1. The combination of paclitaxel (as a 3-hour infusion at 175 mg/m2) and carboplatin (dosed to AUC of 5 to 6 over 1 hour), administered once every 3 weeks for a total of 6 cycles, is the standard first line adjuvant chemotherapy regimen in advanced stage ovarian cancer (Category I recommendation).

2. Single agent platinum (carboplatin or cisplatin) is an appropriate alternative regimen in some patients who are considered unsuitable to receive the combination regimen of paclitaxel and carboplatin.

3. In occasional patients who are considered unsuitable for paclitaxel-platinum (for example due to risk of peripheral neuropathy), appropriate alternative combination regimens include docetaxel (60-75 mg/m2)-carboplatin, gemcitabine-carboplatin or pegylated liposomal doxorubicin (PLD 30 mg/sq m)-carboplatin AUC 5 to be given once in 4 weeks (Category I recommendation)

4. The use of dose dense chemotherapy (paclitaxel 80 mg/m2 once per week instead of once every 3 weeks schedule, plus carboplatin AUC 5-6 on day 1) is supported by the results of one phase III study, in terms of both progression-free (PFS) and overall survival (OS) (Category I recommendation). Although more toxic, it is an acceptable alternative to standard every 3 week regimens. It is reasonable to use this regimen as either 21-day or 28-day schedule in patients who can tolerate this regimen.

5. In elderly patients or those with poor performance status in view of its lower morbidity, a regimen is paclitaxel 60 m/m2 over one hour followed by carboplatin AUC 2 over 30 minutes, weekly for 18 weeks may be given based on the results of MITO-7 trial (Category I recommendation).

6. There is evidence for the benefit of intraperitoneal (plus intravenous) chemotherapy compared to intravenous chemotherapy in terms of PFS and OS and may be offered to patients with completely (nil residual) or optimally debulked (low volume residual disease <1cm) stage III disease- 16 months survival benefit (65.6 vs. 49.7 months, p=0.03) in the GOG 172 trial (Category I recommendation). The recommended regimen is paclitaxel 135 mg/m2 as 24-hour IV infusion on day 1, cisplatin 75-100 mg/m2 IP on day 2 and paclitaxel 60 mg/m2 IP on day 8 – repeated every 3 weeks for 6 cycles. However, because of considerations of toxicity, tolerability, feasibility and trial design issues, it is not a widely practiced standard of care. In institutions where clinicians are experienced in this modality, it is an acceptable alternative to standard intravenous adjuvant regimens. Patients with low performance status, stage IV disease, pre-existing co-morbidities or elderly patients may not tolerate intraperitoneal chemotherapy and should be offered IV chemotherapy. Giving IV fluids hydration is essential before and after IP chemotherapy to reduce renal toxicity and to prevent dehydration. Complications following IP chemotherapy can be severe and may be catheter related,

drug related (e.g. leucopenia, infection, fatigue, renal toxicity, abdominal discomfort, neurotoxicity) or procedure related and may lead to discontinuation of IP chemotherapy.

7. Patients with optimally debulked stage II disease may also be offered intraperitoneal chemotherapy, although there is no evidence from randomized trials to support its use (Category II A recommendation). Intraperitoneal chemotherapy is not recommended for patients with stage I or stage IV disease.

8. Currently, there is no evidence that HIPEC following primary cytoreductive surgery for advanced ovarian cancer improves outcomes and hence is not routinely recommended.

9. The option of HIPEC following neoadjuvant chemotherapy & nterval cytoreductive surgery needs to be discussed with the patient.

10. A combination of chemotherapy and anti-angiogenic drug bevacizumab (used as upfront plus maintenance therapy) may be used as first line adjuvant therapy in patients of advanced ovarian cancer with high-risk features or high post-surgery tumour burden (suboptimally cytoreduced patients)(Category II B recommendation).

11. Maintenance/consolidation chemotherapy with paclitaxel or targeted therapy with pazopanib after completion of standard adjuvant treatment has failed to demonstrate clear overall survival benefit, are associated with increased toxicity and are currently not recommended. Combination therapy with chemotherapy and antiangiogenic agents has shown no statistically significant survival benefit in the pure maintenance setting in a recent meta-analysis. (Wang 2018).

12. Patients with low malignant potential histology do not significantly benefit from adjuvant chemotherapy, except in the subgroup of patients with invasive peritoneal implants (Category IIB recommendation). All other patients should be kept under observation and monitored.

13. There is no proven role of whole abdominal radiation therapy (WART) in patients with low bulk stage III disease as adjuvant therapy.

14. The use of chemotherapy sensitivity and resistance assays to choose a chemotherapy regimen in patients with advanced ovarian cancer is not recommended outside of clinical trial at present, in view of insufficient evidence and lack of demonstrable efficacy of such an approach (category 3 recommendation)

Evidence:

1. The use of platinum.

   Since 1980s, platinum based chemotherapy has been considered the standard of care. A meta-analysis of 49 randomized trials including 8763 patients by the Advanced Ovarian Cancer Trialist's Group has confirmed the value of platinum based chemotherapy (1). In this analysis, platinum chemotherapy resulted in HR of 0.88 (95% CI, 0.79-0.98) compared to non-platinum chemotherapy. The studies included in this analysis were all completed before the advent of taxanes. Thus all modern adjuvant regimens for advanced ovarian cancer are platinum based.

2. Which platinum – cisplatin or carboplatin?

   The initial pivotal trials were done with cisplatin in combination with alkylating agents like cyclophosphamide and later with paclitaxel. However at least 3 trials have now reported the equivalence of cisplatin and carboplatin when combined with paclitaxel (2-4). Because carboplatin

has a more favorable toxicity profile and is easier to administer without the need for meticulous hydration protocols, it is currently the favoured platinum in a dose of AUC 5-7. There is a sequence dependent interaction between paclitaxel and platinum and it is recommended that when used in combination regimens, paclitaxel should be administered prior to platinum.

3. Duration of chemotherapy.

   The optimum duration of adjuvant chemotherapy was analyzed in 3 randomized trials including GOG 178. None of these showed a significant overall survival benefit of longer chemotherapy duration beyond 6 cycles but an increased toxicity with longer chemotherapy (5).

4. The use of taxane-platinum versus single agent platinum.

   A number of studies have firmly established the role of paclitaxel alongside platinum in the first-line treatment of advanced epithelial ovarian cancer. A number of well-conducted phase III randomized studies have been published that have compared a paclitaxel-platinum regimen to a non-paclitaxel-platinum regimen. Paclitaxel-platinum was superior in the two studies where cyclophosphamide-cisplatin was the control arm (GOG 111 and OV 10) in patients with previously untreated stage III-IV disease (6,7). There was no superiority of paclitaxel-platinum in the two studies where single agent platinum was the comparator arm (GOG-132 and ICON-3) (8,9). These results have been interpreted variably. Some have argued for antagonism between cyclophosphamide and cisplatin leading to apparent superiority of paclitaxel-platinum (10). Others have pointed to the considerable cross-over to paclitaxel (in some instances even before disease progression) in the single agent platinum arms to argue that these were really sequential, platinum followed by paclitaxel, strategies rather than true single agent ones. It would suffice to point out that there is current broad consensus that paclitaxel-platinum constitutes the current standard of care as first line regimen in advanced ovarian cancer. However, in the occasional patient who is frail and not considered fit to receive full doses of the combination regimen, single agent platinum is an appropriate alternative.

5. Role of anthracyclines.

   Another question that has been the subject of some debate has been the role and value of anthracyclines (doxorubicin or epirubicin) as additional agents in platinum combinations. Although individual studies failed to show a consistent benefit of anthracyclines, two meta-analyses of published randomized trials suggested a 5-7% survival benefit (11,12). After these analyses, three further studies have been reported. The ICON-2 trial that compared single agent carboplatin to the CAP regimen (cyclophosphamide, adriamycin, cisplatin) failed to show any benefit for the combination (13). Recently two studies have tested the value of addition of epirubicin to the standard paclitaxel-carboplatin regimen (14,15). Both studies failed to reveal any survival benefit from the additional anthracycline, while at the same time subjecting patients to greater toxicity. In aggregate the studies negate any benefit of adding anthracyclines to standard taxane-platinum regimens.

6. Alternative first line adjuvant combination regimens.

   There are occasional patients in whom paclitaxel is relatively or absolutely contraindicated. The presence of pre-existing neuropathy is the most important relative contraindication and a previous episode of severe hypersensitivity an absolute contraindication to the use of paclitaxel. A number of randomized trials have established the equivalence of other combination regimens to paclitaxel and platinum in the first line adjuvant setting. These regimens include docetaxel-carboplatin (16), PLD-carboplatin (17) and gemcitabine-carboplatin (18). One of these regimens could be used in

the adjuvant setting in the occasional patient who, in the judgment of the clinician, is not an appropriate candidate to receive paclitaxel-platinum combination.

7. Addition of a 3rd agent to taxane-platinum or use of sequential doublets.

   In addition to the two anthracycline trials referred to above, that failed to prove the benefit of adding epirubicin, a number of other trials have evaluated the addition of other agents to standard paclitaxel-platinum regimen. These trials have failed to prove the benefit of adding topotecan (19,20) or gemcitabine (21) to the paclitaxel-platinum backbone. Another large trial, GOG-182, tested 2 concepts in a single 5-arm design – addition of a 3rd drug concurrently (PLD or gemcitabine) to paclitaxel-carboplatin or the use of sequential platinum doublets using gemcitabine or topotean (22). There was no benefit of either strategy over use of standard paclitaxel and carboplatin. Thus there is no proof that using a 3rd chemotherapy drug in addition to paclitaxel and platinum as part of the first line regimen improves outcome and this is not recommended as a standard practice.

8. Maintenance or consolidation chemotherapy using paclitaxel or another drug after completion of standard first-line chemotherapy.

   A number of phase III trials have evaluated the continuation of treatment beyond the standard 6-8 cycles of adjuvant chemotherapy in an attempt to `consolidate' or 'maintain' remission. The most recent and important trial (23) evaluated the continuation of monthly paclitaxel (3 vs 12 months) after completion of adjuvant chemotherapy. Although there was improvement in PFS (28 vs 21 months), leading to premature closure of the trial, there was no improvement in OS and there was additional toxicity with maintenance paclitaxel. Because of this, post-remission paclitaxel therapy is only a category IIB recommendation. Other studies have evaluated consolidation/maintenance with intraperitoneal cisplatin (24) and topotecan (25,26) and paclitaxel (27) without any clear benefits. Thus `maintenance' or 'consolidation' therapy after completion of adjuvant treatment is not recommended as a standard of care.

   Pazopanib may be used as maintenance therapy for patients with stages II-IV epithelial ovarian cancer who have had complete clinical remission after first line therapy. This is based on a recent phase III randomized trial showing an increase in PFS (17.9 vs. 12.3 months) in patients treated with pazopanib compared with placebo with no impact on OS and with increased toxicity of pazopanib (28) (Category II B recommendation).

9. Dose dense chemotherapy.

   Administration of paclitaxel in a weekly (`dose dense') schedule (versus once every 3 weeks) has become a routine standard in adjuvant and neoadjuvant settings in breast cancer. One well conducted phase III Japanese study in ovarian cancer (29) has compared weekly versus once every 3 weeks paclitaxel (both in combination with once every 3 weeks carboplatin) and proved the superiority of the weekly regimen in terms of both PFS (28 months vs. 17 months; p=0.0037), OS (72% vs. 65% at 3 years – p=0.03) and median overall survival (100.5 months vs. 62.2 months) in the most recent update (30). There were some additional hematological toxicities and dose delays/modifications in the dose dense arm. However, the dose dense chemotherapy is more toxic and more patients in the dose dense therapy arm discontinued chemotherapy compared to the standard chemotherapy arm. A randomized study comparing dose dense chemotherapy to intraperitoneal chemotherapy showed no significant difference in survival in both the arms (31). Future studies comparing combined intraperitoneal & intravenous chemotherapy with dose dense chemotherapy will identify the optimum approach for adjuvant chemotherapy. In elderly patients

or those with poor PS, a regimen is paclitaxel 60 m/m2 over one hour followed by carboplatin AUC 2 over 30 minutes, weekly for 8 weeks may be given based on the MITO-7 trial (32)(Category I recommendation).

10. Intraperitoneal (IP) chemotherapy.

Intraperitoneal administration of chemotherapeutic drugs, chiefly cisplatin, has several theoretical advantages over intravenous route and has been evaluated in a number of phase III randomized trials as well as a meta-analysis, in patients in whom optimal surgical cytoreduction has been achieved (33-36). High quality pooled data analysis of 8 trials suggested that IP chemotherapy given in the adjuvant setting may significantly reduce the risk of death (HR 0.80, p=0.0003) and disease recurrence (HR 0.79, p<0.0004) as compared to IV chemotherapy and this benefit continued even after 5 years. In the most recent study (GOG-172) (35), there was an improvement in both PFS and OS (65.6 vs. 49.7 months) in the IP arm, as well as a 21.6% reduction in the odds of death in optimally cytoreduced patients. However, the two arms were not balanced with respect to the planned cumulative doses of both paclitaxel and cisplatin and paclitaxel schedule was also different (weekly in IP arm versus once every 3 weeks in IV arm). Besides, there was a concern about the morbidity and tolerability of the IP regimen, since only 42% of the patients completed the planned IP treatment. Therefore the true benefit of intraperitoneal route of administration was uncertain. Moreover IP chemotherapy was considerably more toxic and was associated with significantly more complications with adverse impact on health related quality of life, compared to intravenous administration. Some Indian data also corroborates the substantial toxicity of IP chemotherapy (37). Lower dose IP regimens have not been shown to have equivalent efficacy and are not recommended. Patients with poor performance status, significant co-morbidities especially inadequate renal function, advanced age and stage IV disease may not tolerate intraperitoneal chemotherapy. Because of these considerations and feasibility issues, IP chemotherapy has not been the widely practiced standard adjuvant treatment for advanced ovarian cancer. However, it is an acceptable alternative to standard IV adjuvant regimens when administered by clinicians experienced in this technique. A recent study reported overall survival of 110 months in patients with stage III ovarian cancer and no residual disease who received the IP regimen (38), while another showed that survival improves with each cycle of IP chemotherapy (39).

11. Hyperthermic intraperitoneal chemotherapy (HIPEC)

Till now, there is no randomized controlled study that has shown a survival benefit with HIPEC in the adjuvant setting following primary cytoreductive surgery. A recently published multicentre phase III trial of 245 patients with stage III epithelial ovarian cancer who underwent complete or optimal cytoreduction at interval cytoreductive surgery after 3 cycles of neoadjuvant chemotherapy reported that the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival (10.7 vs. 14.2 months, p=0.003) and overall survival (33.9 vs. 45.7 months, p=0.02) than surgery alone and did not result in higher rates of side effects (40). However, several methodological issues such as imbalance between the 2 arms, small sample size, incremental cost of intervention and extra operating room time, longer hospitalization, increased use of diverting stomas, cost-benefit ratio etc. limit its incorporation into routine clinical practice (41-43). Besides, the results of this trial cannot be extrapolated to other clinical settings in advanced ovarian cancer. New confirmatory clinical investigations of HIPEC are needed to clarify some of the unanswered questions before HIPEC can become a common treatment strategy.

12. Addition of anti-angiogenic targeted therapy (bevacizumab) to taxane-platinum regimen.

There are several lines of evidence suggesting the important role of vascular endothelial growth factor (VEGF) in the maintenance and progression of the malignant phenotype in advanced epithelial ovarian cancer. Bevacizumab, a humanized monoclonal antibody against VEGF, has been evaluated in many smaller and two larger randomized phase III studies in advanced ovarian cancer in the adjuvant setting (44,451). In both studies bevacizumab was added to the standard adjuvant paclitaxel-carboplatin chemotherapy after primary surgery. The patient populations included in the two studies were somewhat different as were their designs, including a midway change of the primary endpoint from OS to PFS in one study (44). In one study (45) bevacizumab was used at a lower dose for 12 cycles and in the other (39) at a higher dose for 16 cycles. Both studies reported a modest improvement in radiologically defined PFS (14.1 vs. 10.3 months in GOG 0218- p=0.001 and 2.4 months improvement in PFS in ICON 7) but no improvement in OS or quality-of-life. Moreover, the PFS curves tended to converge together after bevacizumab was stopped by protocol defined criteria (12 and 15 months respectively in ICON 7 & GOG-218). The updated analysis of ICON 7 showed improved overall survival in the subset of patients with poor prognosis (39.3 vs. 34.5 months; p=0.03) but not in the whole group (46). Similarly, subset analysis of GOG 208 suggests that combination of chemotherapy and bevacizumab leads to better PFS and overall survival compared to chemotherapy alone (47).

Subgroup analysis in one trial (34) suggested preferential benefit in suboptimally cytoreduced stage III/IV patients, but this finding can only be considered exploratory rather than practice changing. Both studies have not yet reported an improvement in HR QOL with bevacizumab. The incidence of severe adverse effects such as hypertension, venous thromboembolism, GI effects (perforation/ fistula/necrosis/leak) and non-CNS bleeding were higher in the bevacizumab arms in one or both studies. In this context, a recent meta-analysis (48) has suggested that treatment related mortality is significantly increased when bevacizumab is combined with platinum or taxane chemotherapy (RR-3.49, 95%CI 1.82-6.66).

A recent meta-analysis of 15 trials (N = 8721 participants) showed that combination treatment with angiogenesis inhibitors and chemotherapy significantly improved PFS and OS in both patients with high-risk of progression and recurrent ovarian cancer, with an increased incidence of common adverse events (49). For newly diagnosed ovarian cancer, combination treatment with angiogenesis inhibitors and chemotherapy yielded a lower risk of disease progression (hazard ratio 0.83); and no improved OS (HR 0.95). In the high-risk progression subgroup, the addition of bevacizumab significantly improved PFS (HR 0.72) and OS (HR 0.84). In view of this, combination of chemotherapy and anti-angiogenic drugs may be used as first line adjuvant therapy in patients of advanced ovarian cancer with high-risk features or high post-surgery tumour burden.

13. Patients with low malignant potential histology do not significantly benefit from adjuvant chemotherapy, except in the subgroup of patients with invasive peritoneal implants (50,51) (Category IIB recommendation). All other patients should be kept under observation and monitored.

14. The use of chemotherapy sensitivity and resistance assays to choose a chemotherapy regimen in patients with advanced ovarian cancer is not recommended outside of clinical trial at present, in view of insufficient evidence and lack of demonstrable efficacy of such an approach (category 3 recommendation) (52-54).

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CHAPTER

8 TREATMENT OF ADVANCED EPITHELIAL OVARIAN CANCER: NEOADJUVANT CHEMOTHERAPY (NACT) AS INITIAL TREATMENT

Recommendations:

1. Patients with extensive radiological stage IIIC or stage IV epithelial ovarian cancer who are deemed unsuitable for primary debulking surgery because of low likelihood of optimal cytoreduction or poor performance status may be offered NACT followed by interval surgery. However, this assessment of resectability should be made by a Gynaecologic Oncologist.
2. However, more data is needed before recommending the approach of neoadjuvant chemotherapy in all fit patients with potentially resectable disease and primary cytoreductive surgery remains the treatment of choice.
3. Three cycles of the combination of intravenous paclitaxel and carboplatin is an appropriate NACT regimen.
4. Histological confirmation of malignancy is mandatory before starting neoadjuvant chemotherapy. To obtain tissue for histology, percutaneous image guided biopsy if feasible or laparoscopic biopsy is recommended. The treatment should be based on cytological confirmation of malignancy only if histology is not appropriate.
5. There is little evidence of use of alternative chemotherapy approaches like IP/IV chemotherapy or dose dense chemotherapy as adjuvant therapy in patients undergoing neoadjuvant chemotherapy followed by interval cytoreductive surgery. Although these approaches have been found to be feasible and safe, there is insufficient data about their efficacy to make a formal recommendation either for or against these approaches.

Background:

NACT followed by interval cytoreductive surgery has since many years been used in patients with advanced Stage III/IV ovarian cancer in most parts of the world other than North America. This was despite the fact that upfront surgery to optimal levels has been a dogma in this disease and there was lack of level 1 evidence to support NACT. The principal reasons for the use of NACT have been the following:

1. Difficulty in performing optimal cytoreductive surgery in patients with extensive peritoneal disease. The required surgery in such patients is often so extensive that it is beyond the capabilities of all but few centres/surgeons.
2. Difficulty in scheduling early surgery because of logistic reasons in many hospitals.
3. The poor performance and nutritional status of many patients with advanced stage disease with presence of anemia, hypoalbuminemia, massive ascites, pleural effusion, etc. This results in prolonged convalescence after surgery with higher chance of morbidity and mortality.

Evidence:

There have been many retrospective and prospective case series and reviews of NACT in ovarian cancer including some from India (1,2) and systematic reviews based on these series. Some authors have also proposed various CT scan and other criteria for selecting patients for NACT. However because of the retrospective nature of most of these reports and the lack of randomized controls there has been lingering doubt about this approach. However, given the fact that neoadjuvant chemotherapy has been non-inferior to upfront local treatment (and in some instances superior) in many other malignancies like breast, esophagus, gastric, urinary bladder etc. there has been a strong rationale to prospectively evaluate this approach in ovarian cancer.

Recently there have been reports from 3 randomized trials that have compared NACT followed by surgery to upfront surgery followed by adjuvant chemotherapy (3-5). In the EORTC-GCG & NCI-CTG phase III well conducted study, 718 patients with advanced stage IIIC or IV epithelial ovarian/peritoneal/fallopian carcinoma were randomized to receive either primary debulking surgery (followed by 6 cycles of platinum-based chemotherapy, which was mostly paclitaxel/carboplatin) or interval debulking surgery (which was preceded and followed by 3 cycles of chemotherapy). The study was powered as a non-inferiority study to prove that NACT was non-inferior to upfront surgery rather than as superiority design that would have required only 400 patients. The median follow-up for all participants was 4.8 years. For the primary end-points of the study there was no difference between the upfront surgery and NACT arms; median OS (29 vs. 30 months) and median PFS (12 vs. 12 months) being almost identical. For the secondary end points of the study, which was the incidence of complications, the NACT arm fared better. Compared to the upfront surgery arm there were fewer postoperative deaths (2.7% vs. 6%), fever (2% vs. 8%), hemorrhage (1% vs. 7%) and thrombosis (0.3% vs. 2.4%) in the NACT arm. All of these were statistically significant. The rate of optimal debulking was also better in the NACT arm (53% nil residual, 82% < 1 cm) compared to the upfront surgery (21% nil residual, 46% < 1 cm). In a multivariate analysis of the entire dataset by the investigators, optimal debulking surgery was the strongest independent prognostic factor for overall survival among the study participants in both groups (P = .0001). In subset analysis, patients with stage IIIC disease and metastatic tumour <45 mm had better survival than those with stage IV disease or larger >45 mm tumours. Other significant prognostic factors included: histological type (P = .0003), largest tumor size at randomization (P = .0008) and disease stage (IIIC vs. IV) (P = .0008). The results of this study provide support for the use of NACT/interval surgery in advanced ovarian cancer, but do not detract from the need for optimal surgery since this was still the strongest predictor of outcome.

Many critics of the EORTC study have cited better optimal reduction rates and PFS/OS with primary debulking surgery (PDS) from single institution American series, compared to the PDS arm of EORTC study, thereby questioning the quality of surgery in this trial (5) However, this trial only accrued higher risk patients (stage III C and above), there is likely a selection bias (6) in these single institution data favouring patients selected for upfront surgery. Moreover there is no convincing evidence that a higher fraction of advanced stage patients are cured in the long-term by performance of supra-radical initial surgery. Thus, the EORTC study remains the best available evidence on the use of NACT as the initial treatment in patients with advanced stage epithelial ovarian cancer (7).

However, more data is needed before recommending the approach of neoadjuvant chemotherapy in all fit patients with potentially resectable disease and primary cytoreductive surgery remains the treatment of choice (8,9)

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CHAPTER 9

MANAGEMENT OF LMP (BORDERLINE) OVARIAN TUMOURS

Borderline (LMP) tumours are epithelial tumours with cytological characteristics suggestive of malignancy but without frank invasion. In general, these tumours have an indolent course with 5-year survival exceeding 80%. These patients in contrast with the invasive ovarian cancer, are generally younger (although they can occur at a wide age range), often have stage I disease and are candidates for fertility sparing surgery (10,11). They can be serous, mucinous or seromucinous. They may also have peritoneal implants, which may be non-invasive or invasive. Although, non invasive peritoneal implants have no deleterious effects on long term survival, invasive peritoneal implants (which represent 12% of all peritoneal implants) are associated with a poor prognosis; the survival is reduced to 66% and more than 50% develop recurrent disease (12-14). The micropapillary pattern and presence of microinvasion within these tumours signify increased risk of invasive implants in extraovarian tissue.

These tumours should preferably be managed by Gynaecologic Oncologists who are familiar with the biological behavior and the prognostic factors. The staging system for these tumours is the same as that for invasive cancer.

Treatment guidelines of borderline epithelial cancer depend on clinico-pathological features, age and desire to preserve fertility, stage of the disease and presence of invasive implants.

Surgery is the main line of treatment for borderline epithelial tumours. Patients with borderline ovarian tumours tend to be younger and are often diagnosed with stage I disease. Young patients desirous of fertility preservation may be offered conservative surgery (unilateral salpingo-oophorectomy) after surgical staging to rule out extraovarian metastatic disease but those who have completed their family may be offered complete surgery with comprehensive surgical staging. Lymphadenectomy does not appear to have an added benefit in these patients, even if the disease is upstaged and hence the decision regarding lymphadenectomy should be individualized.

In terms of histological subtypes, borderline mucinous tumours are more commonly metastatic and thereby warrant an appendectomy, especially when bilateral, considering the fact that their origin is attributed to appendix in certain cases. Such an appendicular specimen needs to be cut and embedded completely to look for any adenomatous or carcinomatous lesion. In view of different chemotherapy options for intestinal and ovarian adenocarcinomas, it is important to differentiate primary and metastatic mucinous adenocarcinomas, especially in cases of large, unresectable tumor involving adnexae and gastrointestinal tract. In such cases immunohistochemistry (IHC) including markers like CK7, CK20, CA125, CEA and CDX2 can be useful to differentiate primary versus metastatic ovarian adenocarcinoma (15).

Patients with advanced stage disease are treated primarily with surgery with limited or no benefit of adjuvant chemotherapy. Patients with invasive implants have a less favourable outcome and hence are frequently treated with chemotherapy (intravenous carboplatin with paclitaxel or docetaxel), although the precise significance of invasive implants remains unclear. However, the role and impact of chemotherapy

in patients with LMP tumours with non-invasive implants is not proved.

It is recommended that patients who have undergone fertility sparing surgery should be monitored by regular ultrasonography and should be encouraged to have completion surgery after the childbearing is completed (Fischerova 2012).

Patients who relapse should be thoroughly evaluated surgically and debulking surgery is indicated. Those with high-grade disease or invasive implants should be treated as per treatment protocols for invasive ovarian cancer including complete surgery and adjuvant chemotherapy. Those without high-grade disease or invasive implants may be kept under observation after surgery.

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CHAPTER

10 FOLLOW-UP & SECOND LOOK SURGERY:

Patients who have a complete response (defined as normal clinical examination, normal serum Ca-125 levels and normal CT scan of abdomen + pelvis) are recommended observation with follow up monitoring. The patients must be educated regarding the symptoms of recurrent disease.

History, physical examination including pelvic examination, CA-125 (in patients with initially elevated Ca-125 levels) and imaging (including CT scan or MRI, PET / PET-CT if indicated) every 3 months for first 2 years, every 4 months during the third year and every 6 months subsequently until documented progression. The follow up then continues annually. Serum Ca-125 is useful if the level was initially elevated. Ultrasonography of the abdomen & pelvis may be adequate if clinical examination and serum Ca-125 are normal. Patients should also be counseled and educated about the symptoms and signs indicative of a recurrence. If the clinical examination and / or Ca-125 levels suggest a possibility of relapse, CT scan or a PET scan (which is more sensitive for detecting multiple sites of relapse and for subsequent planning of therapy) is recommended (1,2).

The value of serum Ca-125 estimation in the follow up of patients and its impact on the final outcome is controversial. A prospective randomized European multi-institutional study of early detection of relapse with Ca-125 and early treatment versus delayed treatment at the onset of clinical manifestation of the disease showed no difference in the overall survival between the immediate and delayed treatment arms (HR1.01, p=0.91). On an average, the immediate chemotherapy arm patients started second line chemotherapy 4.8 months earlier and third line chemotherapy 4.6 months earlier than the delayed treatment group patients. The quality of life of patients in the immediate treatment group was significantly lower than those in the delayed treatment group (3-5). This shows that there is no clinical benefit by detecting the relapse early by routine serum Ca-125 measurement and the treatment should be delayed till the onset of symptoms. It is important to discuss the various aspects of follow up (including pros and cons of Ca-125 monitoring) with the patient before finalizing the schedule for each patient.

Patients with progressive disease, persistent disease or stable disease during initial primary treatment should be considered for second line chemotherapy approaches.

Second look surgery:

This is presently not recommended as a part of routine clinical practice. It is defined as a surgery to assess the status of cancer in patients who are clinically, radiologically and serologically free of disease after the completion of primary treatment (i.e. cytoreductive surgery and 6 cycles of adjuvant chemotherapy). Although sound in principle, it has not been shown to improve survival. Second look surgery may be used a part of clinical trials after obtaining informed consent of the patient.

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CHAPTER

11 RECURRENT OVARIAN CANCER:

A. Serological relapse: (no clinical or radiological evidence of disease in presence of raised Ca-125 levels).

The options of treatment are close observation, immediate treatment or enrolment in a clinical trial. Presently, there is no evidence that early management of isolated CA-125 elevation with chemotherapy is beneficial in terms of improved survival as compared to when treatment is commenced at the time of clinical or radiological relapse. Hence the patients should be advised close observation and monitoring till appearance of clinical disease. There is no consensus about the type of therapy, the chemotherapy regimen and number of cycles to be given, if early treatment is instituted. Treatment must be instituted on an individual basis after counseling the patient about the anticipated benefits and risks of early treatment.

Tamoxifen as well as other hormonal agents are frequently employed in this clinical situation in view of their defined response rate after progression on platinum based chemotherapy in this set of patients with isolated serological relapse and may be recommended for this clinical situation (category 2B)(1-3)

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B. Clinical relapse:

Recurrence of ovarian cancer is defined as evidence of cancer recurrence at least 6 months following completed initial treatment. This has to be differentiated from persistent disease after initial primary treatment where one might complete staging or attempt a second debulking procedure with or without chemotherapy. Recurrence is defined using the RECIST criteria. Diagnosis of recurrence is made by findings on history (details of first illness, review of operation notes, details of chemotherapy received etc), clinical examination, increase in tumour markers (such as CA 125, HE4, AFP, b-hCG, LDH as appropriate for tumour type) and imaging (CT scan / PET-CT scan). Biopsy confirmation of recurrence is not mandatory.

Several factors need to be considered before deciding on the salvage therapy for recurrent ovarian cancer, such as the timing and nature of relapse and the response to previous chemotherapy. Since relapsed ovarian cancer is seldom curable, the potential toxicity of treatment must be weighed against the likely benefit of treatment. A meta-analysis of randomized trials of chemotherapy for recurrent ovarian cancer has been published. (1)

Patients are essentially divided into:

1. Platinum sensitive: Disease free interval of >6 months after completion of adjuvant chemotherapy
2. Platinum resistant: Disease free interval of <6 months after completion of adjuvant chemotherapy
3. Platinum refractory: Patients who progress during treatment with 2 consecutive platinum based chemotherapy regimens without ever obtaining a clinical benefit

Platinum sensitive disease:

Patients with a durable response to first line platinum based chemotherapy have a high probability of responding to a re-challenge with platinum based chemotherapy regimen. The choice of platinum agent – cisplatin or carboplatin depends on previous agent used, its toxicity and tolerability.

The combinations, which may be used in these patients, are:

1. Paclitaxel plus platinum (category I): The evidence suggests that the combination of paclitaxel and platinum based chemotherapy is superior to platinum based chemotherapy as a single agent in "platinum-sensitive" patients relapsing after platinum based chemotherapy with a relapse free interval of >6-12 months (AGO-OVAR 2.2 / ICON 4 trial). (category I recommendation)((2)
2. Carboplatin plus weekly paclitaxel (3)
3. Docetaxel plus platinum (4,5)
4. Liposomal doxorubicin plus platinum: based on non-inferiority of this combination when compared with paclitaxel and carboplatin in a phase III trial and subsequent published data (category 1 recommendation) (6-11)
5. Gemcitabine plus platinum: based on a randomized study (AGO-OVAR) comparing this combination with single agent carboplatin showing superiority of the combination regimen (PFS 8.6 vs. 5.6 months – p=0.0031 and response rates of 47.2% vs. 30.9%)(12-13)
6. Single agent carboplatin or cisplatin may be considered in patients who cannot tolerate combination therapy.
7. Nanoparticle albumin-bound paclitaxel (14)
8. Chemotherapy plus bevacizumab (15)
9. Recent data suggests that PARP inhibitor olaparib is active in select patients of relapsed ovarian cancer especially platinum sensitive patients and have better response rates in patients with BRCA-1 and BRCA-2 mutations. Platinum resistant or refractory patients have a lower response rate to olaparib. Olapraib monotherapy has been shown to have response rate of 34% in women with recurrent advanced ovarian cancer in a recent trial (16) and is now recommended in women who have received 3 or more cycles of chemotherapy and have a germ-line BRCA mutation (17-18). Another phase 2 randomized clinical trial comparing combined olaparib 200 mg twice daily for the first 10 days of a 21-day cycle followed by maintenance olaparib 400 mg twice a day till progression and standard chemotherapy (paclitaxel + carboplatin) versus standard chemotherapy alone and showed improved progression-free survival in the combination arm (median12.2 vs. 9.6 months; p=0.0012), especially in patients with BRCA mutation (19).

Platinum resistant disease:

Typically, the response rates to any chemotherapy are limited, the prognosis poor and the intent of treatment palliation.

1. Re-challenge with paclitaxel and platinum combination yields response rates of less than 10%.
2. Altering the schedule of paclitaxel may produce short-term responses (20-21).
3. Single non-platinum agent is the preferred chemotherapy in this situation – however no particular agent has been found to be better than others to preferentially recommend its use. These drugs can be used as single agent chemotherapy in a sequential fashion (22). Numerous agents eg docetaxel (23), topotecan (24), gemcitabine (25-26), oral etoposide (27), liposomal doxorubicin (25-26), vinorelbine (28-29), ifosfamide, pemetrexed, capecitabine (30), cyclophosphamide, altretamine, irinotecan, oxaliplatin, doxorubicin, nanoparticle albumin-bound paclitaxel etc have been used in the literature with consistently low response rates of about 20-27%.
4. Single agent bevacizumab may be used and is associated with a response rate of about 21%. The combination of chemotherapy (liposomal doxorubicin, weekly paclitaxel, topotecan or gemcitabine) with bevacizumab have been investigated in clinical trials e.g. OCEANS, AURELIA and is associated with an increase in the progression-free survival but has no impact on overall survival and hence not routinely recommended (31-35). A recent meta-analysis demonstrated that combination treatment with angiogenesis inhibitors and chemotherapy significantly improved PFS and OS in patients with recurrent ovarian cancer, with an increased incidence of common adverse events (HR was 0.58 for PFS and 0.86 for OS). Consequently, this combination should be seriously considered in patients with recurrent ovarian cancer (36). The bevacizumab combination regimens are contraindicated in patients at an increased risk for gastrointestinal perforation and unlikely to be beneficial in those patients who have received bevacizumab earlier (37,38).
5. Metronomic chemotherapy with oral etoposide or cyclophosphamide which work mainly as anti-angiogenic agents when given in small doses at more frequent intervals.
6. Patients who cannot tolerate or have failed cytotoxic chemotherapy may be considered for hormonal therapy with tamoxifen, megestrol acetate, LH-RH analogues, aromatase inhibitors etc. (39-41).
7. Patients with platinum refractory / resistant disease may be considered for enrollment into clinical trials of new drugs provided they are eligible for the trials and the patients give their informed consent.

In both **platinum sensitive and platinum resistant** patients, **evaluation of response** is recommended after 2-3 cycles of chemotherapy irrespective of the regimen or agent used. Responding patients may be treated with further chemotherapy and assessed for cytoreductive surgery when appropriate while patients who do not respond to 2 consecutive regimens of chemotherapy are unlikely to respond to further chemotherapy and may be considered for supportive care or clinical trials (42).

The use of **chemotherapy sensitivity and resistance assays** to choose a chemotherapy regimen in patients with recurrent ovarian cancer is not recommended outside of clinical trial at present, in view of insufficient evidence and lack of demonstrable efficacy of such an approach (category 3 recommendation) (43-45)

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CHAPTER

12 SURGERY IN RECURRENT OVARIAN CANCER

Definitions:

Secondary cytoreduction is defined as debulking of tumour after recurrence of ovarian cancer following primary surgery and chemotherapy.

Tertiary cytoreduction is defined as debulking of tumour after a second recurrence following primary and secondary treatments.

Palliative surgery is defined as procedures to alleviate life-threatening problems and improve quality of life in the short term.

Overall perspective and scope of secondary surgery:

When ovarian cancer has recurred, treatments are usually palliative in order to prolong survival or improve quality of life. Cure is not the aim. Since most recurrences are intra-abdominal, they are amenable to cytoreduction. Although there is no level I evidence of survival benefit with secondary cytoreductive surgery in all patients, its role can be supported by the reported improved survival in patients undergoing successful secondary cytoreductive surgeries (1). Numerous studies have shown that the most critical prognostic factor is optimal debulking of tumour to less than 1 cm residual that results in survival of 16-61 months versus 8- 27 months when debulking is sub-optimal (2-4). The AGO DESKTOP I trial showed that the only significant clinical factor associated with improved survival is the ability to achieve complete cytoreduction, with survivals of 45.2 months in those who underwent complete cytoreduction versus 19.7 months in those who did not undergo complete cytoreduction ($p<0.0001$) (5). The same trial tried to identify the factors associated with a higher likelihood of achieving complete cytoreduction. The authors found that ECOG performance score of 0, FIGO stage I/II at diagnosis, no residual disease at primary cytoreduction and ascitis <500 cc as important factors predicting complete cytoreduction. Patients with all these factors (positive AGO score) had a 79% rate of complete cytoreduction in their study. The results of this trial were validated in a subsequent DESKTOP II trial (6). Of the 129 patients with positive AGO score, complete cytoreduction could be achieved in 76% of patients. Other factors which have been reported to be important for a successful secondary cytoreductive surgery are relapse-free interval >12 months, single site relapse, tumour size <10 cm, complete clinical response to primary platinum-based chemotherapy etc (7). Laparoscopic evaluation of successful surgery was published by an Italian group with percentages of complete resections comparable to what obtained with AGO score but at higher price in terms of complications and feasibility of the procedure. Pelvic and para-aortic lymphadenectomy, supracolic omentectomy and appendicectomy may be done if not already done at first surgery. Operation should be done by a Gynaecologic oncologist in a high volume centre, who is prepared to perform extensive resections in order to remove all macroscopic tumour since the surgeon's philosophy and approach to treating recurrent ovarian cancer as well as his technical expertise and experience are important parameters to achieve this goal.

A meta-analysis on cytoreductive surgery for recurrent ovarian cancer (8) showed that among patients undergoing operative intervention (secondary cytoreduction) for recurrent ovarian cancer, the proportion of patients undergoing complete cytoreductive surgery is independently associated with overall post-recurrence survival. Each 10% increase in the proportion of patients undergoing complete cytoreduction was associated with a 3-month increase in the median cohort survival time.

Currently, 2 trials DESKTOP III and GOG 213 are accruing patients with recurrent platinum-sensitive ovarian cancer to secondary cytoreductive surgery followed by chemotherapy versus chemotherapy alone. A better understanding of the benefits and patients selection criteria for this procedure will be achieved after the completion of the ongoing randomized phase III trials and will define the place of secondary cytoreductive surgery more precisely in the treatment algorithm.

Patient selection:

Patients are selected for secondary cytoreduction only if they meet all of the following criteria (9-10)

1. Progression free interval of at least 12 months
2. Isolated recurrence
3. Disease can be potentially excised completely
4. Good response (complete clinical response) to first line chemotherapy treatment
5. Good performance status to tolerate aggressive and extensive multimodality treatment
6. Tumour size <10 cm, preferably <5 cm
7. Ascitis <500 cc

Counseling of patient and relatives regarding the nature of the disease and prognosis: It has to be made clear that recurrent ovarian cancer is not curable and that it can only be kept under control. Risks and benefits of secondary debulking have to be reviewed. Informed consent must be taken for necessary surgical procedures. All alternative options need to be discussed.

Tertiary cytoreduction

This is seldom done and is applicable to very select cases. Favourable features are similar to secondary debulking surgery i.e. longer treatment interval, ability to completely resect the disease and limited sites of disease (11).

Palliative surgery

Generally not recommended as the patient has progressive incurable disease with limited life expectancy. Intestinal obstruction is the commonest clinical situation for which palliative surgery is contemplated. Surgery should be reserved for highly selected patients in whom it seems feasible to relieve the obstruction without a major surgical undertaking and in whom it likely to beneficial for a reasonably long period of time ie those with limited intraperitoneal disease or slowly progressive disease. It is essential that the decision regarding palliative surgery is made by a multidisciplinary team after counseling the patient and her family about the expected benefits and risks. The presence of ascites, performance status, will to live and disease status affect the decision to operate or not.

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CHAPTER

13 LEGENDS

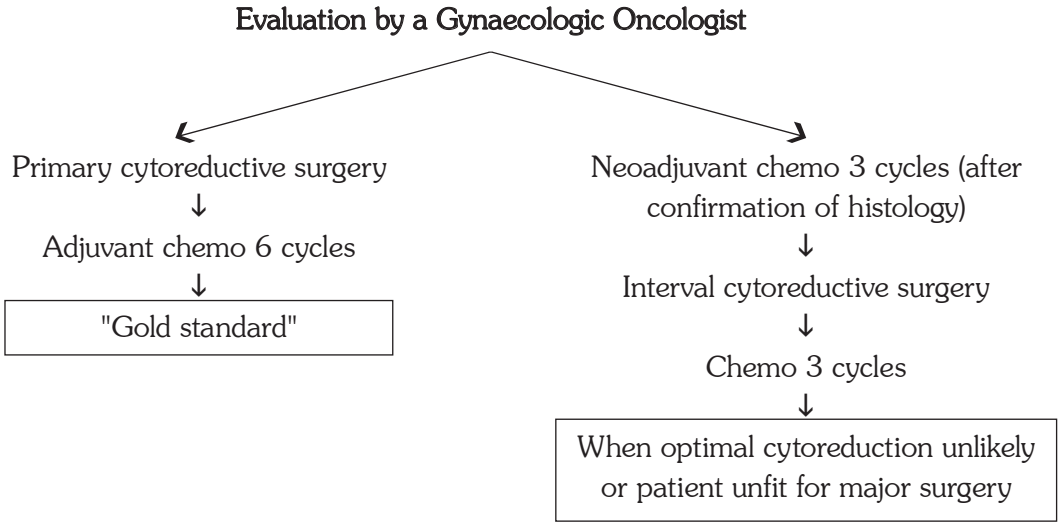
Legend 1
Suspicious pelvic mass: Approach

Detailed history including family history
↓
Clinical examination – abdominal, pelvic, breast & systemic
↓
Imaging: USG, CT scan/MRI of abdomen+ pelvis
(PET scan if clinically indicated)
↓
Tumour markers: Ca-125, CEA, Ca-19.9, AFP & b-hCG as clinically indicated
(X-ray chest)
↓
Cytopathology of ascetic or pleural fluid if present Needle biopsy from ovarian/extraovarian mass only when NACT planned
↓
OGD scopy/Colonoscopy when primary peritoneal carcinoma suspected & to rule out gastrointestinal primary GI evaluation for mucinous tumours Bilateral mammography if clinically indicated
↓
Nutritional & morbidity assessment
↓
Diagnostic laparoscopy if indicated
Proceed to treatment

Legend 2
Early stage ovarian cancer: Management

Laparotomy
TAH + BSO (if fertility not desired) + comprehensive surgical staging
Or
Conservative surgery (USO) for stage IA patients (if fertility desired) + comprehensive surgical staging
↓
Plan for adjuvant therapy
↓
Comprehensively staged stage IA/IB GradeI/II with no high-risk histological features: Close observation
↓
Stage IC or Grade III (high grade) or high-risk histological features: Adjuvant chemotherapy Paclitaxel + Carboplatin 3-6 cycles

Legend 3
Approach to a patient with advanced ovarian cancer



Legend 4
Surgery for advanced stage ovarian cancer

TAH + BSO
Comprehensive surgical staging
Peritoneal washings or ascitic fluid cytology
Total omentectomy
Pelvic & para-aortic lymphadenectomy
Additional procedures as indicated viz. Peritonectomy, diaphragmatic stripping/ excision, bowel resection(s), splenectomy with/without distal pancreatectomy, partial cystectomy, ureteric excision with reimplantation

Adjuvant chemotherapy: Platinum based 6 cycles + maintenance when indicated
(Options, indications & schedules given in text)

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