

Evidence Based Guidelines for the Management of Epithelial Ovarian Cancer – A WHO Initiative

Introduction

Most Indian cancer registries have reported an actual increase in the incidence of epithelial ovarian cancer in India in recent years. It is therefore necessary to generate appropriate evidence-based management guidelines for this disease which would be applicable across the country. India being a vast developing subcontinent, there is understandably a tremendous variation in available medical facilities, infrastructure and medical expertise across the country and this has to be taken into account when such management guidelines are evolved.

On the 8th. October 2006, a team of lead clinicians actively involved in the management of ovarian cancer in regional cancer centers and institutes of excellence were invited to meet at the Tata Memorial Hospital, Mumbai to discuss this issue and the following document highlights the outcome of these discussions.

Objectives

The group was given the following mandate of objectives:

- To generate evidence based standardized management guidelines
- To disseminate these to relevant institutions across India
- To categories treating institutions based upon the available expertise and infrastructure
- To tailor management guidelines according to institutions
- To generate appropriate referral patterns
- To facilitate periodic clinical audit

It was decided that it would be practical to first categories treating hospitals and institutions into groups depending upon the facilities, infrastructure as well as medical expertise as follows:

- Regional cancer centers, teaching institutes of academic excellence
- Large well-equipped private or centrally funded hospitals
- Small hospitals and nursing homes

The management guidelines would then be tailored to suit the conditions available to the hospitals in each of the above-mentioned categories as follows:

- Ideal/Optional
 - Management as per established “Gold Standards” is possible
 - Adequate infrastructure and availability of all the required facilities
 - Availability of trained personnel to allow for a multidisciplinary approach
 - Eg: Regional Cancer Centers, Centers of Excellence
- Standard
 - Management as per established “Gold Standards” is still possible
 - Most of the required infrastructure and facilities are available “in House” or within easy reach
 - Availability of trained personnel to allow for a multidisciplinary approach
 - Eg: Large well-equipped hospitals, private or centrally funded
- Minimal
 - “Gold Standard” management is not possible
 - Required infrastructure and facilities are not available
 - Personnel may or may not be appropriately trained
 - A multidisciplinary approach is not feasible
 - Eg: Small hospitals, nursing homes in smaller towns, semi-rural areas etc

Diagnostic Workup for Epithelial Ovarian Cancer

The diagnosis of epithelial ovarian cancer largely depends upon clinical findings and specific investigations which include serological tests i.e. tumour marker levels and imaging studies. These can be grouped as follows:

- Ideal/Optional
 - Thorough clinical examination
 - Routine biochemistry
 - Imaging studies
 - USG (TAS /TVS +/- Colour Doppler studies)

- X-ray Chest
 - CT Scan
 - MRI (optional)
 - FDG-PET Scanning (optional)
 - Tumour marker panel
 - Women >40
 - Serum CA 125
 - Serum CEA
 - Women <40
 - Serum CA 125
 - Serum CEA
 - Serum AFP
 - Serum βhCG
 - Serum LDH
 - Diagnostic cytology
 - Presence of ascites
 - Presence of pleural effusion
- Standard
 - Thorough clinical examination
 - Routine biochemistry
 - Imaging studies
 - USG (TAS /TVS +/- Colour Doppler studies)
 - X-ray Chest
 - CT Scan
 - Tumour marker panel
 - Women >40
 - Serum CA 125
 - Serum CEA
 - Women <40
 - Serum CA 125
 - Serum CEA
 - Serum AFP
 - Serum βhCG
 - Diagnostic cytology
 - Presence of ascites
 - Presence of pleural effusion
- Minimal

- Thorough clinical examination
- Routine biochemistry
- Imaging studies
 - USG (TAS /TVS +/- Colour Doppler studies)
 - X-ray Chest
- Tumour marker
 - Serum CA 125

The group was unanimous that Fine Needle Aspiration Cytology (FNAC) from the abdomino-pelvic mass is never to be recommended as a routine. It is permissible only in those selected patients where neoadjuvant chemotherapy is being contemplated. These are usually women with Stage IV disease and those who have pelvic masses which are considered to be non-resectable on the basis of physical examination and imaging studies.

Management of The Suspicious Adnexal Mass

The suspicious adnexal mass is defined as one which has a complex morphology on imaging and is associated with normal or mildly elevated serum CA 125 levels. Such masses are very common in general gynaecological practice and the vast majority are benign.

The group unanimously agreed that the diagnostic work up of all such patients should be identical to that for patients with clinically obvious ovarian cancer as outlined above.

The approach to all such patients is necessarily surgical and the following guidelines would be regarded as appropriate:

Ideal/Optional

- Laparoscopic assessment and if trained expertise available
- Conversion to immediate laparotomy if laparoscopic assessment suggests malignant ovarian pathology
- Primary laparotomy if facilities for operative laparoscopy unavailable

Standard

- Laparoscopic assessment if trained expertise available
- Conversion to immediate laparotomy if laparoscopic assessment suggests malignant ovarian pathology

- Primary laparotomy if facilities for operative laparoscopy unavailable

Minimal

- Primary laparotomy

In all cases, adnexal masses larger than 6-7 cms in diameter should be managed by primary laparotomy

Staging of Epithelial Ovarian Cancer

It is now accepted that ovarian cancer is a disease which should be staged on the basis of surgico-pathological data and that staging should be in accordance with the publishes AJCC/FIGO guidelines (1998). The group was unanimous in recommending that an appropriate midline laparotomy was essential in all cases and that use of the laparoscopic approach for this purpose is not to be recommended outside of an established research protocol and in designated centers only.

The group emphasized the need for a uniform staging protocol irrespective of the treating center and the principles of staging are as follows:

- Appropriate midline laparotomy
- Ascitic fluid sample or peritoneal washings for cytology if no obvious ascites (large aliquot)
- Thorough abdomino-pelvic exploration to include
 - Liver
 - Undersurface of diaphragm
 - Bowel serosa and mesentery
 - Paracolic and pelvic peritoneum
 - Retroperitoneum of the para-aortic basin and the pelvis
- Multiple peritoneal biopsies in all cases where disease appears confined to the ovaries
- Infracolic omentectomy even if the omentum is macroscopically normal
- Surgical resection of all macroscopic tumour to include hysterectomy with bilateral adnexectomy and infra-colic omentectomy
- Resection of any palpably enlarged retroperitoneal lymph nodes (para-aortic & pelvic).
- Routine retroperitoneal lymphadenectomy is not indicated in patients with advanced disease

In hospitals where personnel trained in the principles of general surgical or gynaecological oncology are unavailable it would be reasonable for such patients to be operated upon jointly by a surgeon trained in general surgery along with a gynaecologist.

Management of Early-Stage Disease

The management of patients with clinical early-stage disease is surgical. All such patients should be offered an initial exploratory laparotomy which includes the following:

- Primary surgical exploration
- Comprehensive surgical staging
- Peritoneal fluid washings for cytology
- Clearance of all pelvic viscera if fertility is not an issue
- Unilateral adnexectomy is acceptable if fertility is desired
- Infracolic omentectomy
- Retroperitoneal lymph node sampling

A full retroperitoneal lymphadenectomy is indicated to complete the surgical staging in all patients with early-stage disease. This surgery requires training and surgical expertise for its safe performance which may not be available in all settings. In clinical setups where such expertise is unavailable it is acceptable for this procedure to be avoided in interests of patient safety.

Adjuvant Therapy for Early-Stage Disease

All patients treated surgically for early-stage disease should be stratified according into low or high risk groups depending upon histopathological risk factors. Patients with low risk disease should be observed clinically with no adjuvant therapy. On the other hand, all patients with high risk disease require adjuvant combination chemotherapy

- Low risk disease
 - LMP/Borderline tumours
 - Grade I and II
 - Stage IA/IB
 - Non-clear cell histology
 - No adjuvant therapy

- High risk disease
 - Grade III
 - Stage IC and all Stage II
 - Clear cell histology
 - Adjuvant combination chemotherapy with a platinum-based regimen (6 treatment cycles)

All patients treated initially in settings where medical oncology expertise is unavailable or where the available infrastructure does not allow for the safe administration of combination chemotherapy protocols should be referred to larger centers where such facilities are available.

Management of Advanced Disease

80-85% of all patients with epithelial ovarian cancer will present with advanced disease i.e. FIGO Stages III – IV. There are two approaches to the management of such patients as outlined below:

- Primary cytoreductive surgery followed by adjuvant combination chemotherapy - The “Gold Standard”
- Use of neoadjuvant chemotherapy (NACT) - emerging paradigm in selected cases

Neoadjuvant chemotherapy

All neoadjuvant chemotherapy (NACT) protocols in advanced epithelial ovarian cancer involve the upfront use of 3 cycles of a platinum-based combination chemotherapy regimen.

NACT may be used in the following clinical settings:

- Indications
 - All Stage IV except patients with minimal pleural effusion or supraclavicular node involvement
 - Gross upper abdominal tumour on imaging
 - Clinically non-resectable pelvic disease
 - Significant and non-resectable retroperitoneal lymphadenopathy

In other words, NACT may be used in all cases where primary surgery is unlikely to result in an optimum surgical resection of the tumour i.e. no macroscopic tumour at the end of surgery or each residual tumour deposit \leq 1 cm. A cytological diagnosis is acceptable for commencing NACT. It is however essential to make a diagnosis prior to starting NACT.

Most NACT protocols follow the treatment plan outlined below:

- Protocol
 - 3 cycles of upfront platinum-based combination chemotherapy (CAP or Platinum-Taxane)
 - “Interval” cytoreductive surgery within 3-4 weeks of completing the third treatment cycle.
 - The aim is to remove all macroscopic tumour at laparotomy
 - 3 further post-operative treatment cycles

Primary surgery

Primary cytoreductive surgery is the “Gold standard” of care for advanced epithelial ovarian cancer and is indicated in all cases where the diagnostic workup suggests that surgery will result in optimal cytoreduction.

The aim is to remove all macroscopic tumour. The surgical end-points include a complete clearance of all pelvic tumour (TAH + BSO) along with a total omentectomy. Resection of enlarged retroperitoneal nodal masses is an essential component of primary cytoreductive surgery. Bowel resection justified ONLY if it leads to a R0 surgical status.

A routine retroperitoneal lymphadenectomy in the absence of enlarged retroperitoneal lymph nodes is not mandatory in patients with advanced disease as it has not been shown to confer any survival benefit.

Primary cytoreductive surgery should not be routinely undertaken in settings where the necessary surgical expertise is unavailable. It was regarded as appropriate for such patients to be referred to larger centers where the required surgical expertise is either available in-house or can be readily made available.

Adjuvant Therapy for Advanced Disease

All patients with advanced epithelial ovarian cancer will require adjuvant combination chemotherapy.

- If optimal cytoreduction achieved at primary surgery
 - 6 cycles of adjuvant platinum-based combination chemotherapy
- If optimal cytoreduction not achieved at primary surgery
 - 3 cycles of adjuvant platinum-based combination chemotherapy
 - “Secondary” cytoreductive surgery
 - 3 further cycles of chemotherapy post-operatively

If optimal cytoreduction was not obtained at primary surgery, the patient should receive 3 cycles of a platinum-based combination chemotherapy regimen followed by a second surgical exploration in an attempt to achieve “secondary surgical cytoreduction” followed by 3 further chemotherapy cycles. It has been shown that those patients in whom an optimal cytoreduction is achieved at secondary cytoreductive surgery do better than those who have significant residual at the end of secondary cytoreductive surgery.

Considerable surgical expertise is required for these secondary cytoreductive procedures and patients should necessarily only undergo such surgery in larger centers where there is available infrastructure, surgical expertise and supportive care.

Second-Look Surgery in Epithelial Ovarian Cancer

The consensus view on the role of second-look surgical procedures in the management of ovarian cancer can be summed up as follows:

- No indication in routine clinical practice
- Up to 50% of women with a clinical or pathological negative “second-look” assessment will relapse
- Not acceptable outside of a clearly defined research protocol
- Neither laparotomy nor laparoscopy has a role

Follow-Up in Epithelial Ovarian Cancer

The group agreed that the following is a reasonable follow-up protocol irrespective of the clinical setting in which the patient has been managed:

- Ideal/Optional
 - Clinical follow up with a thorough physical exam in all patients
 - Tumour marker panel in all patients where levels were elevated at initial presentation
 - Chest X-ray
 - Imaging studies
 - USG or CT Scan
 - MRI (optional)
 - FDG-PET (optional)
- Frequency (empirical)
 - 3-4 monthly for the first 2 years
 - 6 monthly for the next 3 years
 - Annually thereafter
- Standard
 - Clinical follow up with a thorough physical exam in all patients
 - Tumour marker panel in all patients where levels were elevated at initial presentation
 - Chest X-ray
 - Imaging studies
 - USG or CT Scan
- Frequency (empirical)
 - 3-4 monthly for the first 2 years
 - 6 monthly for the next 3 years
 - Annually thereafter
- Minimal
 - Clinical follow up with a thorough physical exam in all patients
 - Serum CA 125 in all patients where levels were elevated at initial presentation
 - Chest X-ray
 - Imaging studies
 - ?USG if available
- Frequency (empirical)
 - 3-4 monthly for the first 2 years
 - 6 monthly for the next 3 years
 - Annually thereafter

Management of Serological Relapse

A serological relapse in patients with epithelial ovarian cancer is defined as a rising Serum CA 125 level during the course of follow-up after primary treatment in the presence of a normal clinical examination and imaging studies

The group agreed on the following guidelines for the management of serological relapses irrespective of the clinical setting in which the patient has been managed:

- Counsel and observe
- Continue close clinical follow-up
- No evidence that treatment of serological relapses confers any benefit
- No consensus regarding
 - Need to treat
 - Type of therapy

Management of Relapsed Disease

It is generally accepted that patients with relapsed epithelial ovarian cancer can be managed in the following two ways:

- Secondary cytoreduction whenever followed by adjuvant CT X 6
- Adjuvant CT X 3 followed by secondary cytoreduction whenever possible followed by further CT X 3 post-operative treatment cycles

Secondary Cytoreduction for Relapsed Disease

- Selection criteria
 - Localized relapses, whether intraperitoneal or retroperitoneal
 - DFI > 12 months
 - Good performance status
- Aims
 - Removal of all macroscopic tumour
- No Level I evidence to suggest a survival benefit with secondary cytoreduction but some evidence to suggest benefit only in highly selected cases

Primary Chemotherapy for Relapsed Disease

- Indications
 - Disseminated relapse, where optimal cytoreduction is not likely
 - Suboptimal performance status
- Protocol
 - CT X 3 cycles
 - Secondary cytoreduction (if favourable response)
 - Postop. CT X 3 cycles

Selection of Chemotherapy for Relapsed Disease

It is generally accepted that the choice of chemotherapy for relapsed disease is dictated by the duration of the disease-free interval prior to relapse. The following guidelines regarding choice of the chemotherapy regimen were unanimously agreed upon:

- Selection of CT
 - DFI > 12 months (Platinum-sensitive)
 - Re-challenge with same CT regimen as in primary treatment
 - DFI 6-12 months
 - Use second-line CT regimen
 - DFI < 6 months (Platinum-refractory)
 - Experimental CT regimens within the context of a clinical trial
 - Symptomatic palliation only

Conclusions

The group agreed that the following would be a practicable roadmap towards achieving standardization in the management of epithelial ovarian cancer in the Indian setting:

- To redefine management guidelines
- To define “minimal” as well as “standard” requirements necessary to safely manage ovarian cancer in a standardized manner
- To categories treatment centers (?credentialing)
- To disseminate derived guidelines

- To institute a clinical audit policy to include audits of structure, process and outcome
- To evolve hierarchical referral policies appropriate to pre-defined zones

The group was also unanimous in recommending that gynaecological oncology should be recognized as a subspecialty of Obstetrics and Gynaecology in its own right. The general consensus was that there is an urgent need to introduce formal training in gynaecological oncology during the course of the existing postgraduate training programs and that there is a need for a formal nationally recognized certification course for this subspecialty