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Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Gynecological Cancers

AOGD SECRETARIAT
Department of Obstetrics & Gynaecology,
3076, Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029
Tel.: 011-26546603, 26593221 E-mail: secretaryaogd2019@gmail.com
Website: www.aogd.org

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AOGD Secretariat
Department of Obstetrics and Gynecology
3076, Teaching Block, IIIrd Floor
All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029
Tel No: 011-26546603, 26593221
Email: secretaryaogd2019@gmail.com
www.aogd.org

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Dr J B Sharma
Ph. No. 011-26546603; Email: secretaryaogd2019@gmail.com

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From the President's Pen

Dear Friends,

Greetings from AOGD

Current issue of AOGD Monthly bulletin is in your hands. The present issue and the forthcoming issues will be devoted to Gynae Oncology. There has been a tremendous increase in Oncology patients in recentyears. According to WHO data for 2018 there were approximately 1,50,000 new cases of Carcinoma Breast and 98,000 new cases of carcinoma cervix in the year 2018. A sound knowledge about diagnosis and treatment of gynaecological cancers is must for all practicing gynaecologists.

Dr Sunesh Kumar
President, AOGD

From the Secretary's Desk

This month we bring out an issue of AOGD Bulletin on Gynae Oncology, coinciding with celebration of World Cancer Day in the month of February. It covers common gynecological cancers. Hope this will be useful to all the members and will be received with as much appreciation as our previous issues of the Bulletin.

The activities in the month of January included, Gurukul classes organized by Sir Ganga Ram Hospital, CME on management of recurrent pregnancy loss and threatened miscarriage. The monthly meeting was at RML Hospital.

I invite you to participate in the National FOGSI Conference on Women's Reproductive and Sexual Health, organized by AOGD on 29th Feb and 1st March 2020 at The Lalit, New Delhi (surakshitnaritva2020@gmail.com).

We look forward for your support for all AOGD activities

Warm regards

Dr Vatsla Dadhwal
Hon. Secretary

Monthly Clinical Meeting

Monthly Clinical Meet will be held at UCMS & GTB Hospital, New Delhi on **Friday, 28th February, 2020 from 04:00pm to 05:00pm**.

From the Editor's Desk


Dr Neerja Bhatla


Dr Seema Singhal

Guest Editors


Dr J B Sharma
Editor


Dr Reeta Mahey


Dr P Vanamail


Dr Vidushi Kulshreshtha

Co-Editors

We bring you another issue of AOGD bulletin on a very important topic of "Gynecological cancers". The incidence of gynecological cancers is increasing in India. Breast cancer remains the most common cancer among women followed by cervix. According to Globocan 2018, there were 1,62,468 new cases of breast cancer and 1,55,074 cases of gynecological cancers including cervix, ovary, uterus, vulva and vagina. In recent times, India has come out as a fast-growing economy with changes in lifestyle-related behaviour partly accountable for the increasing cancer load. The cancer incidence data are collected by the population-based cancer registries (PBCR) in India. The National Cancer Registry Programme (NCRP) of India compiles PBCR data and publishes cancer statistics from cancer registries. According to the NCRP East/North east region experience the maximum burden of gynaecological cancers. The incidence remain low in rural areas, however, underreporting remain a concern. There is wide disparity in diagnosis and treatment of malignancy in our country owing to lack of awareness, apathy, geographical and financial constraints. There are delays at all levels before women actually reach the specialised centre and majority are already financially exhausted. There is not only a need for upgrading awareness, life style and access to health care but also a need to update the knowledge of gynaecologists to the changing concepts in diagnosis and management. There are several online resources available for the ready reference and FIGO app on management of gynaecological cancers is a free downloadable app which provides a comprehensive step wise management useful for clinical practice.

For this issue we have invited eminent gynaecologic oncologists to contribute articles that are pertinent to recent developments and changing practices in the field of gynaecologic cancers. We have tried to cover almost all the aspects of care of gynaecological cancers, including surgical skills contributed by Prof. Sunesh Kumar. Role of Sentinel nodes has been illustrated by Dr Rupinder Sekhon. The management of Borderline ovarian tumours remain a dilemma and Dr Rama Joshi has provided an update on that. Recently there have been many changes in the management of cervical cancer and Dr Neerja Bhatla has given a concise, one point reference which will be useful for all. Dr Lalit Kumar and Dr Neha have summarised the latest changes in chemotherapy for ovarian cancer. A review of Palliative care is given by Dr Sushma Bhatnagar. Dr Jyoti Meena has given an overview of Fertility preserving management of Endometrial cancer. The latest articles are nicely summarised by Dr Manash Biswas and Dr Kanika Batra in Journal scan. An interesting and stimulating cross word is drafted by Dr Swasti and Dr Satinder Kaur. We would like to thank all our authors for their contributions and hope this bulletin will be useful for all.

Happy reading ….

Editorial Team

Essential Surgical Skills for a Gynaecologic Oncologist

Sunesh Kumar[1], Aarthi S Jayraj[2]
[1]Professor and Head, Department of Obs. & Gynae, [2]Senior Resident, Mch Gynecologic Oncology
All India Institute of Medical Sciences, New Delhi

Over the past few decades, the subdivision of gynaecologic oncology has seen tremendous advances in care for women with uterine, ovarian, cervical, vaginal and vulvar cancers. The surgical aspects of the field are exacting and are quintessential for diagnosis, staging and treating these cancers. Many health systems in different countries have established training curriculums and objectives to be met during the training of a gynaecologist in the field of women's cancers. But, unfortunately, these curriculums are heterogenous without accepted international standardization. In many countries, the surgical management of gynecological cancers is performed by surgical oncologists. Nevertheless, it has been convincingly shown by various studies that women with gynaecological cancers have a better survival when managed by gynaecological oncologists with appropriate training and expertise[1]. As a result, many medical organisations such as the American College of Obstetricians and Gynecologists (ACOG) (2) and Royal College of Obstetricians and Gynaecologists (RCOG) (3) recommend onward referral of women with clinical presentation suggestive of malignancy to a gynaecological oncologist for optimal outcomes.

Recognizing the impact of standard treatment on survival of these patients, this article outlines the appropriate and acceptable surgical skills considered essential for a gynaecological oncologist. The various procedures that would be considered mandatory for a gynaecolgical oncologist would be radical and modified radical hysterectomy, nerve sparing radical hysterectomy, exenteration surgeries, extrafascial hysterectomy, omentectomy, pelvic wash cytology, peritoneal biopsies, methods of lymph node dissection of pelvic, para-aortic and inguinal region, fertility sparing surgeries like radical trachelectomy, Loop Electrosurgical Excision Procedure (LEEP), conization and wide local excision along with modified radical and radical vulvectomy. It is important that the surgeon has considerable expertise in performing the above procedures by minimally invasive approach (MIS), where needed and where oncological outcomes are not compromised.

Surgical Techniques for Managing Cervical Cancer

Radical hysterectomy is considered obligatory for any gynaecologist who aspires to be an oncological surgeon. For completeness of surgical outcome, a gynaecological oncologist must appreciate the differences in the various types of radical hysterectomy as defined by the modified Querleu-Morrow classification of radical hysterectomy and strive towards applying the pertinent surgery according to the stage of cervical cancer in a patient[2]. Where deemed fit, a surgeon must practice nerve sparing radical hysterectomy by identifying the hypogastric nerve plexus and its branches and attempting to preserve them. This reduces the autonomic dysfunction to the bladder, bowel and the sexual dysfunction, which is mediated by these hypogastric nerves and allows early recovery with decrease in rates of prolonged catheterization in the postoperative period amongst these women[3].

With a significant number of women presenting with cervical cancer in early age, with a tendency to delay pregnancy among women, the need for fertility sparing surgery is on the rise. It is, therefore, important for gynecological oncologists to acquire adequate skills in this domain. Fertility sparing options in cervical cancer include conization, LEEP, simple and radical trachelectomy techniques. When performed by a trained surgeon in a properly selected group of patients, the oncological outcomes are reported to be excellent, with live birth rates ranging from 30-40%[4].

There is conflicting evidence on the oncological outcomes of cervical cancer managed through laparoscopic approach, with a randomized controlled trial showing high recurrence and mortality rates in patients treated by the MIS approach[5]. Following this, various retrospective analyses have shown conflicting evidence to the same and the current recommendation is to perform MIS in cervical cancer only in research and trial settings, with a proper informed consent from the patients, till further evidence confirm its safety.

Endometrial Cancer

Extrafascial hysterectomy (Type A) with or without bilateral salpingo-oopherectomy is the ideal surgical procedure. The pelvic, para aortic lymph nodes and omentum are addressed depending on the presence of certain high risk factors. The standard treatment of choice is to perform the above said procedures through a minimally invasive approach, as the oncological and survival outcomes compare favorable to open surgery[6].

Ovarian Cancer

Ovarian cancer present in the third or fourth stage in 75-80% of patients. The singe most important predictor of survival amongst these patients remains the ability to perform "optimal debulking" surgery, which is defined as less than 1 cm by the GOG[7]. More recently, it has been shown that absence of any residual disease (R0) is associated with improved survival than the previously defined optimum.

The gynecologic oncologist who operates on patients with advanced ovarian carcinoma often encounters disease spread involving upper abdominal structures such as the diaphragm, liver, pancreas, and spleen. Debulking of tumor from these areas has been demonstrated to improve the rate of optimal cytoreduction and subsequent survival. The mandatory procedures that a gynecological oncology need to master include infracolic/supracolic omentectomy, pouch of Douglasectomy, peritonectomy and ileostomy/colostomy. The scope of surgical resections undertaken by a gynecologic oncologist has progressively expanded to include small and large bowel resections, diaphragmatic surgery, splenectomy, distal pancreatectomy, subsegmental liver resection, and mesenteric peritoneal resection. In some regions the scope has gone even further to include partial/sleeve gastrectomy, cholecystectomy, and resection of disease from the porta hepatis. But, it should be emphasized that progressively complex upper abdominal surgeries and bowel resections should be undertaken only if the surgeon is able to achieve a complete surgical debulking with no gross residual disease. Incomplete, but complicated, resections should be avoided as this may delay the chemotherapy and have a poorer prognosis.

Vulvar Cancer

Vulvar cancer is a rare gynaecological malignancy, comprising less than 5% of all cases. Needless to emphasize, it is absolutely necessary for women to undergo treatment under a surgeon who has experience in managing such patients, for optimal results. The technique of radical vulvectomy has undergone drastic transformation across the years, with decrease in radicality, use of separate incision, definition of a tumour free margin of 10 mm and resultant decrease in morbidity associated with these surgeries.

Nodal Dissection

Nodal dissection is an important part of gynaecological oncology surgeries. They provide information regarding the staging, prognosis and for tailoring adjuvant therapy in these cases.

Pelvic and para-aortic lymph node dissection has 4 levels:

Level 1: External and internal iliac

Level 2: Common iliac (including presacral)

Level 3: Aortic inframesenteric

Level 4: Aortic infrarenal

Pelvic Lymph Node Dissection

This is an essential part of cervical, ovarian and endometrial cancers. The medial boundary of pelvic nodal dissection is limited by the internal iliac artery and its continuation as the obliterated umbilical/hypogastric artery; lateral boundary by the genitofemoral nerve overlying the psoas muscle; distal boundary by the circumflex iliac vein crossing the external iliac artery; deep limit by the obturator nerve and the proximal boundary is defined by the bifurcation of the common iliac artery.

Para-aortic Lymph Node Dissection

The paracaval, interaorto-caval, and para-aortic (left side) receive lymphatic drainage from the iliac lymph nodes, ovaries, and other pelvic viscera (apart from the alimentary tract), and therefore it is these groups of nodes that are sampled in the surgical staging of gynecologic malignancies. However, systematic para-aortic lymphadenectomy should address all major regions, including paracaval, retrocaval, interaortocaval, preaortic, para-aortic and retroaortic nodes. The para-aortic nodes may be removed by either the direct approach or the lateral approach.

Inguinofemoral Lymph Node Dissection

The nodes are approached by an incision parallel to and just above or below the inguinal ligament. The incision is carried through Camper's fascia, and the lymph node-bearing fat are exposed. There is no need to skeletonize the femoral artery. The saphenous

vein is encountered at the lower medial margin of the dissection, and whenever possible, should be preserved to reduce the risk for postoperative lymphedema.

Additional Procedures

It is desirable for the gynaecological oncologist to command skills in various gastro-intestinal and urological procedures, which they may encounter when managing patients with gynaecological malignancies, particularly those pertaining to ovarian cancers. Procedures that deliver chemotherapy intraperitoneally require some form of surgical interference, such as placement of intraperitoneal chemo-ports, hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC), in which a gynaecological oncologist should profess in.

Conclusion

We have outlined the essential skills that a gynaecological oncologist needs to learn, in course of their surgical journey. Nonetheless, we would like to point out that this is not an exhaustive list. As important as it is for a young surgeon to learn the ropes of an established surgical pathway, it is imperative that an experienced gynaecological oncology surgeon unlearns and relearns the changing surgical paradigm in gynaecological malignancy.

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Current Updates in Cervical Cancer

Neerja Bhatla[1], Sarita Kumari[2]
[1]Professor, Department of Obstetrics and Gynaecology, [2]Senior Resident, M.Ch, Gynaecologic Oncology
All India Institute of Medical Sciences, New Delhi

Cervical cancer is the fourth most common malignancy in females worldwide and constitute a major global health challenge. In 2018, an estimated 569,847 new cases were diagnosed, and 311,365 deathsoccurred. With about 90% of the disease occurring in low-middle income countries, it is a striking example of global health disparity. World Health Organization's International Agency for Research on Cancer (IARC) published the GLOBOCAN 2018 report of global trends across 38 countries in five continents which showed substantial decrease in the age standardized incidence rates in high income countries, whereas the rates have increased or stabilized in low resource settings. In India there were an estimated 96, 922 cases and 60, 078 deaths in 2018.

During the past decade, several changes took place in the field of cervical cancer prevention, diagnosis and treatment. The year 2018-19 particularly saw a lot of changes due to a new staging system, trial results on the outcomes of minimally invasive surgery and neoadjuvant chemotherapy, as well as a remarkable initiative on prevention from the World Health Organisation. This article summarizes these recent advances.

FIGO Staging

Cervical cancer was the first malignancy to be assigned a staging system in 1958. The FIGO staging underwent major revision in 2018. Being mainly a disease of low resource settings with radiation being the most commonly used treatment option, the disease continued to be staged clinically. However, imaging resources have increased significantly even in low middle income countries (LMICs) in the last decade. Non-invasive imaging modalities can accurately assess the disease in pelvis, abdomen and retroperitoneal areas. Para-aortic node sampling is being done by minimally invasive approach to determine the need for extended field radiation.

A major lacuna in clinical staging was non-assessment of major prognostic factors, i.e. tumor volume, nodal metastasis and stromal invasion. Pelvic and para-aortic lymph node status is significantly associated with progression free survival. Reported accuracy of clinical staging ranges from 85% in stage 1A2-1B1, 35% in stage IIA and only 21% in stage IIB. Imaging techniques obviate the need for invasive procedures like cystoscopy and sigmoidoscopy when there is no sign of local extension and moreover, they identify lesion volume and metastatic lymph nodes. Persistent dilemmas in allowing imaging to change the staging included increase in the need for resources, and difficulty in interpretation of enlarged nodes that may be infective, especially in HIV and tuberculosis endemic areas and requiring histological confirmation, as even PET-CT may not be confirmatory. The choice of imaging modality for nodal evaluation has not been fixed by FIGO and it depends upon availability and patients' affordability. Non-availability of an imaging modality should not be a reason for undue delay in initiation of treatment. Pathology remains the gold standard.

In summation, the salient features in the 2018 staging are its applicability to all kinds of resource settings with the option of using clinical, imaging or pathologic findings; an additional cut-off at 2 cm in stage I (1B1, 1B2, 1B3); lymph node positive in stage IIIC – C1 for pelvic nodes and C2 for paraaortic nodes; adding notation of r (imaging) and p (pathology) to indicate the modality used to assign the stage. The best available technology should be used for assessment, and the lowest appropriate stage should be assigned, i.e., when in doubt assign the lower stage. The method of assigning the stage is to be recorded and reported. Table 1 presents a summary of the 2018 FIGO staging for cervical cancer.

Table 1: FIGO staging of carcinoma of the cervix uteri (2018)

Stage I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
I A	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm[a]
I A 1	Measured stromal invasion ≤3 mm in depth
I A 2	Measured stromal invasion >3 mm and ≤5 mm in depth
I B	Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
I B 1	Invasive carcinoma >5 mm depth of stromal invasion, and ≤2 cm in greatest dimension

I B 2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
I B 3	Invasive carcinoma >4 cm in greatest dimension
Stage II	The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
II A	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
IIA1	Invasive carcinoma ≤4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
Stage III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
III A	Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
III B	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
III C	Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases)[c], irrespective of tumor size and extent (with r and p notations)[d]
III C 1	Pelvic lymph node metastasis only
III C 2	Paraaortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IV A	Spread of the growth to adjacent pelvic organs
IV B	Spread to distant organs

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. Pathological findings supercede imaging and clinical findings.

[b]The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.

[c]Isolated tumor cells do not change the stage but their presence should be recorded

[d]Adding notation of r (imaging) and p (pathology), to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r; if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

Surgical Approach

Treatment depends on disease extent at diagnosis and locally available resources, and includes radical hysterectomy or chemoradiation. Radical hysterectomy for early stage (up to IIA) was being done via laparotomy or by minimally invasive approach (laparoscopy or robotic) in the last decade. A meta-analysis of 26 non-randomized studies that included 4013 patients compared the three surgical routes and found that, compared with laparotomy, minimally invasive approach resulted in less blood loss, fewer blood transfusions, faster time to discharge from hospital, less febrile episodes and wound infections, but longer operative time. No differences were found in intra-operative complications and lymph node counts. However, most of the studies included in this meta analysis were either retrospective or observational with small sample size.

The findings of the LACC trial - a large phase 3 randomized trial of laparoscopic or robotic radical hysterectomy versus abdominal radical hysterectomy - in patients with early stage cervical cancer, challenged the perceived oncologic safety of minimally invasive surgery. The primary endpoint was disease free survival at 4.5 years and the study was terminated early by the data safety monitoring committee after 631 women had been randomized. Patients treated by minimally invasive surgery had four times higher recurrence and six times worse overall survival compared to open surgery. Furthermore, in another retrospective cohort of 2221 women with early stage disease, minimally invasive surgery was associated with a higher risk of all-cause mortality compared to laparotomy (4 year survival of 8.4% vs 5.8%, HR 1.48 [95% CI 1.10–1.98]). The findings of the LACC trial have changed clinical practice as most centers have reverted to open surgery till further randomized trials are completed. Currently MIS for cervical malignancy is recommended for selected cases with small tumors, in research setting, after careful counselling and informed consent till more data accrues on its safety.

Role of Chemotherapy

Role of chemotherapy in neoadjuvant as well as adjuvant setting is being explored in several trials. There is conflicting evidence on the value of neoadjuvant chemotherapy in Stage IB2-IIB cervical carcinoma. The EORTC phase 3 randomized trial of neoadjuvant chemotherapy followed by surgery versus primary chemoradiotherapy for stage IB2 to IIB cervical cáncer (NCT00039338) revealed no difference in 5-year overall survival between two arms. Quality of life and long-term toxicity are important to decide optimal treatment. Similar findings were reported by another Indian study and hence, currently NACT followed by surgery for IB2 to IIB disease is not recommended. Neoadjuvant chemotherapy before chemoradiotherapy is also being evaluated in the prospective randomized phase 3 multicenter trial INTERLACE (NCT01566240).

Less Radical Surgery

Meta-analysis of several studies have shown that <1% of patients with early stage cervical cancer with favorable pathologic characteristics have parametrial involvement and there is feasibility and safety of performing less radical surgery consisting of pelvic lymphadenectomy with cone biopsy, simple trachelectomy or simple hysterectomy in women with stage IA1 to IB1. If the results of ongoing studies are favorable, conservative surgery might become the standard of care. The SHAPE trial (NCT01658930) is an ongoing randomized study that aims to assess the oncologic safety of simple extra-fascial hysterectomy and pelvic node dissection versus radical hysterectomy for women with low risk cervical cancer.

Fertility Preserving Surgery

Fertility-preserving surgical procedures have become standard of care for women with low risk, early stage disease. Women younger than 40 years, with stage IA1 disease with lymph-vascular space invasion (LVSI), stage IA2, smaller stage IB1 tumours (<2 cm diameter), without evidence of lymph node metastases on imaging and wishing to preserve fertility, are appropriate candidates for radical trachelectomy. Recurrence rate is similar to that of radical hysterectomy. The prospective CONTESSA-NEOCON-F study will address the safety of neoadjuvant chemotherapy to downsize stage IB1 lesions of more than 2 cm to enable subsequent fertility-sparing surgery.

Conservation of normal appearing ovaries should be considered in women younger than 45 years as the risk of ovarian metastases is low. A meta-analysis of 24 studies that included 892 women found that ovarian transposition was associated with preservation of ovarian function and negligible risk for metastases to the transposed ovaries.

Sentinel Lymph Node Mapping

Sentinel lymph node mapping can reduce lymphadenectomy-associated morbidity and false negative cases have been reported in < 1% in retrospective series. However, the long-term prognosis of sentinel lymph node negative patients is unknown. Role of sentinel lymph node mapping in women with early stage cervical cancer is being investigated in the phase 3 randomized SENTICOL III trial (NCT03386734).

Advances in Radiation Treatment Planning

With the advent of computer based treatment planning with CT and MRI, soft tissue regions at risk can be treated while sparing adjacent tissues using 3 dimensional conformal treatment or intensity modulated radiotherapy. CT and MRI scans enable image guided adaptive brachytherapy (IGABT) to increase the radiation dose to the tumour while avoiding surrounding healthy tissues. IGABT is associated with a 2 year local pelvic control of 70% as compared to 61% (p=0.001) for conventional brachytherapy and a marked decrease in serious urinary and digestive complications (1% vs 14%, p=0.027). The EMBRACE II trial (NCT03210428) 89 is an ongoing study incorporating the latest brachytherapy and external beam radiotherapy technologies.

To clarify the role of adjuvant chemotherapy in high-risk group after surgery, the RTOG 0724 (NCT00980954) trial is in progress, to investigate whether adjuvant chemotherapy following chemoradiotherapy will improve overall survival and local recurrence compared with chemoradiotherapy alone. For locally advanced cervical cancer, adjuvant chemotherapy after chemoradiotherapy is being evaluated in the OUTBACK study.

Role of Immunotherapy

Immunotherapy holds promise in recurrent and metastatic disease. Pembrolizumab inhibits the immune checkpoint programmed cell death 1 protein (PD-1) and has received regulatory approval by the US Food and Drug Administration for use in advanced cervical cancer with progressive disease either during or after chemotherapy, on the basis of the response observed in the KEYNOTE-158 (NCT02628067) trial. The effect of the PD-1 inhibitor Nivolumab has been studied in 19 patients in the phase 1-2 study Check Mate 358 with objective response rate of 26.3%. Therapeutic vaccines are currently being explored. Somatic mutations in the PI3K/AKT/mTOR pathway and in Erb-B2 receptor tyrosine kinase 3 offer potentially actionable targets. However, cost and limited availability remain an important limiting factor before these therapies are recommended routinely.

FIGO Gyn Cancer Management Mobile Application

The FIGO Gyn Cancer Management application was developed by the FIGO Gyn Oncology Committee

in partnerships with IAEA, with an aim to provide latest staging and recommendations for investigation, diagnosis and stepwise management of each Gynaecological cancer (https://apps.apple.com/us/app/figo-gyn-cancer-management/id1153038788). It is available as a free download on both android and iOS platforms and can be used offline once downloaded.

Prevention of Cervical Cancer

In 2018, the Federation of Obstetric and Gynecological Societies of India (FOGSI), Gynaecologic Oncology Committee published Good Clinical Practice and Recommendations on Screening and Treatment of Preinvasive Lesions of Cervix and HPV Vaccination for Indian population. This document provides resource-based options for screening and treatment of preinvasive lesions of cervix. Screening should be started at 25 years for good resource and 30 years for low resource setting. Primary HPV testing is the best method but all screening tests, namely, HPV, cytology, co-testing with both HPV and cytology, and VIA are valid options. Single visit approach is to be practiced wherever possible to minimize non-compliance and loss to follow up.

The bivalent and quadrivalent HPV vaccines are licensed in India for use in females aged 9-45 years; however, the preferred target age group is 9-14 years. Girls aged 9-14 years of age should receive two doses of HPV vaccine at least six months apart, while older age groups need three doses. In 2014 the USFDA approved 9-valent HPV vaccine (9vHPV). This vaccine targets HPV types 6, 11, 16, and 18, as well as 31, 33, 45, 52, and 58. At present the 9-valent vaccine is not available in India. Emerging data suggests that two-dose schedule can be extended till 18 years of age. Moreover, one dose schedule may afford equivalent protection. Older women may be vaccinated although protection would be less. Since 2016 there has been successful introduction of HPV vaccination in immunization program in Punjab and Sikkim (with high coverage and safety) and government sponsored opportunistic vaccination in Delhi. An Indian quadrivalent vaccine has now entered Phase III trials.

In May 2018, WHO Director General gave a call for elimination of cervical cancer by 2030. Targets to be achieved include HPV vaccination of 90% girls by 15 years of age, 70% of women to be screened with a high precision test at 35 and 45 years of age and 90% of women with cervical lesions to receive treatment and care leading to 30% reduction in mortality.

To summarize there has been a tremendous progress in the field of cervical cancer prevention and treatment, with a new staging system, new information on management strategies, powerful prevention strategies and political will to eliminate this disease in foreseeable future.

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Current Concepts in Chemotherapy for Ovarian Cancer

Kumar L, Pathak N
Department of Medical Oncology, Dr. B.R.A.I.R.C.H., AIIMS, New Delhi

Introduction

In absolute numbers worldwide, ovarian cancer has 239,000 new cases (3.6% of total) and causes 152000 deaths (4.3% of total) annually, making it the seventh most common cancer and eighth most common cause of cancer death among females. With 75% cases being diagnosed in advanced stage (III/IV), the five-year survival for ovarian cancer stands at 47%, which compares unfavorably to cancers such as breast cancer (90%) and 5-year cancer survival overall (69%).

Malignant ovarian tumours are the most lethal of all gynaecological cancers. Histologically, such malignant epithelial ovarian cancers can be subdivided into five main subtypes on the basis of immunohistochemistry and molecular genetic analysis; high-grade serous carcinomas (HGSC) (70%), endometrioid carcinomas (EC) (10%), clear cell carcinomas (CCC) (10%), mucinous carcinomas (MC) (3%), and LGSC (<5%) [Table 1]. High grade epithelial ovarian cancer and high grade endometriod tend to be sensitive to chemotherapy,

Table 1: Comparative chart on different histological subtypes of epithelial ovarian cancer*(Adapted from Lheureux S et al 2019, Prat J. et al 2012, Prat J et al 2012)*

Histology/feature	High grade serous	Low grade serous	Clear cell	Endometroid	Mucinous
Characteristic pathology	Tumour cells with atypical, large irregular nuclei High proliferative rate	Micro-papillary pattern Tumour cells with small uniform nuclei Low proliferative rate	Glycogen-containing cells with clear Cytoplasm Tubulo-cystic, papillary, solid, or mixed patterns	Solid and cystic patterns. High grade similar to high grade serous; low grade to low grade serous.	Large size tumours filled with mucus-like material Early-stage diagnosis. Should rule out GI primary
Precursor lesion	Tubal intraepithelial carcinoma	Serous borderline tumor	Atypical endometriosis	Atypical endometriosis	cystadenoma/ borderline tumor?
IHC	TP53 abnormal,WT1 positive High ki67	TP53 Wild, WT1 positive Low ki 67	Napsin positive	Vimentin positive CK7 positive, 97%; CK20 occasional & ER/PR positive	CK7 strong,CK20 and CDX2 weak and focal
Genetic	BRCA1/2, TP53, HRD	MAPK KRAS BRAF	ARID1A, PI3K/AKT RTK/RAS MMR PTEN	PI3KCA ARID1A KRAS Wnt-β catenin MMR	KRAS Her2neu amplification
Hormone receptor positivity PR	30%	57%	8%	67%	16%
Hormone receptor positivity ER	80%	87%	15%	76%	20%
Chemotherapy sensitivity	Sensitive	Relatively resistant	Relatively resistant	Sensitive	Relatively resistant
PARP inhibitor sensitivity	Yes	-	-	Yes for high grade	-
MMR deficiency	-	-	Yes	Yes	-
Aniti-PD1	-	-	Yes	Yes	-
Folate receptor	Yes	-	-	Yes	-
Pattern of spread	Very early trans coelomic spread	Trans coelomic spread	Usually confined to pelvis	Usually confined to pelvis	Usually confined to ovary

AKT indicates AKT serine/threonine kinase 1; anti–PD-1, programmed death 1 antibody; ARID1A, AT-rich interaction domain 1A; BRAF, B-Raf protooncogene,serine/threonine kinase; CNA, copy number alterations; ER, estrogen receptor; GI, gastrointestinal; HER2 amplif., human epidermal growthfactor 2 amplification; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; KRAS, Kirsten rat sarcoma viral oncogenehomolog; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase;PI3K, phosphatidylinositol-4,5-biphosphate 3-kinase; PI3KCA, phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit α; TP53, tumor proteinp53; BRCA1/2, breast cancer type 1 susceptibility protein 1/2; PTEN, phosphatase and tensin homolog.

Table 2: FIGO & AJCC staging of Ovarian cancer

T Category	FIGO Stage	T Criteria
T0		No evidence of primary tumor
TX		Primary tumor cannot be assessed
T1	I	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	IA	Tumor limited to one ovary (capsule intact) or fallopian tube
TIb	IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface
T1c	IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	IC1	Surgical spill.
T1c2	IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface.
T1c3	IC3	Malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	IIA	Extension and/or implants on the uterus and/or fallopian tube(s)and/or ovaries.
T2b	IIB	Extension to and/or implants on other pelvic tissues
T3	III	Microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	IIIA2	Microscopic peritoneal metastasis beyond the pelvis with or without positive retroperitoneal lymph nodes
T3b	IIIB	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension with or without positive retroperitoneal lymph nodes.
T3c	IIIC	Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension including extension to liver capsule or spleen without parenchymal involvement of those organs and with or without positive retroperitoneal lymph nodes
N0	IIIA1	No regional lymph node metastasis
NX	IIIAIi	Regional lymph nodes cannot be assessed
N0(i+)	IIIAIii	Isolated tumor cells in regional lymph node(s) ≤0.2 mm
N1		Positive (histologically confirmed) retroperitoneal lymph nodes
N1a		Metastasis ≤10 mm in greatest dimension
N1b		Metastasis more than 10 mm in greatest dimension
M0	IV	No distant metastasis
M1	IVA	Distant metastasis including cytology-positive pleural effusion; liver or splenic parenchymal involvement; extra-abdominal organ involvement including inguinal lymph nodes; transmural intestinal involvement.
M1a	IVB	Pleural effusion with positive cytology
M1b		Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine

and the others relatively resistant, owing in part to the presence of homologous recombination deficiency (HRD) in DNA repair mechanism seen in this subgroup.

The essential doctrines for management of ovarian cancer that have been established through clinical trials in the past decades involve surgical staging and confirmation of diagnosis, histological subtype and grading, maximal cytoreduction and combination taxane platinum therapy. Ovarian cancer staging has evolved to include fallopian tube, and primary peritoneal carcinomas, and follows the FIGO 2014 and AJCC 8th staging system. (Table 2) The foundation of management of relapsed ovarian cancer relies on the concept of platinum sensitivity. The advent of targeted therapy, in the form of anti-angiogenesis inhibitors and PolyADP-ribosePolymerase (PARP) inhibitors have added to the armamentarium of treatment options.

Antibody drug conjugates and immunotherapy represent the very tip of the spearhead of changing landscape of management of ovarian cancer.

Chemotherapy in Ovarian Cancer: Taxane and Platinum

Post primary debulking surgery most cases of ovarian cancer undergo adjuvant chemotherapy, a platinum doublet, for up to 6 cycles. Few exceptions to this rule include stage IA/IB tumors with the following histological patterns: low grade serous cancers, grade 1 endometriod ovarian cancer and mucinous cancer. For those that do not meet the criteria for upfront surgery, as per institutional protocol, they go for neoadjuvant therapy for 2-3 cycles and are assessed for interval debulking surgery, with adjuvant therapy of the same regimen for up to 6 cycles total.

Two prospective, randomized clinical trials comparing primary debulking surgery (PDS) versus IDS demonstrated no survival disadvantage in the patients who were randomized to IDS; a study conducted in AIIMS New Delhi by Kumar et al found that interval debulking post neo adjuvant therapy led to better quality of life and increased chance of optimal debulking in advanced ovarian cancer. The ongoing TRUST trial is expected to answer the question of preference between the two.(NCT02828618).

Regarding adjuvant therapy, the current standard of care for the last twenty to thirty years has been Paclitaxel (175mg/m2) and Carboplatin (AUC5/6) at 21day intervals for 6 cycles.

Cisplatin (75mg/m^2) and carboplatin have been found to be comparable, however carboplatin is better tolerated. Addition of a third drug (ICON5) or increasing the dose of this doublet was not found to be beneficial.

Weekly dose dense of paclitaxel with 3 weekly carboplatin has recently been evaluated (Table 2). While weekly regimens were well tolerated, they offered no survival advantage, leading to the inference that possibly, there are pharmacogenomic factors in play due to different ethnicity in different studies.

The Role and Question of Intraperitoneal Chemotherapy

Owing to the intra-abdominal pattern of spread of ovarian cancer, the concept of intraperitoneal therapy arose. The concept of intra-abdominal cancer therapy was first intrioduced in the 1950s when nitrogen mustard was used intraperitoneally for malignant ascites. The rationale is that through intraperitoneal therapy, higher concentration of the chemotherapeutic agents can be delivered to the residual microscopic disease site, abrogating the side effects due to such high doses if given systemically instead. A metanalysis published in 2016 of 2119 patients across 9 randomized controlled trials is the strongest evidence of intraperitoneal chemotherapy, showing both OS (HR = 0.81; 95% confidence interval (CI): 0.72 to 0.90) and DFS (HR = 0.78; 95% CI: 0.70 to 0.86) benefit but at the cost of somewhat higher toxicity and poor impact on QOL in one study [GOG 172]. The benefit seen in this analysis is from studies that employed regimens and doses that are not commonly used in practice, nor are standard. In addition, intraperitoneal chemotherapy penetration is limited to the depth of 1mm-2mm or so, hence can be offered to those patients who have low volume residual disease post debulking surgery.

The GOG 252 trial, which incorporated IP carboplatin instead of the cisplatin used classically, also had Bevacizumab in the intravenous arm along with Paclitaxel Carboplatin. This trial failed to demonstrate a PFS benefit. The Ipocc study (NCT01506856) a randomized multicenter trial that will hopefully add information regarding IP carboplatin.

The role of hyperthermic intraperitoneal therapy (HIPEC), i.e, instillation of heated chemotherapy into the abdominal cavity at the time of surgery was addressed by two RCTs. A phase three trial, with 245 patients, demonstrated that HIPEC was feasible and tolerable, and improved outcomes with regard to

Table 3: Summary of trials with weekly Paclitaxel regimen

Trial	N	Phase	Population	Arms	Outcomes
JGOG 3016	637	3 RCT	Stage II to IV ovarian cancer first line	3 weekly TP Vs Weekly T (80mg/m2) plus 3 weekly P	17.5 m vs 28.2 m HR 0.76 (0.62-0.91) OS 62m vs 100.2 m HR 0.79(0.63-0.99)
GOG 262	692	Phase 3 RCT	Stage III and IV incompletely resected	3 weekly TP vs Weekly T (80mg/m2) plus 3 weekly P *84% patients opted to receive bevacizumab in both arms.	PFS 14m vs 14.7m HR 0.89(0.74- 1.06) Those who didn't receive Bevacizumab 10.3m vs 14.2m HR0.62(0.4-0.95)
MITO 7	822	Phase 3 RCT	Stage IC-IV first line	3 weekly TP vs weekly T (60mg/m2)plus 3 weekly P	17.3m vs 18.3m HR 0.96(0.8-1.16)
ICON 8		Phase 3 RCT	Stage IC-IV first line	Group 1: 3 weekly TP Group 2: weekly T (80mg/m2) plus 3 weekly T Group 3: weeklyTP (AUC 2 P and 80mg/m^2 T)	PFS 17.7m 20.8m 21m

decreased risk of recurrence or death (hazard ratio 0.66; 95% CI, 0.50-0.87; p = .003), median recurrence free survival being 14.2 months in the surgery plus HIPEC arm vs 10.7 months in the surgery arm. The median OS was 45.7 months in the surgery-plus-HIPEC group 33.9 months in the surgery group. The other RCT was a negative study of 184 patients with greater toxicity and no PFS or OS advantage. An upcoming multicenter trial, CHIPPI (NCT03842982) will hopefully clarify the stance on this modality. SO far HIPEC in ovarian cancer management should be conducted in research setting and is not yet recommended as standard of care.

Treating Recurrent Disease

Despite best measures, majority of ovarian cancer patients will relapse. The basis of selection of second line therapy, relies on the consideration of the platinum free interval. Patients progressing more than or equal to 6 months post first line therapy, benefit from platinum based combination therapy, either re-challenge with initial regimen, or platinum in combination with paclitaxel, liposomal doxorubicin, gemcitabine etc.

To this combination, there is improvement in the progression free survival on addition of bevacizumab, as noted in subsequent sections. Bevacizumab when added to the doublet regimen should then be continued as maintenance therapy. Indeed, bevacizumab even if included in primary therapy may be utilized in second line therapy as well. Patients who attain a complete or partial response to platinum based therapy in the second line are suitable for and gain benefit from PARP inhibitor switch maintenance therapy as the presence of platinum sensitivity is a soft indicator of susceptibility to DNA damage. (vide infra)

Artificially prolonging the platinum free interval by use of non-platinum regimens is not beneficial.

The patients who are platinum resistant (relapse within 6 months of therapy) and those that are platinum refractory have a poor outcome. The preferred method is to use non platinum single agent therapy, of which a Cochrane meta-analysis found topotecan/paclitaxel/pegylated liposomal doxorubicin to have similar efficacy but different side effect profile. Gemcitabine and oral etoposide seem to have a comparable profile.

The AURELIA trial had 361 patients with platinum resistant ovarian cancer with ≤ two prior lines of therapy tested the idea of single agent chemotherapy of investigator's choice (Paclitaxel/topotecan/liposomal doxorubicin) with bevacizumab at 15mg/kg every 3 weeks was found to impart a progression free survival benefit of 3.3 months, lack of OS benefit was likely due to cross over being allowed in the study. Based on this trial, bevacizumab was approved for this indication in 2014 by FDA. MITO 11 trial showed PFS advantage for Pazopanib in platinum resistant patients. The ATALANTE trial (NCT02891824) which is testing atezolizumab, NRG-GY005 (NCT02446600) using olaparib plus cediranib, and ARIEL 4 (NCT02855944) evaluating Rucaparib, may fill the lacunae in the management of platinum resistant ovarian cancer in future.

Role of Bevacizumab

The reasoning behind VEGF inhibitor benefit in ovarian cancer stems from the angiogenesis driven biology of the disease, ascites which is a manifestation of capillary leak and improvement with reduction of ascites with bevacizumab.

Table 4: Summary of Bevacizumab related trials *(adapted from Wu YS et al 2017)*

Trial/Feature	GOG 218	Icon 7	Oceans	Aurelia	GOG 213
N	1248	1528	484	361	748
Population	Stage III (incompletely resectable) or stage IV	Stage I-III or StageIV or Inoperable Stage III	Platinum-sensitive recurrent ovarian cancer	Platinum-resistant recurrent ovarian cancer	Platinum-sensitive recurrent ovarian cancer
Treatment arms	TP + placebo Vs TP+Bev+Bev(m)	TP Vs TP+Bev+ Bev(m)	GC Vs GC+Bev+ Bev(m)	CT(PLD or PAC or TOP) vs CT+Bev+ Bev(m)	TP Vs TP+Bev+ Bev(m)
Primary end point	PFS	PFS	PFS	PFS	OS
Results	10.3m vs 14.1m HR 0.770 (0.681-0.870)	17.5m vs 19.9m HR 0.930 (0.830-1.050)	8.4m vs 12.4m HR 0.484 (0.388-0.605)	3.4m vs 6.7m HR 0.480 (0.380-0.600)	10.4m vs 13.8m HR 0.614 (0.522-0.722)

TP, Paclitaxel+Carboplatin; GC, Gemcitabine+Carboplatin; Bev(m), Bevacizumab (maintenance chemotherapy);CT, PLD or PAC or TOP; PLD, pegylated liposomal doxorubicin; PAC, weekly paclitaxel; TOP, topotecan; PFS, progressionfreesurvival; OS, overall survival

Bevacizumab was the first targeted therapy approved in ovarian cancer by the EMA in 2011 and it gained its FDA approval in first line adjuvant setting in 2018. The paramount study for this approval, placebo controlled GOG 218, demonstrated a PFS benefit of 6months in incompletely resected stage III/IV ovarian cancers in the first line adjuvant setting along with chemotherapy, followed by maintenance bevacizumab. ICON7 used half the dose and achieved similar results.

In the platinum sensitive recurrent setting, the OCEANS and GOG 213 concurrent and maintenance bevacizumab displayed benefit. The AURELIA trial showed a 3month PFS benefit for platinum resistant relapsed disease. A metanalysis including these three trials concluded an overall OS and PFS benefit with bevacizumab in the recurrent setting.

The common toxicities seen with Bevacizumab are as follows: Hypertension (risk ratio (RR) 21.27, 95% CI 9.42-48.02, I2 = 0%), Proteinuria (RR 4.77, 95% CI 2.15-10.61, I2 = 0%), Wound healing disruption (RR 3.55, 95% CI 1.09-11.59, I2 = 0%), Bleeding (RR 3.16, 95% CI 1.59-6.30, I2 = 0%), GI perforations (RR 2.76, 95% CI 1.51-5.03, I2 = 0%), arterial thrombosis events (RR 2.39, 95% CI 1.39-4.10, I2 = 14%), and venous thrombosis events (RR 1.43, 95% CI 1.04-1.96, I2 = 39%).

The PAOLA 1 trial brought to us some interesting results, a randomized, double-blind, international phase III trial that enrolled patients with newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian cancer, fallopian tube or primary peritoneal cancer, in clinical complete or partial response following platinum-based chemotherapy plus bevacizumab were randomized 2:1 to receive oral olaparib at 300 mg twice daily for up to 24 months or placebo plus bevacizumab at 15 mg/kg on day one every 3 weeks for 15 months, which included doses received during chemotherapy. Primary end point is PFS, and analysis at 59% maturity of the data so far has shown PFS of 22.1 months with olaparib compared to 16.6 months with placebo, and significantly higher PFS gain in subgroups of BRCA (37.2months vs 21.7months) and HRD (37.2 months vs 17.7 months) mutated patients. This is the first trial to use both olaparib and bevacizumab maintenance in the first line setting, in a population unrestricted by BRCA status.

PARP Inhibitors

The phenomenon of synthetic lethality in patients of ovarian cancer with BRCA or Homologous recombination deficiency (HRD) mutation status sparked interest in the use of PARP inhibitors in ovarian cancer. Table 5,6 and 7 summarizes the important trials and their resultant approvals in ovarian cancer and common toxicities of PARP inhibitors respectively. Although there is a range of benefit seen across patients depending on their mutational status with BRCA or HRD, the strongest marker for determining benefit of PARP inhibitor is platinum sensitivity.

Table 5: PARP inhibitors *(adapted from Franzese E et al 2019)*

Drug/Phase	Population	Setting	Results
Olaparib maintenance Phase 3 Moore et al 2018 [SOLO1]	BRCA1,BRCA2 mutated	In first line post CR or PR to therapy	60% vs. 27% (hazard ratio for disease progression or death, 0.30; 95 % confidence interval, 0.23 to 0.41; P < .001
Olaparib maintenance Phase 2 Lederman et al 2012		Platinum sensitive relapsed ovarian cancer	PFS 8.4m vs 4.8m
Olaparib tablet Phase 3 Pujade-Lauraine 2017 [SOLO2]	high-grade serous ovarian cancer with a BRCA1 or BRCA2 mutation	Platinum Sensitive relapse	Median PFS was significantly longer with olaparib than with placebo: 19.1 vs 5.5 m
Niraparib maintenance Phase 3 Mirza 2016	Patients characterized as per germline BRCA& absent germline BRCA	Platinum-sensitive, recurrent ovarian cancer	21.0 vs 5.5 m in patients with gBRCA 12.9 vs 3.8 m in patients with non-gBRCA
Rucaparib maintenance Phase 3 Coleman 2017[ARIEL3]	Stratified as per BRCA and HRD presence or absence	Platinum-sensitive, recurrent, high-grade ovarian cancer	Patients with BRCA-mutant carcinoma: 16.6 vs 5.4 mo Patients with HRD carcinoma: 13.6 vs 5.4 m The intention-to-treat population: 10.8 vs 5.4 m

Table 6: Approval status of PARP inhibitors *(adapted from Franzese E et al 2019)*

Olaparib	Niraparib	Rucaparib
First-line maintenance therapy for *BRCA*-mutated advanced ovarian cancer		
Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status	Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status	Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status
Fourth-line and beyond treatment for advanced ovarian cancer with germline *BRCA* mutations		Third-line and beyond treatment for advanced ovarian cancer with *BRCA* mutations

Table 7: Toxicity of PARP inhibitors *(adapted from Franzese E et al 2019)*

Drug	Olaparib	Rucaparib	Niraparib
Common Side Effects	Nausea (58–76%)/ fatigue (29–66%)/ vomiting (30–37%)/ diarrhea (21–33%)/ dysgeusia (27%)/ headache (20–25%)	Nausea 75%)/fatigue (69%)/vomiting (37%)/ diarrhea (32%)/dysgeusia (39%)/LFTelevation (34%)	Nausea (74%)/fatigue (59%)/LFT elevation (36%)/vomiting (34%)/ headache (26%)/insomnia (24%)/HTN (19%)
Grade 3 Toxcities (CTCAE v 5)	Anemia (16–19%), neutropenia (5–9%	Anemia (19%), neutropenia (7%)	Thrombocytopenia (34%), anemia (25%), neutropenia (20%)

Future Directions

The future of ovarian cancer therapy lies in targeted agents, with purported better efficacy and lesser toxicity. One such viable target is folate receptors. Although normal ovarian tissue does not express folate receptor (FR), approximately 70% of primary EOCs and 80% of recurrent EOCs do. Proof of principle early phase studies of one such drug has shown an overall response rate of 46% (95% CI, 29.5%-63.1%) and a median PFS of 6.7 months (95% CI, 4.1-9.0 months). Mirvetuximab soravtansine soravtansine (IMGN853), which is an Antibody drug conjugate consisting of an anti-folate receptor antibody linked to a potent anti-mitotic drug. DM4 is the foremost in the line of antibody drug conjugates being developed for ovarian cancer. FORWARD1 (NCT02631876) is the phase 3 trial designed to carry this research further.

Immunotherapy, CAR T cell therapy targeting mesothelin, another molecule expressed on ovarian cancer cells and vaccines are areas of active experimental evaluation and research. The future may see further characterization of therapy tailored to ovarian cancer histology and genetic makeup of the tumours. Thus, as we continue to understand and comprehend the complex biology of this disease, our approach will increase in precision and specificity in the management of ovarian cancer.

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Fertility Sparing Management of Carcinoma Endometrium

Jyoti Meena[1], Jayashree N[2]
[1]Associate Professor Department of Obs and Gyane, [2]Senior Resident, M.Ch, Gynaecologic Oncology
All India Institute of Medical Sciences, New Delhi

Introduction

Endometrial carcinoma (EC) is primarily a disease of post-menopausal women, and only 3-5% occurs in less than 40 years with 70% being nulliparous at the time of initial diagnosis. The incidence has increased globally in recent years due to increase in life expectancy, delayed childbearing and lifestyle related disorders such as obesity, diabetes and hypertension. In younger age group EC may associated with Lynch syndrome or obesity, anovulatory cycles, polycystic ovarian syndrome or other hyper estrogenic conditions.

The standard treatment of EC in majority of women is hysterectomy with bilateral salpingo-oophorectomy along with retroperitoneal lymph nodes assessment. In young women EC is often well-differentiated, low grade and carries a good prognosis. Therefore, options for more conservative management for fertility preservation can be considered in these women. For women who are candidates for fertility preservation, the most common approach is progestin therapy and deferral of surgical staging until after completion of childbearing. Use of this approach is limited to women with low-risk disease, and with fertility preservation the risk of recurrent or persistent disease is higher than with hysterectomy. EC treatment with hormone therapy was first reported in 1961, still there is no consensus regarding standardized conservative treatment for EC in young women in terms of the agent to be used, its dosing, duration and the frequency of surveillance after treatment.

Risk of Fertility Preservation

The major concerns while offering conservative approach to women with EC is omission of surgical staging with risk of missing advanced disease, incomplete staging and missing an early stage synchronous ovarian cancer (SOC). There is a moderate risk of extrauterine disease with grade >1 tumors in ~20% women with clinical stage I disease. The risk of a synchronous ovarian cancer may be as high as 25 percent in young women. Deep myometrial invasion may be seen in 10% women with grade 1 disease and even pelvic and paraaortic lymph node involvement can be seen with early stage.

Another important concern with fertility preservation is that the lack of a tumor specimen may limit detection of a genetic cancer, as the young women with EC are at increased risk of hereditary predisposition Lynch syndrome. This results from a genetic mutation in 1 of the mis-match repair proteins (MLH1, MSH2), MSH6, or PMS1 homolog 2(PMS2) or epithelial cell adhesion molecule (EPCAM- regulator of MSH2).

Selection of Right Patient

Fertility preserving management should be considered for women in reproductive age group, desirous of future childbearing with:

- well differentiated stage 1A, grade1 endometrial carcinoma confirmed on histopathology
- No contraindications to hormonal therapy and
- After proper counselling that it is non-standard nature of treatment- including possibility of occult cancer, risk of recurrent and/or persistent cancer

With proper selection, these women have a good prognosis with 5 & 10 year disease free survival (DFS) of upto 99.2% and 98% respectively.

Work up

There is no consensus regarding the optimal workup, however, a thorough pre-treatment evaluation is necessary to evaluate the depth of myometrial invasion, grading of the disease, and presence of ovarian masses. A complete history, physical examination to assess the size of uterus, its mobility and to rule out any features of metastatic or advanced disease. Serum CA125 levels, if raised are suggestive of extrauterine spread of the disease.

Counselling

If the patient is desirous of pregnancy, a geneticist and reproductive medicine specialist should be part of counselling. The women should be properly counselled that the treatment is not the standard treatment of care which is complete surgical staging with total abdominal hysterectomy with bilateral salpingo-oophorectomy. Women should consider the strength of their desire for future childbearing versus the additional oncologic risks.

Endometrial Sampling (Histology & Grade)

The most important predictor of stage and response to treatment with progestins in EC is the grade of disease. Endometrial biopsy is gold standard for histological diagnosis and both D & C and Pipelle biopsy can be used. On comparing both techniques, D & C correlates better with final histology. However, in a retrospective study by Leitao etal in the women with preoperative diagnosis of grade 1 EC, the up-gradation on final histology was 8.7% and 17.4% with D & C and Pipelle biopsy respectively. Also, few women in the biopsy group had no residual tumor at hysterectomy (3.7 vs 14.8%), but this study did no showed statistical significance for this outcome.

Hysteroscopic Evaluation

The accuracy of hysteroscopy in diagnosis of EC or hyperplasia in the case of abnormal bleeding has a sensitivity rate of 86.4 % and specificity of 99.2 %. However, the accuracy seems to be higher in diagnosing cancer rather than excluding it. There have been controversies on use of hysteroscope in EC, because of the risk of dislodging the cancer cells into the abdominal cavity. This leads to upgrading of the stage to IIIA with the need of subsequent adjuvant treatment; however, the clinical impact remains unclear.

Difficulties in Tumor Grading

It is difficult to obtain a consistent diagnosis when differentiating atypical hyperplasia and well-differentiated endometrial carcinoma. 41% of the cases with endometrial hyperplasia were over diagnosed in a study by Crissman et al. Kaku et al, in their study reported that out of 39 only 19 cases of either endometrial hyperplasia or EC were confirmed correctly after a thorough histological review performed by 3 different pathologists. Even the ESGOTF and the ESMO-ESGO-ESTRO consensus recommends that all endometrial specimens should be examined by 2 pathologists or by a specialised gynaecopathologists.

Radiologic Assessment for Staging

Myometrial invasion is the one of the important prognostic factor EC and absence of myometrial invasion is one of most important selection criteria for fertility preservation. Various methods have been studied with varying sensitivities and specificities to evaluate myometrial involvement- transvaginal ultrasound scan (TVUS), computed tomographic scan (CT-Scan), and magnetic resonance imaging (MRI). Contrast enhanced MRI is a preferred imaging modality for endometrial cancer used to assess locoregional disease spread, including cervical extension and deep myometrial invasion. The sensitivity of MRI was found to be 74%, 95% and 88% for detection of superficial, deep myometrial invasion and cervical invasion respectively. TVUS has also shown promising results in identifying the degrees of myometrial invasion especially when performed by experienced radiologists. The reported sensitivity and specificity for TVUS in determining the depth of myometrial invasion are 69% and 70%, respectively.

Thus, Enhanced MRI scan is the option for establishing the depth of myometrial invasion and TVUS by an expert can be considered as an alternative option.

Treatment Options

The most common conservative approach for endometrial cancer is hormonal therapy. Some authors have even proposed hysteroscopic resection of endometrium or repeated curettage, as well as a progesterone containing intrauterine device as local treatment.

The most common options used for conservative management are the progestin derivatives which includes Medroxy Progesterone Acetate (MPA) and Megestrol Acetate (MA). Other hormonal therapy includes GnRH analogues, letrozole, tamoxifen and levonorgesterol containing intrauterine device (LNG-IUD). There are no RCT's so far comparing the efficacy of all the regimens however, studies have been done using different preparations, doses, and regimens. Most of the studies done have evaluated the role of oral progestins in management of endometrial cancer.

Oral Progestins

Oral progestins are commonly used for conservative management of EC - MPA or MA. There are no high-quality data regarding which one is more effective, and the observational data show conflicting results regarding comparison between MPA and MA. According to a meta-analysis. In addition, different dose regimens have been used in various studies.

Agents, Dosage and Duration of Treatment

The dose, duration, route, and follow-up of progestin therapy have not been well defined. The choice of the agent depends on efficacy, safety profile and the tolerance of the patients. The most common

agents used are medroxyprogesterone acetate (MPA) 500–600 mg daily and megestrol acetate (MA) 160 mg daily. Gunderson etal in a systematic review of 45 studies analysed the use of various therapies like medroxyprogesterone acetate(49%), megesterol acetate(25%), LNG-IUS (19%) and others. The overall response to hormonal therapy was 77.7% and was significantly higher for women with hyperplasia than for those with carcinoma (65.8% vs 48.2%, p=.002). Studies have reported different doses of MPA and MA used, ranging from 10-400mg for MA and 2.5-800mg for MPA daily. The decision regarding agent to be used, dose and route of administration should be individualized to minimize risks related to the progestins such as weight gain, headaches, leg cramps, sleep disorders, thrombophlebitis etc.

The median time to response during progestin treatment was documented as 3 months in various studies. However, the median duration of treatment required for disease regression appears to be 4–6 months. Longer treatment duration in obese and anovulatory patients as they tend to be more resistant to treatment.

Response to Treatment

It is important to evaluate the response to treatment not only from an oncologic but also from a reproductive standpoint. The response depends on selection of candidates for fertility preservation and there has been ample evidence to suggest better response in early stage, well differentiated endometrial cancer. There is no universally accepted clear definition of complete disease regression; however, the presence of simple hyperplasia and/or complex hyperplasia without atypia in follow-up biopsies are taken as a complete regression response by some investigators. Documentation from tissue diagnosis either by endometrial curettage or endometrial biopsy, remains the standard criterion to assess response to treatment however, thinning of the endometrial lining on transvaginal ultrasound has also shown to be associated with favourable response to treatment.

The duration required to maintain remission after progestin therapy cannot be predicted, thus women achieving complete response (CR) should be counselled to promptly pursue fertility if desired. Women not planning pregnancy immediately should be placed on maintenance therapy. Maintenance treatment with low-dose cyclic progestin or an LNG-IUD has been shown to lower the risk of recurrence after complete response among young women with EC undergoing fertility-sparing treatment.

Risk of recurrence

Recurrence rates following complete response remains high (24%–40%). Thus, it is necessary to identify the influencing factors to decrease the risk of EC. There is no consensus regarding the optimal management protocol for patients with recurrence after fertility-preserving treatment for early-stage EC. According to the European Society for Gynecological Oncology guidelines 2015 patients who relapse after CR can be retreated with high-dose progestogen therapy, but the guideline is restricted to nulliparous women. Some researchers have suggested the option of standard surgery including hysterectomy immediately in patients with recurrence, while others have proposed repeat conservative treatment which is found to be safe and effective in patients with recurrence who still meet the criteria for initial conservative treatment.

The exact duration of therapeutic benefit from hormonal therapy is unknown. Even patients who initially respond are at significant risk for recurrence. Risk ranges from 24 to 41%, and most of recurrences occur within the first 3 years of successful conservative therapy. However, the recurrences can occur within 2 months to upto 30 years after treatment. In a study by Fujiwara et al 42/59 patients responded to MPA treatment and 22 of these had recurrence. The median onset of recurrence was 12 months (range- 7-84). 20/22 were again treated with MPA and 12 achieved remission without any recurrence and 8 who did not responded underwent hysterectomy.

LNG-IUS

LNG-IUS is considered an alternative management to the systemic progestins. Various studies have demonstrated CR rates, ranging from 64-88% with LNG-IUS alone or with additional oral progestins. It is useful in cases of women with medical co-morbidities or non-compliant as it obviates the need of daily administration. The data from observational studies have shown that the LNG-IUS with oral progestins or Gonadotropin releasing harmone analogues(GnRHa) gives better results than alone.

GnRH Analogues

Zhou etal (2017) compared the efficacy of GnRHa+LNG-IUS or GnRHa+Letrozole in young women with early stage endometrial cancer and complex atypical hyperplasia(CAH). 18 treated with the combination of intramuscular injections of GnRHa every 4 weeks along with insertion of LNG-IUS. 11 treated with the combination of intramuscular injections of GnRHa every 4 weeks with oral letrozole 2.5 mg daily. The

patients were followed up with endometrial sampling to check for response every 3 months. In the EC group 88.2% had complete response with the GnRHa combination treatment and one women had recurrence who underwent hysterectomy.

The ESGOTF and ESMO- ESGO-ESTRO Consensus recommends treatment with either MPA (400-600mg/d) or MA (160-320mg/d). However, LNG-IUS with or without GnRH analogues can also be considered.

Hysteroscopic Resection

Hysteroscopic resection along with progesterone therapy is also one of the conservative treatment modality. It may serve a therapeutic role by removing tumor and thus increasing the efficacy of treatment and decreasing the duration of therapy required for treatment response. It involves resection of the tumor, a small layer of the myometrium underlying the lesion, and the endometrium adjacent to the tumor. Studies have shown favourable outcome of hysteroscopic resection in combination with hormonal therapy. However, the safety and efficacy data are limited to small case series, only patients with unifocal lesions may be candidates and there is the risk of peritoneal dissemination of tumor cells.

Others

A small number of studies have reported the combined use of metformin and progestin for the treatment of EC. Metformin inhibits the expression of key regulator of progestin-resistance the glyoxalase to strengthen the therapeutic effect of progestin on cancer cells . Furthermore, the use of metformin was found to be associated with upregulation of the expression of the progestin receptor in cancer cells due to inhibitory effect of metformin on the mTOR signalling pathway. Thus, indicating that the combined application of metformin and progestin had stronger inhibitory effect on the EC cells than either of the agents when used alone.

Ovarian preservation has an opportunity for fertility preservation in the setting of hysterectomy, given the potential for future oocyte retrieval and surrogacy, which are newer concepts in the field of fertility preservation. However, it is important to recognize that ovarian preservation carries a potentially life-threatening risk of missing occult synchronous ovarian malignancy or metastatic disease.

Follow-up

There is no consensus regarding the optimal follow-up protocol as the available experience is insufficient and based on small series and case reports. Based on the median response time of 12 weeks after progestin therapy, re-evaluation is recommended. An endometrial biopsy is performed at every three months and can be done with an LNG-IUS in situ. Some have also After two consecutive negative biopsies, the patient should be encouraged to pursue pregnancy as soon as possible. But if patient does not wish to conceive the IUS should be left in for a longer duration.

For patients with persistence of disease (EC or atypical endometrial hyperplasia) at three months, the option is either to increase the dose of the oral progestin or another treatment modality should be added. Re-evaluation is done again after three months of the change in therapy and still if no response after nine to twelve months of progestin therapy patient should be counselled about potentially non-hormonally responsive nature of the cancer and need to consider definitive treatment.

Reproductive Outcomes

The pregnancy rates following conservative management reported by several investigators is found to be ~35-40% with a live birth rate ranging from 28-47%. Conservative treatment of endometrial cancer is not always followed by pregnancy and these patients often have infertility issues related to obesity, polycystic ovarian syndrome, and chronic anovulation. Majority will require assisted reproductive technology (ART) for conception. A literature review of 27 studies with 81 patients using variety of hormonal agents, 62 responded to therapy and pregnancy was documented in 20. 12/20 women required fertility treatment to achieve pregnancy.

Conclusion

Fertility sparing management in young women with endometrial carcinoma though feasible, is a therapeutic challenge. Selecting patients through meticulous pathologic and imaging studies is crucial for the oncological outcome of these patients. While hormonal therapy with progestin agents are effective in a majority of treated cases, it is not without risks. Risks include an unrecognized and untreated advanced endometrial cancer or a synchronous tumor. Patients should be carefully selected and extensively counselled regarding the deviation from the standard of care, the oncologic risks, and the subsequent likely need for assisted reproductive techniques to ensure conception. These young women may harbor a genetic predisposition for endometrial and colon cancer. Therefore, once the childbearing is complete, a standard surgical treatment must be considered.

Suggested Reading

1. Koskas M, Uzan J, Luton D, et al. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014; 101:785-94.
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Events Held

- A CME on "High Risk Pregnancy" on 12th January, 2020 at Country Club organized by Gurugram Obs and Gynae Society under and Safe Motherhood Committee AOGD.

- Monthly Clinical Meeting on 17th January, 2020 at Dr Ram Manohar Lohia Hospital, New Delhi.

- Awards at 63 AICOG Conference, Lucknow.

Dr Ashok Kumar (MAMC) Received
Dr C L Jhaveri Award at AICOG

Dr JB Sharma, Dr Radhika and Dr Pikee Saxena
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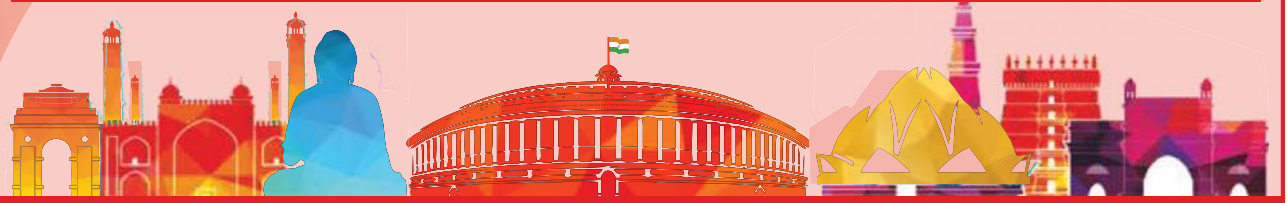
Proposed Scientific Programme

Day 1 - 29th FEBRUARY 2020

TIME	HALL A	HALL B
08:00-09:00	FREE PAPERS / POSTERS Workshop Hours **Session 1:** **The contraception prescription dialogue**	FREE PAPERS / POSTERS Workshop Hours **Session 1:** **Optimizing SRH care : Exploring/breaking the barriers**
09:00-10:10	❖ Medical Eligibility Criteria ❖ The oral hormonal contraception ❖ The basket for Emergency contraception ❖ IUCDs: The right fit/device	❖ Barrier/Natural methods, effective? ❖ Safe Medical abortions ❖ Examination of a rape victim ❖ Midtrimester abortions in Challenging cases
10:10-11:00	**Session 2:** ❖ Non hormonal prescriptions ❖ Injectables: The friendly choice ❖ IMPLANT: New wonder	**Session 2:** ❖ Implementing PPIUCD ❖ Positioning the LARC ❖ Contraception for Clients with special needs
11:00-11:15	**COFFEE TIME**	
11:15-12:30	**Panel discussion** Violence against women in India: Is there Justice?	**Panel discussion** Improving accessibility to Contraception: Lessons learnt
12:30-13:15	**INAUGURATION**	
13:15-14:00	**LUNCH**	**LUNCH**
14:00-14:45	**Session 1:** **Videos-Family Planning Procedures** ❖ Surgical abortion/MVA ❖ Missing IUCD retreival ❖ Removing an elusive IMPLANT	**Session 1:** **Videos-Family Planning Procedures** ❖ The difficult Minilap ❖ Tackling difficulties in Laproscopic sterilization ❖ NSV
14:45-15:30	**Session 2:** **Counselling and Troubleshooting via role plays for contraception** Follow up skills, Post partum/ abortal/ EC Iatrogenic AUB etc.	**Session 2:** **Dealing with Complications: Be legally safe** ❖ Consent/Preparedness ❖ Documentation ❖ Compensation and indemnity schemes
15:30-16:00	**Session 3: The difficult evacuation** ❖ Cervical ectopic ❖ Pregnancy in caesarian scar	**Session 3: Complications of surgical abortion** ❖ Haemorrhage following abortion ❖ Challenges for anaesthesia
16:00-16:15	**Delegate forum**	**Delegate forum**
16:15-17:15	**Panel discussion** Reducing the STD burden	**Panel discussion** Contraception in women with medical disorders/ cancer
17:15-18:00	**QUIZ**	
18:00 Onwards	**Cultural Programme**	

Day 2 - 1st MARCH 2020

TIME	HALL A	HALL B
06:00-07:00	**WALKATHON**	
08:00-09:00	FREE PAPERS / POSTERS	FREE PAPERS / POSTERS
09:00-10:15	**Symposium:** **TAKE AWAYS FROM THE RTMs** ❖ Sexuality education for the teens. ❖ I-CARE ❖ Post Partum contraception ❖ ACTS governing SRH practice ❖ High impact CAC service	**Symposium:** **The other face of SRH** ❖ Male participation for FP ❖ Female sexual dysfunction ❖ Non contraceptive benefits of contraceptives ❖ The MTP POCSO interface
10:15-11:00	**Panel discussion** Case scenarios- SAFE abortion saves lives	**Panel discussion** Case scenarios: The Medicolegal hour
11:00-11:15	**Coffee time**	**Coffee time**
11:15-12:15	**Keynote address** ❖ Ensuring human rights in SRH services ❖ Ten ways to increase uptake of FP services /Harnessing the strength of unlike minds to reach SDG 2030 ❖ Role of FOGSI in achieving SDG 2030	**Keynote address** ❖ MTP beyond 20 weeks: Sorting legal queries ❖ Supporting sexual reproductive health needs for LGBT ❖ Optimizing SRH for the HIV infected
12:15-12:45	**Conference oration: Towards FP 2020**	**Plenary**
12:45-13:45	**Panel discussion** Societal, Religious and Political consensus for Family planning and birth control	**Panel discussion** Plenary
13:45-14:00	**Valedictory**	
14:00-14:30	**Lunch**	
14:30-14:45	**Community banking : meeting unmet medical needs in INDIA**	Plenary
14:45-16:30	**Public Forum on Youth Talk for Sexuality & Reproductive Health**	Plenary
16:30 Onwards	**National Anthem**	



surakshitnaritva2020@gmail.com

Borderline Ovarian Tumours

Rama Joshi
Director & Head, Department of Gynae Oncology, Fortis Memorial Research Institute, Gurugram

Introduction

This group of tumours was first described by Taylor in 1929 as "semi-malignant" ovarian tumours, subsequently described by FIGO (1971) as tumours of "low malignant potential" followed by the WHO in 1973. The current 2014 WHO Classification of Tumours of the Female Genital Organs uses the term "borderline tumour" interchangeable with "atypical proliferative tumour"[1].

Borderline ovarian tumours (BOTs) comprise about 15%-20% of all epithelial ovarian malignancies with incidence of 1.8–4.8 per 100,000 women per year. BOTs differ significantly from ovarian carcinomas with regard to percentile distribution of tumour histotypes, lower FIGO stage, excellent overall prognosis, younger age distribution, higher infertility rate (10-35%), and a lower frequency of BRCA mutations. There is no protective effect of hormonal contraceptives on BOTs as opposed to ovarian cancers[2]; however, the results of further studies concerning BOTs and hormonal contraceptives are controversial. The increased risk of BOTs may also be associated with the use of fertility drugs[3].

The majority of BOTs are serous tumours (53.3%), followed by mucinous tumours (42.5%) and less common histotypes. BOTs are mainly diagnosed at an earlier stage (75% at FIGO stage I) in contrast to ovarian cancer (25% at FIGO stage I).

Pathogenesis

Two pathways have been proposed in the pathogenesis of serous borderline ovarian tumours. First is the "low-grade" pathway that involves BRAF and KRAS mutations. According to this pathway, serous ovarian cystadenomas progress to serous BOTs which eventually lead to low-grade serous epithelial ovarian carcinoma through a continuum of histological precursor lesions[4]. Only 2% of all serous BOTs progress to carcinoma via this "low-grade" pathway. Endometrioid borderline ovarian tumours are characterized by mutations involving the beta catenin gene (50%), PTEN gene (20%), and microsatellite instability gene (up to 50%)[5].

Histology

Pathologic criteria for diagnosis include the absence of stromal invasion in the ovary and at least two of the following characteristics: epithelial tufting, multilayering of the epithelium, mitotic activity, and nuclear atypia.

Serous BOTs are divided into typical subtype (90%) and micropapillary subtype (10%). Serous BOTs are bilateral in 15–40% of cases out of which 15–40% are associated with extraovarian disease (peritoneal implants). These implants are non-invasive in 85% of cases and invasive in only 15%. BOTs with invasive implants have a poorer prognosis[6].

Mucinous BOTs are of two subtypes, intestinal (or gastrointestinal) (85–90%) and Mullerian (endocervical / seromucinous) lesions. The intestinal type is usually unilateral while endocervical type is bilateral in 40% cases. All patients with bilateral ovarian masses should be evaluated for a primary gastrointestinal tumour.

Presentation

Most women with BOT are asymptomatic at presentation ovarian mass usually detected on a screening abdominal ultrasound. Pelvic mass may be an incidental finding on routine pelvic examination. Around 50–60% of patients present with nonspecific symptoms such as dyspepsia, abdominal pain or discomfort, abdominal distension, bowel irregularity, persistent fatigue, or weight loss. Ten percent of patients present with abnormal uterine bleeding[7].

Diagnostic Work-Up

Borderline tumours are difficult to detect clinically until they are huge in size or advanced in stage. Pelvic & abdominal ultrasound helps in identifying the ovarian mass, ascites. Serum CA125 may not be raised in 53.8% of patients with borderline tumours[7]. Serum CA-19-9 may be raised in patients with mucinous BOTs. Serum CEA levels will help in ruling out primary G.I. malignancy. CT does not have any key distinguishing features that would enable differentiating borderline from malignant ovarian cancer but helps in detecting the metastatic disease. Borderline ovarian tumours are not PET-avid and hence are interpreted as "benign" tumours on PET. Ovarian masses that show complex features on MRI that are concerning for malignancy but appear as "benign" on PET are said to be characteristic of borderline ovarian tumours[8]. Upper G.I. endoscopy and colonoscopy are required to rule out primary G.I. malignancy.

Frozen Section Analysis

Intra-operative frozen section analysis is recommended for defining the nature of suspicious ovarian mass on table, based on which the surgical extent of the staging is

decided. However, frozen section accuracy of 58–86% has been reported, varying with the experience of the histopathologist[9]. In absence of frozen section facility the completion surgery and staging should be taken after the final histopathology thus the patient requires to be counselled regarding the same with the initial treatment approach.

Treatment

Radical Surgery

In postmenopausal women or in women who do not wish to preserve fertility, type I hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging is done. Inspection and palpation of the entire abdominal cavity, peritoneal washings , total omentectomy, resection of grossly visible abnormal areas and multiple peritoneal biopsies. Routine retroperitoneal node dissection as the part of surgical staging in clinically ovarian confined disease is not recommended. Lymph node involvement has been reported in up to 6.2% patients with advanced-stage BOT with invasive extraovarian disease implants (FIGO stage III or IV)[10]. lymphadenectomy has not shown any difference in recurrence rate or survival rate. In advanced stages the cytoreduction is performed with the aim of achieving no gross residual disease status which includes complex surgical procedures including modified posterior exenteration, complete peritonectomy, under-surface diaphragm peritonectomy, diaphragmatic resection, bowel resection anastomosis. Appendectomy for mucinous tumours is recommended to exclude synchronous or primitive appendiceal tumour.

Fertility-Sparing Surgery

BOTs are usually diagnosed in younger women where preservation of fertility is an important issue. In patients with tumour confined to one ovary, unilateral salpingo-oophorectomy can be done with complete surgical staging. Biopsy from the normal-looking contralateral ovary is not required as it may interfere with the ovarian reserve and also can form peritoneal adhesions. In case of bilateral ovarian involvement, the option of unilateral or bilateral ovarian cystectomy / a unilateral salpingo-oophorectomy with contralateral cystectomy may be considered with increased risk of recurrence. Relapse rate varies between 12 and 58% for cystectomy and between 2.5 and 5.7% for radical surgery[11]. Thus, the gynaecologic oncologist has to adequately weigh the pros and cons of a fertility preserving approach in selected patients of borderline ovarian tumours with proper counselling of the advantages and disadvantages and the advice of a regular and long-term follow-up.

Role of Laparoscopy

Tumour spillage is the main concern in borderline ovarian tumours as these do not respond to chemotherapy and will have delayed recurrences. Reported cyst rupture is more frequent by laparoscopy compared with laparotomy (33.9 vs. 12.4%)[12]. Hence, laparoscopic surgery for BOTs should be reserved for experienced centres where oncological principles are strictly followed to reduce the risk of intra-abdominal tumour/ cyst rupture and thus reducing the rate of recurrence.

Restaging Surgery

Restaging surgery is recommended if (1) there are histologic features suggestive of invasive recurrence (an invasive peritoneal implant or micropapillary pattern), (2) the peritoneum is not clearly reported as “normal” or if there was no systematic exploration during initial surgery, (3) if macroscopic peritoneal implants are found in the initial surgery, (4) if gross lesions remain after initial surgery, and (5) if the patients are less likely to come for regular follow-up.[13]

Adjuvant Treatment

There is no data to suggest any improvement in survival with adjuvant chemotherapy[14]. Complete surgery plays the key role in the management of Border line tumours.

Fertility After Conservative Treatment of BOT

Following fertility preserving surgery for borderline ovarian tumours, the pregnancy rate is nearly 50%, and most are achieved spontaneously[12]. Ovulation induction is often required in the remaining in order to conceive with the general recommendation to use the minimum number of stimulation cycles. Egg retrieval and egg freezing are alternative options for women with reduced fertility after conservative surgery. This requires a close collaboration of gynaecologic oncologists and reproductive endocrinologists. The presence of postsurgical adnexal adhesions is associated with a 20–30% reduction of pregnancy rate[15].

Treatment of Hormone Deprivation

Hormone replacement therapy (HRT) to prevent cardiovascular disease and osteoporosis and improve quality of life is an important issue, as many patients with BOTs are relatively young women. HRT can be offered to these patients[16].

Treatment of Recurrences

When extraovarian recurrence in the form of borderline tumour or invasive disease occurs, extensive cytoreductive surgery is the treatment option of choice. Residual tumours at the completion of secondary debulking are an important prognostic factor: 12% of patients with optimal debulking died of disease compared with 60% of patients whose tumours were sub-optimally debulked[17].

Follow-Up

Follow up must be carried out for a longer period of time. Studies have reported cases in which relapse and death occurred after more than 10–15 years. The overall recurrence rate for patients previously treated for BOTs is estimated to be up to 11%. The absolute rate for malignant transformation of previous BOTs is about 2%–4%. Usually these malignant tumours are low-grade carcinomas, but in rare cases, serous borderline tumours transform into high-grade serous carcinomas[7].

Follow-up is usually a combination of clinical examination, ultrasound, and CA125 levels. Because mucinous tumours often do not express CA125, CA19–9 can be used for evaluation[18]. During the initial 2 years, follow-up evaluation is performed every 3 months. Patients are then evaluated biannually for 3–5 years after surgery, and then annually thereafter[19].

Survival

Survival of patients with borderline tumours is excellent. Overall 5-year and 10-year survival rates for stage I, II, and III disease are 99 and 97, 98 and 90, and 96 and 88%, respectively[20]. BOTs have a 5-year survival rate of more than 90% across all tumour stages, with a considerable number of patients cured[21].

Conclusion

Borderline ovarian tumours are usually diagnosed at younger age in early stage and have more indolent behaviour, excellent prognosis, longer survival, and later recurrence compared with invasive ovarian cancer. Fertility-sparing surgery is the treatment of choice in young females who desire motherhood with adequate counselling for close and long-term follow-up. Surgery with no macroscopic residual disease remains the mainstay of treatment. There is no benefit of adjuvant chemotherapy, hormonal, or targeted therapy in borderline ovarian tumours. Removal of the preserved ovary, though not mandatory, should be done after completion of childbearing in order to reduce relapse and save the patient from the psychological stress of waiting for relapse since there is always a risk of development of invasive ovarian tumour.

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Role of Sentinel Lymph Node in Carcinoma Endometrium

Rupinder Sekhon[1], Atul Sharma[2]
[1]Professor and Chief of Gynecologic Oncology RGCIRC, New Delhi, [2]Senior Resident (Acad) M.Ch Gynecologic Oncology, AIIMS, New Delhi

Introduction

Sentinel lymph node dissection is a relatively recent alternative staging technique that allows assessment of pelvic/para-aortic lymph nodes, alleviating the need for a complete systematic lymphadenectomy. This has led to a substantial decrease in the morbidities associated with systematic lymphadenectomy and has led to the detection of nodes in unusual nodal basins.

Historical Perspective

French gynecologists, Leveuf and Godard, in the early twentieth century studied the lymphatic anatomy of the cervix by injecting Gerotti blue into the cervices of neonatal cadavers. They found that the dye drained a lymph node found in the obturator space or at the bifurcation of the iliac vessels. They called it the principal lymph node. The concept of sentinel lymph node was formally introduced in 1960 by Ernest Gould while working on parotid gland cancer. But it was not until two decades later that Ramon Cabanas succeeded in mapping the sentinel lymph node in a case of penile cancer. The first gynecological cancer in which this technique was successfully established was in carcinoma vulva. The concept of SLN mapping in endometrial cancer was introduced by Burke in 1996 from the MD Anderson Cancer Center.

Current State of Sentinel Lymph Node Evaluation in Endometrial Cancers

SLND following lymphatic mapping has become a new state-of-the-art option for the assessment of the retroperitoneal lymph nodes in endometrial cancer.

Prospective and retrospective studies have demonstrated that compared to systemic lymphadenectomy, SLN mapping with ultra-staging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. SLN mapping may also be used in high-risk histology like serous and clear cell carcinomas and carcinosarcomas.

Several gynecological organizations, including RCOG, NCCN and the SGO support the role of sentinel lymphadenectomy in the management of women with endometrial cancer.

Technique of Lymphatic Mapping

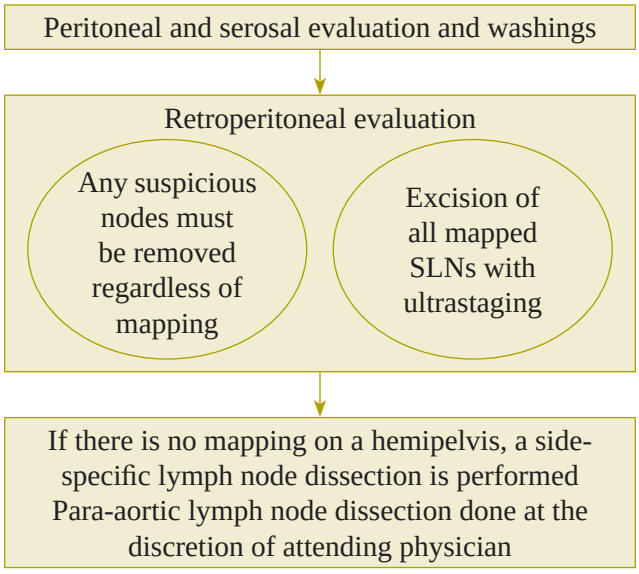
Conventionally, lymph node mapping has been done using technetium-99m (99mTc) radiolabeled colloid injections. Blue-colored dyes (including 1% isosulfan blue and 1% methylene blue) have also been used for direct visualization of lymphatic channels and sentinel lymph nodes. The use of indocyanine green (ICG) with an infrared camera (with or without a colored dye) has replaced use of 99m Tc in many practices. Retrospective data suggest that blue dye alone (either isosulfan blue or methylene blue) is inferior to ICG alone in detection of sentinel lymph nodes, with combined blue dye and ICG having the highest rate of SLND detection.

Whichever dye is used for lymphatic mapping, 2-4 mL is injected using a 27-gauge needle/ spinal needle/ Potocky type needle into the superficial (1-3 mm) and deep (1-2cm) cervical stroma at the 3 and 9 o'clock position prior to hysterectomy.

Following injection of the mapping product into the cervix, optimal detection of the dye or ICG will occur between 15 and 60 minutes. Successful mapping of a hemipelvis is defined by observing a channel leading from the cervix directly to at least one candidate lymph node. Common iliac or aortic sentinel lymph nodes are also dissected if present. Identified sentinel lymph nodes as well as any suspicious nodes are then retrieved and sent for pathologic evaluation. If either hemipelvis does not map, then a side-specific pelvic, common iliac and interiliac lymph node dissection is done. Paraaortic lymph node dissection is at the discretion of operating surgeon.

The key point to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of the side specific nodal dissection in cases of failed mapping and removal of any suspicious and grossly enlarged nodes regardless of mapping.

Algorithm: The SLN algorithm for surgical staging of endometrial cancer



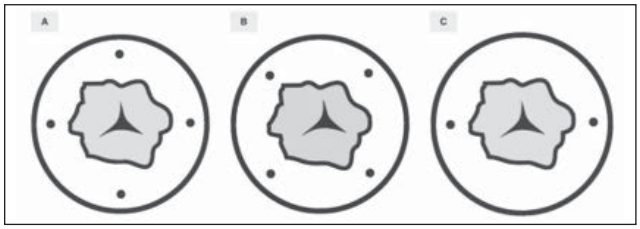


Figure 1: Three different options for direct cervical injection

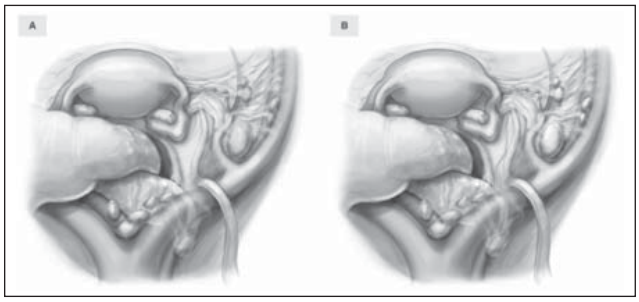


Figure 2: A. Most common locations of SLNs
B. Less common location of SLNs

The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to external iliac, ventral to the hypogastric or in the superior part of the obturator region. (Fig 2A) A less common location is usually seen when the lymphatic trunks do not crossover the obliterated umbilical and move cephalad following the mesoureter; in these cases, SLN is commonly seen in the common iliac and presacral region.(Fig 2B)

Other lymphatic mapping techniques such as fundal injection or hysteroscopic injection have not been shown to have the convenience or the sensitivity for detection of sentinel lymph nodes, though hysteroscopic injection may be associated with an increased detection of aortic sentinel lymph nodes.

The rationale for using the cervical injection includes the following:

1. The cervix is easily accessible
2. The cervix in women with endometrial cancer is rarely distorted or scarred from prior procedures such as conization
3. The main lymphatic drainage of the uterus is from the parametria
4. Uterine fundal serosal mapping does not reflect the parametrial lymphatic drainage of the uterus

The main argument against the cervical injection is that it has a lower paraaortic detection rate, but as is well documented, when the pelvic lymph nodes are negative for metastasis, disease is unlikely to be found in the paraaortic nodes, and to date there has been no definitive association between paraaortic nodal assessment and improved overall survival.

Pathological Assessment of SLN

Utilizing a standardized strategy when intending to perform a SLN dissection in patients with EC has been shown to improve the SLN detection rate and decrease the rate of complete pelvic lymph node dissection. When such an algorithm is applied, bilateral mapping was seen in 81 percent, unilateral in 12 percent, and no mapping of either hemipelvis in 6 percent of patients. If a selective LND strategy is utilized to determine the management of a non-mapping hemipelvis, fewer than 10 percent of patients will require a complete pelvic LND without compromising the ability to detect metastatic disease in the lymph nodes.

The SLN ultrastaging protocol varies among institutions. Standardization of the pathologic assessment of removed SLND is critical to the correct use of this technique. Sentinel lymph node ultrastaging has two components:

1. Serial sectioning with review of multiple H&E stained slides, and
2. Cytokeratin IHC staining

Sentinel lymph nodes are generally cut at 3 mm intervals, in a bread-loaf fashion, or bivalve if less than 1.5 cm in any dimension. Two paraffin-embedded slides are created from each section, each 50 micrometers apart. One slide is generally stained for hematoxylin and eosin (H&E) and the other is reserved for immunohistochemistry staining. If no metastatic disease is identified on the first H&E slide, the reserved slide is generally stained for cytokeratin AE1 and AE3.

Lymph nodes with isolated tumor cells should be clearly reported. When isolated tumor cells are detected in the

absence of macro-metastasis and micro-metastasis, the lymph node stage is designated pN0(i+). Whether these should be included in FIGO stage III remains to be determined.

Advantages of Sentinel Lymph Node Dissection

1. Decreased morbidity as compared to conventional lymphadenectomy
2. Unusual basins of drainage are identified
3. Ultra-staging detects an additional 8% positive nodes in the SLN in endometrial carcinomas with any degree of myo-invasion

Further studies are needed to confirm that utilization of sentinel node biopsy reduces lower extremity lymphedema, particularly given the number of patients ultimately requiring full LND.

Additionally, the populations in which lymphatic mapping and SLND are appropriate are being evaluated. While initially utilized in patients at low risk for lymph node metastasis (with a complete LND in those at higher risk), many centers have moved to utilizing SLND in all patients, with selective complete LND in specific circumstances. It does appear that SLND is feasible in patients with non-endometrioid histology, with lymph node metastasis identified in approximately 20 percent of patients regardless of whether the procedure was performed using an SLND or systematic approach.

Conclusion

The SLN algorithm if applied to all patients with newly diagnosed endometrial cancer, will at a minimum permit bilateral pelvic nodal assessment as part of the surgical staging. It is gradually becoming the standard of care for surgical staging in many institutions. The major factors to successful SLN mapping include the surgeon's experience (30 procedures or more) and adherence to the SLN algorithm published in 2012 and listed in NCCN guidelines since 2014.

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Calendar of Monthly Clinical Meetings 2019-20

Months	Name of the Institute
28th February, 2020	UCMS & GTB Hospital
27th March, 2020	LHMC
24th April, 2020	Apollo Hospital

Gestational Trophoblastic Neoplasia: What's New?

Shalini Rajaram[1], Megha Jindal[2], Pallavi Gupta[2], Bindiya Gupta[4]
[1]Director Professor, [2]Senior Resident, [4]Associate Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi

Introduction

Gestational Trophoblastic Neoplasia (GTN) refers to abnormal proliferation of placental villous and extravillous trophoblast and includes the malignant forms ranging from invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). The latter two are classified as Intermediate Trophoblastic Tumors. While complete hydatidiform mole (CHM) and partial mole (PM) are benign entities and form part of the GTD (Gestational trophoblastic disease) spectrum, early detection of progression to GTN which can occur in 15-20% of CHM and 0.5-5% of PM, is enabled by monitoring of serum **β-hCG**.

While chemotherapy remains the cornerstone of management in persistent trophoblastic disease, invasive mole and choriocarcinoma; surgery with or without chemotherapy forms the mainstay of treatment in PSTT and ETT.

Clinical Presentation & Diagnosis

GTN usually presents as vaginal bleeding and elevated hCG levels. It can follow molar gestation, abortion, tubal pregnancy, term or pre-term gestation and can occur immediately or months or even years after the antecedent pregnancy. Other clinical presentations are due to bleeding in metastatic sites such as the liver, spleen, intestine, lungs, brain or spine. Thus patients can present with pulmonary symptoms, neurological signs, convulsions, acute abdomen, shock etc. GTN should be considered in differential diagnosis of unusual presentations and serum β-**hCG** should be done.

The β-**hCG** assay should be standardized at a central laboratory. In the UK, β-**hCG** surveillance policy has been to measure serum β-**hCG** every two weeks following a molar pregnancy until normalization and then every four weeks for six months. However, for CHM although the risk of post molar trophoblastic neoplasia is reduced in women whose β-**hCG** returns to normal within 56 days of evacuation, the policy is to continue β-**hCG** monitoring after normalization, monthly for six months.

criteria for diagnosis of postmolar gestational trophoblastic neoplasia.

1. When the plateau of β-**hCG** lasts for four measurements over a period of 3 weeks or longer; i.e, day 1, 7, 14, 21.
2. When there is a rise in β-**hCG** for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, 14.
3. If there is a histologic diagnosis of choriocarcinoma.

An important observation here is that the previously used criteria "persistence of β-**hCG** level for more than 6 months" is no longer used.

PSTT and ETT are rare subtypes of GTN with an incidence of 1 in100,00 pregnancies and representing 1–2% of GTN cases. They can appear after any pregnancy event but usually present months to years after a term pregnancy. Since they are slow growing they remain confined to the uterus for a long period of time with a paucity of symptoms like amenorrhoea or vaginal bleeding. Other symptoms depend on the sites of metastases in women with metastatic disease. Lung is the most common site of metastases. Levels of β-**hCG** are usually below 1000IU/L but high levels are also seen[3]. Ultrasound is a good tool to diagnose PSTT and ETT and various types of USG presentation as Type I, II & III have been described. A typical hypoechogenic halo was seen in all cases of ETT suggesting an expansile growth. 30% may be misdiagnosed as ectopic pregnancy.

Once the diagnosis of GTN is made, imaging forms an important tool for staging and scoring. (FIGO staging and Modified WHO scoring, Tables 1 & 2). Chest X-ray is appropriate to diagnose lung metastases and can be used for counting the number of lung metastases to evaluate the risk score. In the event that chest X-ray is normal, chest CT may be used. Liver metastases may be diagnosed by ultrasound or CT scanning. Brain metastases is best diagnosed by MRI or CT scanning.

Immunohistochemistry & Molecular Diagnostics

A cyclin dependent kinase inhibitor p57 is encoded by paternally imprinted and maternally expressed gene and therefore absent in complete mole. Partial mole and non-molar abnormal gestations show strong nuclear staining of p57 and can be used to exclude complete

mole. PSTT show strong positivity for human placental lactogen (hPL) and Mel-CAM (CD 146) while placental alkaline phosphatase (PLAP) is only focally positive. Additionally, marked positivity for Ki-67, alpha-inhibin and cytokeratin 8/18 and negative staining for smooth muscle markers helps confirm diagnosis of PSTT. ETT is positive for pancytokeratin, epithelial membrane antigen, E-cadherin, and EGFR (consistent with their epithelial origin) but all tumors are also strongly positive for PLAP and p63 and only focally positive for hPL, hCG, and Mel-CAM. As p63 is expressed in ETT but not PSTT and hPL and Mel-CAM are only focally/weakly positive relative to the strong positivity seen in PSTT, these markers (p63, hPL, and Mel-CAM) can help distinguish the two entities[3].

SALL4 is a zinc finger transcription factor important in embryonal development by maintaining stem cell pluripotency. Because SALL4 has been identified as a reliable marker of germ cell tumors and non-gestational choriocarcinoma its ability to distinguish gestational choriocarcinoma from PSTT or ETT was studied by immunohistochemistry. All of choriocarcinomas and none of the PSTTs or ETTs expressed SALL4.

Treatment

GTN should be staged and scored according to current FIGO staging (Table 1) and modified WHO prognostic scoring system (Table 2). This scoring determines the course of treatment for the patient. The score has been developed from individual risk factors that are predictive of GTN being resistant to single agent chemotherapy. This predictive scoring system is not valid for PSTT and ETT.

Table 1: FIGO staging system for GTN

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

Table 2: Prognostic scoring Index for GTN

Prognostic Factor			Risk Score	
	0	1	2	4
Age (years)	<40	≥ 40	-	-
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	-
Interval from index pregnancy (months)	< 4	4-6	7-12	>12
Pre-treatment **β-hCG** (IU/mL)	$< 10^3$	10^3 to $<10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3-5	>5	
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal tract	Brain, Liver
Number of metastases identified	0	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	≥ 2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. According to the prognostic score patients are divided into: Low risk: <7, High risk: ≥7, Ultra high risk > 12

Treatment of Low-risk GTN

Patients with low-risk GTN should be treated with single agent chemotherapy methotrexate or actinomycin D (Dactinomycin). While methotrexate has a more favourable adverse effect profile, Dactinomycin may achieve a better efficacy with less frequent infusion schedule. Dactinomycin is usually used as secondary therapy for patients with methotrexate toxicity because of risk of effusions contradicting the use of latter.

Monitoring of response to chemotherapy is done with **β-hCG** assay at least every 2 weeks at the start of each treatment cycle.

- Normal **β-hCG** levels: NCCN recommends continuation of systematic therapy for two treatment cycles (chemotherapy) post normalization of **β-hCG** levels.
- Good response to initial therapy followed by **β-hCG** level plateau or re-elevation: change to alternative single-agent chemotherapy which was not used initially as first-line therapy.
- Poor response to initial therapy OR good response to initial therapy followed by rapid rise in **β-hCG** levels (> 10% change): Switch from single agent chemotherapy to combination therapy and repeat the work-up to look for metastasis.

Special consideration should be given to WHO risk score (5-6) and clinicopathologic diagnosis of choriocarcinoma as both are associated with an increased risk of resistance to single agent chemotherapy. Lowering the threshold for the use of multiple agent chemotherapy in such cases can be considered.

First-line single agent chemotherapy regimens for low-risk gestational trophoblastic neoplasia.

1. MTX-FA 8-day regimen (50 mg MTX intramuscularly on days

1,3,5,7 with folinic acid 15 mg orally 24 hours after MTX on days 2,4,6,8); repeat every 2 weeks.

2. MTX 0.4 mg/kg (max. 25 mg) intravenously or intramuscularly
3. for 5 days every 2 weeks.
4. Actinomycin D pulse 1.25 mg/m2 intravenously every 2 weeks.
5. Actinomycin D 0.5mg intravenously for 5 days every 2 weeks

Not Recommended

Methotrexate 30–50 mg/m2 IM weekly

OR Methotrexate infusion 300 mg/m2 over 12 hours/ leucovorin due to lesser efficacy.

Treatment of High-Risk GTN

High-risk GTN should be treated with multi-agent chemotherapy along with adjuvant surgery or radiation therapy, if needed. This multi-modal approach achieves a cure rate of 70-90%. The most commonly used regimen is EMA-CO. About 20% of patients fail EMA-CO therapy but most can be salvaged with further therapy and the overall survival rates for patients with high-risk GTN is as high as 95%. In patients with CNS metastases, in addition to the chemotherapy, additional treatment with whole brain irradiation (30 Gy in 15 fractions), stereotactic radiosurgery &/or craniotomy with surgical excision may be required. To ensure sufficient blood brain barrier penetration in these patient, methotrexate dose should be increased in EMA-CO or EMA-EP regimens or additional intrathecal methotrexate should be given. Infusion dose is increased to 1000mg/m2 over 24 hrs.

Interventional radiological procedure such as selective arterial embolization is required in emergency situations for management of acute bleed from uterus/vagina or other metastatic sites.

Surgical management may be required for chemotherapy-resistant disease especially for isolated disease in uterus or lungs. Monitoring is done with **β-hCG** assay every 2 weeks during treatment and response is assessed:

A. Normal **β-hCG** levels: Continue chemotherapy for 2-3 cycles past normalization followed by **β-hCG** assay every month for 12 months.

B. Good response followed by low levels **β-hCG** plateau or relapse from remission with EMA-CO: EMA-EP or EP-EMA is the most appropriate therapy.

C. Incomplete response to treatment: Switch to chemotherapy with etoposide/platinum-based regimens with bleomycin, ifosfamide or paclitaxel and consider resection of chemo-resistant disease (especially hysterectomy and pulmonary resection). This leads to cure in 80-90% of such patients.

Ultra-High Risk GTN

Ultra-high risk GTN refers to widespread metastatic disease and high tumour burden. Among the high-risk group, patients with prognostic score > 12 as well as patients with liver, brain or extensive metastases do poorly when treated with first-line multiple agent chemotherapy. For such patients, induction chemotherapy with low dose Etoposide & Cisplatin for 1-3 cycles prior to initiating EMA-CO regimen is recommended. This alteration is to prevent the complications seen with the direct use of standard chemotherapy such as tumor collapse with hemorrhage, metabolic acidosis, myelosuppression, septicaemia &/ or multiple organ failure, possibility of death within 4 weeks.

New Drugs in the Management of Drug-Resistant GTN

PD-L1 (Programmed Cell Death Ligand 1) is normally expressed by trophoblastic tissue. This expression helps in maintaining gestational tolerance towards expression of paternal antigens by the developing embryo. PD-L1 also suppresses the anticancer T-cell activity thus, promoting the survival of neoplastic cells. Monoclonal antibody Pembrolizumab is a PD-L1 inhibitor, thus preventing the suppression of anticancer T-cell activity. Pembrolizumab has been found to have an impressive clinical activity against drug-resistant GTN. **Treatment of Intermediate trophoblastic tumors (PSTT, ETT)**

ITTs are derived from extra-villous trophoblasts, chemo-resistant in nature and therefore the mainstay of treatment is hysterectomy. Ovaries may be conserved in women with disease confined to uterus. The rate of lymph node metastases in PSTT is 5-6% and some centers perform lymphadenectomy in patients with Stage 1 PSTT with deep myometrial invasion or if lymph nodes are enlarged.

Chemotherapy (along with surgical management) is given to patients with metastatic disease or patient with non-metastatic disease who have any of the adverse prognostic factors, which include Interval from index pregnancy ≥ 2 years, deep myometrial invasion, extensive coagulative necrosis, Mitotic count > 5/10hpf and lympho-vascular space invasion. Treatment of

choice is platinum/etoposide containing regimen e.g. EMA-EP, TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide), BEP (bleomycin, etoposide, cisplatin) etc.

Survival rates have been reported to be 50-60% for metastatic disease and 100% for non-metastatic disease. Monitoring is done with either hCG levels or imaging if hCG is not a reliable marker. PET-CT may be considered for follow up at the completion of chemotherapy and then every 6-12 months for 2-3 years.

Suggested Readings

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Forthcoming Events

- CME on 'Preeclampsia- An update' on 19th February, 2020 at Manipal Hospital Safe Motherhood Committee of AOGD.
- Next Monthly Clinical Meeting on 28th February, 2020 (4:00 pm - 5:00 pm) at UCMS & GTB Hospital.
- National FOGSI Conference -"Women's Reproductive & Sexual Health" on 29th February – 1st March, 2020 at The Lalit New Delhi By Sir Ganga Ram Hospital under the aegis of FOGSI & AOGD.
- International Hysteroscopy Congress on 18th & 19th March, 2020 at Cairo, Egypt under the aegis of Endoscopy Committee, Contact: Dr Richa Sharma.
- **FOGSI FORCE PG Program on 21st and 22nd March, 2020 organised by Department of Obstetrics and Gynaecology, AIIMS, New Delhi.**
- Society for Vaginal Surgeons, Delhi will be conducting VagSurgiCon-2020 'State-of-the-Art Vaginal Surgery Workshop-Basics to Advanced' on 21st and 22nd March, 2020 at Sant Parmanand Hospital. Registration fees Rs1000. For Registration, please contact Dr Sonal Bhatla-9811444563, Dr Uma Swain-9811258731.
- CME on "Symposium on Endometriosis" on 22nd March, 2020 at Auditorium, Max Super Speciality Hospital, Saket under the aegis of Endometriosis Committee of AOGD.

Palliative Care in Gynaecologic Oncology

Seema Singhal[1], Sushma Bhatnagar[2]
Associate Professor Department of Obs. & Gynae, [2]Professor & Head, Department of Anesthesia & Palliative Care, AIIMS, New Delhi

Introduction

Palliative care is the critical element of the comprehensive multidisciplinary management of women with gynaecological cancer. The aim is to improve the quality of life of patients as well as their families after diagnosis of cancer. Palliative care is often mistaken as end of life or hospice care because of late introduction during treatment. Approximately 53.9% of gynaecologic oncologists actually postponed end of life discussions until a major change in functional or medical status.[1] The term palliative care was initially introduced to replace "hospice" as the later term was associated with only end of life care. The paradigm of palliative care is rather vast and it needs to be embraced in care right from the beginning, should continue during all the phases of their illness and is applicable even for patients who are likely to be cured or are in the terminal phase of their illness.[1,2]

WHO defines "Palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and treatment of other problems, physical, psychosocial and spiritual". It affirms life and regards dying as a normal process. Palliative care to cancer patients is not the sole responsibility of palliative care specialists but needs to be actively embraced by all those involved in integrated care including Gynaecologists, Gynaecologic oncologists, medical and radiation oncologists and also the nursing staff and family members. Several societies including ASCO (American society of clinical oncology) and SGO (Society of Gynaecologic Oncology) are committed to integrate palliative care into comprehensive gynaecologic oncology care. Palliative care does not need too many sophisticated equipment or technology but its strength lies with compassion and therefore should be offered to all patients irrespective of resources with communication and empathy being the backbone. Table 1 enlists the domains of palliative care as outlined by the American Association of Hospice and Palliative Medicine.[1]

Although there are obvious benefits of integration of palliative services in reducing symptom distress, better management of functional status and thus improving survival of gynae cancer patients. Significant improvement was observed after incorporation of palliative services in symptoms related to pain, anorexia, fatigue, depression, anxiety and shortness of breath. However, there are barriers that have made this integration difficult. Physician related barriers include hesitancy to admit failure to provide cure, optimistic view of prolonging patient's life, lack of awareness and training to provide palliative care. Similarly majority of patients and families do not have realistic expectations from therapy and there is lack of understanding of the meaning of palliative care. Furthermore, there are inadequate resources and poor reimbursement of palliative care services. These factors ultimately lead to delayed referrals for palliative care. Only 18% of gynaecologic oncology patients receive palliative care consultation greater than 30 days before their death and nearly one third died without receiving a referral to palliative care. More than half of women with gynaecological cancers received chemotherapy and procedures in the last 6 months of life despite the limited benefits.[1,3]

Table 1: Domains of palliative care

1.	Rapport and relationship building with patients and family caregivers
2.	Symptom distress and function status management,
3.	Exploration of understanding and education of prognosis
4.	Clarification of treatment goals
5.	Assessment and support of coping
6.	Assistance with medical decision making
7.	Coordination with other providers
8.	Provision of referrals to other providers
9.	Understanding of compassion fatigue and need to support each other

Delivery of Palliative Care

Primary palliative care should be provided by the Gynaecologic oncologists, while managing the complex treatment of patients and speciality palliative care is provided by the providers with dedicated training in palliative care. Referral to specialty palliative care services should be made when "physical, social, psychological, or spiritual unmet needs" are not able to be effectively managed by the primary team. Of note, this may be at a time when the goal of disease management is still curative. This implies that oncologists must regularly assess patient's and

caregivers' needs to ensure timely referral to specialty palliative care services. Timely referral results in added benefits specifically in patients with advanced malignancies.

Team work: Effective palliative care depends on good teamwork. As an ideal, the basic care team should consist of a doctor, professional nurse, and social worker. The team can benefit from a dietician, occupational therapist, physiotherapist, massage therapist, and creative artists, as well as a "Gynaecologic oncologist, a radiation oncologist, a radiologist, an interventional radiologist, a pain specialist from hospice services, and/or a palliative care physician". Leadership and review is essential to prevent burnouts.[1-4]

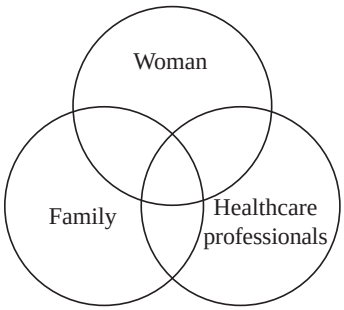

Fig 1: The three stakeholders of palliative care

Strategies to Improve Palliative Care Services for Gynae Cancer Patients[1,2]

Following strategies if used simultaneously may improve use of palliative and hospice care for gynae cancer patients

1. **Identification of indications for referral to specialised palliative care specialists**

   The indications to trigger referral of gynae cancer cases are listed in Table 4. These should be evaluated regularly and early in all gynaecologic oncology patients regardless of diagnosis or symptoms to identify patients who would be benefitted even during management of early stage disease. It is prudent to note that higher medical expenditures and more aggressive care were not associated with increased survival but rather with worse quality of life in the final week.

Table 3: Indications to trigger referral to specialised palliative care teams

Primary Indications	Secondary indications
Frequent admissions	Metastatic or incurable cancer
Admissions prompted by difficulty to control symptoms	Chronic oxygen use
Complex care requirements	Admission from long term care facility
Decline in function	Limited social support

2. **Education of patients and providers**

   According to one study, although 90% of Gynaecologic oncology fellows reported palliative care as an integral part of their training, only 11% actually received any training and they found it useful. Approximately 77% expressed that more training would have been beneficial.

3. **Incorporation of palliative services in Research settings**:

Treatment of Common Clinical Conditions During Care of Gynae Cancer Cases[1,4,5]

Pain Control

Pain management remain an integral part of care during each step of care and the goals which includes indications and approach should be discussed with the woman. As per the WHO analgesic ladder for pain management, pain should be treated in a step wise fashion first using non opioids plus or minus adjunctive analgesics followed by opioid combinations Different types of pains should be treated differently; For treating neuropathic pain, anticonvulsants, antidepressants, Gabapentinoids and transcutaneous stimulation should be used. For treating pain associated with acute inflammation corticosteroids and for treating the associated anxiety and depression anxiolytics and antidepressants should be used. For localized pains respective blocks and indwelling epidural analgesics should be given. Local radiation therapy should be considered for brain or bone metastasis. However, the least invasive option for administration of medications should be considered, e.g oral, sublingual or topical medications are preferred over intravenous or subcutaneous administration. The additional supportive care in form of massage, heat, meditation, physical therapy, positioning, and alternative therapies (aromatherapy, music therapy, etc.) and spiritual care are useful to assist pain and anxiety control. Prior planning to tackle adverse events like constipation, somnolence and nausea can further improve the outcomes.

End of life and Hospice

Patients should transition to hospice when their life expectancy is less than 6 months. It was observed that 20-60% of gynae cancer cases die while on hospice care with a length of stay in hospice only 19-25 days with 55% of patients registered less than 30 days prior to death. In a review of 268 gynaecologic oncology patients admitted in the last 6 months of life, 70.5% were referred to hospice with a median time of

Table 2: Management of common symptoms[1,4,5]

Management of anorexia	
Symptomatic treatment for reversible causes including treatment for constipation, pain, medications, hypercalcemia, mucositis, prokinetic agents, short term administration of low dose corticosteroids, progesterone agents, cannabinoids. Additionally, counselling is needed for patients and caregivers to remain away from meeting nutrition goals to avoid suffering from forced feeding	
Management of constipation	
Rule out bowel obstruction and faecal impaction, initiate bowel regimen with opioid use, add stool softeners, osmotic agents (lactulose), stimulants (senna, bisacodyl), lubricants (glycerine suppositories), enemas (mineral oil, soap suds), opioid antagonist (methylnaltrexone)	
Management of nausea/vomiting	
Use optimal dose/route and scheduled dosing, Maximize primary agents abnd then add secondary agents (do not switch agents), Avoid drugs with similar toxicities (reduces adverse effects)	
Malignant bowel obstruction	
Conservative management with nasogastric tube, intravenous fluids	
Partial bowel obstruction	Prokinetic agents (metoclopramide), steroids (dexamethasone), haloperidol, antispasmodics (hyoscine butylbromide)
Complete bowel obstruction	Avoid prokinetic agents if increased cramping/pain, steroids, dexamethasone, antiemetic, haloperidol, octreotide to reduce secretions. Consider gastrostomy tube, TPN (total parenteral nutrition) to be considered only if there is possibility of surgery in future.
Management of dyspnoea	
General management Relaxation techniques like music, guided imagery, cognitive behavioural therapy, fan (facial cooling/air movement), Oxygen, physiotherapy/chest wall percussion. Systemic opioids, benzodiazepines, anticholinergics	
Aetiology of Dyspnoea	**Treatment**
Pneumonia	Antibiotics, pulmonary toilet
Pneumonitis, radiation or chemotherapy induced	Glucocorticoids
VTE	Anticoagulation, IVC filter
Pleural effusion	Indwelling catheter, thoracocentesis, VATS, pleurodesis
Airway obstruction by tumour or lymphadenopathy	Radiation therapy, glucocorticoids
Retained of excessive secretions	Anticholinergic agents
Massive ascites	Drainage including indwelling catheter
Anxiety including hyperventilation	Anxiolytics, cognitive behavioural therapy
Management of genitourinary symptoms based on aetiology	
Vaginal haemorrhage	Vaginal packing
Bladder haemorrhage	Bladder irrigation, Cystoscopic coagulation > infusion of 1% alum, Administration of PGE2 and silver nitrate, Formalin
Other options	EBRT(hypofractionation, 2# over 2-3 days
	Arterial embolization by interventional radiologist
Management of gastro intestinal complications	
Haemorrhage	Endoscopy, surgical ligation or clipping of bleeding vessels
Management of Hypercalcemia (serum calcium >10.2)	
Hydration with intravenous normal saline, Biphosphonates (pamidronate or Zoledronic acid), Addition of calcitonin in patients with severe hypercalcemia	
Malignant ascites	
Maximize diuretics to decrease albumin loss, Frusemide (40-80 mg IV/PO twice daily) and Spironolactone (50-200 mg PO twice daily), Paracentesis, permanent drains	

enrolment to death of only 22 days suggesting earlier referral may be appropriate. 51% of women with gynaecologic cancer died in an acute care bed as an inpatient and up to 60% of patients have an invasive procedure performed within the last 3 to 6 months of life. End-of-life patients not managed on hospice are more likely to be inpatient, transferred to the intensive care unit, and receive invasive procedures without survival benefit. Thus, to provide optimal end-of-life care, timely hospice referral is essential.[3,4,5]

Conclusion

Patients with advanced gynaecologic cancer, whether inpatient or outpatient, should receive dedicated

palliative care services, early in the disease course and concurrent with active treatment. Referring patients to palliative care teams is essential, and services may complement existing protocols. Gynaecologic oncologists should be well versed with treatment of common symptoms. There is a need to identify methods to improve hospice use in the gynaecologic oncology population to improve patient outcomes.

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Congratulations !!

Dr Neerja Varshney & Dr Rashmi Vyas
for correctly answering the Crossword and Pictorial Quiz of January issue

Answer: January Issue

Crossword

Down
1. Dyslipidemia
2. Aromatase
3. Total
4. Paroxitine
5. PCOS
6. Ospemifene

Across
7. Gonadoblastoma
8. SCOFF
9. Berlin
10. Twenty

Pictorial Quiz

Figure 1: Androgen Insensitivity Syndrome

Figure 2: 46 XY

Journal Scan

Manash Biswas[1], Kanika Batra Modi[2]
[1]Associate Director Gyn Onco Surgery, [2]Consultant Gynaecologic Oncologist, Max Institute of Cancer Care
Max Superspeciality Hospital Saket, New Delhi

N Engl J Med 2019;380:822-32. DOI: 10.1056/NEJMoa1808424

A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms

P Harter, J Sehouli, D Lorusso, A Reuss, I Vergote, C Marth, J W Kim, F Raspagliesi, B Lampe G Aletti, W Meier, D Cibula, A Mustea, S Mahner, I B Runnebaum, B Schmalfeldt, A Burges R Kimmig, G Scambia, S Greggi, F Hilpert, A Hasenburg, P Hillemanns, G Giorda, I von Leffern C Schade-Brittinger U Wagner and A Du Bois

Background: Systematic pelvic and paraaortic lymphadenectomy has been widely used in the surgical treatment of patients with advanced ovarian cancer, although supporting evidence from randomized clinical trials has been limited.

Methods: The Study, intraoperatively randomly assigned patients with newly diagnosed advanced ovarian cancer (International Federation of Gynecology and Obstetrics stage IIB through IV) who had undergone macroscopically complete resection and had normal lymph nodes both before and during surgery to either undergo or not undergo lymphadenectomy. All centers had to qualify with regard to surgical skills before participation in the trial. The primary end point was overall survival.

Results: A total of 647 patients underwent randomization from December 2008 through January 2012, were assigned to undergo lymphadenectomy (323 patients) or not undergo lymphadenectomy (324), and were included in the analysis. Among patients who underwent lymphadenectomy, the median number of removed nodes was 57 (35 pelvic and 22 paraaortic nodes). The median overall survival was 69.2 months in the no-lymphadenectomy group and 65.5 months in the lymphadenectomy group (hazard ratio for death in the lymphadenectomy group, 1.06; 95% confidence interval [CI], 0.83 to 1.34; P=0.65), and median progression-free survival was 25.5 months in both groups (hazard ratio for progression or death in the lymphadenectomy group, 1.11; 95% CI, 0.92 to 1.34; P=0.29). Serious postoperative complications occurred more frequently in the lymphadenectomy group (e.g., incidence of repeat laparotomy, 12.4% vs. 6.5% [P=0.01]; mortality within 60 days after surgery, 3.1% vs. 0.9% [P=0.049]).

Conclusions: Systematic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer who had undergone intraabdominal macroscopically complete resection and had normal lymph nodes both before and during surgery was not associated with longer overall or progression-free survival than no lymphadenectomy and was associated with a higher incidence of postoperative complications.

Comments: Harter and colleagues show in their LION (Lymphadenectomy in Ovarian Neoplasms) trial how meticulous trial design can help overcome many inherent confounders. The Trial's novel design resolved the criticisms of many previous studies. Without an improvement in survival, any potential complications from systematic lymph-node dissection should be avoided. The absence of a difference in overall survival between the two groups in this trial is consistent with the concept that it is the inability to control intraabdominal disease that is the most frequent cause of ovarian cancer–related illness and death. Moreover, any potentially increased rate of disease recurrence in the lymph nodes did not affect survival among these women. Women with ovarian cancer in whom complete primary cytoreduction is achieved have the best prognosis and longest survival. The procedures required to achieve complete cytoreduction already have attendant risks, and eliminating ineffective techniques such as systematic lymphadenectomy is prudent to improve patients' overall recovery. Along the way, we may also have learned a bit about how difficult it can be to overcome our assumptions without a properly controlled trial design.

N Engl J Med 2019;380:822-32. DOI: 10.1056/NEJMoa1708618

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W J van Driel, S N Koole, K Sikorska, J H Schagen van Leeuwen, H W R Schreuder, R H M Hermans
I H J T De Hingh, J Van Der Velden, H.J Arts, L F A G Massuger, A G J Aalbers, V J Verwaal, J M Kieffer
K K Van De Vijver, H Van Tinteren, N K Aaronson and G S Sonke

Background: Treatment of newly diagnosed advanced-stage ovarian cancer typically involves cytoreductive surgery and systemic chemotherapy. A trial was conducted to investigate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer.

Methods: In a multicenter, open-label, phase 3 trial, 245 patients were randomly assigned who had at least stable disease after three cycles of carboplatin (area under the curve of 5 to 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) to undergo interval cytoreductive surgery either with or without administration of HIPEC with cisplatin (100 mg per square meter). Randomization was performed at the time of surgery in cases in which surgery that would result in no visible disease (complete cytoreduction) or surgery after which one or more residual tumors measuring 10 mm or less in diameter remain (optimal cytoreduction) was deemed to be feasible. Three additional cycles of carboplatin and paclitaxel were administered postoperatively. The primary end point was recurrence-free survival. Overall survival and the side-effect profile were key secondary end points.

Results: In the intention-to-treat analysis, events of disease recurrence or death occurred in 110 of the 123 patients (89%) who underwent cytoreductive surgery without HIPEC (surgery group) and in 99 of the 122 patients (81%) who underwent cytoreductive surgery with HIPEC (surgery-plus-HIPEC group) (hazard ratio for disease recurrence or death, 0.66; 95% confidence interval [CI], 0.50 to 0.87; P=0.003). The median recurrence- free survival was 10.7 months in the surgery group and 14.2 months in the surgery- plus-HIPEC group. At a median follow-up of 4.7 years, 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; P=0.02). The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P=0.76).

Conclusions: Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

Comments: The results of the randomized trial by van Driel et al., represent the most convincing informa- tion to date that a single administration of hyperthermic intraperitoneal chemotherapy (HIPEC) delivered at the end of a surgical resection of ovarian cancer may provide a meaningful advantage for a defined group of patients with cancer. The treatment is apparently reasonably safe; the patients who underwent interval cytoreductive surgery with HIPEC and those who underwent the surgery without HIPEC had a similar side-effect profile and a similar rate of grade 3 or 4 adverse events. There was no significant delay in the re-initiation of routine chemotherapy after surgery when HIPEC was performed.

So, is hyperthermia necessary for the incremental effectiveness of the chemotherapy? Does the early intra-operative administration of intraperitoneal therapy offer advantages over routine postoperative chemotherapy? Beyond these mechanistic questions, the overall role of HIPEC in the treatment of ovarian cancer is still uncertain and will depend on additional information regarding clinical outcomes. What is the incremental cost of this intervention? The extra time needed in the operating room, the longer duration of hospitalization, and the increased use of diverting colostomies or ileostomies will all increase the overall cost of treatment. The assessment of a cost–benefit ratio warrants serious consideration. Finally, the results observed in this trial, be expected to be reproduced at canters at which surgeons do not have as much experience in administering HIPEC. New confirmatory clinical investigations of HIPEC are needed to clarify some of the unanswered questions before HIPEC can become a common treatment strategy. These considerations will be important for clinical trial investigators as they focus on the positive effect of HIPEC as an intervention as compared with the effects of promising new agent combinations or immunotherapy treatments.

The INTERNATIONAL MISSION study: Minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy

A Fagotti, S Gueli Alletti, G Corrado ,E Cola2, E Vizza, M Vieira,C E Andrade, A Tsunoda G Favero, I Zapardiel, T Pasciuto and G Scambia. Int J Gynecol Cancer 2019;29:5–9.)

Background: The aim of this retrospective multicenter study was to investigate the extent, feasibility, and outcomes of minimally invasive surgery at the time of interval debulking surgery in different gynecological cancer centers.

Methods/Materials: In December 2016, 20 gynecological cancer centers were contacted by e-mail, to participate in the INTERNATIONAL MISSION study. Seven centers confirmed and five were included, with a total of 127 patients diagnosed with advanced epithelial ovarian cancer after neoadjuvant chemotherapy and minimally invasive interval surgery. Only women with a minimum follow-up time of 6 months from interval surgery or any cancer-related event before 6 months were included in the survival analysis. Baseline characteristics, chemotherapy, and operative data were evaluated. Survival analysis was evaluated using the Kaplan–Meier method.

Results: All patients had optimal cytoreduction at the time of interval surgery: among them, 122 (96.1%) patients had no residual tumor. Median operative time was 225 min (range 60 – 600) and median estimated blood loss was 100 mL (range 70 – 1320). Median time to discharge was 2 days (1–33) and estimated median time to start chemotherapy was 20 days (range 15 – 60). Six (4.7%) patients experienced intraoperative complications, with one patient experiencing two serious complications (bowel and bladder injury at the same time). There were six (4.7%) patients with postoperative short-term complications: among them, three patients had severe complications. The conversion rate to laparotomy was 3.9 %. Median follow-up time was 37 months (range 7 – 86): 74 of 127 patients recurred (58.3%) and 31 (24.4%) patients died from disease. Median progression-free survival was 23 months and survival at 5 years was 52 % (95% CI: 35 to 67).

Conclusions: Minimally invasive surgery may be considered for the management of patients with advanced ovarian cancer who have undergone neoadjuvant chemotherapy, when surgery is limited to low-complexity standard cytoreductive procedures.

Comments: This is a very important and well conducted trial highligting the importance, benefits and practical considerations while using minimally invasive surgery (MIS) for ovarian cancer. Fagotti and colleagues have suggested minimally invasive surgery for ovarian cancer after neoadjuvant chemotherapy to have similar perioperative outcomes and survival rates to women who undergo interval surgery by laparotomy. IS is currently underused to perform interval cytoreductive surgery. The main aim of this study was also to understand that there is no adverse outcome on survival. There has been critical appraisal in the past about this technique not being adequate for peritoneal assessment and possible leading to inferior outcome. But this study has clearly proven that the MIS technique used in trained hands after adequately assessed patients with good or partial response to chemotherapy leading to similar progression free and disease free survival rates as open surgery with decreased peri-operative morbidity and early recover.

Clinical Proceedings of AOGD Clinical Meeting held at Dr Ram Manohar Lohia Hospital, New Delhi on 17th January, 2020

Ohvira Syndrome (Herlyn Werner Wunderlich Syndrome) – A rare entity

Paridhi, Indu Chawla, Anjum Ara

Indroduction

OHVIRA syndrome is a rare congenital anomaly consisting 5% of total mullerian dysgenesis. It consists of a triad of uterine didelphys, obstructed hemivagina and ipsilateral renal agenesis. It usually presents soon after menarche but may have delayed presentation depending upon type. It usually presents with pelvic pain and dysmenorrhea may be associated with urinary complaints.

Case Reports

Mrs X, 31 yr female, P2L2 with previous 2 caesarean deliveries reported in gynec emergency, Dr RML Hospital with complaints of pelvic pain, urinary retention and hematuria since 2 months and with ultrasound report suggestive of bicornuate uterus with large hematocolpos/ hematometra. Patient was catheterized to relieve urinary complaints. Examination under anesthesia was done –a huge cystic bulge on anterior vaginal wall seen. On aspiration, 10cc of blood mixed organized pus collection was obtained. Cystoscopy showed normal bladder wall. Cervical os was seen posterior to bulge. On MRI, bicornuate bicollis uterine anatomy was seen with right hematocolpos. IVP was suggestive of absent right kidney. Laparotomy with Right hemihysterectomy along with drainage of hematocolpos was done.

Discussion

A didelphys uterus is characterized by complete failure of the Mullerian ducts to fuse leading to separate uterine cavities and two cervices. Because the Mullerian ducts develop often in association with Wolffian ducts, abnormalities of the kidneys may be found in conjunction with uterine abnormalities.

Conclusion

This is rare case of a women with didelphys uterus who conceived and delivered successfully by caesarean section. Usually such cases present soon after menarche but rare one present late. The principle management in such cases is drainage of collection obstructing the outflow and channelization of passage.

Rare Mullerian Anomalies - Acum and Roberts Uterus

Preeti Sainia, Alka Goel
Poonam Yadav, Veena Ganju

Developmental anomalies of mullerian duct system are one of the most intriguing and challenging disorders that gynecologist encounter in their practice Roberts uterus and ACUM are rare form of mullerian anomalies seen in young menstruating girls who present with severe dysmenorrhea leading to poor quality of life.

ACUM is acronym for accessary and cavitated uterine masses. These are non communucating accsssary cavities lying within an otherwise normal uterus, lined by functional endometrium and surrounded by smooth muscle cells. The external appearence of the uterus is nearly normal

ROBERTS UTERUS is charectarised by oblique complete uterine septum dividing the endometrial cavity asymetrically, resulting in non-communicating hemi uterus with single cervix with normal external contour. Patient presents with severe dysmenorrea and later on chronic pelvic pain and infertility.

Both these entities are diagnostic delimas as patient keeps menstruating normally amd the severe dysmenorrhea in these girls are often dismissed asprimary dysmenorrea and giving symptomatic treatment,but both these warrant early diagnosis and treatment as these conditions are extremely debilitating and hampers the quality of life of patient and my have future adverse impact on fertility.

Ovarian Myeloid Sarcoma: A rare case report

Shilpi Singh, Bani Sarkar
Sushma Rani, Kamna Dutta

Myeloid sarcoma (chloroma, granulocytic sarcoma, or extramedullary myeloid tumour) is a rare tumor of immature myeloid cells.

Most commonly presents with history of AML or antecedent myeloproliferative disorder or myelodysplastic syndrome.

and it may also present initially as an isolated mass and subsequently develops AML.

we had a rare case of primary ovarian myeloid sarcoma, 43 Years old female, P1L1, known case of recently diagnosed DM, HTN with Nephropathy and unexplained leucocytosis (>27000). Bone Marrow Biopsy was inconclusive and LAP score was negative but due to persistent symptoms, CECT abdomen was done and incidental finding of left adnexal hypoechoic mass of 6.5x4.8x5.4 cm.Tumor markers for ovarian tumor were negative, laparotomy was done for suspicion of torsion of ovarian mass. Left sided solid mass 5x7 cm, no torsion was found. Histopathology and Immuno-histochemistry was suggestive of Myeloid Sarcoma and FDG PET was Suggestive of Metastasis. The patient is on chemotherapy and is under regular follow-up at our centre.

This case illustrate diagnosis of MS requires a multisystem approach with strong clinical suspicion.

Ohvira Syndrome (Herlyn Werner Wunderlich Syndrome) – A rare cause of dysmenorrhea in adolescents

Sonal Gupta, Indu Chawla, Anjum Ara

Introduction

The Herlyn–Werner–Wunderlich syndrome is a rare congenital anomaly characterised by uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis(OHVIRA). This abnormality contributes to 5% of the total Mullerian dysgenesis and belongs to Class III of AFS classification of Mullerian anomalies. It usually presents after menarche with progressive pelvic pain during menses secondary to haematocolpos.

Case Report

A 18 year old unmarried girl presented with severe dysmenorrhoea for past three months. She had attained menarche at the age of 13 years and was having regular menses with cyclical abdominal pain. On Per rectal examination a 3*3 cm bulge was felt on left side anterior to rectum. Ultrasound revealed a bicornuate uterus with left renal agenesis and cervical fibroid of 4.5*3.2 cm. On MRI, bicornuate bicollis uterus with left hematocolpos and left renal agenesis was found. Vaginoscopy was done under anaesthesia and a 3*3 cm bulge was visualized on left antero-lateral wall of vagina with a single cervix seen on right side of the bulge. Diagnostic laproscopy was done, bicornuate uterus with a bulge on lower part of left uterine horn along with left tubo-ovarian mass adhered to bowel was seen. Decision for Laparotomy was taken. While the right uterine horn was communicating with vagina via patent cervix, left utero-vaginal canal was not patent due a vaginal septum covering its cervix. Vaginal resection of septum with left salpingectomy and left ovarian cystectomy was done. Diagnosis of OHVIRA Syndrome with left paratubal cyst was made. During follow-up, patient is relieved of her symptoms. On vaginoscopy and ultrasound, healthy vaginal wound with patent utero-vaginal canal was found.

Discussion

HWW presents with varied conditions, such as abdominal pain, dysmenorrhea, and abdominal mass secondary to hematocolpos, urinary retention, endometriosis, pelvic infection, acute pelvic pain, and infertility. Awareness is necessary in order to diagnose and treat this disorder properly before complications occur. MRI is the gold standard for the delineation of uterine malformation, renal anomalies and associated complications like endometriosis. When renal anomalies are encountered, a screening should also be made for congenital abnormalities of the reproductive tract and vice versa. Single stage vaginoplasy is the treatment of choice.

Conclusion

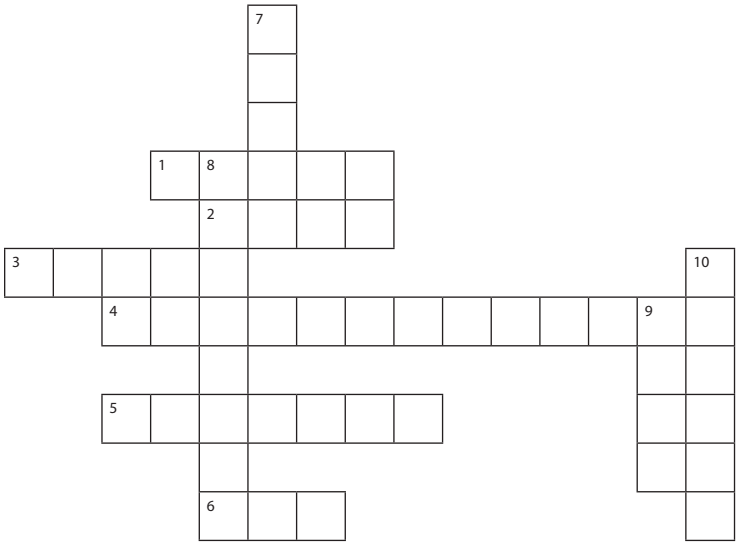
An unusual presentation of regular menstruation and nonspecific abdominal pain makes the diagnosis of HWW syndrome difficult and requires special clinical suspicion. Early identification warrants awareness of such an anomaly in order to diagnose and treat this disorder properly before complications occur. Routine laparoscopy is not essential to management. Vaginal stenosis is a postoperative possibility, and may be associated with vaginal adenosis.

The Maze of Knowledge

Swasti[1], Satinder Kaur[2]

[1]Senior Consultan, Gynae Oncology, Max Vaishali, Patparganj & Noida, [2]Clinical Head & Senior Consultant, Gynae Oncology, Dharamshila Narayan, Super Speciality Hospital, New Delhi & Gurugram

CROSSWORD



Across

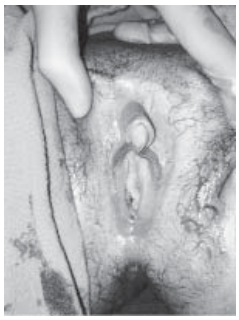
1. Colposcopic scoring system (5)
2. Performance status (4)
3. Old classification of radical hysterectomy (5)
4. Surgery for advanced ovarian cancer (13)
5. Author of recent classification on radical hysterectomy (7)
6. Deficiency of this protein is associated with better survival in endometrial cancer (3)

Down

7. Novel technique of chemotherapy delivery in ovarian cancer management (5)
8. Earlier name of radical hysterectomy for cervical cancer (8)
9. Precancerous lesions of vagina (4)
10. Most common gynaecological cancer in India (6)

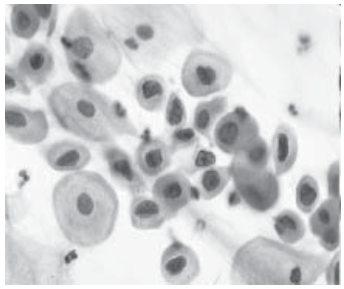
PICTORIAL QUIZ

Q1. 19 year old girl with Large 20 X 20 cm solid cystic ovarian mass. AFP, BHCG and LDH normal. Clinical examination showed the findings as seen in the picture above. What could be the probable diagnosis?

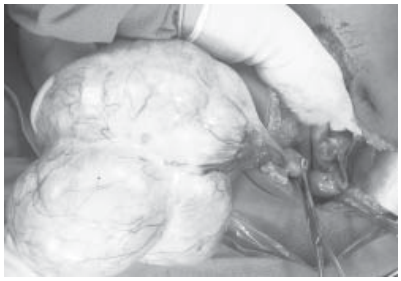


Q2. 54 year old lady underwent a screening pap smear. This was the picture on Cytology.

She underwent Colposcopy, on which transformation zone could not be seen. What should be the next step?



Q3. Spot the diagnosis?



Whatsapp your answers to **9211656757.**
Names of first three correct entries will be mentioned in the next issue

Refer page 42 for previous answer key.

I.F.C.P.C

IFCPC INDIA 2020

Eliminating Cervical Cancer-Call for Action

1-4 October 2020, Hyderabad, India

17th World Congress for Cervical Pathology and Colposcopy

SAVE THE DATE

1-4 October 2020, Hyderabad, India

Hyderabad International Convention Centre, Hyderabad

HIGHLIGHTS

Plenary Sessions On

- Eliminating Cervical Cancer - The Landscape Science and Politics
- The Biology of Cervical Premalignancy and Malignancy: The Transformation Zone
- Screening and Vaccination
- Clinical Challenges
- Multi-zonal disease
- IFCPC session- Terminology and Training
- New Technologies and Artifical Intelligence
- Patient Advocacy

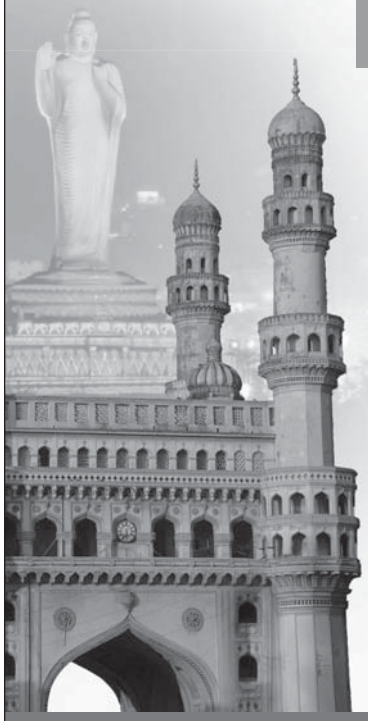
PRE-CONGRESS WORKSHOPS

Wednesday, 30 September 2020

- Training the Trainer
- Vulva with Hands-on Module
- Screen 'n' Treat

Thursday, 1 October 2020

- Comprehensive Colposcopy Course & Hands-on LEEP
- Cytopathology & HPV
- Surgical Options for CIN & Cervical Cancer (Live Surgery)
- Vulvar Reconstructive Surgery



ONLINE ABSTRACT SUBMISSION OPEN!

Who should submit?	Publication	Prizes
Medical Students Nurses Trainees Researchers in related disciplines	Abstracts will be published in an indexed journal	Prizes for best papers in all categories

THEMES

1. Basic Research in HPV and Cervical Cancer
2. HPV Testing and HPV Vaccination
3. Cervical Cancer Screening
4. Management of CIN
5. Quality Assurance
6. Cervical Cancer
7. Public Health
8. Think Beyond Disease
9. Other Precancerous Lesion and Cancers Related To HPV
10. STDs and HPV
11. Training and Education in Colposcopy
12. Miscellaneous and Case Reports

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North Zone

All India Coordinating Committee
Royal College of Obstetricians & Gynaecologists (RCOG)
Northern Zone
Website: **www.aiccrcognzindia.com**

"Early Pregnancy Symposium What Every Obstetrician Needs To Know"

Date: **Sunday 1st March, 2020** | *Timing:* **08:00 am to 06:00 pm**
Venue: **Auditorium, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, 110076**

Programme

08:00 am	Registration	
08:20 am	Welcome Address and Lamp Lighting	
08:30 am	**Session 1:** 4-10+6 weeks	
	Chairpersons: Dr Anjila Aneja, Dr Ranjana Sharma, Dr Jyoti Bhaskar	
08:30 am - 08:50 am	Imaging Based Embryology	Ashok Khurana
08:50 am - 09:10 am	Dating in Early Pregnancy Scan	Ashok Khurana
09:10 am - 09:30 am	Viable Pregnancy vs Non-Viable Pregnancy. RCOG criterion	Dr Kuldeep Singh
09:30 am - 09:50 am	Can We Pick Up Structural Anomalies Before 10+6 Weeks?	Dr Kuldeep Singh
09:50 am - 10:10 am	Pregnancy of Unknown Location	Dr Arbinder Dang
10:10 am - 10:20 am	**Discussion**	
10:20 am - 10:50 am	Code of Ethics	Dr Shekhar Agarwal
10:50 am - 11:00 am	**Coffee Break**	
	Chairpersons: Dr Nirmala Agarwal, Dr Sohani Verma, Dr Neema Sharma, Dr Uma Pandey	
11:00 am - 11:20 am	Assessment of Cesarean scar in early pregnancy: Is it useful?	Dr Poonam Tara
11:20 am - 11:40 am	Work Up of Early Pregnancy Losses	Dr Mala Arora
11:40 pm - 12:10 pm	Spectrum of Ectopic Pregnancy: Diagnostic criterion on Imaging	Dr Mala Sibal
12:10 pm - 12:40 pm	Management of Tubal, Cervical, Ovarian, Cesarean Scar Pregnancies	Dr Sangeeta Gupta
12:40 pm - 01:10 pm	Molar Pregnancy: Diagnosis and recent advances in management and follow up	Dr Mala Sibal Dr Arbinder Dang
01:10 pm - 01:30 pm	**Discussion**	
01:30 pm - 02:30 pm	**Lunch**	
02:30 pm	**Session 2:** 11-13+6 weeks	
	Chairpersons: Dr Asmita Rathore, Dr Jayasree Sunder, Dr Jasmine Chawla, Dr Mamta Sahu	
02:30 pm - 03:00 pm	Overview of Different Protocols for Down's Screening in the First Trimester	Dr Anita Kaul
	Components of Screening Process	
03:00 pm - 03:30 pm	How to do NT/NB Scan: Image optimizing and Screening	Dr Smriti Prasad
03:30 pm - 04:00 pm	Explaining Biochemistry in First Trimester: What these terms mean? • Just Ultrasound • Combined Screening • Enhanced Screening • Extended Screening	Dr Akshatha Sharma
	Chairpersons: Dr Sweta Gupta, Dr Jharna Behura, Dr Shelly Arora, Dr Shweta Gupta	
04:00 pm - 04:30 pm	Quality Control for Risk Calculation (Ultrasound and Biochemistry) in First Trimester for T21, T18/13, Preeclampsia	Dr Anita Kaul
04:30 pm - 05:00 pm	Structural Abnormalities Picked Up between 11-13+6 weeks	Dr Chanchal Singh
05:00 pm - 06:00 pm	**General Body Meeting**	

Dr Nirmala Agarwal
Organizing Chairperson
& Head North Zone

Dr Anita Kaul
Organizing Co-Chairperson

Dr Arbinder Dang
Organizing Secretary

RCOG North Zone Secretariat
OT Complex, 3rd Floor, Sant Parmanand Hospital, 18 Shamnath Marg, Civil Lines, Delhi-110054
Mr Asif Muniri (Administrative Assistant) +919560069925 / 9716801190
Tel No.: 91-11-23981260, 23994401-10, Ext 314 | **Email:** rcognz2017@gmail.com/ n.menoky@gmail.com/ arbidang@gmail.com

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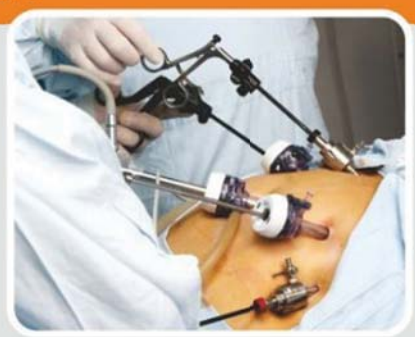

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