CONSENSUS DOCUMENT FOR MANAGEMENT OF UTERINE CANCER

Prepared as an outcome of ICMR Subcommittee on Uterine Cancer

INDIAN COUNCIL OF MEDICAL RESEARCH
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Disclaimer

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

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

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Head (Publications & Information) : Dr. Neeraj Tandon

Compiled & Edited by: Dr. Tanvir Kaur, Dr. Neerja Bhatla, Dr. Selvalaxmi

Production Controller : Mr. JN Mathur

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Foreword

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

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

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

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

Message

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

The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, esophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2016 was reviewed while formulating consensus document and accordingly recommendations are made.

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

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

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

Preface

The incidence of cancer is rising in India – slowly and steadily. The increase in some cancers is attributed to lifestyle factors. Uterine cancer is one of these. it has a relatively low incidence in India compared to the western world. However, increasing urbanization in India, coupled with an increase in the metabolic syndrome, changing lifestyle patterns and delayed child bearing have resulted in an increase in the incidence of uterine cancer not only in postmenopausal women but in younger women too. Many of the latter may have concerns about future fertility. Among all the gynaecological cancers, uterine cancer has the best prognosis, largely due to early presentation and diagnosis, and the availability of effective multidisciplinary treatment options. The ICMR consensus document on Uterine Cancer has addressed all the controversial aspects of diagnosis and management, including the place of minimally invasive surgery, role of lymphadenectomy and its extent, sentinel lymph node sampling, and adjuvant therapy. The other less common but more controversial topic, uterine sarcoma, is also presented in this document, with all the important diagnostic and management related take home points.

It has been a privilege to serve as the Chairperson of this subcommittee. I take this opportunity to appreciate the initiative by the Indian Council of Medical Research to set up a task force to develop this consensus document for management of uterine cancer in India. Experts from all corners of India have come together to glean and analyse the available literature, gather the evidence and develop practical guidelines that will not only update the busy clinicians. While keeping up with the international standards, these guidelines are adapted to the Indian scenario and I am confident that they will be helpful to formulate therapy tailored to the patient's requirements. I thank all the national experts and the coordinators for their tireless work in bringing shape to the final consensus on these controversies. I would also like to thank Dr. G. K. Rath and Dr. Tanvir Kaur for their help, support and encouragement, which went a long way in successfully concluding this endeavour.

It is our hope that clinicians, researchers and students will find these guidelines useful in their day-to-day practice. The field of gynaecologic oncology is a rapidly evolving one. These guidelines would be updated from time to time, and we look forward to your constructive feedback as we strive to further improve our understanding and deliver the best care to our patients.

(Dr Neerja Bhatla)
Chairman
Sub-committee on Uterine Cancer

Preface

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

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

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

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

Acknowledgement

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

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

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

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

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

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

Tanvir Kaur

(Dr.Tanvir Kaur)
Program Officer & Coordinator

Members of the Sub-Committee

Chairpersons

Dr. Neerja Bhatla
Professor and Unit Head,
Department of Obstetrics & Gynaecology,
All India Institute of Medical Sciences,
New Delhi - 110029, India

Dr Selvalaxmi,
Professor,
Department of Radiotherapy,
Cancer Institute, Adyar, Chennai

Members

1) Dr. Abraham Peedicayil
Porfessor and Head,
Department of Gynecologic Oncology,
Christian Medical College,
Vellore

2) Dr. Amita Maheshwari
Professor, Department of Gynecologic Oncology, Tata Memorial Centre,
Mumbai

3) Dr. Asima Mukhopadhyay
Senior Consultant,
Department of Gynecologic Oncology,
Tata Medical Centre,
Kolkata

4) Dr. D.N. Sharma
Professor, Department of Radiation Oncology, BRAIRCH, All India Institute of Medical Sciences,
New Delhi

5) Dr. Lalit Kumar
Professor and Head, Department of Medical Oncology, BRAICH, All India Institute of Medical Sciences,
New Delhi

6) Dr. Sunesh Kumar
Professor and Head,
Department of Obstetrics and Gynaecology,
All India Institute of Medical Sciences,
New Delhi

7) Dr. Sushil K.Giri
Professor and Head, Department of Gynecologic Oncology, Acharya Harihar Regional Cancer Centre, Cuttack,
Odisha

8) Dr. Sushmita Pathy
Professor, Department of Radiation Oncology, BRAIRCH, All India Institute of Medical Sciences,
New Delhi

9) Dr. Umesh Mahantshetty
Professor, Departent of Radiation Oncology,
Tata Memorial Centre,
Mumbai

10) Dr. Uttam D. Bafna
Former Professor and Head, Department of Gynecologic Oncology, Kidwai Memorial Institute of Oncology,
Bangalore

Coordinators:

1) Dr. Seema Singhal
Associate Professor,
Dept of Obstetrics & Gynaecology, All India Institute of Medical Sciences, New Delhi

2) Dr. Jayashree Natarajan
Acad Senior Resident,
MCh Gynaecological Oncology,
Dept of Obstetrics & Gynaecology, All India Institute of Medical Sciences, New Delhi

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1 CARCINOMA ENDOMETRIUM

1. Introduction

Carcinoma endometrium is the most common gynecological cancer in developed countries with an age standardized incidence rate (world) of 8.4 per 100,000 women.(1) In developing countries, cervical cancer still remains the leading gynecological cancer but recently there has been an increase in the incidence of endometrial cancer. In India, the total number of estimated new cases of endometrial cancer in 2018 is 13,328 with an estimated 5010 deaths. The age standardized incidence rate (ASIR) of endometrial cancer in India is 2.3/100,000 women. (1,2) The rise in endometrial cancer in India is mainly attributed to changing trends in the lifestyle and reproductive profile of women, especially in urban areas. The majority of cases present in the 6th and 7th decades of life, with the mean age being 60 years at the time of diagnosis. (3)

EPIDEMIOLOGY AND RISK FACTORS:

The effect of estrogens in the pathogenesis of endometrial cancer has been proved by several epidemiological studies. The strong association of endometrial cancer with long-term unopposed estrogenic action, either exogenous or endogenous, in women with an intact uterus has been postulated to be causative. Unopposed estrogens lead to increased mitotic activity of endometrial cells, resulting in more frequent errors in DNA replication and somatic mutations. These changes are manifested clinically as hyperplasia and carcinoma.(3) However, this carcinogenic effect of estrogen on the endometrium is opposed to some extent by the effect of progesterone.(2) Other risk factors include genetic factors, which account for less than 5% of endometrial cancers (hereditary non-polyposis colorectal cancer, Lynch syndrome due to defect in mismatch repair gene) and previous pelvic irradiation. Table 1 shows the risk of developing carcinoma endometrium with respect to epidemiological risk factors.(3,4,5)

Table 1: Relative risk of developing carcinoma endometrium with some epidemiological risk factors (3,4,5):

RISK FACTOR	RELATIVE RISK
Prolonged estrogen exposure	
Estrogen-only hormonal therapy	2-10
Early menarche	1.5-2
Late menopause	2-3
Nulliparity	2.0
Anovulation (Polycystic Ovarian Syndrome)	3.0
Demographic Characteristics	
increasing age (> 55 years)	1.4
High socioeconomic status	1.3
Family history of uterine malignancy (Lynch syndrome)	22-50% life time risk

Associated Medical Illness	
Diabetes mellitus	2.0
Obesity **For type I endometrial cancer:** • BMI 25.0 to <30 kg/m^2 • BMI 30.0 to 39.9 kg/m^2 • BMI 40.0 kg/m^2	2-4 OR 1.5 OR 2.5-4.5 OR 7.1
For type II endometrial cancer: • BMI 25.0 to <30 kg/m^2 • BMI 30.0 to <39.9 kg/m^2 • BMI 40.0 kg/m^2	 OR 1.2 OR 1.7-2.2 OR 3
Hypertension	1.5
Prior pelvic RT	8
Tamoxifen	2

HISTOPATHOLOGIC TYPES

Endometrioid adenocarcinoma is the most common histopathological type of endometrial malignancy. Two distinct types were described by Bokhman in 1983, which have different incidence, clinical picture, molecular pattern and biological behavior.

Type 1 Endometrial Carcinoma:

Type 1 endometrial cancers comprise 80% of uterine carcinoma. These tumors are estrogen responsive and are seen in pre- or perimenopausal age group. They are of endometrioid histology and are usually well differentiated. Type 1 endometrial carcinomas are usually linked with chronic and unopposed estrogen exposure as seen in women with obesity, anovulatory cycles, infertility, and estrogen-secreting tumors.(3) These tumors usually have a favorable prognosis with >90% 5-year survival rate. (6) They are characterized by K-RAS over expression, PTEN, PiK3CA, K-RAS mutations, and microsatellite instability.

Type 2 Endometrial Carcinoma:

Type 2 endometrial cancers comprise the remaining 10-20% of cases. They are estrogen independent and usually arise in an atrophic endometrial background. They occur in women who are older, postmenopausal, multiparous, non-obese, smokers, and tamoxifen users. The histological types include grade 3 endometrioid adenocarcinoma, serous, clear cell, mucinous and squamous varieties. They are aggressive tumors and often show deep myometrial invasion and extrauterine spread.(3) Type 2 tumors have worse prognosis with a recurrence rate of 50% and overall survival (OS) of 35%.(6) They are associated with genetic alteration in E-cadherin, p53 and HER2/neu expression.

Molecular typing: Next generation sequencing has shown four molecular subtypes of endometrial cancer. The four types of endometrial cancer proposed by the Cancer Genome Atlas (TCGA) in the ProMisE study showed a new reproducible way of classification of endometrial cancer beyond the histological phenotypes, but it was not cost-effective. Testing has been made practical with immunohistochemistry (iHC) based surrogate typing of the endometrial cancer. Somatic copy number alteration (CAN), Somatic mutation number, MSI status could classify endometrial cancer into four subtypes. (7,8)

1. *POLE* mutations and their ultra-mutated phenotype associated with highly favourable clinical outcomes
2. Microsatellite instability (MSI)
3. Copy-number (CN low)
4. Copy-number high (CN high)

The iHC based classification has its own caveats. Clear cell carcinomas are not included in any of the subtypes, endometrioid grade 3 are spread over almost all four subtypes. Hence the main areas of decision making are yet to be addressed and more data needs to accrue on the results of the patients managed on the basis of molecular subtypes before the significance is fully recognized.

CLINICAL FEATURES

The usual presenting complaints are abnormal uterine bleeding in younger women and postmenopausal bleeding in older women. The risk of carcinoma endometrium in a woman with postmenopausal bleeding is approximately 10%. Occasionally asymptomatic women may be diagnosed during investigation for infertility. The previous menstrual history may reveal a history of early menarche or late menopause, or menstrual abnormalities during the perimenopausal transition.

Clinical presentation with advanced disease includes urinary or rectal bleeding, constipation, pain, lower extremity lymphedema, abdominal distention due to ascites, hepatomegaly, jaundice, cough and/or hemoptysis.

A past history of diabetes, hypertension, use of hormones or tamoxifen use may be present. Family history of uterus, colorectal, or genitourinary cancer should be inquired into, especially if endometrial cancer is diagnosed at age <50 years.

General physical examination is to be done, including assessment of lymph node enlargement (supraclavicular and inguinal lymph nodes) and breast examination; complete systemic and gynecological examination (per speculum, per vaginum and bimanual pelvic examination): assessment of uterine size and mobility, and involvement of cervix, parametrium, lateral pelvic wall, bladder or rectum.

DIAGNOSTIC WORKUP:

Transvaginal sonography (TVS): TVS is the first line imaging modality to triage these symptomatic patients, to assess uterine size, endometrial thickness, endo-myometrial interface, myometrial echotexture, and adnexa. Endometrial thickness greater than 4 mm in a post-menopausal woman, perimenopausal women with intermenstrual bleeding or prolonged heavy bleeding and premenopausal women with anovulatory cycles warrant further evaluation. In tamoxifen users, the endometrium may be thickened due to subendometrial cysts. Other causes of thickened endometrium include endometrial hyperplasia, polyp, and collection of fluid, blood or pus. (9)

- **Endometrial and endocervical sampling**: Endometrial biopsy with endometrial aspiration devices like Pipelle or a fine Karman's cannula (4 mm) can provide adequate tissue for histopathology. The accuracy of identifying cancer with an aspiration device is higher in post- than in pre-menopausal women, up to 91-99% (10). In all cases with suspicion of endometrial cancer, endocervical curettage is to be done prior to endometrial aspiration. Asymptomatic women with abnormal glandular cells (AGC) on cytology should also undergo colposcopy, endocervical and endometrial evaluation.

- **Dilatation and curettage**: Routine dilatation and curettage (D&C) is not required after an office endometrial sampling shows malignancy. (11)
- **Hysteroscopy**: Further evaluation with hysteroscopy is advised for women with negative or inadequate sampling and strong suspicion of malignancy. The indications for hysteroscopy and directed biopsy are as follows:
    - Abnormal findings on TVS with negative biopsy
    - Inaccessible uterine cavity
    - Women with high risk factors having persistent symptoms even after negative endometrial aspiration biopsy.

Hysteroscopy is useful for diagnosing endometrial polyps that can be removed simultaneously.

There has been a concern of transtubal migration of tumor cells after hysteroscopy that may be detected as malignant pelvic washings on cytology. Though definite peritoneal spillage does occur after hysteroscopy, the significance of its result is not clear.(12) Several studies have shown increased incidence of positive cytology (30% vs 12%) but there was no impact on outcome (disease specific survival or recurrence). (13,14) Kudela et al found that the percentage of positive peritoneal cytology after hysteroscopy does not differ from the percentage after D&C. (15)

FURTHER EVALUATION:

After confirming the diagnosis, further laboratory investigations and detailed imaging is done to assess the extent of disease, surgical risk, and to plan the appropriate surgical treatment.

Advanced imaging

Magnetic Resonance Imaging (MRI): In case hysteroscopy findings are inconclusive, these cases should also be further evaluated with MRI to rule out any abnormality. In proven cases of endometrial cancer, MRI of the abdomen and pelvis is recommended where available as it is the most accurate modality for assessing the size and extent of tumor, myometrial invasion, extension to cervix and adnexa, and lymph node involvement. Contrast enhanced (CE) MRI to exclude myometrial invasion and cervical extension is mandatory when planning fertility preserving options. (17)

Computed Tomography (CT): The accuracy of CT for assessing myometrial invasion is low with sensitivity and specificity being 40%-83% and 42%-75%, respectively. Poor soft tissue differentiation is the main limitation in accurate delineation of disease extent in the pelvis.(18,19) CT scan is mainly utilized for assessing extrapelvic disease and lymph node involvement. (19)

Positron emission tomography-computed tomography (PET/CT): This has little benefit in assessing primary tumor extension and therefore not indicated for preoperative staging purpose. PET/CT is highly sensitive (50-100%) and specific (87-100%) for assessing nodal status as well as distant metastases in selected cases with high-risk disease and those with recurrent disease.(20) PET/MR provides additional benefit of better soft tissue resolution along with accurate assessment of anatomical details.

Other preoperative work up

Complete blood count, renal and liver function tests, serum electrolytes, urinalysis, blood sugar and viral markers are recommended.

Serum Cancer Antigen 125 (CA 125) - The preoperative serum levels of CA 125 could be elevated in patients with extrauterine spread of the disease especially nodal involvement in high risk types and can be utilized for monitoring the clinical response after therapy in selected patients.(21)

Serum Human Epididymis Protein (HE4) - The serum level of HE4 is known to correlate with aggressive types of disease and is, therefore, useful in identifying high risk endometrial cancer cases. It is also useful for detecting early disease recurrence.(22)

Chest X-ray should be done to rule out lung metastasis. If the chest X-ray is suspicious of metastasis, CT chest without contrast is advised.

Genetic evaluation – Patients diagnosed with endometrial malignancy at a younger age (< 50 years) and those with known related genetic syndrome or family history of uterine and colorectal malignancies should undergo genetic evaluation.

Diagnostic dilemmas

1. When the differential diagnosis is between primary endocervical and endometrial adenocarcinoma, a panel consisting of vimentin and p16 may be utilized when clinical and histological evaluation is inconclusive. Vimentin negative and positive p16 expression favours endocervical primary; vimentin positive and negative p16 expression is suggestive of endometrial primary tumour.(23)
2. When the tumor involves multiple sites and there is a dilemma whether these are synchronous tumors or metastasis, immunohistochemistry is useful to derive the diagnosis

Histological Classification of Endometrial Carcinoma (2014 WHO)(22)

Endometrioid adenocarcinoma

Endometrioid adenocarcinoma variants

- With squamous differentiation
- Secretory variant
- Ciliated cell variant

Mucinous adenocarcinoma

Serous endometrioid intraepithelial carcinoma

Serous adenocarcinoma

Clear cell carcinoma

Mixed cell carcinoma

Undifferentiated carcinoma

- Monomorphic type
- De-differentiated type

Neuroendocrine tumors

- Neuroendocrine tumor (carcinoid tumor): Well-differentiated
- Small cell neuroendocrine tumor: Poorly differentiated
- Large cell neuroendocrine tumor: Poorly differentiated

Staging of Carcinoma Endometrium

Endometrial cancer should be surgically staged with histological assessment of grading and extent of disease. The FIGO 2009 staging for carcinoma endometrium is depicted in Table 2, along with the AJCC (American Joint Cancer Committee) Tumor-Node-Metastasis (TNM) classification.

Table 2: Staging of Endometrial carcinoma and carcinosarcoma (25)
Primary Tumor (T):

TNM STAGING	FIGO STAGING	SURGICO- PATHOLOGICAL FACTORS
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1b	IA	Tumor limited to endometrium or invades less than one half of myometrium
T1b	IB	Tumor invades one half or more than one half of myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond the uterus
T3a	IIIA	Tumor involves serosa and/ or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
	IIIC	Metastasis to pelvic and/ or paraaortic nodes
	IV	Tumor invades bladder and/ or bowel mucosa and / or distant metastases
T4	IVA	Tumor invades bladder mucosa and/ or bowel
	IVB	Distant metastases including intra-abdominal metastasis and inguinal lymph nodes

Lymph nodes (N):

TNM STAGING	FIGO STAGING	SURGICO- PATHOLOGICAL FACTORS
Nx		Regional lymph nodes cannot be assessed
N0		No evidence of regional lymph nodes
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes (Positive pelvic nodes)
N2	IIIC2	Regional lymph node metastasis to paraaortic nodes, with or without positive pelvic lymph nodes

Metastasis (M):

TNM STAGING	FIGO STAGING	SURGICO- PATHOLOGICAL FACTORS
M0		No distant metastasis
M1	IV B	No distant metastasis

Cases should also be stratified based on degree of differentiation (3)

- G1: 5% or less of a non-squamous or non-morular solid growth pattern
- G2: 6%-50% of a non-squamous or non-morular solid growth pattern
- G3: more than 50% of a non-squamous or non-morular solid growth pattern

Pathological grading : Important considerations

- Notable nuclear atypia that is not appropriate for the architectural grade of tumor, raises the grade by 1.
- Nuclear grading takes precedence in serous adenocarcinomas, clear cell adenocarcinomas and squamous cell carcinomas.
- Nuclear grading of the squamous component should be used to grade adenocarcinomas with squamous differentiation.
- Endometrial carcinoma is surgically staged hence the fractional D&C is not needed or change the stage.
- Some of the patients although small in number may be treated by primary radiotherapy, FIGO 1971 staging should be used to stage the disease clinically.
- Peritoneal wash cytology will not change the staging, but documentation of the result is needed.

PROGNOSTIC FACTORS: The following prognostic variables have been identified (3,26)

FiGO stage

Age

Histological type Histological grade Nuclear grade

Myometrial invasion

Cervical stromal invasion

Lymphovascular space invasion

Tumor size >2 cm

Positive peritoneal cytology

Hormone receptor status

DNA ploidy and other biological markers

Type of primary therapy - surgery or radiation

However, nuclear grade, hormonal status, DNA ploidy, peritoneal wash cytology are not independent prognostic factors.

TREATMENT

Surgical treatment remains the mainstay of therapy for both early as well as advanced disease. The standard surgical management for uterine cancer is staging laparotomy with extrafascial total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node assessment. For younger women who are desirous of future child bearing, fertility preserving management can be advised after thorough evaluation and detailed counseling.

The route of surgery can be open or minimally invasive (laparoscopic or robotic) (22,23,24). Several studies have proved the feasibility, safety, and efficacy of the minimally invasive approach with comparable survival rates. However, during laparoscopic surgery, morcellation or tumor fragmentation is not permissible.

Complete surgical staging involving examination of the bowel, peritoneum, liver and splenic surface should be done. Biopsy(s) should be taken from suspicious areas.

Though peritoneal cytology does not change staging, both FiGO and TNM systems recommended that peritoneal washings should be collected for cytology.

Omental biopsy or omentectomy is indicated in patients with non-endometrioid histology, G3 endometrioid tumor and carcinosarcomas.

Lymphadenectomy in Endometrial carcinoma - *Evidence Review*:

The extent of lymphadenectomy in endometrial cancer has been a matter of considerable debate and has been extensively investigated in several studies. The baseline rate of nodal disease in endometrial cancer is approximately 9%. (3) The extent of lymphadenectomy is important to decide the need to administer adjuvant therapy but may also impart some therapeutic benefit, though this is still debated. The overall surgical complication rate of lymphadenectomy varies from 6% to 20%, depending mainly on the surgical expertise. In order to determine the patients with a lower risk of nodal metastasis in whom lymphadenectomy can be safely omitted, several risk stratification systems have been developed.

1. In 2000, a model was suggested by Mayo Clinic that could help in identifying cases with low risk of nodal spread and high disease-free survival (DFS) based on frozen section evaluation of uterus. They found that women with Grade 1 to 2 endometrioid tumors, myometrial invasion 50% and tumor size <2 cm were at lower risk of lymph node involvement. Approximately 40% patients of carcinoma endometrium met the low-risk criteria and, if followed, the risk of missing the nodal disease was only 0.8%. (31)
2. The Korean GOG group suggested another criterion. Women with <50% myometrial invasion, absence of enlarged lymph nodes, absence of extrauterine disease on MRI and serum CA 125 <35 IU/mL were at low risk of nodal disease. The risk of nodal disease was 1.7% in thus identified low risk women with carcinoma endometrium. (32)

Intraoperative assessment may be inaccurate and disease may be upstaged in 28% cases. Only 10% women with lymph node metastasis will have enlarged nodes and may be missed on direct palpation through the overlying peritoneum. Therefore, systematic lymphadenectomy including external iliac, hypogastric, obturator, common iliac, and para aortic nodes is considered by several investigators. The incidence of paraaortic lymph node positivity in cases where pelvic lymph nodes are positive is 50% and approximately 2% if pelvic nodes are negative (in well-differentiated cases). In stage III, isolated paraaortic nodes may be involved with negative pelvic nodes in 7-21% cases and with positive pelvic nodes in 30-40% cases. (31) The SEPAL trial (2010) compared the practice of pelvic lymphadenectomy, with or without paraaortic lymphadenectomy. Patients were classified into low versus intermediate to high-risk groups and outcomes were compared based on lymphadenectomy. Type of lymphadenectomy was identified as independently associated with improved survival. Therefore, it was concluded that if lymphadenectomy was to be conducted, both pelvic and paraaortic should be considered. (34) According to the Mayo group, when paraaortic nodes were positive, 77% of cases had involvement above the inferior mesenteric artery. (35)

In women having endometrial cancer with high risk features, e.g., myometrial invasion >50% or reaching up to serosa, extrauterine disease, grade 3 disease and histology of serous carcinoma, clear cell carcinoma or carcinosarcoma, a complete systematic lymphadenectomy up to the level of renal vessels is recommended. (36) The accurate extent and grade of disease is possible only after final histopathological assessment.

The role of lymphadenectomy in advanced endometrial cancer in improving of progression free survival and overall survival is a controversial issue. The decision regarding lymphadenectomy should be taken judiciously when operating on elderly, frail patients, or patients with multiple comorbidities.

Treatment

The stage-wise treatment for uterine cancer is as follows:

FIGO STAGE I

Surgical treatment

- For stage 1A disease, total extrafascial hysterectomy with bilateral salpingo-oophorectomy with or without lymphadenectomy is recommended. Lymph node dissection can be omitted in patients with well-differentiated non-invasive tumors with tumour size less than 2 cm.(34,36))
- A complete surgical staging comprising of total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic and paraaortic lymph node dissection upto the level of left renal veins is advisable for patients with intermediate and high-risk disease. (Stage 1A G3, 1B)
- In tumors with non-endometrioid histology complete surgical staging including paraaortic lymph node dissection and omentectomy is recommended.

Considering the high morbidity of extensive lymphadenectomy, the role of sentinel lymph node (SLN) sampling has been investigated recently with encouraging results.(37,38) Sentinel lymph node mapping can be done with indigo cyanine green (iCG) dye, methylene blue dye, isosulphan blue, patent blue and Technetium 99 radiocolloid. The near infrared technique with ICG has been found to be more sensitive and specific in detecting sentinel nodes. The FiRES trial evaluated the diagnostic accuracy of sentinel lymph node biopsy using iCG dye during robotic staging for endometrial cancer and found the sensitivity and NPV as high as 97.2% and 99.6% respectively. (38) In high-risk histologic variants, SLN mapping is not routinely recommended.(39)

In resource-poor settings with less than adequate infrastructure and technical issues, the lymph node dissection strategy needs to be individualized. When the tumour grade and myometrial invasion are not likely to be ascertained fairly accurately, pelvic node dissection should be done so that unnecessary pelvic radiotherapy, which would increase both the cost and the morbidity, is not administered.

Pelvic and paraaortic lymph node dissection should be offered in the following cases:

- All type I tumours with deep myometrial invasion and grade 2/3.
- All type ii tumours.

SLN protocol

The dye is injected into the cervix at 3 and 9 o'clock positions, both superficial (1–3 mm) as well as deep (1–2 cm). The dye passes along the uterine lymphatic trunks into the parametria leading to pelvic and paraaortic sentinel nodes. Lymphatics from the uterine body pass over the obliterated umbilical artery goes into pelvic SLN, most common being medial to the external iliac, in the superior part of the obturator or ventral to the hypogastric vessels. Sometimes, the lymphatic trunks move cranially along the mesoureter and go into the common iliac presacral region. SLN should be evaluated pathologically by ultra-staging to detect low volume disease. in situations where mapping fails or grossly enlarged lymph nodes are found intraoperatively, a side-specific nodal dissection is recommended regardless of mapping. (39)

SLN mapping should be undertaken for surgical staging of uterine-confined disease with no obvious extrauterine spread on exploration and where imaging reveals no evidence of distant metastasis or enlarged nodes.

Risk Stratification

The following risk factors may predict the high risk of disease recurrence in women with early stage endometrial cancer: non endometrioid or high grade endometrioid tumours, positive lymph nodes, deeper myometrial invasion, LVSI, and tumor diameter >2 cm. Based on the presence of these factors, stage 1 can be further sub-divided into risk categories (Table 3). This stratification is useful to plan adjuvant therapy.(40)

Table 3: Risk stratification of endometrial carcinoma to guide adjuvant therapy	
Low risk	Stage 1A (G1,2), endometrioid type No LVSI
Intermediate risk	Stage 1B (G1,2), endometrioid type No LVSI
High Intermediate risk	Stage IA G3 ±LVSI Stage IG1-2+ LVSI ±MI
High risk	Stage 1B (G3), endometrioid type ± LVSI Stage II, Stage III with no residual disease All stages non-endometrioid type or carcinosarcoma
Advanced	Stage III with presence of residual disease and stage IV A
Metastatic	Stage IV B

Recommendation for adjuvant management based on risk stratification:

Radiotherapy plays an important role in the management of endometrial cancer.

Stage I A G1–G2: Observation

The risk of pelvic node positivity is as low as <3% and the 5-year PFS is 95-98%. (41)

IA G3: Vaginal brachytherapy or observation is also an option.

I B G1,G2: Observation or vaginal brachytherapy if other high risk features are present.

IB G3: Node Negative: External beam radiation therapy (EBRT) to reduce locoregional recurrence

IB G3: No nodal staging: EBRT + chemotherapy.

FIGO STAGE II

Surgical treatment

Type A (Type I) radical hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic ± para-aortic lymphadenectomy is the standard procedure.

Parametrial spread cannot be predicted by cervical involvement alone but may be predicted by various lymphovascular space invasion (LVSI)-related histopathological factors. Radical hysterectomy is indicated if parametrium is involved in order to obtain free margins (40).

When surgery is not feasible due to medical contraindications (in ~5%–10% of patients), or because of non-resectable disease, external beam radiation therapy with or without intracavitary brachytherapy can be considered.

Adjuvant treatment

Pelvic RT is used as adjuvant therapy if stromal invasion is diagnosed afterType i hysterectomy.

Chemotherapy may be administered in addition to EBRT and/or vaginal brachytherapy in patients with G3 disease.

In patients who have had radical hysterectomy with negative nodes and free margins, pelvic radiotherapy may be avoided.

Medically inoperable Stage I / II

Intracavitary application with or without pelvic RT is recommended with intracavitary application, 70-75 Gy to point A.

When combined with pelvic RT 45-50 Gy and intracavitary 30-35 Gy, with total dose to point A being 80-85 Gy.

FIGO STAGE III

Surgical treatment- Optimal cytoreduction is recommended in patients with resectable disease and good performance status.

Stage III A

In selected patients with ovarian involvement and with intact ovarian capsule, possibility of concurrent synchronous ovarian malignancy must be kept in mind and such patients should be advised chemotherapy with EBRT.

Stage III B

A combination of EBRT and chemotherapy is advised. However, women vaginal extension may be advised for intracavitary / interstitial radiation that is individualized according to the disease extent.

Stage III C

If positive nodes are detected concurrent chemo radiotherapy consisting of platinum and taxane based chemotherapy followed by EBRT during the last cycle of chemotherapy is recommended. if paraaortic nodes are involved, extended field EBRT is preferred.

FIGO STAGE IV

Systemic therapy ± pelvic radiotherapy

If positive nodes are detected, radiotherapy can be considered.

The 5-year survival for patients with stage III-IV disease is 30%–40% and 60%–70% for paraaortic and pelvic nodal involvement, respectively.

For locally advanced disease extending into cervix or parametria the surgical staging with radical hysterectomy followed by adjuvant therapy is the treatment of choice. Studies have shown that neo-adjuvant therapy consisting of EBRT (45 Gy in 25#) and image guided HDR (5.5 Gy 3-4 #) + chemotherapy followed by less extensive, Type A hysterectomy is also a feasible less morbid treatment in such cases.(42)

High Risk Serous and Clear Cell Carcinoma Uterus: Chemotherapy is recommended along with radiation therapy except for stage IA, LVSI negative disease, when patient may be given only brachytherapy without chemotherapy.

High risk carcinosarcoma and undifferentiated tumors: Consider chemotherapy along with EBRT.

Supporting Evidence Review:

Administration of adjuvant therapy is usually decided on the basis of presence of risk factors. Use of adjuvant RT does not improve survival for stage 1 low risk and low intermediate disease, although it is associated with slight improvement in locoregional disease control but there is no difference in distant metastasis and higher treatment related morbidity was seen in women who received adjuvant radiation therapy. Therefore, stage 1 low risk and low intermediate disease may be considered for observation only. The landmark trials ASTEC/EN-5, PORTEC-1, Key's trial (GOG 99), showed that addition of radiation therapy after surgery did not improve overall survival of patients, although the risk of pelvic recurrence was lower in this group.(43,44,45)

GOG 99:

In this trial, 392 women with stage 1B-IIB after surgery (TAH with BSO with pelvic or paraaortic lymph node sampling were randomized to either observation (n=202) or radiation treatment (n=190). The median follow-up was 68 months with no difference in 4-year survival (86% vs 92% respectively, p=0.55). Recurrence was significantly lower in the irradiation arm (3% vs 12%, p=0.007). They defined the high intermediate risk (HIR) group as a combination of age and risk factors including grade 2/3, myometrial invasion>50% and LVSI+. This HIR group was benefitted by radiation therapy by reduction in the incidence of cumulative recurrence rates. (27% with only observation vs 13% after EBRT).

PORTEC 1 trial:

In this trial, 714 women with stage 1B grade 2,3 and IC grade 1,2 were randomized after total hysterectomy and salpingo oophorectomy without lymph node evaluation to either an observation arm (n=360) or EBRT arm(n=354). After a median follow-up of 52 months the 5-year locoregional recurrence rates were high in the observation cohort (14% vs 4%, p=0.001). However, this advantage did not translate into survival benefit to patients (5year survival rates were 81% vs 85%, p=0.37), as most of the recurrences were vaginal and amenable to curative treatment. They defined HiR group according to the presence of two out of three defined factors including age >60 years, myometrial invasion >50% and G3 disease. The recurrence rates in this group reduced from 23% with observation to 5% after EBRT.

These studies did not include the most controversial group of uterine confined disease, and deep myometrial invasion with grade 3 tumor patients, hence the role of EBRT in this group of patients is controversial.

The high intermediate risk group as classified by PORTEC 1 and GOG 99 will benefit from pelvic RT. As per GOG 99, high risk factors other than age are myometrial invasion, grade and LVSI. Patients with age less than 50 years and all three risk factors, age between 50-70 years with two risk factors and age more than 70 years with at least one risk factor are considered high intermediate risk groups. As per PORTEC-1 study, those who have two out of three risk factors (>60 years, LVSI, grade) are considered high intermediate risk groups.

PORTEC-2 compared compared the effect of vaginal brachytherapy in comparison with pelvic RT in women with high intermediate risk group and showed no difference in outcome. (46)

In this trial, 427 high intermediate risk patients from PORTEC 1were randomized to either adjuvant EBRT or vaginal brachytherapy (VBT) with an aim to establish optimum effective modality with fewer adverse effects and better quality of life (QOL). After a median follow-up of 45 months the 5-year loco regional recurrence (EBRT vs VBT 2.1% vs 5.1%; p=0.17) was comparable between the two groups, but pelvic recurrence rates were more in the VBT group (EBRT vs VBT 0.5% vs 3.8%; p=0.02). There was

no significant difference in OS and DFS but the quality of life (QOL) and toxicity profile were better in the vaginal brachytherapy arm.

The addition of adjuvant cisplatin combination chemotherapy compared to pelvic RT was compared by Susuma et al. and they observed a higher PFS in women with intermediate risk disease who received adjuvant chemotherapy but no difference in low to intermediate risk well differentiated disease group. (47) Aalder's randomised trial found that RT does not improve overall recurrence free survival but improves local control. After a mean follow up of 20.5 years also there was no statistical difference in overall survival but the risk of secondary cancers increased in patients younger than 60 years who received pelvic RT.(48)

PORTEC-3 trial investigated the role of adjuvant chemotherapy(concurrent or sequential) in women with endometrial cancer. In this trial, 686 women with high-risk stage IB-III endometrial carcinoma were randomized to either a group which received concurrent chemoradiotherapy followed by adjuvant chemotherapy or another group which received pelvic radiotherapy alone. There was no difference in OS but the 5-year failure free survival was higher in the chemoradiation arm. Patients with stage iii disease showed clinically relevant (11%) improvement in failure free survival than those with stages I–II with chemo-radiotherapy. (49)

In the GOG-122 trial, conducted with 396 cases of stage III and IV disease after optimal cyto reduction. The chemotherapy arm (doxorubicin–cisplatin) had a better PFS (50% versus 38%; P = 0.07) and OS (55% versus 42%; P = 0.004) than whole abdominal radiation arm.

Hence in conclusion, in comprehensively staged patients with intermediate risk one may either observe (low intermediate risk) or may add vaginal brachytherapy to reduce the risk of vault recurrence. Conversely, if comprehensive surgical staging has not been done then patients with LVSI positivity should be recommended in addition to undergo EBRT to reduce the risk of pelvic recurrence. Grade 3 LVSI negative cases, who had not undergone comprehensive surgical staging should be advised for adjuvant vault brachytherapy. Patients with stage II disease should receive adjuvant EBRT. In women with high risk stage III endometrial cancer and those with no residual disease, radiation therapy in combination with chemotherapy is advisable, in stage IIIC2 the field of radiation should be extended to cover the para aortic lymph nodes. Women with high risk non endometrioid cancers are advised chemotherapy in addtion to EBRT and vaginal brachytherapy. In stage IV disease, role of radiation therapy is mainly palliative.

LACE TRIAL

Randomized equivalence clinical trial by Janda et al. was designed to determine if outcomes following total laparoscopic hysterectomy (TLH) were the same for disease-free survival as total abdominal hysterectomy (TAH) for patients with treatment-naïve endometrial cancer called Laparoscopic Approach to Cancer of the Endometrium (LACE) trial. Total number of 760 patients with stage I treatment-naïve endometrial cancer were randomized to either receive TLH (407 women) or TAH (353 women). The primary outcome was disease-free survival, defined as the time between surgery and first recurrence (disease progression or development of a new primary cancer or death). At 4.5 years out, 81.3% of the TAH group and 81.6% of the TLH group were disease-free respectively. With a difference of only 0.3%, the two approaches were considered equivalent. There were no statistically significant differences in recurrence of endometrial cancer between the groups nor overall survival. While 2 patients in the TLH group had metastases in the port site, 2 women in the TAH group had metastases in the surgical site. Overall survival was 92.4% in the TAH group and 92.0% in the TLH group. The authors concluded that use of TLH for women with stage I endometrial cancer is supported by the data in this study. The results from the LACE study

likewise showed no difference in intraoperative complications, but shorter hospital stays (2 vs. 5 days), and fewer postoperative adverse events (13% vs. 19%) in addition to overall improvement in quality of life in the TLH group at 6 weeks postoperative. This study also showed longer operating time compared to open surgeries. The study did not include women with large uterus (more than 10 weeks size) and suggest these patients should be 'approached with greater caution'. The surgeons in the study performing TLH were highly trained group and reflect a particular skill set that is not generalizable to all surgeons.(50)

RECURRENT ENDOMETRIAL CANCER

Widely metastatic recurrence carries poor prognosis. Treatment depends on the site and extent of recurrent disease and the previous treatment modality.

Treatment for Local Recurrence

Distant metastasis should be ruled out by imaging with PET/CT or CECT. Treatment should be individualized based on the following factors (51-55):

- Whether recurred in previously irradiated area
- Whether complete resection is possible
- Disease free interval
- Grade of disease

After optimal therapy, a 5-year overall survival rate of 31%–53% can be achieved. (52) However, a high incidence of adverse effects is reported, including rate of grade 4 complications as high as 9%. Other commonly reported adverse effects include vaginal stenosis, proctitis, chronic diarrhea and cystitis.

Surgery

In cases where complete surgical resection appears possible, surgical exploration and resection with negative free margins and intraoperative radiotherapy if available.

Radiotherapy

Isolated vaginal recurrence: Surgical excision and pelvic radiation + brachytherapy.

Inoperable pelvic recurrence: Consider palliative pelvic radiation.

Chemotherapy

If the patient has been previously irradiated and found inoperable, palliative chemotherapy is to be considered. Platinum and taxane based chemotherapy regimens are used.

Treatment for nodal recurrence:

If not irradiated previously, external beam radiotherapy + chemotherapy are recommended.

Special situations

Endometrial Cancer diagnosed after hysterectomy:

The situation is best avoided by proper preoperative evaluation of women with abnormal uterine bleeding prior to surgical management. Once encountered this situation poses a dilemma especially when diagnosed after vaginal hysterectomy with retained ovaries. The following investigations are recommended in this situation::

i. PET scan or CT scan of the abdomen, pelvis and chest

ii. Serum CA-125 assay

If serum CA-125 is elevated or if the PET/CT scan reveals lymphadenopathy or other evidence of metastatic disease, staging laparotomy and completion surgery should be done.

Patients with a grade 1 or 2 lesion with 50% myometrial invasion and no LVSI generally require no further therapy, although laparoscopic oophorectomy is advisable to prevent risk of ovarian cancer, particularly necessary in women with a familial cancer syndrome.

If high risk factors are identified, complete surgical staging with removal of both the adenexa is recommended. Alternately, external beam radiation therapy to the pelvis may be used.

TREATMENT FOR METASTATIC DISEASE

Palliative chemotherapy

Palliative chemotherapy is recommended if previously not exposed to chemotherapy or there has been a long disease-free interval after previous chemotherapy. Chemotherapy regimens based on single cytotoxic agents have shown response rate as high as 40% in chemotherapy-naïve patients. (39,55)

Platinum based compounds, anthracyclines and taxane are the commonly used agents. For chemoresistant disease recurring after first line chemotherapy, paclitaxel-based therapy has shown >20% response rates (3,10,39) and is recommended in this setting.

Response rate with chemotherapy is only 20% in women who present with systemic metastasis and progression-free survival of 3–6 months, and overall survival of less than 12 months is observed in this setting. (53)

Hormonal therapy:

- For endometrioid histology only
- Several progestational agents are used with response rates as good as 25%
- Tamoxifen and aromatase inhibitors can also be used.
- Characteristics including well-differentiated tumours, long disease-free interval and the location and extent of extrapelvic (particularly pulmonary) metastases may predict better response to hormonal therapy.

Palliative radiation:

Palliative radiation can be considered for bone metastasis and for control of vaginal bleeding.

PRINCIPLES OF RADIOTHERAPY IN THE MANAGEMENT OF UTERINE CANCER

Pelvic Radiotherapy

Pelvic radiation should include gross disease (if present), parametria, vagina (depending on extent of involvement), paravaginal tissues, iliac nodes (internal, external, lower common iliac), presacral nodes (if cervix is infiltrated).

Extended field radiotherapy should cover the entire pelvic and common iliac region along with the paraaortic lymph nodes up to the level of renal vessels.

External beam radiotherapy dose for microscopic disease 45-50 Gy, preferably with CT based planning and conformal therapy.

Brachytherapy

Brachytherapy (BT) should be administered 4-6 weeks from the time of surgery / when the vaginal cuff has healed well but not beyond 12 weeks. The treatment volume should include the vault and upper 3-4 cm of the vagina.

For vault BT alone : High Dose Rate brachytherapy (HDR) 7Gy x 3 fractions, calculated at 0.5 cm depth from vaginal surface or 6Gy x 5 fractions, calculated at vaginal mucosal surface.

For vault BT boost after EBRT, HDR 6-7 Gy x 2 fractions prescribed at 0.5 cm from vaginal mucosal surface.

Palliative Radiation

Palliative radiation should depend upon patient's performance status and needs to be tailored as per the need / extent of disease.

Medically inoperable Stage I / II

Intracavitary application with or without pelvic RT is recommended.

Intracavitary application 70-75 Gy point A, when pelvic RT is combined 45-50 Gy and intracavitary 30-35 Gy.

Whole body irradiation was compared with systemic therapy and was found to have more side effects than systemic therapy, hence it is not preferred. (54)

Role of systemic therapy

Adjuvant systemic therapy plays an important role in extrauterine disease. Paclitaxel with carboplatin has been used in systemic therapy. in patients with high grade, deeply invading tumors of the uterine endometrium, systemic therapy is used to prevent distant metastasis. (57) Progression free survival (PFS) is shown to improve with adjuvant sequential chemotherapy/RT.(58)

Hormonal Therapy

In patients with endometrioid histology, hormonal therapy has been tried. Patients with recurrent or metastatic endometrioid tumors who have low-grade tumors with an indolent course should be offered hormonal treatment. Several hormonal agents have been investigated including megestrol acetate alternating with tamoxifen, progestational agents alone, aromatase inhibitors, tamoxifen alone or fulvestrant, with variable response rates as seen in Table 4.(59-63) Response depends upon ER/PR receptor positivity, long disease free interval, location and extent of metastasis. Tamoxifen, acting through ER, would increase expression of PR and thus likely to enhance the sensitivity to medroxyprogesterone acetate (MPA) or megestrol acetate (MA). It was found that 11-56% low grade tumors responded to progestins especially the PR-positive tumors. The risk of grade 3 or 4 adverse effects was low being less than 5%. (64)

Table 4: Studies showing impact of hormonal therapy in treatment of recurrent and metastatic endometrial carcinoma				
Trial	**Treatment given**	**PFS (months)**	**OS (months)**	**Response rate**
GOG 81(59)	Group 1: MPA 1000 mg daily (n=154) Group 2: MPA 200 mg daily (n=145)	2.5	7	15%
GOG 12(60)	MA 800 mg daily	3.2	11	25%
GOG 119(61)	MPA 100 mg BD on alternating weeks +Tamoxifen 20 mg daily continuous	33	3	13%
GOG 168(62)	Anastrozole 1 mg/day	1	6	9%
Ma et al (63)	Letrozole 2.5 mg daily	4	9	9.4%

PFS=Progression-free survival: OS=Overall survival; MA=Megestrol acetate: MPA=Medroxyprogesterone acetate

Progestin therapy is recommended for the following cases of carcinoma endometrium:

1. Women with receptor-positive disease who have recurred after chemotherapy;
2. Women with well differentiated (low-grade) hormone receptor positive endometrioid adenocarcinomas who are not suitable for chemotherapy.

Menopausal hormone therapy (MHT) in survivors:

Endometrial cancer is considered hormonal dependent hence the use of MHT in patients who have undergone oophorectomy was previously considered harmful. The use of estrogen replacement therapy in patients with profound hypoestrogenic symptoms may be considered after counseling the patient, especially in women who had early stage low-grade endometrioid disease. In advanced stage and high-risk cases use of selective estrogen receptor modulators (SERMs) and non-hormonal options should be considered as first line.(39)

Fertility preserving therapy:

Patients who want to preserve childbearing function may be considered for fertility preserving options after thorough evaluation and explaining the deviation from standard therapy. Preoperative counseling with reproductive medicine and genetics specialists is desirable. Young women with stage IA grade 1 disease without myometrial or cervical involvement can be considered for medical management with progestational agents. They should be carefully evaluated for other risk factors like breast cancer, deep vein thrombosis, myocardial infarction, stroke, pulmonary embolism, and smoking. Various drugs including medroxyprogesterone acetate (400–600 mg/day), megestrol acetate (160–320 mg/day), and levonorgestrel releasing intrauterine systems, with or without GnRH analogues, have been tried with variable success rates as seen in Table 5. Patients need to be on follow-up 3-monthly with endometrial biopsy with or without hysteroscopy.(65,66) Treatment should be discontinued if disease persists for more than 6-12 months, or if there is progression of disease (proven by histology) in patients with stable disease after 6 months of treatment. Imaging should be repeated after 6 months to rule out myometrial involvement or extrauterine or ovarian involvement. Definitive treatment should be considered when child bearing is complete, if there is progression of disease or if there is no reversal of disease after 12 months of treatment. Patients on high dose progesterone should also be monitored for the side effects of progesterone. (69)

Table 5: Response to medical therapy for fertility preserving management of carcinoma endometrium		
Author, Year	**Drug used/Intervention**	**Response rate**
Qin et al, 2016 (65)	MPA/MA	83%
Simpson et al, 2014(66)	MPA/MA	55%
Gallos et al, 2012(67)	MPA/MA Endometrial resection Others	76%
Ramirez et al, 2004(68)	MPA/MA	75%

MA=Megestrol acetate: MPA=Medroxyprogesterone acetate

FOLLOW UP

Follow-up is recommended every 3-4 months up to a period of two years, then 6-monthly up to 5 years, and annually thereafter.

At each visit the patient is asked in detail for symptoms of potential recurrence, and complete systemic examination and pelvic examination is performed. The use of imaging and serum CA-125 is advised according to symptoms.(3,39) Vault cytology has limited significance and is reserved for patients with no prior radiation therapy. Mammography can be done as per standard guidelines for breast cancer screening. For patients at risk of colon cancer (Lynch syndrome), colonoscopy should be requested every one to two years, starting at 20-25 years or 10 years before the age of the youngest case detected in the immediate family (American Cancer Society recommendation for colorectal cancer early detection).

Survival: Prognosis for carcinoma endometrium is generally favourable. The stage of the disease is the most significant prognostic factor with respect to stage wise survival (Table 6). (70)

Table 6: Stage wise survival rates for carcinoma endometrium (70)	
STAGE	**SURVIVAL**
I A	88%
I B	75%
II	69%
IIIA	58%
III B	50%
III C	47%
IV A	17%
IV B	15%

SCREENING:

Currently routine screening for endometrial cancer for asymptomatic populations with average risk or with the above-mentioned risk factors including tamoxifen intake has not proven beneficial and is not recommended. (71) It is recommended that women at the onset of menopause should be counselled and explained about the risks and symptoms of endometrial cancer, i.e., unexpected bleeding or spotting, and should be encouraged to report immediately if these symptoms occur.

Women who are taking tamoxifen therapy for prevention of recurrence or development of contralateral breast cancer have a higher risk of developing uterine cancer. However, routine screening with ultrasound or endometrial biopsy is not recommended. These women should be advised to report if there is any abnormal vaginal discharge or bleeding per vaginum. (72)

Women with family history of Lynch syndrome are at high risk of developing carcinoma endometrium and should be advised to undertake regular screening. In these women screening should start from 35 years of age, or 5-10 years before the diagnosis of any Lynch associated cancer in the youngest family member and consist of annual endometrial sampling.

Clinical algorithms for management of endometrial carcinoma are available at https://play.google.com/store/apps/details?id=app.com.figostaging&hl=en_iN

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CHAPTER

2 UTERINE SARCOMA

Introduction

Uterine sarcoma is an uncommon gynecological malignancy accounting for <1% of all gynecological cancers and 3-7% of all uterine cancer variants.(1) Uterine sarcomas are usually diagnosed after surgery done for benign conditions. The incidence of uterine leiomyosarcomas (uLMS) being found in women operated on for presumed uterine fibroids is about 0.5%.(2) There is a lack of consensus in their management options because of their rare occurrence, unknown etiology, variable prognosis, associated genetic aberrations and limited therapeutic options. Their biological behavior is largely dependent on tumor type and histological grade. (1, 3)

EPIDEMIOLOGY AND RISK FACTORS

The underlying etiology for uterine sarcoma is not clear and most of the cases are sporadic in nature. Recently genetic factors and specific chromosomal translocations have been implicated (4) however few risk factors are identified (Table 1).(1,2,3)

Table 1: Risk factors for Uterine Sarcoma

S. No.	Risk Factor
1	Age 50 years and above
2	Nulliparity
3	Obesity, Diabetes, Hypertension
4	Past history of radiation exposure
5	History of tamoxifen intake
6	Black race
7	Unopposed estrogen therapy

CLASSIFICATION AND PATHOLOGY

Uterine sarcomas are mesenchymal tumors and based on the tissue of origin, can be classified into two types according to WHO 2003 classification system (1,3).

Non-epithelial: Uterine leiomyosarcoma (uLMS) - epithelioid and myxoid variants: 30%; endometrial stromal sarcoma (ESS): 15%, undifferentiated uterine sarcoma (UUS): 5%.

Mixed non-epithelial/ epithelial malignancy: carcinosarcoma: 50%: adenosarcoma: 5%.

Subsequently carcinosarcoma was considered as a de-differentiated or metaplastic form of endometrial carcinoma in which the mesenchymal part retains epithelial features. it has a more aggressive behavior with a different pattern of spread. In the WHO 2014 classification they were kept as a separate section of mixed epithelial and mesenchymal tumors. (Table 2) After exclusion of uterine carcinosarcoma the distribution of various histological subtypes is as follows:

uLMS 63%, ESS 21%, UUS 6%, adenosarcoma 6%, other types (rhabdomyosarcoma, PEComa (perivascular epithelioid cell neoplasm) 5%.(3)

Two systems are used for staging uterine sarcomas, including the 2014 Federation International Gynecology and Obstetrics (FIGO) and 2010 American Joint Committee on Cancer tumor, lymph node, and metastases system (Table 2). The FIGO staging is more frequently applied in clinical practice. For grading purpose the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system or the Broder's system is used. This incorporates tumor differentiation, mitotic count, and tumor necrosis and stratified as following (4).

Grade 1: mild cytologic atypia
Grade 2: more nuclear irregularity
Grade 3: between Grades 2 and 4
Grade 4: presence of bizarre cells

While evaluating cytological atypia, medium power magnification is used and a comparison of cytological features of tumor should be done with surrounding myometrium to look for background nuclear atypia and not a bizarre type atypia. Apart from this, presence of more than one of the features, which includes high nucleo-cytoplasmic (N/C) ratio, hyperchromatic nuclei, irregular nuclear membrane, prominent nucleoli or more than one nucleoli should be identified.

STAGING:

Tumor stage is the most significant prognostic factor. The new staging system has two sub divisions, one for the staging of LMS and ESS and the other one for staging of adenosarcoma. Carcinosarcomas are staged similar to endometrial carcinoma (Table 2).

Table 2: FIGO and AJCC staging systems(6)

FIGO Stage (2014)	DEFINITION	American Joint Committee On Cancer TNM system 2010
Stage I	Tumor limited to uterus	
I A	< 5 cm	T1aN0M0
I B	> 5 cm	T1bN0M0
Stage II	Tumor extends beyond the uterus but limited within the pelvic cavity	
II A	Adnexal involvement	T2aN0M0
II B	Involvement of other pelvic tissues	T2bN0M0
Stage III	Tumor invades abdominal tissues	
III A	1 site	T3aN0M0
III B	>1 site	T3bN0M0
III C	Pelvic and/or para-aortic lymph node metastases	T3bN1M0
Stage IV		
IV A	Tumor invades bladder and/or rectum	T4NxM0
IV B	Distant metastasis	T4NxM1

FIGO- International Federation of Gynecology and Obstetrics; TNM- Tumor, lymph node, and metastases staging system.

Staging of Adenosarcoma

FIGO Stage (2014)		Definition
Stage I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	1 site
	IIIB	>1 site
	IIIC	Pelvic and/or para-aortic lymph node metastases
IV		
	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

HISTORY AND CLINICAL PRESENTATION:

Overall the median age of clinical presentation is 47-56 years of age (range 22-89 years). The median age of presentation is 50.7, 56.6, 58.8 and 65.7 years for ESS, LMS, UUS and adenosarcoma, respectively. (3) The clinical features are nonspecific and largely depend on the histological subtype.(7) Symptoms include abdominal pain (13%), enlarged abdominal circumference (17%), abnormal uterine bleeding (50%) and rapid increase in uterine size in peri- or post-menopausal women despite lower levels of estrogens. (2,3) Most of the time, the condition is diagnosed postoperatively as an incidental finding. (7) However, one study by Parker et al found the incidence of uterine sarcoma to be as low as 0.23% in women operated for benign uterine fibroids and they also found that the criteria for rapid growth did not substantiate the risk of sarcoma as the incidence of sarcoma was similar in fibroids operated after rapid growth and controls (0.27% vs 0.23%). All uterine sarcomas disseminate through the hematogenous route, most often to the lungs and less commonly to the liver, bone and brain. (3).

Table 3: Comparison of various types of uterine sarcoma

	ESS	LMS	UUS	Adenosarcoma	Others
Distribution	21%	63%	6%	6%	5%
Median age (3)	50.7	56.6	58.8	65.7	
5 year survival for localized disease (8)	84%	51%	57%	76%	43%

ESS=Endometrial stromal sarcoma; LMS=Leiomyosarcoma; UUS=Undifferentiated uterine sarcoma

DIAGNOSIS:

Initial work up

Diagnosis is based on initial clinical assessment, imaging and histology. Transvaginal sonography with color doppler is the first triage modality. The ultrasound features may be the same as those of a leiomyoma, or there may be an irregularly vascularized myometrial mass lesion with an irregular or regular margin often with anechoic areas of necrosis.(9) Contrast enhanced MRI has a better predictive accuracy. The most common MRI finding is the presence of a large heterogeneous mass. On T1-weighted images, there may be a high signal intensity indicative of hemorrhagic necrosis in the sarcomas, not seen in other lesions, and on T2-weighted images, they are of intermediate to high signal intensity.(10) On diffusion weighted imaging (DW1) high intensity signals along with diffusion restriction might be suggestive. PET-CT has limited utility as even benign lesions may show increased FDG uptake. However, for clarifying ambiguous findings, PET-CT is a useful modality (11). To summarize, there are no definitive imaging findings that can diagnose sarcoma reliably. CT pelvis, abdomen and chest are useful to confirm extra pelvic metastasis of disease. For further management metastasis to distant sites should be ruled out.

- For cases diagnosed after surgery (total hysterectomy, supracervical hysterectomy, myomectomy, possible tumor fragmentation, intraperitoneal morcellation): Chest/abdominal/pelvic CT or abdominal/ pelvic MRi and chest CT without contrast is advisable to evaluate for metastatic disease.
- For cases where there is no or incomplete resection of uterus or adnexa, evaluate for residual abnormality with the use of contrast pelvic MRi.

Hysteroscopy and D&C:

Preoperative D&C was diagnostic in 70% of ESS patients, but only in 30% of LMS patients (7,12). Serum CA 125 may be raised in uLMS especially with extra uterine spread. (3)

A wide variation of gross and morphologic appearance exists in leiomyoma and its variants, that often raises suspicion for malignancy. (7)

UTERINE LEIOMYOSARCOMA (uLMS):

On cut section, a fleshy, variegated cut surface with areas of hemorrhage and necrosis is seen. On microscopy, LMS is characterized by marked nuclear atypia, high mitotic rate, and tumor cell necrosis. High mitotic index with more than 10 mitoses/10 high-power fields is suggestive of spindle LMS and, 4 mitoses/10 high-power fields or 2 mitoses/10 high-power fields are suggestive of epithelioid, and myxoid uLMS, respectively (5). Tumor cell necrosis is characterized by abrupt change from necrotic to non necrotic areas without any granulation tissue in between. Tumors with size >5 cm, infiltration, high-grade cytologic features, high mitotic rate or more high-power fields, necrosis, or lymph vascular invasion have a poor outcome.

Prognostic factors for uLMS: Tumour stage and size are the two most important prognostic variable that affect survival. Depending on these, LMS can be stratified into three different risk groups –

Low risk group- Tumor diameter <10cm and MI <10

Medium risk group- Tumor diameter>10cm or MI >10

High risk group- Tumor diameter >10cm and MI >10.

High risk group has 5.3 times higher risk of death. (8)

Age (>50 years : RR 11.07 [95% CI 1.53-80.34]), tumor size (>11cm versus < 11 cm: RR, 11.63 [95% CI 2.14-63.12]), stage (III and IV versus I: RR, 21.24 [95% CI 2.20-204.98]), and adjuvant chemotherapy (yes versus no: RR, 0.08 [95% CI 0.01-0.81]) are other significant predictors of death.(12)

Treatment

En bloc removal of the uterus with efforts to avoid intraoperative spill or morcellation, along with resection of adherent organs even if not overtly infiltrated, is the primary surgical treatment. Previous studies have demonstrated worse outcome after morcellation. Sub optimal resection is associated with a poor prognosis. Ovarian conservation can be done in younger women and lymphadenectomy has not been associated with any benefit on survival. However it can be done as a component of cytoreductive surgery in advanced symptomatic cases. Optimal resection with no residual disease following primary surgery, tumor size <5 cm is the most significant prognostic factor determining survival for patients with LMS.

Adjuvant therapy: Conflicting evidence exists on the role of adjuvant thereapy, limited by heterogeneity and sample size.

Recommendation:

1. Adjuvant radiation therapy is not recommended for stage 1 and II uLMS.
2. The benefits of adjuvant chemotherapy for women who had optimal debulking in stage I or II is not clear and thus not recommended. (13)
3. The choice of chemotherapeutic agents is also not clear. First line therapy includes doxorubicin alone, or ifosfamide alone, or doxorubicin plus ifosfamide combination.
4. For management of advanced disease, chemotherapy is a preferred modality than radiation.
5. Gemcitabine based chemotherapy may be suggested as first line therapy for cases not amenable for surgical management.
6. Other alternatives can be single agent liposomal doxorubicin or paclitaxel or ifosfamide. Combination chemotherapeutic regimens consist of gemcitabine and docetaxel with or without bevacizumab.
7. Trabectedin, a tetrahydroisoquinoline alkaloid, in combination with doxorubicin has been used in the management of advanced or recurrent disease.
8. Metastatectomy (pulmonary wedge resection for isolated pulmonary metastasis) may be considered for selected cases.

For cases with incidental diagnosis after hysterectomy or with morcellated specimen, further management consists of imaging and re-exploration based on the extent of disease. if patient is not suitable for primary surgery then pelvic EBRT ± brachytherapy and/or systemic therapy should be considered. (11)

ENDOMETRIAL STROMAL SARCOMA

The cells in ESS resemble the endometrial stroma in the proliferative phase and it accounts for <1% of uterine malignancies. (14) According to the WHO 2014 classification (15) endometrial stromal tumors can be divided into four categories:

ESN (Benign)

Low grade endometrial stromal sarcoma(LG-ESS)

High grade endometrial stromal sarcoma (HG-ESS)

Undifferentiated uterine sarcoma (UUS)

LOW GRADE ENDOMETRIAL STROMAL SARCOMA (LG-ESS)

Low-grade endometrial stromal tumor constitutes the second most common variant of uterine sarcoma after uLMS. This usually affects pre- or perimenopausal women with most common clinical presentation of abnormal uterine bleeding (AUB), pelvic pain and dysmenorrhea. Most of these women have high risk factors including obesity, diabetes, tamoxifen intake, or younger age at menarche.(16) Approximately 25% cases do not have any symptoms and 30% present with features related with extrauterine spread, which is often associated with endometriosis. (17)

On gross examination LG-ESS usually has vague borders and shows worm-like permeation into the adjacent myometrium and parametrium. There are usually fleshy tan to yellow soft nodules but sometimes it may present as pale, firm and grayish masses. On microscopy LG-ESS is characterized by extensive permeation of myometrium with tongue like areas of LVSI and myometrial invasion. The nuclei are oval to spindle shaped and mitotic activity is low <5/10 HPF and without areas of necrosis. (18)

Immunohistochemistry is useful to differentiate LG ESS from uLMS or leiomyoma. There is no single marker but a panel consisting of CD10 and at least two smooth muscle markers (desmin, caldesmon, smooth muscle heavy chain myosin, HADC8) is useful.(21) LG ESS is usually positive for CD10, vimentin, actin,WT1, ER, PR and androgen receptors. (18,19)

Investigations

Iimaging: Presence of multi-septate cystic areas and multiple small areas of cystic degeneration are the most frequently seen features on USG (20). On contrast MRI, presence of a polypoid endometrial mass with low signal on T1 weighted images and heterogeneously increased high T2 signals. Worm-like extension bands of low signal intensity within areas of myometrial involvement on T2 weighted images may also be seen.(21) Tumor-free resection margin is the most significant prognostic factor. (3)

Treatment

The prognosis of LGESS is good but there is a high risk of late recurrences even in stage 1 tumors, warranting long-term follow-up. Prognosis depends mainly on stage of disease with 5-year survival over 90% for stage 1, decreasing to 50% for stage III and IV.(14) Lymphatic involvement is seen in 7%-9% cases. (19) The role of lymphadenectomy remains debatable. Removal of enlarged lymph nodes as a component of optimal cytoreduction is required, lymphadenectomy does not confer any survival advantage. (22)

Recommendations

1. Surgical treatment consisting of hysterectomy and bilateral salpingo- oophorectomy is the primary treatment.
2. Lymph nodes should be removed only if enlarged.
3. Role of adjuvant therapy – Observation is recommended for women with LG ESS who have undergone compete surgery with no evidence of residual disease. (11). Alternatively, estrogen blockade may be recommended for stage I ESS. Aromatase inhibitors (AI) (anastrozole 1 mg daily) are recommended as it has been seen that AI might have partial or even complete response in women with LG-ESS. (23)
4. Postoperative hormone therapy to block estrogen receptors is advised for stages II to IV ESS.
5. Adjuvant EBRT may be recommended for stage ii-iVA to reduce local recurrence but has no significant impact on survival; palliative RT may be added for stage IVB.

6. Typical hormone therapy includes agents like megestrol, medroxyprogesterone, or aromatase inhibitors and gonadotropin-releasing hormone [GnRH] analogs.
7. Hormone therapy for those that have recurred or are unresectable.
8. Menopausal hormone therapy is contraindicated for management of menopausal symptoms.

The role of AIs in the management of 16 ESS patients was investigated retrospectively and, an overall response rate of 67% and a stable disease rate of 20% was observed to justify the use of AIs in these women(23).

Prognostic factors

LG-ESS carries a favorable prognosis but 36-56% cases are known to recur (24). Most of the recurrences occur in abdomen and pelvis followed by lung. (25) For recurrent cases complete surgical resection and postoperative adjuvant therapy is recommended with reportedly good survival outcome. (26)

HIGH GRADE ENDOMETRIAL STROMAL SARCOMA (HGESS)-

This is an intermediate group between LG-ESS and UUS presenting in advanced stage with more than 75% cases having tumor size >5 cm, and a majority with myometrial and cervical invasion at the time of presentation.(27) HG-ESS typically has a tendency for frequent, and early recurrence.(28). The prognosis is usually poor with 5-year OS rate of 51.4% and 43.5% for FIGO Stage IA and FIGO Stage IB, respectively. (29) Due to rarity, evidence is limited to guide the management. Stage and extent of residual disease after surgery remain the most important prognostic factors.(30)

Primary surgical therapy consisting of total hysterectomy and bilateral salpingo-oophorectomy. Preservation of adnexa even with early stage disease is not advisable. in advanced stages, cytoreductive surgery including lymphadenectomy is recommended. (19)

Post operative EBRT may decrease locoregional recurrence risk. Addition of chemotherapy can be considered to prevent the risk of distant and visceral recurrences. (SARCGYN study). Doxorubicin and ifosfamide or gemcitabine + docetaxel and doxorubicin has been utilized in women with HG-ESS. (19)

UNDIFFERENTIATED UTERINE SARCOMA (UUS))

UUS is an extremely rare high grade disease without a specific line of differentiation, and is usually a diagnosis of exclusion. Women usually present with postmenopausal bleeding or features of extrauterine disease. They are associated with a poor prognosis. Grossly, UUS is a fleshy, large tumor with infiltration into uterine wall along with extensive necrosis and or hemorrhage.(31)

Primary surgical treatment consisting of total hysterectomy and BSO with or without lymphadenectomy followed by adjuvant treatment with either chemotherapy (doxorubicin and /or ifosfamide) is frequently used.

ADENOSARCOMA

Adenosarcoma is a biphasic tumor consisting of a mixture of both benign epithelial as well as a sarcomatous mesenchymal element. The mesenchymal element can be homologous or heterologous depending upon the presence or absence of elements of uterine or non-uterine origin. (3) Adenosarcoma appears as a polypoid mass occupying the entire uterine cavity with a fleshy, hemorrhagic, necrotic cut surface.(19) The treatment consists of total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. The prognosis is usually favorable. The role of adjuvant therapy is not clearly established. (31)

Post treatment surveillance

Follow-up is recommended every 3 months up to a period of two years, then 6-monthly up to 5 years, and annually thereafter. Patients should seek prompt care if they have any symptoms of recurrent disease, e.g. abnormal bleeding (vaginal, rectal, bladder), decreased appetite, weight loss, pain, cough, shortness of breath, abnormal swelling.

TREATMENT OF RECURRENT/METASTATIC DISEASE

Local recurrence

Patients without prior RT-

Surgery with IORT or EBRT ± vaginal brachytherapy, with (or without) systemic therapy is recommended for women with local recurrence who have not received RT in past. Hormone therapy (e.g Anastrozole) is preferred for women with ESS. Preoperative EBRT followed by resection can be considered in selected cases.

Patients with prior RT:

Surgery with iORT and/ or chemotherapy, or chemotherapy, or selected re-irradiation with EBRT and/ or brachytherapy

Hormonal therapy may be considered in patients with ESS. Pre-operative EBRT may be considered, followed by surgery and followed by adjuvant EBRT with or without brachytherapy. For patients with isolated resectable metastasis, surgical resection may be appropriate. (11)

Clinical algorithms for management of Uterine sarcoma are available at https://play.google.com/store/apps/details?id=app.com.figostaging&hl=en_iN

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