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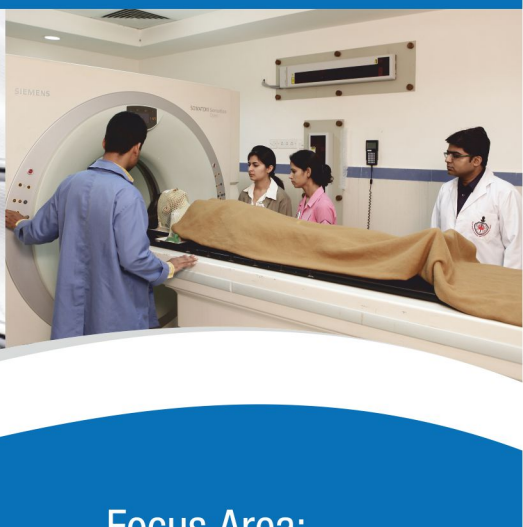

Focus Area:

ENDOMETRIAL CANCER

Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
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From the Desk of Director Research

Endometrial cancer is the sixth most common cancer in women worldwide. It is mainly a disease of high-income countries, where the highest incidence of endometrial cancer is in North America, and Central and Eastern Europe; and the lowest incidence in Middle and Western Africa. The incidence of ca Endometrium is very low in India but highest being observed in Bangalore and Delhi. Factors that increase the risk of endmometrial cancer is increased or prolonged oestrogen exposure, either because of early menarche or late menopause, obesity, nulliparity, anovulation and unopposed exogeneous oestrogen including tamoxifen.

Endometrial Cancers need to be clinically staged for appropriate management. FIGO advocates surgical staging also in addition to clinical staging. There have been many changes in the management of endometrial cancer. Minimally invasive surgery is now an acceptable alternative. Treatment paradigms for endometrial cancer are rapidly evolving. New minimally invasive surgical techniques have helped to reduce the morbidity of women with early-stage tumors undergoing hysterectomy. Although there is more data on pelvic and para-aortic lymphadenectomy, their role continues to be debated. A growing body of evidence has helped to stratify women with intermediate-risk endometrial cancer to optimize adjuvant therapy in this subset of patients. There have been important developments in chemotherapy in endometrial cancer, which may be promising in an adjuvant setting. For women with high-risk and metastatic endometrial cancer there has been a renewed interest in incorporating chemotherapy into treatment paradigms. Hormonal therapy remains an important option in recurrent disease and our understanding of the biology of the disease may help determine which patients may benefit most.

The most notable development in the treatment of endometrial cancer, as with many tumors, is the increasing understanding of tumor genomics, which seeks to identify mutations in genes in the tumor that might “drive” or cause the tumor to grow. One such example in endometrial cancer has already shown that mutations in a pathway called PI3K/AKT/MTOR are commonly found, and patients with recurrent disease may benefit from using a drug that targets this pathway called everolimus (Afinitor, RAD001). Another type of targeted therapy recently shown to have activity for patients with endometrial cancer are called angiogenesis inhibitors, such as with the drug bevacizumab (Avastin) that targets blood vessel growth that feeds tumors as one mechanism of its action.

In spite of the overall good prognosis during the early stages of the disease, the survival is poor in advanced stages or recurrences. Diagnostic measures are able to detect asymptomatic recurrences. These only seem justified if patients’ chances are likely to improve, otherwise such measures increases costs as well as decrease the patients’ quality of life. To date neither current nor improved concepts of endocrine treatment or chemotherapy have been able to substantially increase patients’ chances of survival. The protected measure could be regular physical activity, prudent and balanced diet with high intake of carotenoides. Suspicion helps in timely diagnosis and therapy with better survival. However there are grey areas, so research needs to be continued.

The present issue of the Cancer News highlights the newer advances in the field of "Ca Endometrium" and features regular articles, such as Special Feature, Guest Article, Perspective, and In Focus. We are grateful to Prof Neerja Bhatla, Professor, Dept of Obstetrics & Gynaecology and Dr Kusum Lata Senior Resident, All India Institute of Medical Sciences, Delhi for the "Guest Article"; Dr Shalini Rajaram, Director Professor, Dept of Obstetrics & Gynecology UCMS & GTBH; Dr Anupama Rajanbabu, Associate Prof, Dept of Gynecological Oncology, Amrita Institute of Medical Sciences and Research Centre for "Perspective".

Suggestions/ comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

ENDOMETRIAL CARCINOMA

Introduction

Cancer of the endometrium is the second most common genital cancer in Indian women, second only to carcinoma of the cervix. In the western countries it continues to be the most common genital cancer in women.[1] The major predisposing factors for endometrial cancer are obesity, diabetes and hypertension, though genetic predisposition and familial incidence are also known. Unopposed and continual use of estrogen can also predispose to endometrial cancer.[2,3]

Epidemiology

Worldwide, in 2008, 288,000 women were diagnosed with uterine cancer. The incidence was found to be as high as 12.9 per 100,000 women and mortality rate was 2.4 per 100,000 in developed countries. In developing countries, its incidence is 5.9 per 100,000 with a mortality rate of 1.7 per 100,000.[4] It is estimated that in India each year there are about 8,800 new cases of endometrial carcinoma with an age adjusted incidence rate of 1.9 per 100,000. The Network of Cancer Registries has reported a variable incidence rate within different parts of India, with a very high rate of 4.3 per 100,000 in Delhi.[5]

Histopathology

Endometrial carcinomas are classified into two major types (I and II) based upon light microscopic appearance, clinical behavior, and epidemiology. Most endometrial are carcinomas. However, carcinosarcomas and other rare malignant neoplasms arise in the endometrium.

Type I tumors include tumors of endometrioid histology, are grade 1 or 2; and comprise approximately 80 percent of endometrial carcinomas. These tumors typically have a favorable prognosis, are estrogen responsive, and may be preceded by an intraepithelial neoplasm (atypical and/or complex endometrial hyperplasia).[3,6]

Type II tumors account for 10 to 20 percent of endometrial carcinomas. They include grade 3 endometrioid tumors as well as tumors of non-endometrioid histology: serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated. These tumors are often high grade, have a poor prognosis, and are not clearly associated with estrogen stimulation. A precursor lesion is rarely identified.[3,6]

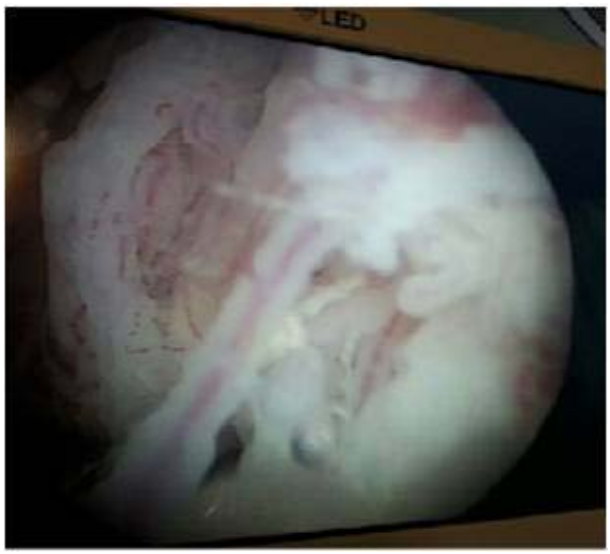
Type I	Type II
40 - 60 years	Elderly
H/O Chronic anovulation or estrogen replacement therapy	No H/O Hyperestrogenism
Endometrial hyperplasia is common	Atrophic non-neoplastic endometrium
Well-differentiated, Stage I, Nonmyoinvasive	High stage with deep myoinvasion present
Endometrioid histology	Special variant carcinomas High grade Endometrioid carcinomas
ER/PR Positive, p53 Negative, Low Ki-67	ER/PR Negative, p53 Positive, High Ki-67 index
Good prognosis after surgery	Molecular genetic abnormalities present
	Poor prognosis after surgery

Modified FIGO Grading System[7]

Grade 1: Five percent or less of a nonsquamous or nonmorular solid growth pattern.
Grade 2: Six to fifty percent of a nonsquamous or nonmorular solid growth pattern.
Grade 3: More than 50% of a nonsquamous or nonmorular solid growth pattern.

Cytologic features which are used in formulating final grade:

- Notable nuclear atypia inappropriate for the architectural grade raises the grade of a Grade 1 or Grade 2 tumor by one level.
- In serous adenocarcinomas, clear cell adenocarcinomas and areas of squamous differentiation, nuclear grade takes precedence over architecture.



Hysteroscopic findings of endometrium in a case of carcinoma endonectrium

Risk Factor	Relative Risk
Increasing Age	Women 50 - 70 years of age have 1.4 % risk
Unopposed estrogen therapy	2 – 10
Tamoxifen therapy	2
Early Menarche	NA
Late Menopause > 55 years age	2
Nulliparity	2
Polycystic Ovary Syndrome	3
Obesity	2 – 4
Diabetes Mellitus	2
Estrogen Secreting Tumors	NA
Hereditary Non Polyposis Coli	22 – 50 % lifetime risk
Cowden Syndrome	13 – 19 % lifetime risk
Family history of Ovarian, Breast or Colon cancer	NA

NA: Relative risk not available

Adapted from data in Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society Guidelines for Early Endometrial Cancer Detection: Update 2001.

Serous papillary carcinoma constitutes 5–10% of all endometrial carcinomas. It is characterized by complex papillary architecture, high grade nuclear features, psammomatous calcifications, lack of association with hyperestrogenism and endometrial hyperplasia and aggressive behavior. These tumors show a tendency to develop deep myometrial invasion, extensive lymphatic invasion and presentation with extrauterine spread.(8)

Clear cell adenocarcinoma constitutes 1–5% of all endometrial carcinomas. It is composed of clear or "hobnail" cells arranged in solid, tubulocystic or papillary patterns. It is frequently diagnosed in advanced clinical stage and has poor prognosis. However, if limited to the uterine corpus it has a better prognosis than serous adenocarcinoma of the same stage.(9)

Mixed adenocarcinoma tumor is composed of admixture of endometrioid carcinoma or mucinous carcinoma and serous or clear cell carcinoma in which the minor type must comprise at least 10% of the total volume of the tumor.

Squamous cell carcinoma is often associated with cervical stenosis and pyometra. Primary pure squamous cell carcinoma of endometrium is rare and it is necessary to exclude predominantly squamous differentiation of an endometrioid adenocarcinoma and cervical squamous cell carcinoma extending into endometrium. Prognosis is poor.

Other variants are rare and include transitional cell carcinoma, small cell carcinoma and undifferentiated carcinoma.(3,6-11)

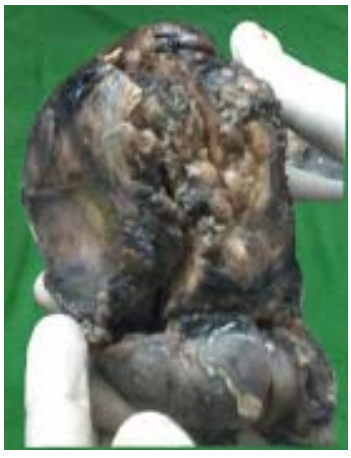
Clinical Features

Endometrial carcinoma typically presents with abnormal uterine bleeding and is most common in women who are postmenopausal and with increasing age in premenopausal women. Occasionally, women with no abnormal uterine bleeding present with abnormal findings on cervical cytology.

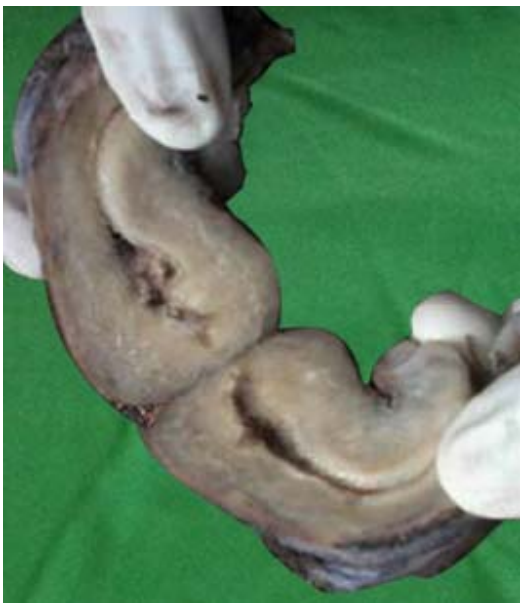
Suspicion of the presence of endometrial neoplasia (neoplastic endometrial hyperplasia or carcinoma) depends upon symptoms, age, and the presence of risk factors. Abnormal uterine bleeding is present in approximately 75 to 90 percent of women with endometrial carcinoma. The amount of bleeding does not correlate with the risk of cancer.(13)

For different patient populations, the following bleeding patterns should prompt endometrial evaluation:

Pic 1: Multiple Fibroids



Pic 2: T^0 involves > 1/2 of myomtrium also isthumus and cervix



Pic 3: T^0 involves less then half of myomtrium

Postmenopausal women: Any bleeding, including spotting or staining. Three to 20 percent of women withpostmenopausal bleeding are found to have endometrial carcinoma and another 5 to 15 percent haveendometrial hyperplasia.

Age 45 to menopause - Any abnormal uterine bleeding, including intermenstrual bleeding in women who are ovulatory, frequent (interval between the onset of bleeding episodes is less than 21 days), heavy (total volume of >80 mL), or prolonged (longer than seven days). In addition, endometrial neoplasia should be suspected in women with prolonged periods of amenorrhea (six or more months) and with an ovulation. Among cases of endometrial carcinoma, 19 percent occur in women aged 45 to 54 years compared with 6 percent in thoseaged 35 to 44 years.

Younger than 45 years: Abnormal uterine bleeding that is persistent, occurs in the setting of a history ofunopposed estrogen exposure (obesity, chronic anovulation) or failed medical management of the bleeding, or in women at high risk of endometrial cancer[13]

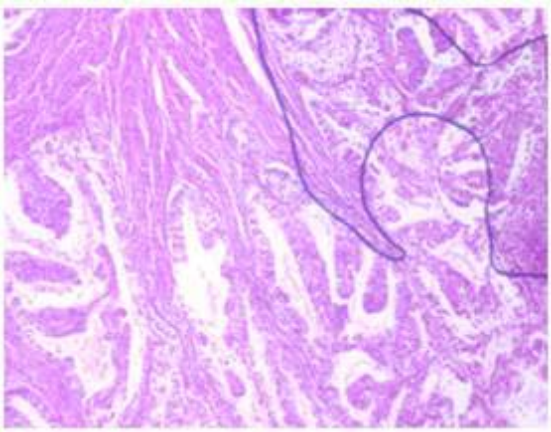
Diagnosis

Endometrial carcinoma is a histologic diagnosis based upon the results of evaluation of an endometrial biopsy, endometrial curettage, or hysterectomy specimen. Routine preoperative hematology and biochemistry should be performed, and a Chest, Pelvic and Abdominal Computed Tomographic scan is usually performed. It has limited usefulness in determining the depth of myometrial invasion or presence of nodal disease, but has been traditional investigation to exclude liver or lung metastasis, adnexal masses or hydronephrosis in high risk cases. An MRI has been shown to have 83.3% accuracy for differentiating deep from superficial myometrial invasion and a positive predictive value of 89.8% for detection of cervical involvement. PET scan has an overall diagnostic accuracy of 89.5% for detection of lymph node metastasis in patients with untreated endometrial cancer, but it is not considered part of routine workup. An elevated CA-125 levels have been demonstrated to correlate with advanced stage of disease including positive lymph node status.[13,14]

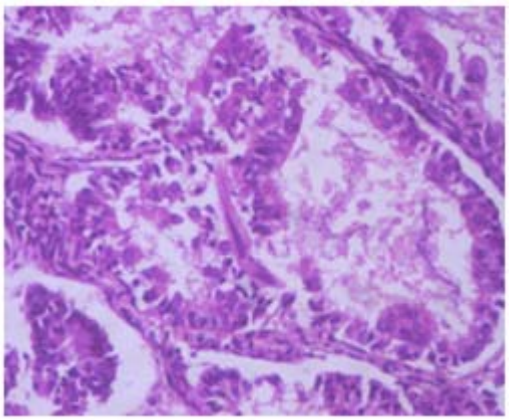
Staging[15]

Revised 2009 FIGO staging for carcinoma of the endometrium:

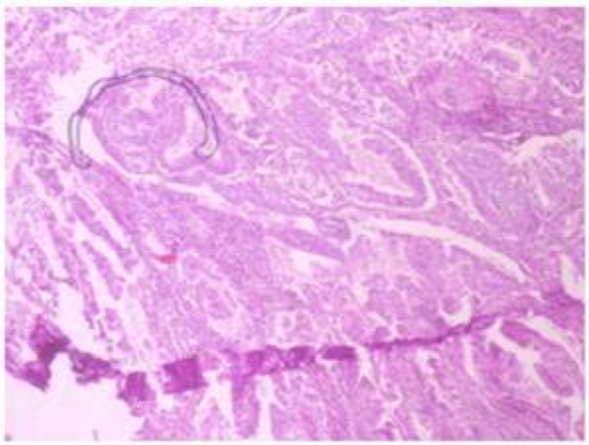
- Stage 0 - carcinoma in situ
- Stage I - limited to the body of the uterus
- Ia - no or less than half myometrial invasion
- Ib - invasion equal to or more than half of the myometrium
- Stage II - cervical stromal involvement
- endocervical glandular involvement only is stage I
- Stage III - local or regional spread of the tumour



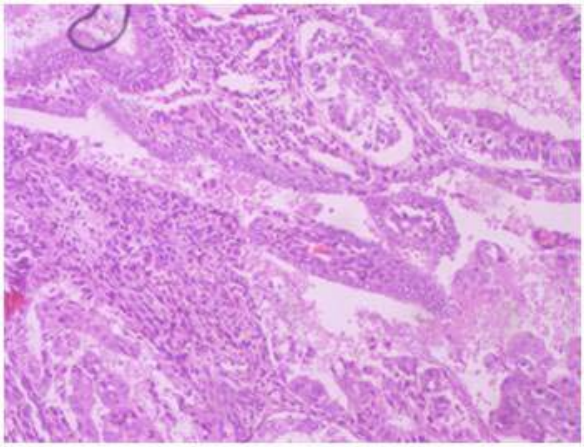
Pic 4: Villo-glandular architecture irregular mazelike glands



Pic 5: Well formed glands mild nuclear plemorphism



Pic 6: Irregular bronching glands



Pic 7: Stratified nuclei in gland solid areas

- IIIa - tumour invades the serosa of the body of the uterus and or adenexae
- IIIb - vaginal or parametrial involvement
- IIIc - pelvic or para-aortic lymphadenopathy
- IIIc1 - positive pelvic nodes
- IIIc2 - positive para-aortic nodes with or without pelvic nodes
- Stage IV - Involvement of rectum and or bladder mucosa and or distant metastasis
- IVa - bladder or rectal mucosal involvement
- IVb - distant metastases, malignant ascites, peritoneal involvement

Spread Patterns[16]

Endometrial carcinoma spreads by the following routes:

1. Direct extension to adjacent structures - Direct extension is the most common route of spread, and it results in penetration of the myometrium and eventually the serosa of the uterus. The cervix, fallopian tubes, and ultimately the vagina and parametrium may be invaded.
2. Transtubal passage of exfoliated cells - The presence of malignant cells in peritoneal washings and the development of widespread intra-abdominal metastases in some patients with early-stage endometrial cancer strongly suggest that cells may be exfoliated from the primary tumor and transported to the peritoneal cavity by retrograde flow along the fallopian tubes.
3. Lymphatic dissemination - Lymphatic dissemination is clearly responsible for spread to pelvic and para-aortic lymph nodes. Although lymphatic channels pass directly from the fundus to the para-aortic nodes through the infundibulopelvic ligament, it is rare to find positive para-aortic nodes in the absence of positive pelvic nodes. It is quite common to find microscopic metastases in both pelvic and para-aortic nodes, suggesting simultaneous spread to pelvic and para-aortic nodes in some patients. This is in contrast to cervical cancer, where para-aortic nodal metastases are virtually always secondary to pelvic nodal

Adjuvant Treatment for Endometrioid Histology

Surgically Staged: Stage I

Histological Grade	Stage IA (<50%) Myometrial Invasion		Stage IB (≥50%) Myometrial Invasion	
	Adverse Risk Factors Not Present	Adverse Risk Factors Present	Adverse Risk Factors Not Present	Adverse Risk Factors Present
G1	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT
G2	Observe Or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (Category 2B for pelvic RT)	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT
G3	Observe Or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT	Vaginal brachytherapy and/or pelvic RT or Observe (category 2B for observation)	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy)

Adverse risk factors include age, positive lymphovascular invasion, tumor size, and lower uterine segment or surface cervical glandular involvement.

Endometrial Carcinoma Stages I and occult stage 2 patients requiring Surgical Staging
1. Grade II tumors > 2 cm in diameter
2. Grade III lesions
3. Clear cell or serous carcinomas
4. Greater than 50% myometrial invasion
5. Cervical extension

Adjuvant Treatment for Endometrioid Histology	
Surgically Staged: Stage IIIA	
G1	Chemotherapy ± RT Or
G2	Tumor directed RT ± chemotherapy Or
G3	Pelvic RT ± Vaginal brachytherapy

metastases.

4. Hematogenous dissemination - Hematogenous spread most commonly results in lung metastases; liver, brain, bone, and other sites are involved less commonly.

Treatment[17-20]

The cornerstone of treatment for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy; this operation should be performed in all cases whenever feasible. Many patients require some type of adjuvant radiation therapy to help prevent vaginal vault recurrence and to sterilize disease in lymph nodes. The surgery has traditionally been via laparotomy, but many of these patients are elderly and have comorbidities such as diabetes, hypertension, and obesity. Minimally invasive approaches are replacing open laparotomy for most patients with endometrial cancer.

The decision to undertake surgical staging is usually based on the histopathology from the uterine curettings, the gross findings on opening the uterus on the operating table, and possibly a frozen section of the resected uterus.[17,18]

Adjuvant Treatment for Endometrioid Histology	
Surgically Staged: Stage II	
G 1	Vaginal brachytherapy And/or Pelvic RT
G 2	Pelvic RT + Vaginal brachytherapy
G 3	Pelvic RT + Vaginal brachytherapy ± Chemotherapy (category 2B for chemotherapy)

Adjuvant Treatment for Endometrioid Histology		
Surgically Staged: Stage IIIB, IIIC, IV		
Stage IIIB	Chemotherapy and/or Tumor directed RT	
Stage IIIC1 Stage IIIC2	Pelvic Lymph node positive Paraaortic Lymph node positive ± Pelvic Lymph node positive	Chemotherapy and/ or Tumor directed RT
Stage IVA, IVB	Debulked and with no gross residual disease or microscopic abdominal disease	Chemotherapy ±RT

Treatment for Serous or Clear Cell Adenocarcinoma		
Includes surgical staging with maximal tumor debulking for gross disease		
Stage IA (No myometrial invasion)	Stage IA (with myometrial invasion) Stage IB, II	Stage III Stage IV
Observe Or Chemotherapy ± Vaginal brachytherapy Or Tumor directed RT	Chemotherapy ± Tumor directed RT	

Stage I & Stage II (Occult) – Total Abdominal Hysterectomy with Bilateral Oopherectomy. A subset of such patients require additional surgical staging.

Stage II (Clinical) – Total Abdominal Hysterectomy with Bilateral Oopherectomy with surgical staging. In staging, the surgery is as follows:

1. Modified (Type II) radical hysterectomy
2. Bilateral salpingo-oophorectomy
3. Peritoneal washings for cytologic study
4. Pelvic lymphadenectomy to the midcommon iliac area
5. Resection of grossly enlarged para-aortic nodes
6. Omental biopsy
7. Biopsy of any suspicious peritoneal nodules

Stage III – Debulking surgery

Stage IV – Treatment must be individualized and may require some type of modified pelvic exenteration. There may be some role of cytoreductive surgery, though data is limited to small retrospective studies.

Fertility Preservation

Women with low-risk endometrial carcinoma who wish to preserve fertility may be candidates for treatment with progestin therapy.[21]

All of the following criteria for considering fertility sparing options for management of endometrial carcinoma must be met:

1. Well differentiated (grade I) endometrioid adenocarcinoma on dilatation and curettage confirmed by expert pathology review
2. Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound

3. Absence of suspicious or metastatic disease on imaging
4. No contraindication to medical therapy or pregnancy
5. Patient should undergo counselling that fertility sparing option is NOT standard of care for the treatment of endometrial cancer

Post Treatment Surveillance

Post treatment surveillance is aimed at the early detection of recurrent disease. For women with endometrial carcinoma, surveillance mainly consists of monitoring for symptoms and physical examination[22]:

1. Speculum and bimanual examination every 3 to 6 months for two years, then every 6 months or annually
2. The frequency of examination depends on risk of recurrent or persistent disease
3. Routine use of serum CA-125 and imaging varies across institutions

Prognosis

The prognosis of endometrial carcinoma is determined primarily by disease stage and histology (Including both grade and histologic subtype). In general, the rate of five-year survival for stage I disease is approximately 80 to 90 percent, for stage II it is 70 to80 percent, and for stages III and IV it is 20 to 60 percent.[13, 23]

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.
2. Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematology/oncology clinics of North America. 2012;26(1):1-12.
3. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(20):2607-18.
4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.
5. NCRP. Two-year Report of the Population Based Cancer Registeries - 2006-2008. National Cancer Registery Programme, Indian Council of Medical Research, 2009, Bangalore, India.
6. Yang HP, Wentzensen N, Trabert B, Gierach GL, Felix AS, Gunter MJ, et al. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. American journal of epidemiology. 2013;177(2):142-51.
7. Creasman WT. New gynecologic cancer staging. Gynecologic oncology. 1995;58(2):157-8.
8. Jordan LB, Abdul-Kader M, Al-Nafussi A. Uterine serous papillary carcinoma: histopathologic changes within the female genital tract. International journal of gynecologicalcancer : official journal of the International Gynecological Cancer Society. 2001;11(4):283-9.
9. AbelerVM, VergoteIB, KjorstadKE, Trope CG. Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. Cancer. 1996;78(8):1740-7.
10. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecologic oncology. 1983;15(1):10-7.
11. Sturgeon SR, Sherman ME, Kurman RJ, Berman ML, Mortel R, Twiggs LB, et al. Analysis of histopathological features of endometrioid uterine carcinomas and epidemiologic risk factors. Cancer epidemiology, biomarkers &prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1998;7(3):231-5.
12. Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection. CA: a cancer journal for clinicians. 2001;51(1):38-75; quiz 7-80.
13. Creasman WT. Endometrial cancer: incidence, prognostic factors, diagnosis, and treatment. Seminars in oncology. 1997;24(1 Suppl 1):S1-140-S1-50.
14. American College of O, Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstetrics and gynecology. 2005;106(2):413-25.
15. BenedetJL, Bender H, Jones H, 3rd, NganHY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2000;70(2):209-62.
16. Bigelow B, Vekshtein V, Demopoulos RI. Endometrial carcinoma, stage II: route and extent of spread to the cervix. Obstetrics and gynecology. 1983;62(3):363-6.
17. CreasmanWT, Odicino F, Maisonneuve P, Quinn MA, Beller U, BenedetJL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006;95Suppl1:S105-43.
18. Bakkum-GamezJN, Gonzalez-Bosquet J, LaackNN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. Mayo Clinic proceedings. 2008;83(1):97-112.
19. NicklinJL, Petersen RW. Stage 3B adenocarcinoma of the endometrium: a clinicopathologic study. Gynecologic oncology. 2000;78(2):203-7.
20. Aalders JG, Abeler V, Kolstad P. Stage IV endometrial carcinoma: a clinical and histopathological study of 83 patients. Gynecologic oncology. 1984;17(1):75-84.
21. RCOG. Fertility Sparing Treatments in Gynaecological Cancers. Scientific Impact Papaer No. 35. Feb. 2013.
22. Sartori E, Pasinetti B, Chiudinelli F, Gadducci A, Landoni F, Maggino T, et al. Surveillance procedures for patients treated for endometrial cancer: a review of the literature. International journal of gynecologicalcancer : official journal of the International Gynecological Cancer Society. 2010;20(6):985-92.
23. Lewin SN, Herzog TJ, BarrenaMedel NI, Deutsch I, Burke WM, Sun X, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstetrics and gynecology. 2010;116(5):1141-9.

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GUEST ARTICLE

CA ENDOMETRIUM - CURRENT MANAGEMENT PERSPECTIVE

Introduction

Endometrial cancer is the fifth most common cancer in women, affecting 318,000 women per year globally.[1] Endometrial carcinoma is the commonest type of female genital tract malignancy in the developed countries, accounting for nearly 50% of all new gynecologic cancers diagnosed in the Western world(2).

In India(3) the incidence of endometrial carcinoma is showing an increase. It is reported to be 4.6/100,000 women (Delhi cancer registery, 2013). Most (75–85%) of endometrial carcinoma occur in the sixth and seventh decades of life, and 95% occur in patients over 40 years of age (4).

The main risk factors are obesity and chronic unopposed oestrogen stimulation of the endometrium. Endometrial cancer can be divided into two major types: Type 1 cancers-account for 80-90%, are oestrogen dependent endometrioid adenocarcinomas and have good prognosis. Type 2 tumours (nonestrogen dependent) usually present late, behave more aggressively, and carry a poor prognosis and the risk of relapse and metastasis is high.

Endometrial carcinoma is usually confined to the uterus at the time of diagnosis and as such usually carries an excellent prognosis with high curability (5,6). However, patients with high-risk factors including increased age, higher tumor grade, aggressive histology and advanced stage represent real challenges.

There have been many changes in the management of endometrial cancer. Minimally invasive surgery is now an acceptable alternative. Although there is more data on pelvic and para-aortic lymphadenectomy, their role continues to be debated. There have been important developments in chemotherapy in endometrial cancer, which may be promising in an adjuvant setting (7). Hormonal therapy remains an important option in recurrent disease and our understanding of the biology of the disease may help determine which patients may benefit most (8).

Screening

Many Type 1 endometrial cancers develop by way of a precursor lesion. However, there is no tumour marker or screening method that can be applied to the general population.

Although most cases of endometrial carcinoma are sporadic, some have a hereditary basis, the prototype being the Lynch syndrome hereditary nonpolyposis colorectal cancer (HNPCC). This is an autosomal-dominant cancer susceptibility syndrome associated with early onset colon, rectal, ovary, small bowel, ureter/renal pelvis cancers, and endometrial cancer. The lifetime risk of endometrial cancer in Lynch syndrome women is 40% to 60%, a risk similar to that of developing colon cancer (9).There is no uniform screening strategy for these women. Currently, the American Cancer Society recommends annual endometrial biopsies starting at age 35 years for women known to have or be at risk for HNPCC and does not recommend ultrasound scans.

Management

A gynecologic oncologist should be involved in the initial care of every woman seeking treatment for endometrial cancer. Such involvement enhances the preoperative and intraoperative decision process, allows completion of any necessary procedure (comprehensive staging or debulking), facilitates decision regarding the need for additional therapy, and results in a comprehensive and cost-effective clinical approach.

Carcinoma of the Endometrium : Staging FIGO 2009	
IA	Tumor confined to the uterus, no or < ½ myometrial invasion
IB	Tumor confined to the uterus, > ½ myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumor invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumor invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

Extent of Surgical Procedure

The standard treatment for endometrial carcinoma remains surgical and includes exploration with collection of peritoneal fluid for cytologic evaluation,total extra fascial hysterectomy with bilateral salpingo-oophorectomy and appropriate surgical staging in patients considered at risk for extrauterine disease.

Role of Peritoneal Cytology

Positive peritoneal cytology may carry a prognostic significance only when the endometrial carcinoma has spread beyond the uterus (10–13). In patients with clinical stage I and II endometrial carcinoma, positive peritoneal cytologic results did not influence survival when the disease was confined to the uterus. However, when the disease had spread to the adnexa, lymph nodes, or peritoneum, then positive peritoneal cytologic findings decreased the survival rate from 73% to 13% at 5 years, but all recurrences were at distant sites (14).

Role of Lymphadenectomy

The prognostic value of lymph node status has been well defined, with 5-year recurrence free survival of 90% with negative nodes, 75% with positive pelvic nodes and 40% with positive para-aortic nodes (15,16).

It is suggested that lymphadenectomy does not appear to benefit patients with grade 1 and 2 endometrioid lesions with myometrial invasion but it improves the overall survival and the recurrence-free survival in high-risk endometrioid adenocarcinoma patients (17).

In the absence of nodal disease, recurrence risk is low and overall survival is high, with no radiation or with the substitution of vaginal vault brachytherapy. This has encouraged many gynaecologic oncologists to move towards performing routine surgical staging including pelvic and para-aortic lymphadenectomy for nearly all patients with endometrial cancer. The rationale for routine uniform staging is the inaccuracy of preoperative or intraoperative assessments predicting the risk for nodal disease, the potential for therapeutic benefit in node-positive and -negative patients, and the lack of significant morbidity associated with the procedure, with major complication rates of 2% to 6%. It could thus be argued that routine nodal dissection is the best method to determine which few patients will require adjuvant therapy. In addition, there is a significant risk of lymph node spread even for patients with seemingly low-risk disease.

Among patients who underwent systematic pelvic and paraaortic lymphadenectomy, 96.2% had negative para-aortic nodes when the pelvic nodes were negative. However, when the pelvic nodes were positive, 48% also had positive para-aortic nodes (18, 19). Hence, systemic para-aortic lymphadenectomy is advocated on all high-risk patients, or in patients with two or more positive pelvic lymph nodes (19, 20).

Thus controversy remains over the indications for, the anatomic extent of and the therapeutic value of lymphadenectomy in the management of the disease.

Sentinel Lymph Node Mapping

In an attempt to avoid complete lymphadenectomy, the concept of sentinel node identification has been investigated in endometrial carcinoma. Several protocols have been examined using injection of blue dye, Technetium 99, or both into the cervix and/or uterine fundus. But the long-term outcome data are not yet available for SLN mapping and it should be done in institutions with expertise in this procedure.

Role of Laparoscopic Hysterectomy

Current evidence on the safety and efficacy of laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer is adequate to recommend the use of this procedure. Together with reduced post operative analgesic requirements and an improved short-term quality of life, laparoscopy from the patients' perspective is far superior to laparotomy. In Gynecologic Oncology Group Study (GOG)LAP2, 2616 women with endometrial cancer were randomized in 2:1fashion to undergo comprehensive surgical staging via either laparoscopy or laparotomy (21).

Conversion from laparoscopy to laparotomy occurred in 25.8% of cases, primarily due to poor exposure. Laparoscopy was associated with fewer moderate-to-severe post-operative adverse events than laparotomy (14% vs 21%; P b 0.0001) and similar rates of intraoperative complications. Although operative time was longer for laparoscopy, the incidence of hospitalization of more than 2 days was significantly lower compared to laparotomy (52% vs 94%; P b 0.0001). Laparoscopy patients reported higher scores on several quality-of-life measures over the 6-week recovery period compared to laparotomy patients(22) but the outcomes were similar after 6 months of life in both the arms.

The second trial that randomized endometrial cancer patients to either laparotomy (n = 142) or laparoscopy (n = 190) was performed in Australia, New Zealand, and Hong Kong (LACE study) also showed significantly shorter hospital stay and improved quality of life at both 4 weeks and 6 months (23).

Role of Robotic Assistance in Laparoscopic Surgical Management

Robotic-assisted laparoscopy has not been prospectively compared in a randomized trial to conventional laparoscopy for the performance of endometrial cancer surgical staging. However, the existing literature suggests that robotic-assisted laparoscopy has benefits similar to those established for traditional laparoscopy in comparison to laparotomy. Although traditional laparoscopy is typically the least expensive surgical approach, robotic-assisted laparoscopy appears to be less costly than laparotomy, especially when societal costs associated with recovery are considered.

Risk of Port Site Metastases after Laparoscopic or Robotic Staging

The rate of port-site tumor implantation after laparoscopic procedures in women with malignant disease is low and almost always occurs in the setting of synchronous, advanced intra-abdominal or distant metastatic disease. The risk of port-site metastases should not be used as an argument against offering women with early stage endometrial cancers either a conventional or a robotic approach to their disease.

Adjuvant Radiation Therapy

Radiation therapyhas a role as adjuvant treatment after surgery or sometimes as definitive treatment for patients who are medically inoperable or with local recurrence. The need for postoperative radiotherapy is usually determined by prognostic features obtained from the pathology review. Radiation therapy decreases the risk of pelvic recurrence. Postoperative radio therapy in women with Stage II endometrial carcinoma patients led to an improved 5-year disease-free survival (24-25). Similar results were observed in women with Stage IIIC endometrial carcinoma receiving adjuvant EBRT and EBRT/BT.

The benefit of adjuvant radiation is most pronounced in women with high-risk pathologic features (26). In the PORTEC-1 trial, the 5-year risk of vaginal and pelvic recurrence for high/ intermediate risk patients was 19% without further treatment, compared to 5% after EBRT.

Brachytherapy is perceived to be a more convenient mode of treatment compared to external beam radio therapy and might be associated with less toxicity. PORTEC-2 compared the efficacy of vaginal BT and EBRT and suggested that vaginal brachytherapy was effective in preventing vaginal recurrence. Despite the slightly but significantly increased pelvic failure rate in the VBT arm, rates of distant metastases, OS, and RFS were similar (27). Vaginal brachytherapy provided a better quality of life than external-beam radiotherapy for endometrial carcinoma and should be the preferred treatment (28).

Role of Chemotherapy

The value of adjuvant systemic chemotherapy in patients with high-risk early stage endometrial cancer is not very clear. The GOG 34 trial, using single-agent doxorubicin, did not show any benefit for women with clinical Stage I or II (occult) disease who had one or more risk factors for recurrence after surgical staging (29). Comparing 5 cycles of cisplatin, doxorubicin, and cyclophosphamide with external pelvic radiation, there was no difference between therapies in terms of progression-free or overall survival (30).

Follow-Up

Survival outcomes vary with each FIGO stage (see table). In general, prognosis depends mainly on the age and health of the patient and the histological grade and stage of the tumor. Any pelvic pain or vaginal or rectal bleeding may indicate disease recurrence which should be investigated. Both patients and healthcare professionals should be alert for general symptoms of malignancy and metastasis such as anorexia, unexplained weight loss, and bowel, urinary, or respiratory symptoms. Follow-up should be conducted every three months with careful history and pelvic examination at each visit in the first two years after diagnosis. Appointments every six months are recommended for the next three years. Radiological images, including CT scans, are not indicated for routine follow-up of patients who do not have symptoms. Serum CA 125 measurement has been suggested for post treatment surveillance but it should be obtained in patients with elevated levels at the time of diagnosis or with known extra uterine disease.

Conclusion

Endometrial cancer is the most common gynecologic malignancy, and an understanding of presentation, surgical management, and treatment options is required for gynecologic oncologists. Although there continues to be controversy regarding treatment of early-stage endometrial cancer, considerable progress has been made over the past several decades.

Advancement in minimally invasive surgical techniques has allowed extensive staging procedures to be performed with significantly reduced patient morbidity. Using surgical staging, it is possible to avoid unnecessary adjuvant treatment in low risk patients, while defining a group of higher risk early-stage patients who may benefit from more aggressive adjuvant therapy, such as systemic chemotherapy. Combination therapy with radiation and chemotherapy is under evaluation.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012: cancer incidence and mortality worldwide 2012. IARC CancerBase 11. Lyon, France: International Agency for Research on Cancer; 2013. Available at globocan.iarc.fr (accessed 10 December 2014)
2. Zhang Y, Wang J. Controversies in the management of endometrial carcinoma. Obstet Gynecol Int. 2010; vol. 2010, Article ID 862908.
3. Julka PK, Manoharan N, RathGK.Cancer incidence and mortality in Delhi UT Urban. Delhi Cancer Registry,2008 & 2009.
4. Norris HJ, Tavassoli FA, Kurman RJ. Endometrial hyperplasia and carcinoma. Diagnostic considerations. Am J Surg Pathol. 1983;7(8):839– 847.
5. E. L. Trimble, L. C. Harlan, L. X. Clegg, and J. L. Stevens, "Pre-operative imaging, surgery and adjuvant therapy for women diagnosed with cancer of the corpus uteri in community practice in the United States," Gynecologic Oncology, vol. 96, no. 3, pp. 741–748, 2005.
6. W. T. Creasman et al., "Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer," International Journal of Gynecology and Obstetrics, vol. 95, supplement 1, pp. S105–S143, 2006.
7. M. E. Randall, V. L. Filiaci, H. Muss et al., "Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study," Journal of Clinical Oncology, vol. 24, no. 1, pp. 36–44, 2006.
8. M. Singh, R. J. Zaino, V. J. Filiaci, and K. K. Leslie, "Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group study," Gynecologic Oncology, vol. 106, no. 2, pp. 325–333, 2007
9. K. H. Lu, M. Dinh,W. Kohlmann et al., "Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome," Obstetrics and Gynecology, vol. 105, no. 3, pp. 569–574, 2005.
10. Y. Hirai, N. Takeshima, T. Kato, and K. Hasumi, "Malignant potential of positive peritoneal cytology in endometrial cancer," Obstetrics and Gynecology, vol. 97, no. 5, pp. 725–728, 2001.
11. R. N. Grimshaw,W. C. Tupper, R. C. Fraser,M. G. Tompkins, and J. F. Jeffrey, "Prognostic value of peritoneal cytology in endometrial carcinoma," Gynecologic Oncology, vol. 36, no. 1, pp. 97–100, 1990.
12. T. Kasamatsu, T. Onda, N. Katsumata et al., "Prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus," British Journal of Cancer, vol. 88, no. 2, pp. 245–250, 2003.
13. P. M. Tebeu, Y. Popowski, H. M. Verkooijen et al., "Positive peritoneal cytology in early-stage endometrial cancer does not influence prognosis," British Journal of Cancer, vol. 91, no. 4, pp. 720–724, 2004.
14. N. Kadar, H. D. Homesley, and J. H. Malfetano, "Positive peritoneal cytology is an adverse factor in endometrial carcinoma only if there is other evidence of extrauterine disease," Gynecologic Oncology, vol. 46, no. 2, pp. 145–149, 1992
15. J. K. Chan,M. K. Cheung,W. K. Huh et al., "Therapeutic role of lymph node resection in endometrioid corpus cancer: astudy of 12,333 patients," Cancer, vol. 107, no. 8, pp. 1823– 1830, 2006.
16. W. T.Creasman,C. P.Morrow, B. N. Bundy,H.D.Homesley, J. E. Graham, and P. B. Heller, "Surgical pathologic spreadpatterns of endometrial cancer. A gynecologic oncology group study," Cancer, vol. 60, no. 8, pp. 2035–2041, 1987
17. C. V. Lutman, L. J. Havrilesky, J. M. Cragun et al., "Pelvic lymph node count is an important prognostic variable forFIGO stage I and II endometrial carcinoma with high-risk histology," Gynecologic Oncology, vol. 102, no. 1, pp. 92–97,2006.
18. H. Nomura, D. Aoki, N. Suzuki et al., "Analysis of clinicopathologic factors predicting para-aortic lymph node metastasis in endometrial cancer," International Journal of GynecologicalCancer, vol. 16, no. 2, pp. 799–804, 2006.
19. Mariani, S. C. Dowdy, W. A. Cliby et al., "Efficacy of systematic lymphadenectomy and adjuvant radiotherapy innode-positive endometrial cancer patients," Gynecologic Oncology, vol. 101, no. 2, pp. 200–208, 2006.
20. T. Fujimoto, H. Nanjyo, A. Nakamura et al., "Para-aortic lymphadenectomy may improve disease-related survival inpatients with multipositive pelvic lymph node stage IIIc endometrial cancer," Gynecologic Oncology, vol. 107, no. 2, pp.253–259, 2007.
21. Walker JL, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009;27(32):5331–6.
22. Kornblith AB, et al. Quality of life of patients with endometrial cancer undergoinglaparoscopic international federation of gynecology and obstetrics staging comparedwith laparotomy: a Gynecologic Oncology Group study. J Clin Oncol 2009;27(32):5337–42.
23. M. Janda, V. Gebski, A. Brand et al., "Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomized trial," The Lancet Oncology, vol. 11, no. 8, pp. 772–780, 2010
24. D. E. Cohn, E. M. Woeste, S. Cacchio et al., "Clinical and pathologic correlates in surgical stage II endometrial carcinoma," Obstetrics and Gynecology, vol. 109, no. 5, pp. 1062– 1067, 2007.
25. P. J. Rossi, A. B. Jani, I. R. Horowitz, and P. A. S. Johnstone, Adjuvant brachytherapy removes survival disadvantage of local disease extension in stage IIIC endometrial cancer: a SEER registry analysis," International Journal of RadiationOncology Biology Physics, vol. 70, no. 1, pp. 134–138, 2008.
26. J. D. Wright, J. Fiorelli, A. L. Kansler et al., "Optimizing the management of stage II endometrial cancer: the role of radical hysterectomy and radiation," American Journal of Obstetricsand Gynecology, vol. 200, no. 4, pp. 419–e1, 2009
27. R. A. Nout, V. T. H. B. M. Smit, H. Putter et al., "Vaginal brachytherapy versus pelvic external beam radiotherapy forpatients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomisedtrial," The Lancet, vol. 375, no. 9717, pp. 816–823, 2010.
28. R. A. Nout, H. Putter, I. M. J¨urgenliemk-Schulz et al., "Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial," Journal of Clinical Oncology, vol. 27, no. 21, pp. 3547–3556, 2009.
29. T. Thigpen, R. B. Vance, L. Balducci, and J. Blessing, "Chemotherapy in the management of advanced or recurrent cervical and endometrial carcinoma," Cancer, vol. 48, no. 2, pp. 658– 665, 1981.
30. R. Maggi, A. Lissoni, F. Spina et al., "Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial," British Journal of Cancer, vol. 95, no. 3, pp. 266–271, 2006.

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PERSPECTIVE

FUTURISTIC PURVIEW ON CARCINOMA ENDOMETRIUM

Introduction

Endometrial cancer is the commonest genital tract cancer in women in the developed world and is fast becoming a leading cancer among women in urban India given the life style changes, akin to that of western women. In 2012 and estimated were 319605 new cases of endometrial cancer were diagnosed and 76155 deaths were recorded (Globocan 2012) with a five-year prevalence of 121,504 cases[1]. There have been interesting new developments in the classification of uterine cancers, particularly related to genetic profiles and this may pave the path to more rational treatment. The Cancer Genome Atlas Research Network (TCGA) studied sequencing- based techniques and indicated that endometrial cancers can be classified into at least 4 subtypes on the basis of molecular characteristics[2].

Integrated Genomic Characterization by the TCGA Network[2]

The recent work by TCGA research network has subclassifed endometrial cancers into four different types based on proteomic, transcriptomic and genomic analysis. They performed a molecular analysis of 373 patients with endometrial cancer (307 endometrioid and 66 serous) and found micro-satellite instability (MSI) in 40% of endometrioid adenocarcinomas and 2% of serous tumors. They sub-classified endometrial carcinomas into four clusters based on (i) MSI status, (ii) copy number clusters and (iii) nucleotide substitution frequencies and patterns. Cluster 1 was the ultra-mutated group with very high mutation rates and this group had mutations in the exonuclease domain of POLE (catalytic subunit of DNA polymerase epsilon involved in DNA replication and repair). Cluster 2 had hyper mutated tumors showing increased MSI and most of them with promotor 1 hypermethylation. Cluster 3 was microsatellite stable (MSS) and had a lower mutation frequency and most of the tumors were endometrioid. Cluster 4 had a low mutation frequency but a high rate of Somatic Copy Number Alterations (SCNAs) and the group contained most of the serous and mixed histology tumors with frequent TP53 mutations. When the progression-free survival was analyzed after a median follow up of 32 months it was found that Cluster 1 had a significantly better progression-free survival (PFS) compared to other clusters and cluster 2 having better PFS than Cluster 3 and Cluster 4 having significantly worse PFS than others.

Thus the integrated molecular analysis of endometrial carcinomas by TCGA led to the identification of four different groups of endometrial carcinomas as opposed to the traditional classification of Type I and Type II tumors. The new POLE sub type (Cluster 1) comprised about 10% of the endometrioid tumors. This group is characterized by hotspot mutations in the exonuclease domain of POLE, ultrahigh somatic mutation frequency and MSS. The survival analysis showed a significantly high progression-free survival for this group. The analysis of SCNAs also added new information about endometrial cancers, showing that the extent of SCNAs correlated with the progression-free survival. 25% of high-grade endometrioid carcinomas had extensive SCNAs and increased TP53 similar to that of uterine serous carcinomas.

Therapeutic Implications

The improved knowledge about the molecular characteristics of endometrial carcinoma should ideally translate into targeted therapy offering better survival with less treatment related toxicity to the patient. Gynecologic oncology group (GOG) conducted Phase II trials for Trastuzumab, Bevacizumab, Lapatinib and Geftinib in the treatment of endometrial cancers.

Trastuzumab is a monoclonal antibody directed against HER 2 receptor and has proven survival advantage in HER 2 positive women affected with breast cancer. GOG 181-B looked into treating patients with advanced or recurrent HER 2 – positive endometrial carcinoma with Trastuzumab[3]. Trastuzumab did not show any activity against HER 2 positive endometrial cancer in this Phase II trial. Serous tumors have high frequency of HER 2 amplification and trials have shown that uterine serous carcinoma may respond to HER 2 inhibition [4]. Further research is warranted in this area.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor–A (VEGF-A). It is used in the treatment of many malignancies including ovarian and cervical malignancies. The GOG 229-E Phase II trial assessed the activity of Bevacizumab in recurrent or persistent endometrial cancer

and found that 40% patients survived progression free for 6 months and 13.5% patients had objective clinical response[5]. The results were similar across all histologies. The results of GOG 086-P, a randomized Phase II trial combining Bevacizumab with chemotherapy is awaited.

Lapatinib is a member of the 4-anilinoquinazoline class of kinase inhibitors and acts as a dual inhibitor of both EGFR and HER2 tyrosine kinase activity[6]. GOG 229-D assessed the efficacy of Laptinib in endometrial cancer and found that it had insufficient activity to warrant its use as a single agent in endometrial cancer[7]. The GOG 229-C trial involving Geftinib, yet another tyrosine kinase inhibitor did not show improved response rates for patients with persistent or recurrent endometrial cancer [8].

Konency et al. assessed the activity of fibroblast growth factor receptor (FGFR) inhibitors Dovitinib and NVP-BGJ398 in human endometrial cancer cells and found that both molecules had significant antitumor activity in FGFR2 mutated endometrial cancer xenograft models[9]. The antiproliferative effect of Metformin in obese endometrioid endometrial cancer patients was analysed by Schuler et al. and found that 65% patients responded to metformin and it reduced proliferation by 11.75% supporting further therapeutic clinical trials using metformin[10]. Metformin has shown to reduce cell proliferation in endometrial cell lines [75]. Treatment with metformin resulted in G1 phase arrest, induction of apoptosis and reduced HER 2 expression. In this study metformin reduced endometrial cancer cell proliferation, establishing its potential role in prevention of endometrial cancer in obesity and metabolic syndrome.

Conclusions

The recent work by TCGA research network has subclassified endometrial cancers into four different types based on proteomic, transcriptomic and genomic analysis. Survival analysis also showed distinctive progression free survival curve; the POLE mutated group having very good survival rates. This classification may lead to changes in the management of endometrial cancers in the future. The anti-proliferative effects of Metformin, may in the time to come, be harnessed for prevention of endometrial cancer in obese women.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on , 18th May, 2015.
2. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497 (7447):67-73.
3. Fleming GF, Sill MW, Darcy KM, Mcmeekin DS, Tate J, Adler LM, et al. Phase II Trial of Trastuzumab in Women with Advanced or Recurrent, HER2-Positive Endometrial Carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2010; 116(1): 15–20.
4. Schwab CL, Bellone S, English DP et al. Afatinib demonstrates remarkable activity against HER2-amplified uterine serous endometrial cancer in vitro and in vivo.Br J Cancer. 2014;111(9):1750-6.
5. Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin. Oncol. 2011;29(16):2259–65.
6. Aertgeerts K, Skene R, Yano J, Sang BC, Zou H, Snell G, et al. Structural analysis of the mechanism of inhibition and allosteric activation of the kinase domain of HER2. J Biol Chem. 2011; 286:18756–65.
7. Leslie KK, Sill MW, Lankes HA, Edgar G, Godwin AK, Gray H, et al. Lapatinib and Potential Prognostic Value of EGFR Mutations in a Gynecologic Oncology Group Phase II Trial of Persistent or Recurrent Endometrial Cancer. Gynecol Oncol. 2012 ; 127(2): 345–50.
8. Leslie KK, Sill MW, Fischer E, Darcy KM, Mannel RS, Tewari KS, et al. A Phase II Evaluation of Gefitinib in the Treatment of Persistent or Recurrent Endometrial Cancer: A Gynecologic Oncology Group Study. Gynecol Oncol. 2013; 129(3): 486–94.
9. Konecny GE, Kolarova T, O'Brien N a, Winterhoff B, Yang G, Qi J, et al. Activity of the fibroblast growth factor receptor inhibitors dovitinib (TKI258) and NVP-BGJ398 in human endometrial cancer cells. Mol. Cancer Ther. 2013 ;12(5):632–42.
10. Schuler KM, Rambally BS, DiFurio MJ, et al. Antiproliferative and metabolic effects of metformin in a preoperative window clinical trial for endometrial cancer. Cancer Med. 2014 Nov 21. doi: 10.1002/cam4.353. [Epub ahead of print]
11. Cantrell LA1, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy.Gynecol Oncol. 2010;116(1):92-8.

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IN FOCUS

MOLECULAR BIOLOGY OF ENDOMETRIAL CANCER

Endometrial cancer is a common gynecologic malignancy. Based on Globocan 2012 data an estimated 320,000 new cases are diagnosed with a mortality of 2.1% every year. Amongst these 90% of cases of endometrial cancer are sporadic, whereas the remaining 10% of cases are hereditary. A dualistic model proposed by Bokhman for endometrial tumorigenesis is used for its classification. It is broadly termed Type 1 and Type 2. This model serves as a useful way to categorize these cancers in terms of both etiology and clinical behavior. However, this classification lacks in not addressing the endometrial cancers with shared characteristics. Also, the correct biologic and pathologic assignment of some uterine cancers is controversial, such as carcinomsarcomas that may represent extremely poorly differentiated (ie, grade 4) endometrial cancers.

Type 1 endometrial cancers represent the majority of sporadic cases, accounting for 70% to 80% of new cases. These cancers are typically of endometrioid type and therefore are primarily associated with unopposed estrogen exposure. Risk factors include obesity, anovulation, nulliparity, and exogenous estrogen exposure. Type 1 endometrioid lesions arise in a background of hyperplasia and commonly express estrogen and progesterone receptors. Clinically, these cancers are more often low-grade tumors with a favorable prognosis. In contrast, the remaining 10 to 20% of endometrial cancers are Type 2. Their histology is often high-grade, usually papillary serous or clear cell and are unrelated to hormonal exposure. They typically arise in a background of atrophic endometrium. Clinically, Type 2 cancers have an aggressive clinical course with a propensity for early spread and poor prognosis.

Theses types are also diverse in genetic alterations. Type 1 endometrial cancer is most commonly characterized by mutation of PTEN, and also by mutations in Kras, â-catenin, phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) and phosphatidylinositol 3-kinase (PIK3). Some cases also have inactivation of mutS homolog 6 (MSH6), which is associated with microsatellite instability (MSI).

Genetic Alterations of Type 1 Endometrial Cancers

Genetic Alteration	Type 1 Carcinoma(%)	Type 2 Carcinoma (%)
PTEN inactivation	50-80	10
K-ras mutation	15-30	0-5
β-catenin mutation	20-40	0-3
Microsatellite instability	20-40	0-5
p53 mutation	10-20	80-90
HER-2/neu	10-30	40-80
p16 inactivation	10	40
e-cadherin	10-20	60-90

Table 1: Genetic Alterations in Endometrial Cancer: Percentage Frequency of Genetic Mutations Identified in Type 1 and 2 Endometrial Cancers

On the other hand Type 2 endometrial cancers show mutations of p53 and p16, reduced expression of E-cadherin and overexpression of human epidermal growth factor receptor 2 (Her-2/neu). The percentage frequency of occurrence of each alteration is given in table 1.

PTEN

Endometrioid carcinomas are characterized by a variety of genetic alterations, the most frequent of which been PTEN which is altered in up to 83% of endometrioid carcinomas and 55% of precancerous lesions. PTEN, located at chromosome 10q23, encodes a protein with tyrosine kinase function and behaves as a tumor suppressor gene. PTEN inactivation is caused by mutations that lead to a loss of expression and, to a lesser extent, by a loss of heterozygosity. The proteinhas both lipid and protein phosphatase activity, with each serving different functions. The lipidphosphatase activity of PTEN causes cell cyclearrest at the G1/S checkpoint. Also, the up regulation of proapoptotic mechanisms involving AKT-dependent mechanisms is mediated through PTEN, as is the down regulation of antiapoptotic mechanisms through Bcl-2. PTEN further acts in opposition to phosphotidylinositol 3-kinase (PI3KCA) to control levels of phosphorylated AKT. Mutation of PTEN increases the PI3KCA activation, resulting in phosphorylation of AKT. PI3KCAmutation is seen in 36% of endometrioid endometrialcancers and is most common in tumors that also bear the PTEN mutation. The protein phosphatase activity of PTEN is involved in the inhibition of focal adhesion formation, cell spread, and migration, as well as the inhibitionof growth factor-stimulated MAPK signaling. Thus, loss or altered PTEN expression results in aberrantcell growth and apoptotic escape. Loss of PTEN isfurthermore likely an early event in endometrial

tumorigenesis, as evidenced by its presence in precancerous lesions, and is likely initiated in response to known hormonal risk factors.

Microsatellite Instability (MSI)

Microsatellite in stability (MSI) has been demonstrated in 20% of sporadic endometrioid endometrial cancers. MSI refers to the propensity to develop changes in the numberof repeat elements in microsatellites (ie, short segments of repetitive DNA bases found predominantlythroughout noncoding DNA) compared with normal tissue due to DNA repair errors made during replication. Inactivation of any number of components of the mismatch repair system can lead to MSI. MLH1 inactivation is the most common mechanism in the endometrium and is accomplished by hypermethylation of CpGislands in the gene promoter. Inherited or somatically acquired mutations of MSH6, although relatively uncommon in endometrial cancers in general, are often seen inMSI endometrial cancers. MSI also represents an earlyevent in endometrial carcinogenesis and has been demonstrated in precancerous lesions, likely targeting those genes that contain susceptible repeat elements. Interestingly, higher rates of mutations (60% to 80%) in the PTEN gene have been described in tumors with MSI compared to tumors without MSI (24% to 35%).

K-ras

K-ras mutations have been identified in 10% to30% of type 1 endometrial cancers. Most studies demonstrate a higher frequency of K-ras mutations in MSI cancers.

β-catenin

Gain of function mutations in the β-catenin gene at 3p21 is seen in 25% to 38% of Type 1cancers as well. Whereas PTEN, MSI, and K-ras mutations often coexist with each other, mutations in β-catenin are usually seen alone. β-catenin also acts as a downstream transcriptional activator in theWnt signal transduction pathway. These mutations result in stabilization of protein that resists degradation, thus resulting in cytoplasmic and nuclear accumulation and constitutive target gene activity. The accumulation of β-catenin has been demonstrated by immunohisto chemistry. Alterations in β-catenin expression have also been demonstrated in atypicalhyperplasia, thus representing an early event in endometrial tumorigenesis.

Genetic Alterations in Type 2 Endometrial Cancers

The most common genetic alteration in Type 2 serous carcinomas is in p53, the tumor suppressor gene. The p53 gene is located on chromosome 17 and is important in preventing the propagation of cells with damaged DNA. Mutations in p53 are present in about 90% of serous carcinomas. The exact mechanism for the causeof this mutation is still unclear. After DNA damage,nuclear p53 accumulates and causes cell cycle arrest byinhibiting cyclin-D1 phosphorylation of the Rb gene and thereby promoting apoptosis. Thus, mutated p53 results in a non functional protein that accumulates inthe cell and acts as a double negative inhibitor of thewild-type p53, leading to propagation of aberrant cells. Mutations in p53 are present in about 80% of endometrial intraepithelial carcinoma lesions, the putative precursor lesion to serous carcinomas. It is postulated thatmutation in one allele occurs early during the developmentof serous carcinoma, and loss of the second normalallele occurs late in the progression to carcinoma.

P16 inactivation was foundin 45% of serous carcinomas and some clear cell cancers. The p16 tumor suppressor gene is located onchromosome 9p21 and encodes for a cell cycle regulatoryprotein. Thus, inactivation of p16 leads to uncontrolled cell growth.

HER-2/neu

HER-2/neu overexpression and gene amplification were found in about 45% and 70% of serous carcinomas, respectively. HER-2/neu is an oncogene that codes for a transmembrane receptor tyrosine kinase involved in cell signaling.

E-cadherin

Negative and reduced E-cadherin expression occurred in 62% and 87% of serous and clear cell cancers, respectively. E-cadherin is a transmembrane protein with five extra cellular domains and an intracellular domain that connects to the actin cytoskeleton through a complex with cytoplasmic catenin. Decreased expression of E-cadherinis associated with a loss of cell-cell cohesive forces and has been shown to precede tumor cell motility.E-cadherin negative tumors are more likely to be poorly differentiated or non endometrioid and are associated with poorer prognosis.

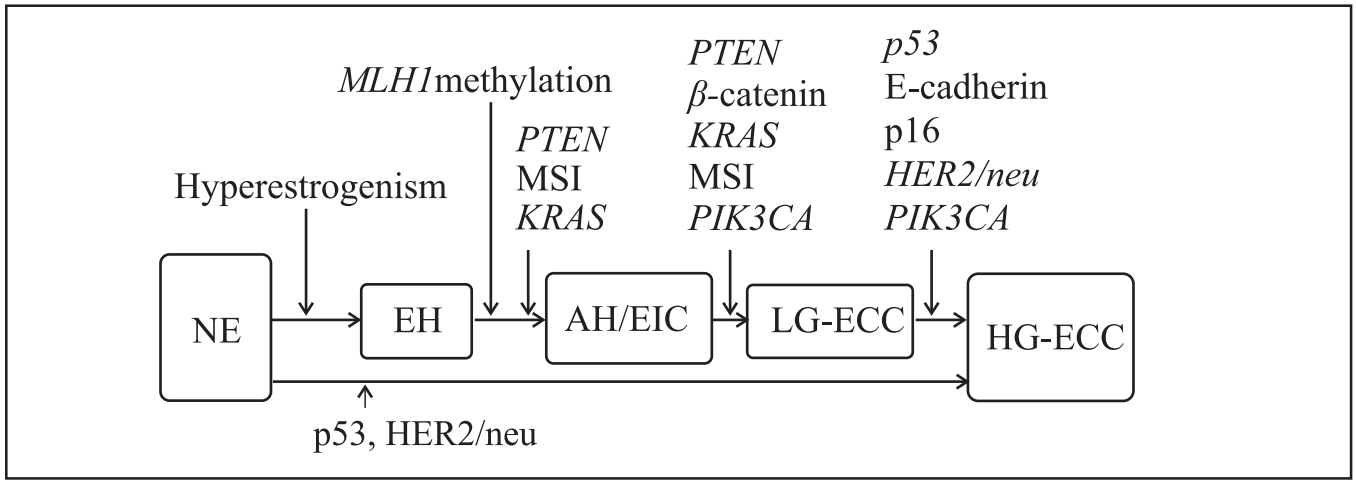

Fig1: NE, normal endometrium; EH, endometrial hyperplasia without hyperplasia, AH, atypical endometrial hyperplasia; EIC, endometrial intraepithelial carcinoma; LG-ECC, low grade endometrioidendometrial carcinoma; HG-ECC, with endometrioid endometrial carcinoma

Progression Model for Type I Endometrioid Carcinomas

A progression model of endometrioid carcinoma resembling the colorectal carcinoma has been proposed. Tumor initiation and progression are characterized by acquisition of various molecular alterations. PTEN alterations appear central to the initiation of proliferative lesions that then acquire mutations in other cancer-causing genes (e.g., DNA mismatch repair genes, KRAS, β-catenin) in the carcinogensis. An alternative pathway bypasses atypical hyperplasia and low-grade carcinoma to high grade carcinoma by p53 mutation and HER2/neu amplification.(Fig 1).

Progression Model for Type 2 Carcinomas

Mutations of p53 were found in approximately 80% of EIC, but in contrast to most serous carcinomas,there is no LOH at the locus TP53. Thus, it is hypothesized that p53 mutation of one allele occurs early, whereas loss of the normal second allele accompanies progression into serous carcinoma. The alterations of E-cadherin, p16, and HER2/neu seem to affect the progression from EIC to serous carcinoma. Another group hypothesizedthat serous carcinoma may develop from endometrioid carcinoma through p53 mutation based on findings in mixed endometrioid and serous carcinomas. (Fig 2).

Endometrial Cancer as a Familial Tumor)

Cases of multiple occurrence of endometrial cancer in a single family suggest involvement of genetic abnormalities. The most typical are cases of Lynch syndrome, an autosomal dominant disorder characterized by juvenile-onset of malignant tumors and colorectal cancer as the core malignant tumor. Patients with Lynch syndrome have risks for gastric, small intestinal, biliary and urologic cancer, in addition to colorectal cancer, and females have increased risks for endometrial and ovarian cancer. Mutations of MMR genes, MLH1, mutS homolog 2 (MSH2), mutS homolog 3(MSH3), MSH6,

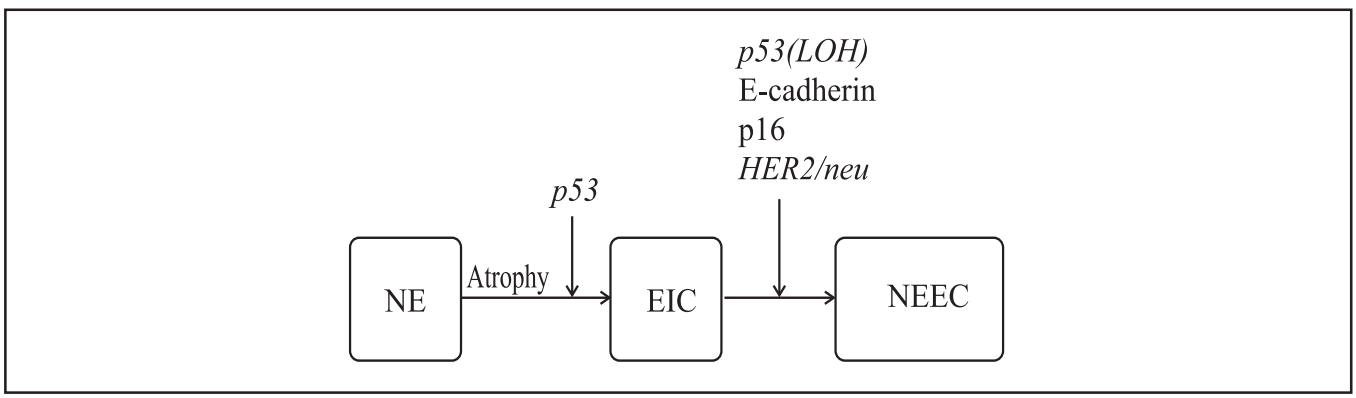

Fig 2: A progression model for non endometrioid (Type II) carcinomas. NE, normal endometrium; EIC, endometrial intraepithelial carcinoma; NEEC, non-endometrioid endometrial carcinoma

Tissue biomarkers	Serum biomarkers
p53	CA125
PTEN-PIK3-mTOR signaling pathway *(PTEN, PIK3, mTOR, 4E-BPI)*	CA15-3
MSI	YKL-40
β-catenin	VEGF
Ras-MAPK-ERK Signaling pathway *(K-ras, RASSF1A, ERK)*	
VEGF	
DNA aneuploidy	

Table 2 : Biomarkers in Endometrial Cancer

postmeiotic segregation increased1 (PMS1) and PMS2, are involved in the pathological mechanism of Lynch syndrome through inhibition of MMR during DNA replication, whichleads to subsequent MSI and carcinogenesis. MSH6 is the most important MMR gene in endometrial cancer thatmay be related to Lynch syndrome. Lynch syndrome can also occur without mutation of MMR genes, but with epimutation in the MLH1 and MSH2 promoter regions. Conversely, epimutation in germ cell lines maybe a cause of Lynch syndrome, based on a family with mutation in the epithelial cell adhesion molecule (EPCAM) germ cell line, which causes hypermethylation in CpG islands in the MSH2 promoter.This epigenetic abnormality is also transmitted genetically. Cowden syndrome (CS) and Peutz-Jeghers syndrome (PJS) are also genetic diseases associated with endometrial cancer. The onset of CS involves the PTEN gene, and approximately 80% of patients with CS have a PTEN mutation. The lifetime risk of endometrialcancer is 2% to 4% in the general population, but 5% to 10% in patients with CS. Patients with Peutz-Jeghers syndrome (PJS) have a higher risk ofdeveloping a malignant tumor in the gastrointestinal tract and other organs compared to the generalpopulation. LKB1/STK11 has been identified as a disease-related gene with autosomal dominant inheritance, and LKB1 mutation is found in 80% to 94% of patients with PJS.These patients have a 9% lifetime risk of developing endometrial cancer.

Upregulation	Downregulation
mir-200a	miR-410
miR-200b	miR-15b
miR-200c	miR-17-5p
miR-429	miR-20a
miR-203	miR-34b
miR-205	miR-152
miR-210	miR-125a
	miR-214
	miR-221
	miR-222
	miR-424

Table 3:Expression of mRNA in Endometrial Cancers

Biomarkers in Endometrial Cancer

The most important factors for diagnosis and outcome prediction in endometrial cancer are surgical stage, tumor differentiation, invasion depth and vascular invasion, based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines.

Useful histological biomarkers for endometrial cancer include p53, PTEN, MSI, β-catenin, Ras-mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), vascular endothelial growth factor (VEGF) and DNA aneuploidy. Serummarkers include carbohydrate antigen 125 (CA125), carbohydrate antigen 15-3 (CA15-3), chitinase3-like 1 protein (YKL-40), VEGF and human epididymal secretory protein E4 (HE-4).(Table 2).

microRNA Abnormalities in Endometrial Cancer

miRNAs are short non-coding RNAs of 20 to 23 base pairs that regulate gene expression at the post-

transcriptional level . miRNAs play an important role in carcinogenesis by targeting tumor suppressor oncogenes or by functioning as oncogenes with elevated expression. In endometrial cancer and, particularly, in endometrioid adenocarcinoma, various miRNAs are down- or up-regulated. The miR-200family (miR-141, miR-200a, miR-200b, miR-200c and miR-429) and miR-203 , miR-205 and miR-210 are all upregulated, whereas miR-410 [28], miR-15b, miR-17-5p, miR-20a, miR-125a, miR-214, miR-221, miR-222 and miR-424 are all down regulated (Table 3).

Studies have show that patients with recurrence can be differentiated by the levels of miR205 and miR-200a with high significance and that lymph node metastasis is associated with expression of miR-200a, miR-203 and miR-429. Aberrant DNA hypermethylation also inactivates expression of miRNAs.

Ongoing work suggests that miRNAs may serve as biomarkers for diagnosis and monitoring of treatment outcomes in endometrial cancer.

Targeted Therapies

Advances in the understanding of molecular events leading to the developments in endometrial cancer have led to the development of targeted anticancer therapies. Detailed description of these therapies is beyond the prerview of this article.Common targets for therapeutics include drugs that affect apoptosis, signal transduction, epigenetic modification, drug resistance, protein folding and degradation,cell cycle progression, hormone receptor activity,and angiogenesis. These new targeted agents are being investigated alone and with conventional therapy in the treatment of endometrial cancer.

The mammalian target of rapamycin (mTOR) are used in variety of trials.A number of other agents targeting components of the mTOR-AKT- PI3K-PTEN pathway have also been developed. Epidermal growth factor receptor (EGFR) family members — ERBB1 (EGFR or HER-1), ERBB2 (HER-2/ neu), ERBB3 (HER-3), and ERBB4 (HER-4) — have been shown to be highly expressed in endometrial cancers.Therefore, anti-EGFR targeted therapies are currently being investigated. Of all types of endometrial cancers, 60 to 80% overexpress EGFR, and 20 to 30% overexpress HER-2/neu.17. Trastuzumab, a monoclonal antibodydirected against HER-2/neu, has showed minimal activity, even in cancers with high overexpression of HER2/neu. Vascular endothelial growth factors (VEGF) and their receptors play a key role in normal and pathologic angiogenesis, and antiangiogenic agents have been developed to target this pathway.

Folate receptor alpha (FR-α) targeted therapy in high-risk endometrial carcinomas has been studied and found to be expressed in nonendometrioid, high-grade, and advanced-stage endometrial cancers, therefore making it an attractive therapeutic target.

Another proposed target lies in cells with an alteredfibroblast growth factor receptor 2 (FGFR2) gene. In such cells, researchers at the Translational Genomics Research Institute (TGen) showed that a pan-FGFR inhibitor drug, PD173074, both inhibited growth and induced cell death. The altered FGFR2 gene causes the receptors to become active, leading to cell proliferation. Therefore, although PTEN inactivation is a common event, the targeting of cancers with altered FGFR2 in this scenario may be part of the pathway to the future of personalized medicines.

Conclusions

Improved understanding of the molecular basis for endometrial cancer has led to the identification of molecular targets for novel therapeutic strategies of treatment. Additionally, molecular targeted therapies can be combined to deliver increased benefit to patients. Molecular markers are also showing promising predictive and prognostic role. This however is a continuous evolution and future will translate more of molecular jargon for clinical use.

Suggested Reading

1. Molecular Profiling of Endometrial Malignancies: Obstetrics and Gynecology International, Volume 2010.
2. Current Treatment of Metastatic Endometrial Cancer: Cancer Control: January 2009, Vol. 16, No. 1.
3. The Molecular Biology of Endometrial Cancers and the Implications for Pathogenesis, Classification, and Targeted Therapies : Cancer Control : January 2009, Vol. 16, No. 1
4. Candidate Biomarkers for Genetic and Clinicopathological Diagnosis of Endometrial Cancer : International Journal of Molecular Sciences : Int. J. Mol. Sci. 2013, 14, 12123-12137
5. MicroRNAS in endometrial cancer: recent advances and potential clinical applications: EXCLI Journal 2015;14:190-198 - ISSN 1611-2156

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