Diagnosis and Surgical Treatment of Endometrial cancer

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Introduction...

- Most common gynaecological malignancy worldwide
- Mean age of diagnosis: 63 years
- 90% of cases occur in women > 50 years

- Most common presentation: post menopausal bleeding
- 20% diagnosed before menopause
- 4-5% before the age of 40 years
REFERENCES FOR TODAY

- NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY
- APRIL 2017

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer
Diagnosis, Treatment and Follow-up

Endometrial Cancer

Management of Endometrial Hyperplasia
Green-top Guideline No. 67
RCOG/BSGE Joint Guideline | February 2016
Important points to ponder----

- Who are at risk…whom to screen and how??
- Approach to postmenopausal lady with bleeding P/V
- Approach to postmenopausal lady with incidentally diagnosed thick ET/ fluid
- Premenopausal lady: when to suspect EC

- Once decided for biopsy: how to sample
- Once diagnosed: how to work-up

- Evidence based treatment options
SCREENING FOR ENDOMETRIAL CANCER

- RISK FACTORS
- EVIDENCE ABOUT SCREENING
Risk Factors

- Prolonged estrogen exposure
- Tamoxifen
- Obesity
- Diabetes
- Age (15% less than 50 years)
- Hypertension
- Reproductive factors (Early menarche, nulliparity, Late menopause)

Genetic predisposition
- Lynch/ HNPCC
- Autosomal dominant
- Germline mutations in mismatch repair genes

OCPs
- Medroxy progesterone
- Progesterone IUCD
- Smoking
Recent meta-analysis of >3000 EC patients

- RR with metabolic syndrome: 1.85
- Largest association with obesity (RR2.2)
- Strength of association between obesity and cancer risk increases with increasing BMI
- Independent RR of diabetes questionable
- Infertility and nulliparity proven risk factors
- Unopposed estrogen: highest association
- Estrogen producing tumors: 20% have associated EC
There is no evidence for endometrial cancer screening in the general population.

- Level of evidence: II
- Strength of recommendation: A
Screening in high risk groups

- Routine surveillance in **asymptomatic women** with obesity, PCOS, diabetes mellitus, infertility, nulliparity or late menopause is not recommended

- Level of evidence: III
- Strength of recommendation: B
Tamoxifen....overall RR 2.53

- Premenopausal women treated with tamoxifen have no known increased risk of endometrial Cancer
- Relative risk in postmenopausal women is 4.0
- The level of risk of endometrial cancer is also dose and time dependent.

Routine screening for endometrial cancer in asymptomatic tamoxifen users is not recommended
Level of evidence: III
Strength of recommendation: B
Clinical presentation

- Abnormal uterine bleeding
- Vaginal discharge
- Abdominal pain, distension, bowel and bladder symptoms in advanced disease
How to approach a postmenopausal woman with AUB
Recommendations...

- Any vaginal bleeding in a postmenopausal woman requires assessment to exclude malignancy.

- Women with postmenopausal BPV may be assessed initially with either endometrial biopsy or TVS; this initial evaluation does not require performance of both tests.

- When EB is performed and tissue is insufficient for diagnosis, some further investigation is necessary and TVS may be performed.
Recommendations

• When TVS is performed and ET is less than or equal to 4mm, endometrial sampling is not required.

• ET >4mm should trigger alternative evaluation, as should an inability to adequately visualize thickness.

Because of extremely high negative predictive value, non-invasive nature, low cost and easy availability: TVS is a reasonable first approach to PMB
TVS

- ACOG $\leq$ 4mm
- SRU $\leq$ 5mm

- supported by a meta-analysis of 35 prospective studies that included data from almost 6000 women with postmenopausal bleeding.

- sensitivity and specificity of TVUS for detection of endometrial cancer at a 4 mm thickness threshold were 96 and 53 percent, and at a 5 mm threshold the sensitivity and specificity were 96 and 61 percent.

- At 3 mm: sensitivity is 98%
Post menopausal lady with incidentally diagnosed thick ET

- 15-20% endometrial cancers occur in women without vaginal bleeding

- Significance of ET>4mm in asymptomatic postmenopausal lady has not been established, does not routinely trigger evaluation
How thick is too thick?

• **Symptomatic patient**: ET > 5mm: 7.3% risk of malignancy vs <0.07% if ET ≤5mm or less

• 11 mm ET yields similar separation between low risk and high risk in asymptomatic post-menopausal women

  • 6.7% risk if ET ≤11 mm vs 0.002% if ET ≤11 mm

• By decreasing cut-off from 11 to 7 mm, cancer detection rate increases from 87 to 95%, but false positives will quadruple

**Cut-off of 11mm acceptable trade-off between cancer detection and unnecessary biopsies**
What to do with endometrial fluid??

- No separate recommendations

- In most of these women, endometrial fluid is related to cervical stenosis

- Observational studies have consistently found that asymptomatic postmenopausal women with endometrial fluid and an endometrial thickness smaller than 3 mm do not have endometrial cancer or hyperplasia

- However, there is an increased risk of endometrial cancer in women with endometrial fluid and endometrial thickening >3 mm; therefore, biopsy is advised
Pre-menopausal lady

• Endometrial evaluation for abnormal bleeding at > 40 years or history suggestive of excess estrogen exposure irrespective of endometrial thickness

• For asymptomatic women:
  • Optimal cut-off not defined
  • Cut-off of 16mm recommended by some
Once decided we need to sample...

how to sample??
How to sample

- Pipelle aspiration: accepted first choice:

- When sample adequate: PPV: 81.7%
  NPV: 99.1%

- Inadequacy of sample: results vary from 0 to 54% in studies

- Referral for D&C should be considered if sample inadequate or symptoms persist
Evidence

- A meta-analysis of 39 studies involving 7914 women compared the results of endometrial sampling with histopathology at D&C, hysteroscopy, and/or hysterectomy.

- Pipelle device more sensitive for detection of endometrial cancer and atypical hyperplasia than all other sampling devices.

- Sensitivity for diagnosis of EC (by Pipelle) in postmenopausal women: 99.6%
  premenopausal women: 91%

- Sensitivity for diagnosis of atypical endometrial hyperplasia: 81%

- Specificity for diagnosis of endometrial carcinoma: 98 to 100 percent.

- Fewer than 5 percent of patients had an insufficient or no sample.

No dilatation, no anaesthesia, cost effective.
D&C...indications...

- When a patient is not able to tolerate an office endometrial biopsy (e.g., due to pain or anxiety)
- After a non-diagnostic office biopsy in women who are at high risk of endometrial carcinoma
- After benign histology on office biopsy in women who have persistent abnormal uterine bleeding
- When there is insufficient tissue for analysis on office biopsy and ET is thick
- When cervical stenosis prevents the completion of an office biopsy
- When a concomitant operative procedure, such as laparoscopy, is deemed necessary

Diagnostic hysteroscopy at the same time
Higher accuracy and diagnostic yield but positive cytology more

Cochrane: no evidence of worse prognosis
Once diagnosed;

how to work-up
ESMO recommendation

Mandatory work-up must include:

- Family history
- General assessment and inventory of comorbidities
- Geriatric assessment, if appropriate
- Clinical examination, including pelvic examination
- Transvaginal ultrasound
- Complete pathology assessment (histotype and grade) of an endometrial biopsy or curettage specimen
Optional pre-op work up

• **In clinical stage I, grade 1 and 2:** At least one of the three following tools should be used to assess myometrial invasion if LND is considered:
  - Expert ultrasound and/or MRI and/or intra-operative pathological examination

• Level of evidence: IV
• Strength of recommendation: A
Recommendation for CT/MRI/PET-CT

- Other imaging methods (thoracic, abdominal and pelvic CT scan, MRI, PET scan) should be considered to assess ovarian, nodal, peritoneal or metastatic disease

- Level of evidence: IV
- Strength of recommendation: C
Place of MRI

- Endometrial carcinomas are divided into two histologic subtypes. Endometrioid adenocarcinoma (type 1), Type 2 endometrial carcinomas include serous papillary and clear cell adenocarcinomas.

- Serous papillary, clear cell, and grade 3 endometrioid adenocarcinomas demonstrate more aggressive tumor biologic characteristics and have a 50% pretest probability of locally advanced or distant disease at manifestation.

- Information provided by MR imaging is invaluable in managing endometrial carcinoma. In response to growing evidence, the National Cancer Institute in France incorporated preoperative MR imaging into its guidelines for managing endometrial carcinoma. MR imaging is also recommended by the ESUR for staging high-risk endometrial carcinoma, including all histologic subtype 2 and high-grade subtype 1 tumors.

- MR imaging plays an important role in the treatment stratification of patients with endometrial carcinoma. Accurate preoperative delineation of local disease extent and involved lymph nodes is essential.
There is evidence that CA-125 and HE-4 are significantly correlated with histological grade, stage, lymph node metastases, myometrial invasion and cervical involvement.

However, the appropriate cut off has not been established and evidence that serum marker assessment is clinically useful is lacking.

There is no evidence for the clinical usefulness of serum tumour markers, including CA-125.

Level of evidence: IV

Strength of recommendation: B

Selective in unstaged patients and serous tumors.
Whom to offer genetic screening??
Facts

- 2-4% of all those with endometrial cancer have Lynch Syndrome
- 10% in women diagnosed under the age of 50
- EC is the first malignancy in 50% of LS women
- Lynch syndrome, an autosomal dominant cancer-prone syndrome caused by germline mutations in genes encoding components of the DNA mismatch repair (MMR) pathway.
- At risk of metachronous colorectal cancer and other Lynch syndrome-associated cancers, and their first-degree relatives are at 50% risk of Lynch syndrome.

If age <50 used as cut-off: 30 to 70% cases of LS will be missed
Detailed family history must for all cases of EC
Universal molecular testing is the preferable method
IHC for MLH1, MSH2, MSH6, and PMS2 expression
Management
MANAGEMENT OF ENDOMETRIAL CANCER

- TAH with BSO: mainstay of treatment till 30 years back

- In 1988: mounting evidence that extrauterine disease was associated with poor outcomes and that patients with advanced disease required more than just surgical intervention

- EC: converted to a surgically staged disease
Comprehensive surgical staging

- Advantages of comprehensive surgical staging: **diagnosis, prognosis, and proper triage of patients for adjuvant therapy**
- FIGO’s surgical staging system for endometrial cancer is based on surgical pathology, and comprehensive staging allows for accurate definition of disease extent
- Hence, the recommended initial management of endometrial cancer should include comprehensive surgical staging (**total hysterectomy, BSO, pelvic and para-aortic lymphadenectomy, and the collection of peritoneal cytology [pelvic washings]**)
- Cytology to be taken (though does not affect prognosis)
- Omental biopsy: for clear cell, serous and carcinosarcoma
- Thorough visual inspection of all peritoneal surfaces of abdomen
Route of surgery

- Minimally invasive surgery should be embraced as the standard surgical approach whenever feasible.
- Power morcellation should not be used in women with known or strongly suspected uterine malignancy.
- Robotic-assisted laparoscopic staging: feasible and safe alternative.
- Vaginal route precludes thorough abdominal survey and lymphadenectomy may be an appropriate treatment for early-stage endometrial cancer in select patients who are at very high risk of surgical morbidity.

GOG lap 2
Meta analysis
Survival rate 89% same for laparotomy and laparoscopy
Short term benefits better with laparoscopy
Port site metastasis is less than 1%
Clinical stage 1
TH+ BSO*

Clinical stage II
Radical hysterectomy with BSO

Clinical stage III-IV
Complete cytoreduction

Ovarian preservation can be considered in women <45 years old with <50% myometrial invasion, no obvious extra-uterine disease and no family history of ovarian cancer risk.

Patients with A1EIN or G1 EEC requesting fertility-preserving therapy must:
- Be referred to specialised centres
- Undergo D&C with or without hysteroscopy
- Have A1EIN or G1 EEC confirmed by a specialist gynaecopathologist
- Undergo pelvic MRI to exclude overt myometrial invasion and adnexal involvement
- Be fully informed that fertility-sparing treatment is a non-standard treatment
- Be willing to accept close follow-up
For patients undergoing fertility-preserving therapy, MPA or MA is recommended; progesterin-loaded IUD is also an option.
After completion of childbearing, hysterectomy and salpingo-oophorectomy is recommended.
Clinical Stage 1

Low risk: clinical stage 1A, G1/2 Endometrioid

Intermediate risk: clinical stage 1A, G3 or clinical stage IB, G1/2 Endometrioid

High risk: clinical stage 1B, G3 Endometrioid
All stages with non-endometrioid
Clinical Stage 1

- Low risk: Not recommended
- Intermediate risk: Can be considered
- High risk: recommended

Lymphadenectomy
Lymphadenectomy

Recommendations

- Patients with grade 1–2 endometrioid tumors, less than 50% myometrium invasion, and tumor of 2 cm or less seem to be at low risk for recurrence and may not require a surgical lymphadenectomy (level of evidence: B)
- Lymphadenectomy may alter or eliminate the need for adjuvant therapy and its associated morbidity (level of evidence: B)
- Sentinel lymph node dissection may reduce the morbidity associated with standard lymphadenectomy and may enhance the therapeutic benefit of surgical staging in early endometrial cancer (level of evidence: I)
This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.
Advanced-stage or recurrent endometrial cancer

- 10–15% of all new cases
- account for more than 50% of all uterine cancer-related deaths
- Is there a benefit from cytoreduction?

- Optimal surgical cytoreduction (variably defined as less than or equal to 1 cm or 2 cm) has been found to improve progression-free and overall survival rates in patients with advanced-stage or recurrent endometrial cancer.
Post-operatively...

- Appropriate pathological assessment
- Decision for adjuvant therapy
- Discussion in tumor board (Team of pathologists, Radiotherapist)
The commonest cancer of genital tract in women worldwide (second in India)
Women in the US have a 2.8 percent lifetime risk of being diagnosed with uterine cancer
Known high risk factors
Clinical staging for deciding extent of surgery
Adjuvant treatment based on surgico-pathological staging
Role of lymphadenectomy in early stage?
Role of chemotherapy?
Targeted therapy, Immunotherapy--

No role of screening till now---
Prevention is possible? Genetic testing---, metformin and OCP in PCOS?