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A comparison of various endometrial cancer management guidelines

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Abstract

This is a comparison review article of the various existing guidelines for the management of uterine neoplasms. The guidelines being compared include National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS), European Society of Gynaecological/Medical Oncology (ESGO/ESMO), Society of Gynaecology and Obstetrics (SGO), British Gynaecological Cancer Society (BGCS) and International Federation of Gynaecology and Obstetrics (FIGO). This article serves to highlight the key differences and similarities between those guidelines with regards to screening, Lynch Syndrome (Hereditary Non polyposis Colorectal Cancer) (HNPCC), prevention, diagnosis, staging, risk assessment, adjuvant therapy, treatment of advanced disease-and surveillance. Comparisons are displayed in both a comprehensive table and in the form of a discussion.

Abbreviations: ACS: American Cancer Society; ASCO: American Society of Clinical Oncology; BGSO: British Gynaecological Cancer Society; BMI: Body Mass Index; BSO: Bilateral Salpingo-oophorectomy; CT: Computed Tomography;

D&C: Dilatation and curettage; EBRT: External Beam Radiotherapy; EC: Endometrial Cancer; ESGO: European Society of Gynaecological Oncology; ESMO: European Society of Medical Oncology; FIGO: International Federation of Gynaecology and Obstetrics: HNPCC: Hereditary Non polyposis Colorectal Cancer; MRI: Magnetic Resonance Imaging; NCCN: National Comprehensive Cancer Network; SGO: Society of Gynaecology and Obstetrics; TAH: Total Abdominal Hysterectomy

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy worldwide [1-5]. It is also the sixth most common cancer in women and more than 90% of those diagnosed are older than 50 years of age [4,6,7]. The increase in incidence of EC is attributed to the increased incidence of obesity, prolonged exposure to oestrogen and the use of tamoxifen as an adjuvant therapy for breast cancer [1,2,6]. Patients mostly present with abnormal uterine bleeding while some present with vaginal discharge [1,2,4]. In 2017, almost two-thirds of patients had the disease confined to the uterus at the time of diagnosis [1]. EC tends to present early with symptoms that compel patients to seek healthcare, which could explain why it is mostly detected at an early stage[1]. Since patients with Lynch syndrome are at a higher risk of developing EC, and the fact that EC is a potentially life-threatening condition, they require annual screening as opposed to asymptomatic patients who do not need to be screened [1,4,5].

Introducing guidelines for managing EC has resulted in a reduction in the incidence, morbidity and mortality due to uterine neoplasms [1]. Establishing guidelines undoubtedly results in the early detection of the disease and hence, early treatment and better outcomes. Detecting pre-malignant states also helps in possibly preventing the progression to invasive cancer [6]. Different countries and societies worldwide have formed a set of recommendations and guidelines for managing EC from screening to prevention and treatment. These guidelines do not necessarily agree on all aspects as there is no universally agreed upon approach to manage patients with EC.

An optimal strategy to manage endometrial neoplasms is not very well established by the currently available evidence. This review article discusses the current international uterine neoplasms guidelines. We compared the following guidelines: American Cancer Society (ACS), European Society of Gynaecological/Medical Oncology (ESGO/ESMO), Society of Gynaecology and Obstetrics (SGO), British Gynaecological Cancer Society (BGCS) and the International Federation of Gynaecology and Obstetrics (FIGO). We highlighted the key differences and resemblances between those guidelines in terms of screening, diagnosis, prevention, staging, risk assessment, treatment and surveillance in addition to screening for Lynch Syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC).

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Key words: *uterine neoplasms, management guidelines, hnpcc, adjuvant therapy, risk assessment, staging, advanced disease and surveillance*

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Summary of Recommendations of Different Guidelines for Management of Uterine Neoplasms

Parameters	National Comprehensive Cancer Network (NCCN)	American Cancer Society (ACS)	European Society of Gynaecological/ Medical Oncology (ESGO/ESMO)	Society of Gynaecology and Obstetrics (SGO)	British Gynaecological Cancer Society (BGCS)	International Federation of Gynaecology and Obstetrics (FIGO)	American Society of Clinical Oncology (ASCO)
Screening	• No recommendation for screening of asymptomatic women				• High-risk groups only (e.g. Lynch syndrome)		• No recommendations
Screening for Lynch Syndrome (HNPCC)	• Annual endometrial sampling for carriers of *MLH1* or *MSH2* • Annual colonoscopy	• Annual screening for endometrial cancer with endometrial biopsy from 35 years for women with or at risk for HNPCC	• Annual surveillance by Transvaginal ultrasound and biopsy starting at 35 years until hysterectomy for all Lynch syndrome mutation carriers	• Genetically screen all women diagnosed with endometrial cancer for Lynch syndrome • Endometrial sampling and colonoscopy every 1-2 years	• Annual screening with Transvaginal scan and endometrial biopsy from 35 years of age	• Annual aspiration biopsy and Transvaginal Ultrasonography starting from the age of 35 years until hysterectomy	• No recommendations
Prevention	• Oral contraceptives containing oestrogen and progesterone for ≥ 1 year	• Add progestin to oestrogen for hormone replacement therapy • Offer prophylactic hysterectomy ± oophorectomy to women undergoing surgery for colorectal cancer and do not wish to preserve fertility	• Avoid unopposed oestrogen treatment in women with a uterus in-situ.		• Maintain a healthy BMI • Weight loss for obese women through bariatric surgery or lifestyle changes	• No recommendations	
Diagnosis	• Expert pathology review to determine histopathologic subtype	• Endometrial biopsy • If unsatisfactory, a D&C hysteroscopy	• Hysteroscopy with biopsy	• Pelvic ultrasonography, endometrial biopsy ± hysteroscopy	• Women with abnormal uterine bleeding should undergo abdominal, speculum and pelvic examination for • Women ≥45 years with menorrhagia, irregular bleeding, or failure of • Treatment need endometrial sampling	• Transvaginal ultrasound with endometrial biopsies by D&C	• No recommendations
Staging	• FIGO staging system • The TNM system developed by AJCC					• FIGO staging system	
Risk assessment	• The categories for endometrioid cancer treatment groups: • Disease limited to the uterus • Suspected or gross cervical involvement • Suspected extrauterine disease	• Vaginal hysterectomy for women at high risk for surgical morbidity	• Treatment groups based on the estimated risk of disease recurrence • Low risk: Endometrioid cancers confined to the endometrium • Intermediate risk: Disease that is confined to the uterus but invades the myometrium, or demonstrates occult cervical stromal invasion; • High risk: gross involvement of the cervix	• Stratify patients based on the FIGO staging	• No recommendations	• Stratify patients based on the FIGO staging	• No recommendations
Adjuvant therapy	• TAH+BSO and complete surgical staging with pelvic washings, bilateral pelvic and paraaortic lymphadenectomy. • Closely monitor women receiving fertility-sparing treatment with endometrial biopsy every 3 months:		• TAH+BSO • Approach: minimally invasive surgery such as laparoscopy		• The uterine size and extent of tumour to determine the safety and appropriateness of total or vaginal approach and laparoscopic or open surgery	• Minimally invasive surgery preferably laparoscopy	• TAH +BSO • Post TAH: no radiation therapy is a reasonable option for the following patients: 1 - without residual disease in the hysterectomy specimen, despite positive biopsy of any grade 2- grade 1 or 2 cancers with either no invasion or <50% myometrial invasion

Treatment of advanced disease	• Hormone therapy followed by chemotherapy on progression for low-grade metastases • Chemotherapy and palliative radiation therapy for symptomatic, high-grade, or large-volume metastases • Persistent progression should be treated with best supportive care and enrolment in a clinical trial	• Concurrent chemo-radiation followed by adjuvant chemotherapy; alternative sequencing strategies with EBRT and chemotherapy	• Combination chemotherapy and radiation therapy should be considered before a single-modality treatment	• Further imaging by abdominal-pelvic MRI or CT. • Patients with unexpected high-risk findings in definitive histology (post-operatively) require CT chest, abdomen and pelvis to plan appropriate adjuvant radiotherapy or chemotherapy.	• The indication for adjuvant radiation therapy is based on the presence of risk factors. • External beam radiotherapy or vaginal brachytherapy • Adjuvant platinum-based chemotherapy with EBRT in patients with risk factors (grade 3 or deep invasion or adverse histological features)	• Vaginal cuff brachytherapy may be considered in patients with negative node dissection, with grade 3 tumour without myometrial invasion, and patients with grade 1 or 2 tumours with 50% myometrial invasion • Concurrent chemoradiation followed by adjuvant chemotherapy for patients with positive nodes or involved uterine serosa, ovaries/ fallopian tubes, vagina, bladder, or rectum • Alternative sequencing strategies with external beam radiation and chemotherapy
Surveillance	• Review of symptoms and pelvic exam every 3- 6 months for the first 2 years and every 6 -12 months thereafter.	• Pelvic exam every 3-4 months for the first 2-3 years, then every 6 months until 5 years to monitor for disease recurrence • Prefer PET/CT over CT alone for assessment of suspected recurrence.	• Review of symptoms and pelvic exam every 3-6 months for the first 2 years and every 6 -12 months thereafter.	• Clinical examinations every 3 months for the first 3 years and then annually for the subsequent two years	• Non irradiated patients would benefit from regular follow-up	• No recommendations

Discussion

Screening

All of the guidelines reviewed agree that low-risk and asymptomatic women should not be screened for EC since that does not result in decreased mortality [6]. About 25% of endometrial biopsies do not yield sufficient tissue for diagnosis and this subjects women to further investigations, a few of which were guided by false positive results [4,6]. This is particularly unwarranted in asymptomatic women due to the increased risk of anxiety and procedure complications including discomfort, bleeding and infection [6].

In the case of Lynch Syndrome (carriers of *MLH1* or *MSH2),* annual screening is recommended with an endometrial biopsy from the age of 35 years. NCCN, ESGO, ESMO, BGCS and FIGO recommend offering prophylactic surgery (hysterectomy and BSO) to Lynch Syndrome carriers [1,4,7,8].

All patients should also be informed of the risks and symptoms of endometrial cancer, as well as the potential benefits, risks, and limitations of testing for early endometrial cancer detection[4].

Prevention

Prolonged unopposed oestrogen is highly associated with an increased risk of developing EC by 10-30 times [2,4,5]. The risk of EC is proportional to the duration of use of unopposed estrogen [5]. This risk can be reduced by adding progestin to estrogen [2,5]. However, high-dose progesterone must be avoided due to the increased risk of cardiovascular disease, stroke, thrombosis and breast cancer [6]. NCCN states that the use of combined oral contraceptives for at least one year reduces the risk of developing EC [1].

ACS recommends that women undergoing surgery for colorectal cancer and those who do not wish to preserve fertility should be offered prophylactic hysterectomy and/or oophorectomy [5]. BGSO stresses on the importance of maintaining a healthy BMI, through lifestyle modifications or bariatric surgery, to reduce the risk of developing EC [4,6]. Obese women have an increased risk of 2-4 times relative risk of getting EC [5]. Additionally, every 5 kg/m^2 increase in BMI is associated with a 1.6-fold increased risk of EC [6]. FIGO does not have any recommendations for prevention of EC probably because their guideline mainly focuses on staging the disease and its treatment.

Diagnosis

Measuring endometrial thickness is easier with a transvaginal ultrasound compared to a transabdominal ultrasound [6]. The cut-off point for endometrial thickness is ≥ 4mm[6]. Endometrial biopsy is associated with 10% false-negative results, which may warrant further investigation, especially in patients with high suspicion of EC, such as unexplained uterine bleeding[1]. While abdominal, pelvic and speculum examination are imperative for clinical assessment of a patient, all the guidelines are in agreement that an expert pathological review of an endometrial biopsy is the gold standard to determine the histopathological subtype [4,5]. D&C with or without hysteroscopy is reserved to those with a high risk of EC or had an inadequate biopsy[6]. It can help detect endometrial polyps seen on ultrasound [6].

All women diagnosed with EC must be tested for Lynch syndrome since they might need to be screened for colorectal cancer [1,2]. Patients with Lynch syndrome have a lifetime risk of up to 60% of developing both EC and colorectal cancer [1,4-7].

Staging and risk assessment

The FIGO staging system and the TNM system developed by the AJCC is universally agreed upon for staging EC [1,2,4,6-9]. Staging through pelvic examination and ultrasound can help assess the size of the tumor, the extent of myometrial invasion, cervical involvement and also rule out ovarian disease [4].

FIGO Staging System [6-9]:

I. Tumor confined to the uterus

I A. Invading < 50% of myometrium

I B. Invading ≥ 50% of myometrium

II. Tumor invades cervical stroma

III. Tumor extends locally/regionally

III A. Invading serosa ± adnexa

III B. Involving vagina ± parametrium

III C. Metastasis to pelvic/para-aortic lymph nodes

III C1. Positive pelvic nodes

III C2. Positive para-aortic lymph nodes ± positive pelvic lymph nodes

IV.Tumour invades bladder ± bowel mucosa ± distant metastases

IV A. Invades bladder ± bowel mucosa

IV B. Distant metastases (including intra-abdominal) ± inguinal lymph nodes

Patients are stratified into treatment groups based on the estimated risk of disease recurrence as follows: low risk, intermediate risk and high risk [4,7]. Low risk patients are those with endometrioid cancer confined to the endometrium. Intermediate risk includes stage IA and IB and a subset of patients with stage II disease. High risk cases are those in which there are gross involvement of the cervix (a subset of stage II disease; stage III or IV disease, regardless of grade; papillary serous or clear cell uterine tumours) [4,7]. Risk groups are defined to guide adjuvant therapy [4].

Conclusion

Effective screening methods and patient education can lead to early detection of EC. All women should be educated on the signs and their individual risks of developing EC. The gold standard method of screening is an endometrial biopsy. The treatment involves hysterectomy with or without oophorectomy with a possible addition of chemotherapy or radiation. Surveillance of recurrence involves a review of symptoms and pelvic examination initially every few months and then at longer intervals.

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