Review article

Management of endometrial cancer: An update to a gynaecologist

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Abstract

Endometrial carcinoma, the most common gynaecological malignancy in high income countries and increasingly rising in low-middle income countries, has a predominantly favorable outcome. Although the majority of cases of endometrial cancer are diagnosed at an early stage, differences in patient characteristics and histopathological features of the disease impact on both patient prognosis and the recommended treatment approach. Irrespective of the vast literature on the different management options for endometrial cancer, this article gives an updated summary on management principles to a practicing gynaecologist.

Key words: endometrial carcinoma, endometrial cancer, management, gynaecology

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Introduction

Endometrial cancer is the commonest gynaecological cancer in high income countries, while it is the second most common when the whole world is considered[1,2,1]. With nearly 80% of the patients being diagnosed in stage 1, endometrial cancer has an overall five year net survival reaching 80%[4,2]. Incidence of endometrial cancer has risen up by 50% in the United Kingdom between 1990 and 2012, causing a significant amount of the resource uptake of gynaecological cancer services[2,3]. Around 96% of the patients were diagnosed beyond the age of 40 years[4]. However, a better prognosis was observed in women less than 40 years of age[4].

With regards to Sri Lanka, endometrial cancer is the third commonest gynaecological cancer with 491 new endometrial cancers in 2018[5]. In the same year, 192 endometrial cancer patients were referred to National Cancer Institute (Apeksha Hospital), Maharagama, Sri

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Lanka out of which 7.0% (n=15) were less than 40 years (Unpublished data).

Pathophysiology

Endometrial cancer is histologically categorised into two groups[6]. Type 1 tumours represent the estrogen sensitive endometrioid type cells which has the best prognosis. Depending on the percentage of solid component in the cell architecture, these tumours are graded from 1 to 3. Type 2 tumours include endometrial serous carcinomas and clear cell carcinomas which represent a heterogeneous group of non-endometrioid type cells that are associated with poor prognosis as well as non-hormone dependent pathogenesis.

Risk factors

This rising incidence might reflect changes in the demographics of the risk factors (i.e. obesity) as well as aging of the population[3]. Risk factors for type 1 endometrial cancer are related to unopposed endometrial exposure to estrogen such as tamoxifen therapy, early menarche, late menopause, nulliparity, infertility, anovulation, obesity and polycystic ovary syndrome[7,8]. Other non hormonal risk factors include family history of endometrial cancer, age more than 50 years, hypertension, diabetes mellitus, thyroid disease, and Lynch syndrome[7,9]. Type 2 tumors although less common, predominantly occur in postmenopausal women[9]. Protective factors include prior use of combined oral contraceptives for at least one year and multiparity[9].

Diagnosis

Diagnosis: postmenopausal women

Summary of the basic steps for diagnosis and management of postmenopausal bleeding is illustrated in Figure 1. Transvaginal ultrasonography (TVS) is an accurate triaging tool for endometrial cancer. TVS reliably identifies postmenopausal women with vaginal bleeding who were unlikely to have cancer (thickness of 3mm or less). A large meta-analysis in 1998 found that an endometrial thickness (ET) of ≤4mm reduced the probability of EC to <1%[10]. However, in the recent past several alternative cut-offs for ET have been proposed. Latest accepted cut-off ET is ≥4 mm and in patients with a TVS endometrial thickness measurement of ≥4 mm, an outpatient endometrial biopsy (Pipelle aspirator device) is recommended. It is important to note that the Pipelle aspirator device has to be inserted more than 4cm through the cervical canal to obtain reliable results[11]. Further evaluation with hysteroscopy is warranted in cases of persistent abnormal vaginal bleeding despite inadequate sampling or negative histology[12]. Hysteroscopy should also be carried out in women with ultrasound irregularities in the ET and at high risk of endometrial cancer[12].

A 5mm cut-off has also been suggested for post-menopausal women on tamoxifen[12]. The upper endometrial thickness limit for postmenopausal women on hormone replacement therapy (HRT) is 8mm if asymptomatic, but if vaginal bleeding is present a biopsy should be taken if the thickness is ≥5mm[12].

Diagnosis: pre/peri-menopausal women

Women presenting with persistent prolonged or intermenstrual bleeding, heavy menstrual bleeding over 45 years, or those with irregular bleeding or failure of treatment over 45 years, should receive a clinical assessment (an abdominal, speculum and pelvic examination) and endometrial sampling as described above.

Staging

Traditionally endometrial cancer is staged surgico-pathologically according to the FIGO staging system. Pelvic lymph nodes are the commonest site of metastasis. Less commonly para aortic lymph nodes can be involved, which sometimes 'Skip' the pelvic lymph nodes. Characteristics of lymph node involvement in endometrial cancer depends on tumour type, differentiation, depth of myometrial invasion and plays as a key factor when planning surgery.

Initial clinical workup to plan management

All the patients diagnosed with endometrial cancer should be adequately staged before treatment. Even though the final staging is surgico-pathological, provisional radiological staging helps to plan treatment. It is recommended to perform Magnetic Resonance Imaging (MRI) scans of the pelvis and abdomen in all the patients with endometrial cancers to assess the myometrial invasion, extension to cervix, direct extra uterine spread and pelvic lymph nodes involvement. This is complimented by chest X-ray to assess for pulmonary metastasis. It is recommended to perform Computerised Tomography (CT) of chest, abdomen, and pelvis in high risk patients to exclude abdominal and pulmonary metastasis.

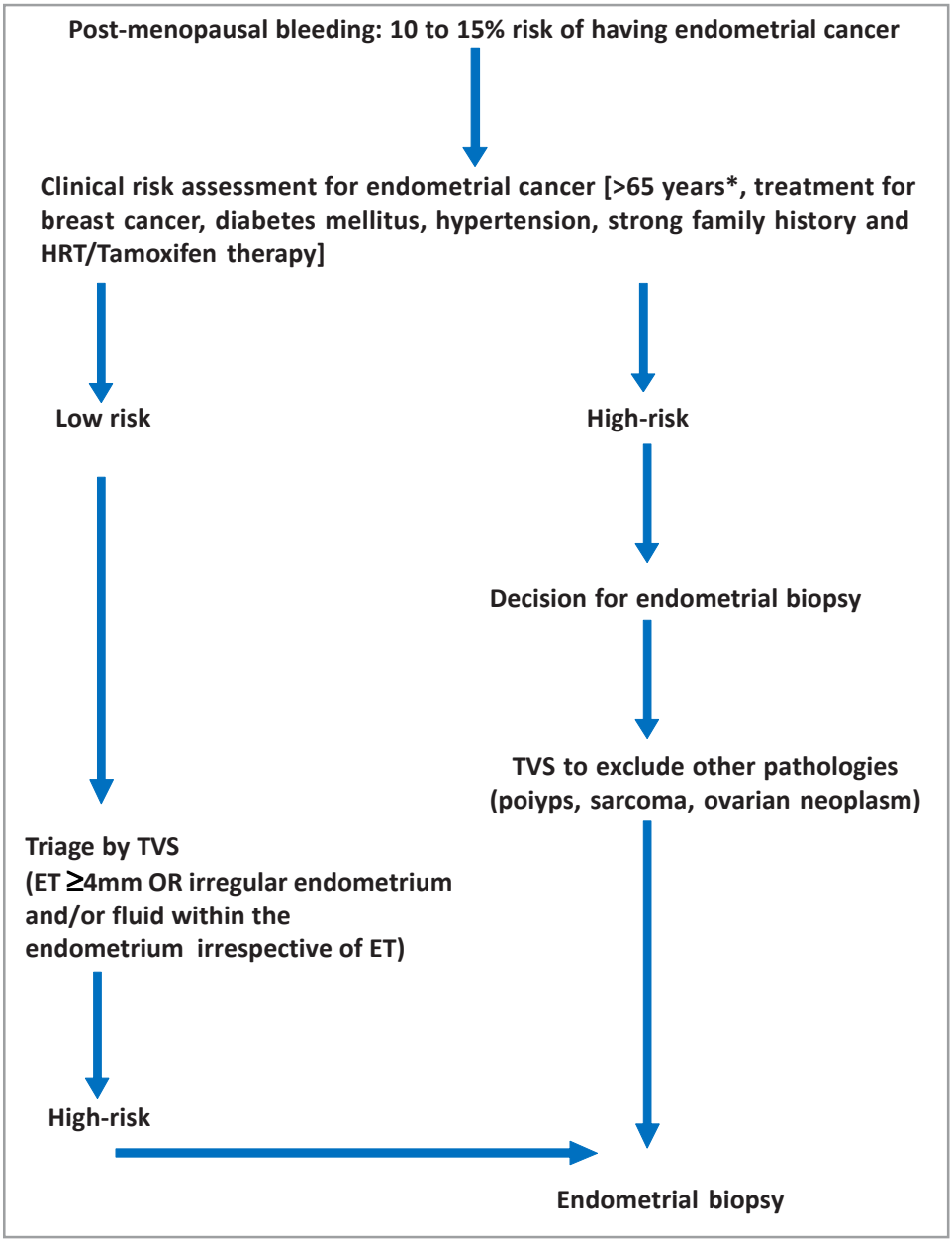

Figure 1. **Summary of management of post-menopausal bleeding.**

*risk increases with rising age and highest risk after 80 years
HRT: Hormone replacement therapy; TVS: Transvaginal ultrasonography; ET: Endometrial thickness.

All the patients who are having MRI or clinical evidence of FIGO stage 2 or more disease and/or Type 2 tumours or Grade 3 endometrioid cancer are considered high risk for metastatic disease. Clinical details, radiological findings and histology should be discussed in a multi-disciplinary group including gynaecological oncologist, Clinical/Medical Oncologist, Pathologist and Radiologist to plan the management that is optimal for each patient.

Management of early endometrial cancer (Stage 1 and stage 2)

a. Surgical management

Surgery is the first line of treatment in FIGO Stage I and 2 endometrial cancer. In Addition, adjuvant radiotherapy with or without chemotherapy is offered to those with risk factors for recurrence. All the patients with early endometrial cancer should undergo total

hysterectomy and bilateral salpingo-oophorectomy (BSO) as a minimum. Due to stimulatory effects of oestrogen on the endometrium, shared lymphatics between ovary and endometrium and possibility of synchronous ovarian cancer, ovarian preservation is not recommended.

Pelvic lymph node assessment plays a crucial part in the surgical management of endometrial cancer. The principle behind lymph node assessment is to identify patient with FIGO Stage 3c disease who would need external beam radiotherapy to achieve local disease control. However, lymph node assessment is also associated with both intra operative as well as long term complications. In order to balance the risks and benefits, the current recommendation is to perform pelvic lymph node assessment in high risk patients. There are considerable variations in the practices of pelvic lymph node assessment among different parts of the world as well as different cancer centres. To make matters more complicated, data from some randomised controlled trials are considered of good quality by some while, doubted by others. However, the positive association between depth of myometrial invasion and lymph-node metastasis was evident in early studies[13].

ASTEC trial is one of the most famous yet controversial studies which assesses the outcome of pelvic lymph node dissection in endometrial cancer[14]. It included 1408 patients with clinical stage I or II endometrial cancer assigned to systematic pelvic lymph node dissection (LND) versus removal of lymph nodes if suspicious at the discretion of the surgeon[14]. Subjecting this study to much controversy second randomization to radiation versus no radiation was performed in a subset of patients (intermediate- and high-risk early-stage patients) regardless of the status of the lymph nodes. After 37 months of median follow-up, removal of suspicious lymph nodes compared with systematic LND showed no difference in overall survival (HR 1.04, 95% CI 0.74-1.75) and recurrence-free survival (HR 1.25, 95% CI 0.93-1.66). Subgroup analysis (low, intermediate, high risk, and advanced) showed no difference in overall or recurrence-free survival. However, a second randomisation into 'radiotherapy' Vs 'no radiotherapy' is a significant confounder as disease progression of both surgical arms are affected by radiotherapy. It should be also noted that in real life, patients with positive lymph nodes are almost always offered adjutant radiotherapy. The average number of lymph nodes removed in this study was also low compared to previous studies. Due to these reason some authorities would consider this study to be methodologically flawed.

Deep myometral invasion and higher histological grade are well recognised risk factors for lymph node metastasis. Grade 2 tumors [7.3% in < 50% Versus 17.1% in > 50% invasion] and grade 3 tumors [6.9% in <50% Versus 35.3% in >50% invasion] have higher risk of pelvic nodal metastasis compared to grade 1 disease [3.8% in <50% Versus 15.2% in > 50% invasion][15]. Para aortic nodal involvement also follows a similar pattern in which isolated para-aortic (negative pelvic nodes) metastasis is highest in grade 3 tumours [27.3%] compared to grade 2 [12.5%] and grade 1 [0] in those with deep myometral invasion[15]. It should be noted that depth of myometrial invasion act as an independent risk factor in both para aortic and pelvic lymph node metastasis.

Due to above facts, many authorities agree for a compromise, in which lymph node assessment in the low risk patients (Grade 1 or 2, Stage 1a disease) could be avoided while all other patients are considered for lymph node assessment. Traditionally, lymph node assessment is done by bilateral pelvic lymph node dissection which is sometimes supplemented by para aortic lymph node dissection up to the level of renal vessels. However this surgical approach is associated with significant short and long term complications. Therefore less invasive sentinel lymph node assessment is currently emerging as an equally effective alternative for full dissection. Different indicators such as blue dye, Tc99 radio colloids as well as Indo Cyanine Green (ICG) have been used in different centers to identify the sentinel nodes. When combined with pathological ultra-sectioning and immunohistochemistry, this method has shown sensitivity up to 100% with negative predictive value of 93%[6,16].

b. Adjuvant treatment in early endometrial cancer

Risk of recurrence of endometrial cancer depends on multiple variables and adjuvant treatment is aimed at minimizing this risk. Many studies have been conducted to quantify the risk and efficacy of adjuvant treatment. First joint European Society for Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) held in 2014, stratified endometrial cancer patients into risk categories, reflecting their risk of recurrence and recommended adjuvant treatment[6]. These risk factors are illustrated in table 1.

Table 1. New risk groups to guide adjuvant therapy use in adequately staged patients with early stage endometrioid endometrial cancer

Risk group	Stage and description	Management
Low risk	FIGO grade 1, Stage Ia, Ib, no LVSI FIGO grade 2, Stage Ia, no LVSI	No adjuvant treatment
Intermediate risk	FIGO grade 2, Stage Ib, no LVSI FIGO grade 3, Stage Ia, no LVSI	Vaginal brachytherapy
High-intermediate risk	FIGO grade 3, Stage 1a, regardless of LVSI FIGO grade 1, grade 2, LVSI unequivocally positive, regardless of depth of invasion	Consider external beam radiation versus vaginal brachytherapy if nodal status unknown. Consider adjuvant brachytherapy versus no adjuvant therapy if node negative
High risk	FIGO grade 3, Stage Ib	Consider external beam radiation versus vaginal brachytherapy.

Adapted from ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group[6] and BGCS Uterine Cancer Guidelines[12].
FIGO 2009 staging has been used. LVSI – Lymphovascular space invasion.

Thus it is of paramount importance that these patients are reviewed post-operatively by a senior clinician familiar with managing endometrial cancer in order to identify and refer high risk patients for adjuvant treatment.

c. Management of patients who are medically unfit

Radiotherapy is the first line treatment in this group. Palliative high dose progesterone is used as a second line to control bleeding[17].

d. Fertility preserving treatment

Standard treatment for early endometrial cancer is surgery involving hysterectomy and bilateral salpingo oophorectomy irrespective of the age of the patient and any conservative treatment should be regarded as non-standard. Thus, all the patients who are offered with conservative treatment should be selected carefully and discussed in a multi-disciplinary setting[6]. This involves reassessment of the histology by a consultant pathologist specialized in gynae-oncological disease. Patients which had initial biopsy by Pipelle aspiration should undergo dilatation and curettage as it is superior in assessing the histological grade of the disease[6]. Pelvic MRI is also performed in all the patients to exclude overt myometrial invasion and pelvic lymph node involvement[6].

Following the initial assessment, patient with Grade 1 endometrioid type tumour without myometrial invasion who are appropriately counselled could be offered with conservative treatment[6]. High dose Medoxy progesterone acetate (MPA) is considered as the standard treatment while Levenogestrel Intra-uterine System (LNG-IUS) is increasingly being used in the recent times[18]. Oral MPA 400-600 mg and oral Megestrol 160 to 320 mg daily are considered as the standard regimens[12,19].

All the patients should be assessed with endometrial biopsy at 3 to 6 months and repeat MRI scan at 6 months from initiation of treatment. If remission is achieved, these patients should be referred to reproductive medicine specialist for assisted reproduction[18]. Those patients who do not respond by 6 months should be offered with standard surgical management. Those patients who achieve remission but not planning to

become pregnant at the end of 6 months of treatment should continue progesterone treatment and have endometrial biopsy every 3 to 6 months. Overall live birth rate among these women was 14.9% with improvement to 39.4% when assisted reproduction technology is used[18]. However, there is no consensus on the appropriate duration of treatment. Most authors have sampled the endometrium at 3 monthly intervals and the time to response varies between 3 and 12 months in all series[19].

Management of advanced endometrial cancer

FIGO Stage IIIA and above is considered as advanced disease and surgery is associated with survival advantage only when complete debulking is achieved. Thus radical surgery with curative intent should be selected with caution. Otherwise surgery should be limited to palliation in instances like uncontrolled bleeding and intestinal obstruction.

Management of locally confined advanced disease (FIGO Stage 3) is controversial. Evidence on the outcome of each treatment is lacking and usually dictated by local experience, preferences and policy. Thus multi-disciplinary discussion is mandatory. Normal practice is to surgically debulk locally advanced, operable disease followed by radiotherapy and/or chemotherapy. Brachytherapy with or without external beam radiotherapy (EBRT) is the preferred option for those with an inoperable disease which is confined to the genital tract.

For advanced disease with distance metastasis, multi agent chemo therapy has shown survival advantage. Hormonal treatment with low dose progesterone (MPA 200mg/d) can be used as 3rd line treatment in well differentiated endometrioid type disease with response rate of 37%[20]. Response in poorly differentiated and Type 2 tumours are less than 10%.

Management of recurrent disease

Nearly 70% of the recurrences in endometrial cancers occur within three years from the primary treatment. Treatment in these patients are heavily influenced by the extent of the disease free interval, number of lesions, previous treatment and surgical resectability. Therefore, these patients should undergo MRI scan of the pelvis and abdomen as well as CT scan of chest abdomen and pelvis to assess pelvic and distant diseases.

Single recurrent lesion in a medically fit and willing patient with a disease free interval of more than one year should be considered for radical treatment aiming for cure. Surgery followed by radiotherapy or radical radiotherapy alone should be considered in patients with isolated resectable disease[21]. For large volume (>4cm) isolated resectable disease, commonly as in lymph node recurrences, surgical excision is the common practice even though evidence of benefit is lacking. In isolated vaginal vault recurrences without previous irradiation, radical radiotherapy can achieve disease remission nearly in 90% of the cases.

Central, isolated pelvic recurrence in a patient who previously underwent pelvic radiotherapy, should be considered for exenterative type procedure as these patients are not suitable for further radio therapy. Positron Emission Tomography (PET) scan to exclude any distance metastasis is a compulsory investigation before carrying out an exenterative procedure.

Patients who recurred within one year and those with multi focal disease would not be suitable for radical surgery or radiotherapy. Treatment in this patient group is palliative in intent and chemotherapy and hormonal therapy is considered as the first line. Low dose progesterone (MPA 200mg/d) is preferred over high doses[6,20]. Other options include palliative radiotherapy and palliative surgery.

Conclusion

When treated scientifically, endometrial cancer is a curable disease in most instances. Adherence to basic principles such as surgico-pathological staging, assessment of risk of recurrence following surgery and timely referral of high risk patients for adjuvant treatment is crucial in managing these patients.

Abbreviations

MRI: Magnetic Resonance Imaging

CT: Computerised Tomography

LND: Lymph Node Dissection

ESMO: European Society for Medical Oncology

ESRO: European Society for Radiotherapy & Oncology

ESGO: European Society of Gynaecological Oncology

MPA: Medoxy Progesterone Acetate

EBRT: HR - Hazard ratio

LNG: Levenogestrel Intra-uterine System

PET: Positron Emission Tomography

Author Declarations

Author contributions: All authors contributed equally to this work.

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