18 Endometrial Cancer with High-Risk Histology

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Introduction

Endometrial cancer (EC) has traditionally been classified into two histological categories that differ in incidence, hormone responsiveness and prognosis [1]. The type 2 tumours or the tumours with high risk histology consist of uterine papillary serous (10% of all EC), clear cell (2–4%) and carcinosarcoma (2–5%), undifferentiated (5%) and squamous cell (0.1–0.5%) [2]. These tumours are rare, comprising of <15% of all endometrial cancers, but their behaviour is more aggressive and they remain at a higher risk of recurrence and deaths than endometrioid subtype, when stage to stage comparison is done. Serous carcinoma leading to 39%, clear cell carcinoma leading to 8% and high grade endometrioid carcinoma leading to 27% of deaths due to disease [3, 4]. These tumours are seen usually in older women, women with BRCA mutations, post radiation therapy and also in breast cancer survivors using tamoxifen therapy. Surgery is the primary treatment followed by adjuvant combination chemo and radiotherapy. Several recent advances in understanding of molecular and genetic factors have led to tailoring of appropriate adjuvant therapy for these women [3, 4].

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Q: What Is WHO Classification of Endometrial Cancer. How To Classify Endometrial Cancer into Risk Categories (Low, Intermediate, High Intermediate, Intermediate)?

Ans

WHO Classification of Endometrial Cancer [5]

According to the recent WHO classification tumours of uterine corpus can be divided into following categories-

1. Endometrial epithelial tumours and precursors
2. Tumour like lesions
3. Mesenchymal tumours specific to the uterus
4. Mixed epithelial and mesenchymal tumours
5. Miscellaneous tumours

These categories have further sub divisions as below

Endometrial Epithelial Tumours and Precursors

Endometrioid adenocarcinoma harbours varying degrees of glandular, papillary and solid architectural pattern with the cells showing endometrioid differentiation

- Endometrial hyperplasia without atypia
- Atypical endometrial hyperplasia
- Endometrioid adenocarcinoma NOS
- Serous carcinoma NOS
- Clear cell adenocarcinoma NOS
- Carcinoma undifferentiated NOS
- Mixed cell adenocarcinoma
- Mesonephric adenocarcinoma
- Squamous cell carcinoma NOS
- Mucinous carcinoma, intestinal type
- Mesonephric-like adenocarcinoma
- Carcinosarcoma NOS

Tumour-Like Lesions

- Endometrial polyp
- Endometrial metaplasia
- Arias-Stella reaction

Mesenchymal Tumours Specific To the Uterus

- Leiomyoma NOS
- Intravenous leiomyomatosis
- Smooth Muscle tumours of uncertain malignant potential
  - Epithelioid
  - Myxoid
  - Spindle types
- Metastasizing leiomyoma
- Leiomyosarcoma NOS
- Endometrial stromal nodule
- Endometrial stromal sarcoma-low grade
- Endometrial stromal sarcoma-high grade
- Undifferentiated sarcoma
- Uterine tumor resembling ovarian sex cord tumor
- Perivascular epithelioid tumor (Benign, Malignant)
- Inflammatory myofibroblastic sarcoma

Mixed Epithelial and Mesenchymal Tumours

- Adenomyoma NOS

Table 18.1 Molecular risk stratification based on TCGA (The Cancer Genome Atlas Program) [3]

Group	Histology	Grade of disease	Mutation rates	Mutated genes
POLE ultramutated	Endometrioid	Any	High >200 × 10^6/Mb	POLE, PTEN, ARID1A, PIK3CA
MSI hypermutated	Endometrioid	Any	18 × 10^6/Mb	PTEN, PIK3CA, PIK3R1, ARID1A
Copy number low/ MMRp	Endometrioid	Low grade	2.9 × 10^6/Mb	PTEN, PIK3CA, CTNNB1, ARID1A
Copy number high	High-risk histology	High grade	2.3 × 10^6/Mb	TP53, PIK3CA, PPP2R1A, HER2

- Atypical polypoid adenomyoma
- Adenosarcoma

Miscellaneous Tumours

- Primitive neuroectodermal tumour NOS
- Germ cell tumour NOS (Yolk sac, mature and Immature teratoma NOS)

Risk Categories

For planning the adjuvant therapy, EC needs to be stratified into prognostic risk groups, including Low-risk, Intermediate-risk, High-Intermediate risk and High-risk groups. The prognostic risk groups be stratified based on availability of resources for molecular characterization of tumours. Integration of microscopic and molecular features is the best approach to stratify the patients to predict prognosis [6]. Based on the TCGA molecular classification POLE ultra-mutated tumours represent 6.4% of low-grade and 17.4% of high-grade endometrioid tumours. MSI-hypermutated tumours represent 28.6% of low-grade and 54.3% of high-grade endometrioid EC (EEC). Copy-number low tumours represent 60% of low-grade and 8.7% of high-grade EC (Table 18.1) [3]. The most commonly seen genetic mutation in the above three subtypes is PTEN. Copy-number high predominantly represents serous type (97.7%), mixed histology tumours (75% cases) and are characterized by TP53 mutation.

Risk Stratification if Molecular Characterization Is not Available

Risk stratification can be done based on stage histology, grade and LVSI into low risk, intermediate, high-intermediate, high-risk and advanced/metastatic categories as below (Tables 18.2 and 18.3).

Table 18.2 Risk stratification when molecular characterization is not available [6]

	Low	Intermediate risk			High-intermediate risk			High-risk		Advanced/Metastatic	
Stage	IA	IB	IA	IA	IA or IB	IB	II	III-IV A	I-IV A	III-IV A	IV B
Histology	Endometrioid	Endometrioid	Endometrioid	Non-endometrioid	Endometrioid	Endometrioid	Endometrioid	Endometrioid	Non-endometrioid	Endometrioid	Any
Grade	Low	Low	High		Any	High	Any	–			
LVSI + or -	Absent	Negative	Negative		Present	Any	Any				
-LVSI focal or substantial	Focal	Focal	Focal		Substantial	Any	Any				
MI				None	Any	Any	Any	Any	Present		
Residual disease								None	None	Present	Any

Table 18.3 Risk stratification when molecular characterization is available [6]

	Low		Intermediate risk			High-intermediate risk			High-risk			Advanced/metastatic	
Stage	I-II	IA	IB	IA	IA	IA or IB	IB	II	III-IV A	I-IV A	I-IVA	III-IV A	IV B
Histology	Any	Endometrioid	Endometrioid	Endometrioid	Any	Endometrioid	Endometrioid	Endometrioid	Endometrioid	Any	Non endometrioid	Endometrioid	Any
Grade	Any	Low	Low	High	Any	Any	High	Any					
LVSI + or -	Any	Negative	Negative	Negative	Any	Present	Any	Any					
LVSI focal or substantial	Any	Focal	Focal	Focal	Any	Substantial	Any	Any					
Myometrial invasion	Any	No or < 50%	>50%	No or < 50%	None	Any	>50%	Any	–	Present	Present		
Residual disease									None	None	None	Present	+/–
Molecular characterization	POLE mut	MMRd/ NSMP	MMRd/ NSMP	MMRd/ NSMP	P53 abn	MMRd/ NSMP	MMRd/ NSMP	MMRd/ NSMP	MMRd/ NSMP	P53 abn	NSMP/ MMRd	Any	Any

Q: Discuss Type 1 and Type 2 Endometrial Cancers? [3]

Traditionally endometrial cancers are divided into two sub groups based on clinical (by Bokhman et al.), biochemical and morphological components-.

	Type I	Type II
Clinical characteristics		
Distribution	60–70%	30–40%
Onset of menopause	>50 years	<50 years
Background endometrium	Hyperplastic	Atrophic
Oestrogen association	Yes	No
Tumour grade	Low (G1,2)	High (G3)
Myometrial invasion	Superficial	Deep
Potential for lymphatic spread	Lower	High
Prognosis	Favourable	Unfavourable
Sensitivity to progestogens	High	Low
5-year survival	High	Low
Stage at diagnosis	I, II	III, IV
Clinicopathological and molecular correlates		
Histopathology	Endometrioid	Non endometrioid (serous, clear cell, Carcinosarcoma, poorly differentiated)
ER, PR receptor status	High	Low
Genetic alterations		
Predominant genetic mutations	PTEN, PIK3CA, PIK3R1, KRAS, ARIDIA, MSI, CTNNB1	TP53 (80–90%), HER2 (30–40%), PPP2R1A (10–40%)

Comments

The clinical distribution in real life is heterogenous and following disparities may be observed

1. Not all patients with type I be obese and also not all type 2 are lean. It has been observed that >20% of serous endometrial cancer will be obese and also Type 1 tumours with lynch syndrome will be thin with no evidence of surrounding hyperplastic endometrium.
2. >20% of endometrioid adenocarcinoma type I tumours are high grade and their behaviour and outcome fall somewhere between type I and II, rather more like type II tumours. Thus these patients clinically present with advanced disease and have worse prognosis than other type I tumours.
3. 20% cases with serous adenocarcinoma will be associated with endometrial hyperplasia and 20% patients lack deep myometrial invasion.

Such a heterogeneity may be explained due to underlying molecular variations, therefore prognostic stratification is revised and now incorporates molecular features to determine the adjuvant therapy and prognosis.

Case 1

Age, Parity, PS	60 years P4L4; ECOG = 1
Presenting complaints	Post menopausal bleeding
Co morbidities	Hypertension, type 2 diabetes mellitus controlled on oral hypoglycaemics
Transvaginal sonography	Uterus normal size, growth in the cavity 3 × 4.5 cm with myometrial thinning, bilateral adnexa normal
Endometrial biopsy	Poorly differentiated endometrial carcinoma Serous papillary carcinoma
MRI	Growth in endometrial cavity, >50% myometrial invasion seen No retroperitoneal lymphadenopathy, bilateral ovaries normal
Surgery	Total abdominal hysterectomy with bilateral salpingo oophorectomy+ pelvic and paraaortic lymphadenectomy
Histology	Undifferentiated carcinoma, >50% MI No LVSI; nodes (0/18) FIGO Stage (2009) IB

Table 18.4 Incidence of lymph node involvement in type 2 endometrial carcinoma

Type 2 Endometrial cancer			
Site of nodal metastasis	Myometrial invasion		
	MI nil	MI <50%	MI >50%
Pelvic nodes	12.5%	19.4%	30%
Para aortic	9.5%	18.2%	10%
Isolated paraortic (Negative pelvic)	5.6%	3.8%	0%
Type 1 grade 3 endometrioid adenocarcinoma			
Site of nodal mets	NA	MI <50%	>50%
Pelvic	NA	6.9%	35.3%
Paraortic	NA	0%	25%
Isolated paraortic	NA	0%	27%

Q: How Do You Tailor Pelvic and Para-aortic Lymphadenectomy in High Risk Endometrial Cancer?

In high risk endometrial cancers the risk of nodal metastasis is high. According to a study by Kumar et al. 2014 [7] the risk of nodal metastasis in high risk endometrial cancer according to the myometrial invasion is shown in Table 18.4.

The standard surgical approach for patients with high-risk endometrial cancer is peritoneal wash cytology+ Total hysterectomy + bilateral salpingo-oophorectomy + pelvic and para-aortic lymphadenectomy + multiple peritoneal biopsies; Infracolic omentectomy be considered for serous, carcinosarcoma and undifferentiated carcinomas, while may be omitted for clear cell carcinoma [6].

For high-risk endometrial cancers, all the guidelines recommend pelvic (PLND) and infra renal para-aortic lymph node dissection (PALND). For high-risk patients lymphadenectomy not only aids for accurate staging but might also has therapeutic value for both node negative and positive cases as seen in some retrospective analysis. Approximately 20% of these patients are likely to have nodal metastasis [1, 6]. The number of nodes also had an impact on survival. Removal of more than 11 nodes in those with high-risk histologies had survival benefit. In a subgroup of PORTEC trial, 99 patients who had grade 3 disease with deep myometrial invasion did not undergo lymph node dissection were treated with External beam radiotherapy (EBRT). The outcome of these patients was worse (5-year OS was only 58% and 12% had pelvic or vaginal failures) than the historical cohort with similar grade and myometrial invasion, but who had undergone lymph node dissection followed by EBRT [8, 9].

In the retrospective SEPAL trial, that compared the practice of two centres with one centre practicing Pelvic LND (n = 325) and another centre doing complete pelvic and para-aortic LND for intermediate and high risk endometrial cancer. The systematic pelvic and para-aortic group was found to have survival benefit (HR 0.53, 95% CI 0.38–0.76) which was maintained after controlling the post operative chemotherapy [10].

The sentinel node biopsy has recently come as a viable option to reduce lymphadenectomy associated morbidities and at the same time safely predicting the nodal involvement. The role of SLNB for the high-risk endometrial cancer, has been investigated in several trials. In the SHREC trial (The pelvic SLN detection in high-risk endometrial cancer), out of 257 cases with high-risk histology, 54 had pelvic nodal metastasis [11]. Using the Sentinel Node algorithm, 52 cases could be detected; in one case mapping failed and in another one patient it was false negative. 95% patients had bilateral mapping. The sensitivity and NPV of the overall SLN algorithm was 98% (95% CI 89–100) and 99.5% (95% CI 97–100) respectively. Isolated para aortic metastasis was seen in only 1% cases. Another study by Cusimano et al. (2021), conducted on 156 patients with EC, out of which 126 cases had high risk histology. The detection rates were 97% per patient, bilateral mapping could be done in 77.6% cases and false negative rate was 4% [12]. The SLNB had sensitivity of 96% and NPV of 99%. Similarly the SENTOR trial in 106 patients with high-risk endometrial cancer observed a high sensitivity (96%) high NPV (99%) and low FNR (3.9%) for detection of SLN [13]. However, more randomized data is needed to ascertain the oncological safety of this technique in women with serous cancer.

Q: Discuss Transperitoneal Versus Extraperitoneal Approach to Lymphadenectomy?

The extraperitoneal approach for lymph node dissection is associated with reduced risk of intra-abdominal adhesion formation (transperitoneal vs extra peritoneal: 76% vs 43%), paralytic ileus and intestinal obstruction. A laparoscopic extraperitoneal access to nodes also has added benefits of rapid access, lesser risk of injuries to bowel and vessels during entry and electrosurgical injuries are reduced [14, 15]. Lymphocyst formation has been cited as the most frequent complication of extra peritoneal approach. Several additional procedures may be done like paracolic gutter peritoneum incision to allow intra peritoneal drainage of the dissected area or applying systematic clipping of any large lymphatic vessel. The transperitoneal approach was limited by obesity, previous abdominal surgeries and intolerance to trendelenburg position, thus making visualization of ureter and large vessels more difficult [14]. STELLA-2 was a prospective randomized multicentric study conducted in 209 women with endometrial or early-stage ovarian cancer into extraperitoneal (N = 103) and transperitoneal groups (N = 100). The extra peritoneal approach was associated with better nodal retrieval ((median, interquartile range [IQR] 12 [7–17] vs 14 [10–19]: P = .026). There was no difference in surgical duration, conversion rates or survival outcome between the two groups. The surgical complications were lower using extraperitoneal robotic approach [16].

Q: Role of Omentectomy Versus Omental Biopsy in High-Risk Endometrial Cancer

The behaviour of serous endometrial cancer being more aggressive, having propensity for extra uterine involvement, resembles more closely with serous ovarian cancer than the endometrioid endometrial carcinoma. Hence, comprehensive surgical staging remains the primary treatment modality. Omentum is involved in 10–18% cases and out of these 50% might have occult involvement [17]. Omental metastasis is commonly seen in those with advanced disease, being involved of other extra uterine sites like uterine serosa, adnexa, pelvic or para-aortic nodes. 35% cases with omental metastasis may also show positive peritoneal cytology [1, 6, 20]. Involvement of adnexa and deep myometrial invasion were identified as risk factors for omental involvement with OR of 2.82 and 2.03 respectively [6]. Other factors like age, tumor diameter, peritoneal cytology and LVSI did not have any significant impact on omental metastasis. Omental involvement upstages the patient to stage IV B and is an independent prognostic variable. (PFS HR 1.48; OS HR 1.39) [18, 19]. However, whether to do omental biopsy or omentectomy has been a matter of debate. The NCCN guidelines recommend omental biopsy, while the European guidelines recommend omentectomy [1]. However, the visual assessment is not appropriate (sensitivity only 55%) to recognize microscopic involvement. Therefore, considering the high rate of occult metastasis, significant number of cases getting upstaged if positive, omentum being a common site of recurrence (27%) if not tackled appropriately and omentectomy being a relatively simple surgical procedure not adding significant morbidity, is justified as a part of staging surgery for serous endometrial cancer. Similarly, for carcinosarcoma, the omental metastasis was seen in 20.4% cases, and thus omentectomy should be done for all the cases [20, 21]. For the clear cell variants, the probability of finding omental metastasis was lower than other histology and therefore the European guidelines do not recommend omentectomy for staging apparent stage I clear cell carcinoma [6].

Q: Role of MIS in High-Risk Endometrial Cancer?

Staging using minimally invasive approach is now standard of care for endometrial cancer. MIS is found to be beneficial and oncologically safe for early stage uterus confined serous endometrial cancers. While providing all the benefits of MIS in terms of early recovery, lesser morbidities

and early resumption of routine activities, the PFS and OS was same with MIS and open approach. Considering that majority of patients are elderly, and often need adjuvant therapy, reduction of surgical morbidities is of utmost relevance. However, for the advanced disease, MIS may not be a safer option [1, 6, 21, 22].

Q: What Are the Histological Prognostic Indicators

USC is an aggressive disease and accounts for 40% mortality from uterine cancer. It has high recurrence rates (30–80%) even for early stage disease Several prognostic indicators affect outcome in women with high risk endometrial cancer [2, 3, 21, 23].

Lymphovascular Space Invasion (LVSI)

LVSI is presence of tumour cells in a space lined by endothelial cells outside the immediate invasive border i.e. within the lymphatics or venous or capillaries or both. 10% cases are likely to have LVSI. It has been an independent variable predicting recurrent disease. Presence of LVSI is not only is associated with five times higher risk of pelvic nodal involvement but also an independent predictor for distant metastasis irrespective of nodal disease. LVSI is labelled as extensive/ substantial if more than or equal to 5 vessels are involved.

Depth of Myometrial Invasion

The 5-year OS for stage I USC without any MI is reported as 90%, and for those with <50% and >50% as 80% and 66% respectively. Stage III and IV USC have 5-year-OS as low as 33%. MELF pattern of invasion has been associated with nodal metastasis, even when compared to other infiltrative cases, and shows multiple patterns of growth in positive LNs. MELF cases additionally trended toward decreased time to extra-vaginal recurrence.

FIGO stage

Surgical stage is the most important variable affecting outcome.

Table shows the year survival rates for each FIGO stage.

Histology	Stage 1	Stage II	Stage III	Stage IV
Serous	80%	41%	38%	–
Clear cell	85%	63%	48%	–

Molecular Alterations in USC

According to the TCGA molecular classification USC are mostly p53 mutant group.

Others

Presence of tumour infilterating lymphocytes (TILs) determine their responsiveness to immunotherapy agents.

Q: Discuss Further Management and Adjuvant Therapy?

The use of adjuvant therapy in high-risk endometrial cancer has been refined by several investigators. The uterine serous carcinoma was excluded from the famous trials like GOG 99, PORTEC 2 [2]. Even the ASTEC and GOG 249 had 10% and 15% cases of USC respectively. External beam RT alone has a limited role as observed in GOG 94 trial, where 5-year-survival for stage I and II USC was only 35% for those who received only abdominal RT as the risk of vaginal vault recurrence was very high in these women. Hence, vaginal brachytherapy be needed for these women. Using combination chemoradiotherapy the 5 year survival for stage I disease was 73%, stage II was 100%, stage III 59% and 0% for stage IV disease. Other modalities like sandwich therapy (EBRT was sandwiched using 6 cycles of platinum and carboplatin-based combination chemotherapy) and sequential radical pelvic RT (4 cycles of Carboplatin and Paclitaxel combination followed by radical pelvic RT), but the outcome was similar [1–4, 23, 24].

A high rate of relapse and probability of having extra pelvic and multisite recurrence, chemotherapy is the preferred option for women with USC in adjuvant setting. Addition of chemotherapy led to reduced recurrence risk (P=0.04) and better PFS (P = 0.01). A NCDB study with stage

I-II USC (N = 7320), reported 22% mortality reduction by using chemotherapy (HR 0.78) and 33% reduction in the VBT group (HR 0.67). Regardless of surgical staging combined chemotherapy and radiotherapy regimen were found to have best OS. PORTEC 3 trial established the benefit of combining chemotherapy with radiotherapy in improving failures, PFS and OS in high-risk endometrial cancer [1–4, 6].

In a subset of GOG 249, women having high-risk histology in stage I, II, role of chemotherapy +VBT was compared with EBRT alone. However, there was no difference in PFS or OS [24]. Chemotherapy alone was compared with combined chemotherapy with pelvic radiotherapy in GOG 258 trial for women with advanced disease; although the OS was not improved by adding EBRT, but there was significant reduction in the incidence of local and nodal failures [25].

The preferred combination chemoradiotherapy regimen to administer to women with high-risk EC is the one used in PORTEC, RTOG 9708 and NRG/GOG 258 trial. EBRT was given to a dose of 48.6 Gy in 1.8 Gy fractions, 5 days a week, total duration should not exceed 50 days. First two cycles of chemotherapy using intravenous cisplatin 50 mg/m2 in the first and fourth week of external beam radiotherapy. The vaginal vault brachytherapy with the dose equivalent to 14 Gy in 2 Gy fractions be given to those with endocervical stromal involvement, substantial LVSI, and or stage IIIB or IIIC disease. The adjuvant chemotherapy be started within 3 weeks of completion of EBRT and with a 4-week interval from the second concurrent CRT cycle [6].

Q: Discuss the Prognosis of the Case

Serous adenocarcinoma of uterus is aggressive disease with a poor prognosis and high risk of relapse. The FIGO stage and residual tumour after surgery are the most significant prognostic variables affecting survival. The OS rates for early-stage disease are reported as 65–85% and cure rates as 35–50%. In advanced stages, the patients with stage III-IV have cure rates reported as 0–15%. Survival is better for those who are optimally cytoreduced than those with residual disease. (Median survival 52 vs. 16 months) [1–4, 6] The most significant variable affecting OS was depth of myometrial invasion. The 5-year-OS was 66% for patients with >50% myometrial invasion, 80% for those with superficial and 90% for those with no myometrial invasion [3, 4].

Q: Follow Up Protocol for High-Risk Early-Stage Endometrial Cancer?

After completing the treatment patient should be called for surveillance every 3–6 months for 2–3 years, then every 6 months or yearly for 5 years. Patients should be educated about the symptoms of recurrence. At every visit detailed history including any complaints like abnormal bleeding or discharge or pain or bladder bowel complaints, also loss of weight or appetite etc. should be elicited. A thorough physical examination including general, systemic, and local examination should be done. If clinically indicated appropriate imaging should be advised. CA 125 is advisable only if raised preoperatively. Apart from symptomatic treatment, patient should be educated to maintain a healthy lifestyle, weight reduction, nutrition, exercise, smoking cessation and potential late effects of treatment and their management. Evaluation of sexual health should be done and if needed patients should be advised use of lubricants, vaginal dilators as indicated [1, 6].

Case 2

Age, Parity, PS	56 years P5L5; ECOG = 0
Presenting complaints	Post menopausal bleeding, foul smelling watery discharge
Co morbidities	Nil
Trans vaginal sonography	Uterus normal size, endometrial thickness = 21 mm, bilateral adnexa normal
Endometrial biopsy	Clear cell cancer endometrium ER-ve, PR-ve, Ki-67 70%

MRI	Endometrium thickened 20 mm, no myometrial invasion seen Pelvic lymph nodes not enlarged, bilateral ovaries normal
Surgery	Total abdominal hysterectomy with bilateral salpingo oophorectomy+ pelvic, paraaortic lymphadenectomy, infracolic omentectomy
Histology	Clear cell cancer endometrium, <50% myometrial invasion 0/28 lymph nodes LVSI +ve FIGO Stage (2009) IA

Q: What Are the Pathological Hallmarks and Immunohistochemical Markers for Diagnosing Clear Cell Endometrial Cancer

Clear cell carcinoma of endometrium is a rare tumour (<10% of all ECs) and is associated with higher risk of venous thromboembolism (VTE). Pathologically clear cell carcinoma is characterized by presence of papillary, tubule-cystic, and/or solid architectural patterns. The papillae are short, rounded and have hyalinized stroma. Presence of hobnail cells with clear or eosinophilic cytoplasm are typical but not mandatory for diagnosis. Nuclear pleomorphism is variable and most of the tumours have <5 mitosis/2 mm^2. For the diagnosis of clear cell carcinoma, the tumour should depict at least 25–50% of clear cell component.

IHC tumours are positive for HNF1beta, Napsin and AMACR (P504S) in 70–100%, 60–90% and 75–80% respectively. ER, PR are either negative mostly or only focally positive. Somatic mutations include mutations in TP53 in 36–60% cases. The hypoxia-inducible protein 2 (HIG2) gene has been recently investigated as a novel biomarker to diagnose clear cell carcinoma [5, 21].

Q: Discuss Adjuvant Therapy in this Case? (EBRT Versus VBT, Role of Chemotherapy)

The clear cell tumors are known to be less chemo responsive. Adjuvant therapy in these cases is tailored depending on MI, LVSI and FIGO stage at the time of presentation. For patients with completely staged FIGO stage 1, observation is advised as there was no difference in 5-year survival in RT vs observation group (78% vs 75%). For those with more advanced disease, chemotherapy with or without VBT or concurrent chemotherapy and EBRT with or without VBT is practiced. Adjuvant Platinum/Taxol based combination chemotherapy is preferred in patients with high-risk histology with acceptable toxicity profile. Whole abdominal radiation therapy was traditionally used for clear cell carcinoma, however, the evidence to support its utility is limited. VBT alone is not an optimal modality for these patients. There is no role of hormonal therapy [1, 6, 25].

Q: What Is the Prognosis?

The prognosis of uterine clear cell carcinoma is usually worse than other endometrial adenocarcinomas. The 5-year-OS rate is 55–75%. The recurrence is predominantly extra-pelvic. The advanced FIGO stage and age remain the most significant prognostic variable affecting outcome. The other prognostic variables include TCGA molecular subgroup, high expression of L1CAM, IMP3, Cyclin E and loss of expression of ARID1A, aberrant p53 phenotype. The positive peritoneal cytology, adjuvant therapy, tumor size, architectural pattern along with LVSI have also been found to affect the prognosis [3, 6].

Case 3

Age, Parity, PS	53 years P4L4; ECOG = 1
Presenting complaints	Post menopausal bleeding
Co morbidities	Hypertension, type 2 diabetes mellitus, depression, BMI = 35
Transvaginal sonography	Uterus normal size, growth 3.5 × 4 cm, fluid in endometrial cavity, bilateral adnexa normal

Endometrial biopsy	Serous carcinoma endometrium Diffuse strong nuclear P53 staining (aberrant), P16 negative, ER and PR patchy +ve, WT1 negative, MMR proficient
MRI	Exophytic growth 4.8 cm in lower uterine segment; proximal hematometra Myometrial invasion<50%, cervix normal
CECT chest abdomen + pelvis	Endometrial growth 4.8 cm. 16 mm node right external iliac lymph node, inguinal lymphadenopathy with diffusion restriction 16 mm, lower retroaortic lymph nodes above aortic bifurcation 13.7 mm, abdominal para aortic lymph node enlarged 14 mm, haziness in omentum with cardio oesophageal node enlarged
PET CT	Non avid inguinal lymphnode and cardio oesophageal node
Tumor markers	CA125 = 14 IU/L

Q: Discuss Further Management of the Above Case. Role of Neoadjuvant Chemotherapy Versus Surgery? Discuss the Type of Surgery

Surgical treatment remains the mainstay of therapy for serous endometrial cancer. The debulking surgery with an intention to remove all macroscopic disease is recommended in this condition if morbidities are acceptable. In the above case laparotomy is preferred over NACT because of following reasons

1. According to the imaging findings, the disease appears resectable.
2. The role of chemotherapy in these cases is not well established and is limited to cases which appear unresectable. Chemotherapy followed by delayed surgery is an option if there is response after chemotherapy.
3. The role of MIS in advanced disease is not established.

The surgical staging using open surgical approach is preferred. The surgical steps include peritoneal wash cytology, thorough exploration of abdomen for accurate assessment of disease extent, random peritoneal biopsies, or biopsy from suspicious or sites of adhesions, type 1 extra fascial hysterectomy with bilateral salpingo-oophorectomy with systematic pelvic and para-aortic lymphadenectomy.

Surgery	**Laparotomy: TAH+ BSO+ Bilateral pelvic and para aortic lymphadenectomy + infracolic omentectomy**
Histology	**Histology** Serous carcinoma, 3 × 2 × 1 cm, <50% myometrial invasion, cervix normal, LVSI +ve; lymph nodes +ve; Para aortic nodes (3/12), pelvic 2/14 Omentum positive deposit 1 × 1 cm **Serous carcinoma** FIGO stage IVB HER2neu negative

Q: Adjuvant Treatment

For the advanced stage IV B serous carcinoma with Her 2 neu negative status, chemotherapy is the standard choice of treatment based on data from GOG 122 and GOG 258 trials. Out of many chemotherapeutic agents, Paclitaxel and Carboplatin combination is the most preferred option. Targeted or immunotherapy may be added based on Her2 neu status or MSI status. For the patients expressing 3+ Her 2 neu receptor expression, Trastuzumab has been used [1, 4, 6].

Q: What Are the Recent Developments in Management of Advanced Uterine Serous Cancers

With the evolution of precision medicine, novel targeted therapy has been investigated for improving the outcome of uterine serous cancers [4]. HER2/neu overexpression is reported in 30% cases of uterine serous carcinoma and Trastuzumab (humanized anti HER2/neu antibody) therapy along with Paclitaxel-Carboplatin cytotoxic therapy has led to 4.6 months benefit in median PFS in recurrent endometrial cancer.

Another agent Pertuzumab (humanized monoclonal antibody targeting the epidermal growth factor type II receptor) in combination with Trastuzumab has been effective in primary USC cell lines exhibiting HER2 neu overexpression. Hence, for USC expressing 3+ or 2+ expression of HER2neu Trastuzumab be added to the combination chemotherapy in primary setting [4, 26].

Other targeted agents include small molecule tyrosine kinase inhibitors like Niratinib which selectively target the ErbB family of receptors including HER2neu, Dacomitinib which is an oral pan-ErbB TKI and Taselisib which is an oral selective inhibitor of PIK3CA pathway, has been investigated in pre-clinical studies. Adavosertib that targets protein kinase involved in cell cycle check points, leading to formation of unstable DNA replication molecules is another novel therapeutic targeted agent under research [4, 27].

BRCA1 mutation was seen to be associated with higher risk of development of USC. According to one study 20% cases of USC expressed BRCA1 mutation. However, other studies observed lower association (8 cases observed vs. 4.3 expected). However, association of PTEN mutation with HRD has been well established and thus the concept of synthetic lethality is applicable to PTEN deficient endometrial tumors, if treated with PARPi. Few studies have shown promising role of PARPi in EC either alone or in combination of immunotherapeutic agents. Several trials are ongoing to investigate the role of PARPi in advanced, metastatic, and recurrent disease [28].

Immunotherapy has emerged as a promising modality to treat endometrial carcinoma. Serous cancer are reportedly less immunogenic than the endometrioid variant and also do not express MSI or PDL1 receptors. Role of immunotherapy (combination of Lenvatinib and Pembrolizumab) in recurrent disease has been seen in trials-Keynote 146 and 775. Both PFS and OS were better in those who received immunotherapy than those who received chemotherapy. (PFS 7.2 vs 3.8 months, HR 0.5; OS 18.3 vs 11.4 months, HR 0.62) [6].

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