High-Grade Endometrial Cancer—Behaviour and Outcomes at a Tertiary Cancer Centre

Prerna Lakhwani, Priya Agarwal, Ashish Goel, Nidhi Nayar, Pankaj Pande & Kapil Kumar

Indian Journal of Surgical Oncology

ISSN 0975-7651

Indian J Surg Oncol
DOI 10.1007/s13193-019-00970-1

Springer

Indian Journal of Surgical Oncology
https://doi.org/10.1007/s13193-019-00970-1

ORIGINAL ARTICLE

High-Grade Endometrial Cancer—Behaviour and Outcomes at a Tertiary Cancer Centre

Prerna Lakhwani[1] · Priya Agarwal[1] · Ashish Goel[2] · Nidhi Nayar[1] · Pankaj Pande[2] · Kapil Kumar[2]

Received: 8 April 2019 / Accepted: 7 August 2019

Abstract

High-grade endometrial carcinomas are a heterogeneous group of clinically aggressive tumours. They include FIGO grade 3 endometrioid adenocarcinoma, uterine papillary serous carcinoma (UPSC), clear cell carcinoma, undifferentiated carcinoma and carcinosarcomas or malignant mixed Mullerian tumour (MMMT). The aim of this study is to look at clinicopathological features and survival outcomes of high-grade endometrial cancers of the uterus in our centre. A tertiary care centre in India. The study design is retrospective with survival analysis. We did a retrospective analysis of all patients admitted with a diagnosis of high-grade uterine carcinoma. Data regarding baseline characteristics, disease profiles, surgical outcomes, complications, extent of surgical staging, duration of surgery, blood loss, length of hospital stay, drain output, wound infection, surgico-pathological stage and grade, tumour size and location, myometrium and lymphovascular invasion, node positivity, adjuvant treatment, overall survival and recurrence-free survival. Survival analysis was done using the Kaplan–Meier method. We had 115 females diagnosed with endometrial cancer. Of these, 40 patients had high-grade endometrial cancer. Mean age at presentation was 64.7 years (range 33–80 years). Of this, endometrioid adenocarcinoma grade III was the commonest (37.5%), followed by UPSC in 32.5% and MMMT in 22.5% patients. Clear cell variant and mixed dedifferentiated variant were reported in 5% and 2.5%, respectively. Over 48 months of follow-up, recurrence was detected in eight patients (20%) and median time to recurrence was 11 months. Mean recurrence-free survival was 32.8 months and mean overall survival was 38.6 months High-grade endometrial cancers are aggressive tumours of postmenopausal women. Surgical staging and combination chemotherapy along with radiation therapy are the mainstay of treatment. In spite of adequate debulking followed by adjuvant therapy, survival remains poor.

Keywords High-grade endometrial cancer · Uterine papillary serous carcinoma · Carcinosarcoma · Malignant mixed Mullerian tumour

✉ Priya Agarwal
priyaagarwalmar26@gmail.com

Prerna Lakhwani
preleo2020@gmail.com

Ashish Goel
dr.goelashish@gmail.com

Nidhi Nayar
nidhi_nayar@rediffmail.com

Pankaj Pande
pankaj.pande@blkhospital.com

Kapil Kumar
kdrkapil@yahoo.com

[1] Gynae Oncology, BL Kapur Super Specialty Hospital, Pusa Road, Delhi, India

[2] Surgical oncology, BL Kapur Super Specialty Hospital, Pusa Road, Delhi, India

Introduction

Endometrial carcinoma (EC) is the most common malignancy of the female genital tract in developed countries. [1] The incidence rate in developing countries is four to five times lower than the developed nations. Two different clinicopathologic subtypes of endometrial cancer are recognized: the estrogen related (type I, endometrioid) and the non-estrogen related (type II, non-endometrioid). [1] Patients with type II tumours are more likely to be older, non-white, multiparous, current smokers and non-obese. [1]

High-grade endometrial carcinomas are a heterogeneous group of clinically aggressive tumours. They include FIGO grade 3 endometrioid adenocarcinoma, uterine papillary serous carcinoma (UPSC), clear cell carcinoma, undifferentiated carcinoma and carcinosarcomas or malignant mixed Mullerian tumour (MMMT). These tumours usually present as postmenopausal bleeding,

Published online: 21 August 2019

discharge per vaginum, abdominal mass or distension and occasionally as distant metastasis.

The aim of this study is to look at clinicopathological features and survival outcomes of high-grade endometrial cancers of the uterus in our centre.

Materials and Methods

This study was conducted at a tertiary care centre in North India. We did a retrospective analysis of all patients admitted with a diagnosis of high-grade uterine carcinoma between January 2015 and March 2018 (39 months) in a Super Specialty hospital in Delhi after ethical clearance from institutional review board. Data regarding baseline characteristics, disease profiles, surgical outcomes, complications, extent of surgical staging, duration of surgery, blood loss, length of hospital stay, drain output, wound infection, surgicopathological stage and grade, tumour size and location, myometrium and lymphovascular invasion, node positivity, adjuvant treatment, overall survival and recurrence-free survival along with follow-up were collected from the electronic records and supplemented with patients' letters and phone calls. All high-grade endometrial cancers, operated in our tertiary care cancer centre, were included.

Recurrence was diagnosed based on clinical and radiologic imaging. A local recurrence was defined as any disease confirmed by histopathology examination at the vault region. Distant recurrence was defined as disease out of the pelvis as shown clinically or on imaging. Overall survival was defined as duration from start of treatment (either surgery or neoadjuvant chemotherapy) till the date of death or last follow-up. Recurrence-free survival was defined as duration from start of treatment till recurrence was detected. Overall survival was assessed over 48 months. IBM SPSS version 21 (IBM, Chicago, USA) was used for the analysis of data. Kaplan–Meier method was used for survival analysis. Linear regression was used to study the determinants of survival and recurrence.

All patients were staged according to the 2009 FIGO criteria. [2] All patients underwent surgical staging including hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic ± para-aortic lymphadenectomy, following standard surgical guidelines and peritoneal fluid cytology either upfront or after neo adjuvant chemotherapy. Type of hysterectomy done was named according to Piver–Rutledge classification.

Adjuvant treatment was offered as per institutional guidelines following a discussion at a multidisciplinary tumour board. Patients were followed up once every 3 months for the first 2 years, then once every 6 months for 5 years.

Results

During this 39-month period, we had 115 females diagnosed with endometrial cancer. Of these, 40 patients had high-grade endometrial cancer. Mean age at presentation was 64.7 years (range 33–80 years). Seven patients were nulliparous and rest multipara. All patients were postmenopausal (97.5%) except one. Demographic data is shown in Table 1. Most common presenting symptom was postmenopausal bleeding. Most of the patients were thin built as 60% of the patients had BMI of < 25. Only one patient (2.5%) had serum CA 125 levels of > 1000.

Preoperatively, all patients were subjected to endometrial sampling either by endometrial aspiration or by hysteroscopy-guided biopsy. Review of slides was done in case biopsy was done outside our hospital. Of this, endometrioid adenocarcinoma grade III was the commonest (37.5%), followed by UPSC (Table 2).

All patients were worked up thoroughly with clinical history and examination along with blood investigations and imaging. After complete workup, further management was

Table 1 Patient characteristics ($n = 40$)

Factors	$N = 40$
Age	
< 60	13 (32.5%)
> 60	27 (67.5%)
Parity	
Nullipara	7 (17.5%)
Primipara	3 (7.5%)
Multipara	30 (75%)
Menopausal status	
Premenopausal	1 (2.5%)
Postmenopausal	39 (97.5%)
BMI	
19–25	24 (60%)
25–30	7 (17.5%)
> 30	9 (22.5%)
Comorbidites	
HTN	18
DM	17
Hypothyroid	15
Presenting complains	
PMB	39 (97.5%)
Pain abdomen	1 (2.5%)
CA125 levels(IU)	
< 35	14 (35%)
35–100	14 (35%)
100–1000	11 (27.5%)
> 1000	1 (2.5%)

Table 2 Type of high-grade endometrial cancer

Histology	Number of patients $N = 40$	Percentage
Endometrioidadenocarcinoma grade III	15	37.5%
Uterine serous papillary carcinoma (UPSC)	13	32.5%
Carcinosarcoma or MMMT	9	22.5%
Clear cell carcinoma	2	5%
Mixed (endometrioidadenocagrade III and dedifferentiated)	1	2.5%

decided, the details of which are shown in Table 5. Out of 40 patients, 29 patients (72.5%) underwent upfront surgery, 10 patients (25%) had neoadjuvant chemotherapy followed by surgery and 1 patient (2.5%) had neoadjuvant chemotherapy followed by surgery along with heated intra peritoneal chemotherapy (HIPEC). Two patients clinically had DVT on first presentation of which one also developed pulmonary embolism which was managed with IVC filter, thrombolytic and anticoagulants.

The average duration of surgery was 3–4 h with a blood loss of approximately 100 ml to 700 ml. Of 40 patients, 34 had type I hysterectomy and 6 underwent type II/III radical hysterectomy in view of gross cervical involvement. Only two patients had bowel resection and anastomosis in the form of low anterior resection.

On final histology as depicted in Table 3, peritoneal cytology was positive in six patients (15%) and all these cases were in advanced stage (IVB). Tumour size was more than 2 cm in 35 patients (87.5%). Lymphovascular invasion was positive in 16 patients (40%). Eleven patients (27.5%) had positive pelvic lymph nodes while only nine patients (22.5%) had positive para aortic LN. One patient had skip metastasis to para-aortic nodes without pelvic lymph node involvement.

As is clear from Table 4, 35% (14 patients) were in stage IVB which was the most common stage encountered and was mainly associated with UPSC variant.

Average hospital stay in our study was 8–9 days, except approx. 15 days in patient who underwent CRS with HIPEC. Almost 50% of the patients had sub-acute intestinal obstruction in early post op period which was managed conservatively. Fourteen patients (35%) needed blood or blood product transfusion. Surgical site infection was seen in 30% cases, mostly managed conservatively, only two patients requiring resuturing. Increased drain output was noted in 20% cases which decreased gradually. Readmission rate was 22% mainly for sub-acute intestinal obstruction. Lymphocyst formation was seen in 35% of patients on follow-up.

The final histopathology of these patients was discussed at a multidisciplinary tumour board meeting, and decisions on adjuvant treatment were made. Depending on the histological stage and performance status, patients were subjected to adjuvant treatment in the form of either systemic therapy and/or EBRT ± brachytherapy as described in Table 5. Standard NCCN protocols were followed for chemo and radiotherapy.

Patients were followed up every 3 months for initial 2 years and then every 6 monthly thereafter. Total follow-up period ranged from 9 to 48 months. Three patients (7.5%) were lost to follow-up. Seven (17.5%) patients died due to disease, of whom all but one had advanced disease. Three patients who died had endometrioid adenocarcinoma grade 3, another three patients had UPSC and one had MMMT as histology.

Twenty percent patients recurred in 48-month follow-up (Table 6). In three cases (7.5%) who recurred within 6 months, one was UPSC stage IIIB, one MMMT stage IIIC and one was mixed histology stage IIIC2. Five cases (12.5%) had recurrence after 6 months, of which two had endometrioid

Table 3 Histopathological findings

Variables	
Positive peritoneal cytology	6
Tumour site	
Endometrium	6
Fundus	7
LUS	10
Whole body	18
Tumour size	
< 2 cm	5 (12.5%)
> 2 cm	35 (87.5%)
Myometrial invasion	
No invasion	6 (15%)
< 50%	5 (12.5%)
> 50%	29 (72.5%)
LVSI	
Positive	16 (40%)
Negative	24 (60%)
Cervical involvement	10 (25%)
Pelvic nodes	
Negative	29 (82.5%)
Positive	11 (27.5%)
Para aortic nodes	
Negative	31 (77.5%)
Positive	9 (22.5%)
Adnexa/parametrium/vagina involvement	8 (15%)
Distant metastasis	13 (32.5%)

Table 4 Distribution according to stage and histology

	Endometrioid adenoca grade III (15)	UPSC (13)	MMMT (9)	Clear cell (2)	Dedifferentiated (1)
Stage I $n = 10$	$n = 5$	$n = 1$	$n = 4$		
IA(4)	1	–	3	–	–
IB(6)	4	1	1	–	–
Stage II $n = 3$	$n = 2$	$n = 1$	–	–	–
Stage III $n = 13$	$n = 5$	$n = 4$	$n = 3$	–	$n = 1$
IIIA(1)	1		–	–	–
IIIB(1)	–	1	–	–	–
IIIC1(3)	–	2	1	–	–
IIIC2(8)	4	1	2	–	1
Stage IV $n = 14$	$n = 3$	$n = 7$	$n = 2$	$n = 2$	–
IVA(1)	1	–	–	–	–
IVB(13)	2	7	2	2	–

adenocarcinoma grade three stage IIIC2, two UPSC stage IVB and one MMMT stage IIIC1. Forty-seven percent ($n = 19$) of patients are disease free till date. Median time to recurrence was 11 months. Mean recurrence-free survival was 32.8 months and mean overall survival was 38.6 months (Figs. 1 and 2).

Discussion

Type II endometrial carcinomas are considered more aggressive histologic variants of uterine malignant epithelial tumours as they have a higher incidence of extra uterine disease at presentation and are staged using the same FIGO/AJCC staging system as endometrial cancers. [2] UPSC carries a poor prognosis (70% at 5 years for stages I and II). Clear cell carcinoma (CCC), another relatively rare cancer of the endometrium, also carries a poor prognosis (50.8% at 5 years for stages I and II). [3] Carcinosarcoma uterus is a rare, but aggressive cancer which comprises about 1.5% of all uterine malignancies. [4] It is a biphasic tumour with malignant mesenchymal and epithelial components. They have a less favourable outcome compared to other uterine malignancies with 5-year survival rates between 33 and 39% [4] One of the reported reasons for the poor prognosis of these histological variants is the fact that they have a propensity for spreading outside of the uterus early in the disease process.

In our study, 67.5% of cases had advanced stage disease, i.e. stage III and IV, and only 25% and 7.5% cases were in stages I and II, respectively.

According to Benedetti et al., survival is more in patients who are younger, have early-stage disease and have lower-grade disease. In addition to histological type and grade, depth of myometrium invasion, increasing age, lymph node status, tumour size, lymphovascular space invasion (LVSI) and tumour involvement of the lower uterine segment are the risk factors associated with poor prognosis. [5]

Ninety percent of these patients present with postmenopausal bleeding, but can also present with pain in abdomen,

Table 5 Treatment of high-grade endometrial cancer

Treatment	
Surgical staging	
Upfront	29 (72.5%)
Post NACT	10 (25%)
Post NACT with HIPEC	1 (2.5%)
Hysterectomy type	
Type 1	34 (85%)
Type 2/3	6 (15%)
Bowel resection and anastomosis	2 (5%)
Adjuvant therapy	
Observation	3 (7.5%)
EBRT	1 (2.5%)
EBRT + brachytherapy	3 (7.5%)
Brachytherapy	6 (15%)
Chemotherapy	7 (17.5%)
EBRT + Brachy + Chemo	19 (47.5%)
Defaulted treatment	1 (2.5%)

Table 6 Recurrence and survival analysis

S. NO.	Parameter	Value
1	Recurrence	$n = 8$
2	Median time to recurrence	11 months
3	Overall survival(months), mean ± SD	38.61 ± 2.49
4	Recurrence-free survival (months), mean ± SD	32.89 ± 2.89

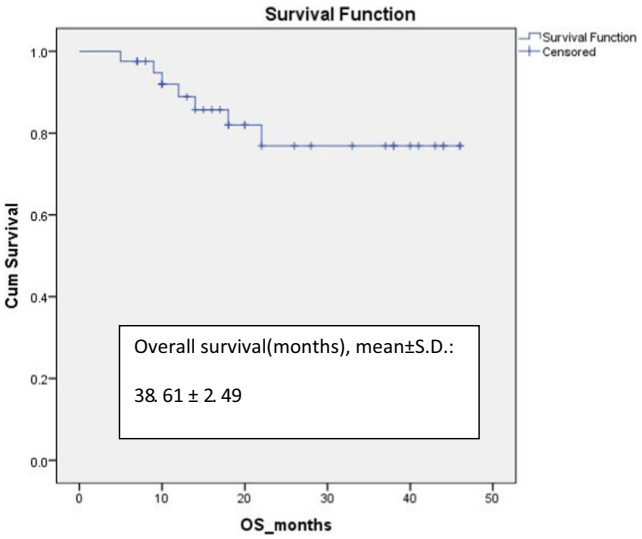

Fig. 1 Kaplan–Meier graph showing overall survival of entire cohort of patients

pelvic masses, abnormal cervical cytology or ascites. In our study, almost all patients presented with postmenopausal bleeding except one who presented with abdominal distention and pain.

Diagnosis can usually be made by an office endometrial biopsy. Hysteroscopy can be useful for endometrial lesions like polyp or where there is undiagnosed or recurrent bleeding episodes. Imaging modalities such as CT, MRI and/or PET/CT are also useful to assess extent of disease and for metastatic workup. A serum CA-125 assay may be helpful in monitoring clinical response and follow-up in UPSC and other metastatic cases. [6]

Multimodality therapy is typically recommended for these histologically aggressive tumours. In high-risk histology, patients with apparent early-stage disease may have distant

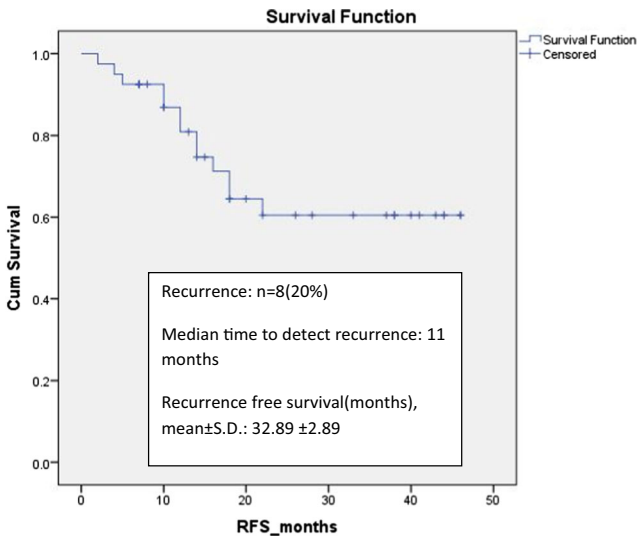

Fig. 2 Kaplan–Meier graph showing recurrence-free survival of entire cohort of patients

metastases. Thus, fertility-sparing therapy is not recommended for these aggressive tumours.

Primary treatment includes total abdominal hysterectomy with bilateral salpingo oophorectomy, peritoneal cytology, omental and peritoneal biopsies, pelvic and para aortic lymphadenectomy and consideration of maximal tumour debulking for gross disease or patient can be subjected to neoadjuvant chemotherapy followed by surgery. [7] In our study, out of 40 patients, 29 patients underwent upfront surgery, 10 patients had neoadjuvant chemotherapy followed by surgery, 1 patient had neoadjuvant chemotherapy followed by surgery with heated intra peritoneal chemotherapy (HIPEC).

Surgery for advanced endometrial cancer has undergone significant advances. A women with high-grade endometrial cancers staged by minimally invasive techniques experienced fewer complications and similar survival outcomes compared to those staged by laparotomy. In countries like India, where gynecologic oncology as a specialty is in its early phase of development, comprehensive open surgery with appropriate and adequate lymphadenectomy, when indicated, is the need of the current time. In this group of patients, open surgery was performed in all cases. Pelvic and para-aortic dissection was performed in all except three patients. The most common serious complications were postoperative ileus and subacute intestinal obstruction. In this series, the recurrences ($n = 5$) were predominantly at distant locations especially in the lungs and mediastinal nodes. Few patients ($n = 3$) had loco regional as well as distant metastases.

Adjuvant therapy is highly individualized. For patients with stage IA without myometrium invasion, options include either chemotherapy with or without vaginal brachytherapy (preferred approach), or observation if no residual serous or clear cell carcinoma in hysterectomy specimen, or EBRT with (or without) vaginal brachytherapy. For all other patients with more advanced disease, systemic therapy with (or without) tumour-directed RT is the preferred option. [15] Adjuvant platinum/taxane-based therapy appears to improve survival in patients with uterine serous carcinoma and clear cell carcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcoma. [8]

In our study, one patient underwent CRS with HIPEC due to advanced stage disease with peritoneal metastasis. In a recent study by Ahmed Abu-Zaid et al., CRS with HIPEC was studied for advanced stage endometrial cancer and they concluded that aggressive CRS supplemented with perioperative HIPEC emerges to be a well-tolerated, achievable and feasibly promising treatment modality that yields favourable results in managing patients with PC from primary and recurrent endometrial carcinoma with a good disease-free survival interval. [9] In our study, also this patient is having disease-free survival period of 1 year from surgery.

About 50% to 70% of patients present with recurrence of endometrial carcinoma within 24 months after the primary management. [10] Recurrence rates range from 2 to 15% in

patients with an early-stage disease (stages I and II). Conversely, recurrence rates can reach as high as 50% in patients with an advanced stage disease (stages III and IV) with a biologically aggressive tumour histologic lesion. [10] In our study, 55% of patients are disease free till date. Over 48 months of follow-up, recurrence was detected in eight patients (20%) and median time to recurrence was 11 months. Mean recurrence-free survival was 32.8 months and mean overall survival was 38.6 months (Figs. 1 and 2).

The 3-year survival probability for patients with stage I and II disease was 84%, while for patients with stages III and IV disease, it was 50%. It was concluded that radiotherapy sandwiched between carboplatin and paclitaxel was well tolerated and appeared to be effective in women with completely resected uterine serous cancers. [10]

Most recurrences occur within the first 3 years after treatment. The suggested frequency of follow-up is every 3–4 months with physical and gynecological examination for the first 2 years, and then with a 6-month interval until 5 years. Further investigations can be carried out if clinically indicated. PET/CT has been shown to be more sensitive and specific than CT alone for the assessment of suspected recurrent endometrial cancer. [11] The biology of tumour, its behavioural pattern and the outcome may vary with race and ethnicity, thus suggesting the concepts of genetics, unique molecular markers and personalized medicine. The limitations of this study were that it was a retrospective study, and some follow-up details were not obtainable. The follow-up of patients and their compliance with further treatments were less than satisfactory. It is probable that the results could have been different if the follow-up had been extended up to 5 years.

Conclusion

High-grade endometrial cancers are aggressive tumours of postmenopausal women who present with bleeding or discharge per vaginum. Surgical staging and combination chemotherapy along with radiation therapy are the mainstay of treatment. In spite of adequate debulking followed by adjuvant therapy, survival remains poor.

Financial Support and Sponsorship Nil.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent Informed consent was taken from patient and attendant.

References

1. Brinton LA, Felix AS, McMeekin DS et al (2013) Etiologic heterogeneity in endometrial cancer: evidence from a gynecologic oncology group trial. Gynecol Oncol 129:277–284
2. Amin MB, Edge SB, Greene FL et al (2017) AJCC CancerStaging manual, 8th edn. Springer, New York
3. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P (2004) Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol 95(3):593–596
4. Cherian AG, Thomas A, Sebastian A, Sebastian T, Thomas V, Chandy RG, Peedicayil A (2018) Outcomes of carcinosarcoma in a tertiary care institution in India. South Asian J Cancer 7(1):31–33
5. Benedetti Panici P, Basile S, Salerno MG et al (2014) Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 210:363 e361–363 e310
6. Vogel TJ, Knickerbocker A, Shah CA et al (2015) An analysis of current treatment practice in uterine papillary serous and clear cell carcinoma at two high volume cancer centers. J Gynecol Oncol 26: 25–31
7. ACOG practice bulletin (2005) Clinical management guidelines for obstetrician-gynecologists, number 65, august 2005: management of endometrial cancer. Obstet Gynecol 106:413–425
8. Vandenput I, Trovik J, Vergote I, Moerman P, Leunen K, Berteloot P, Neven P, Salvesen H, Amant F (2011) The role of adjuvant chemotherapy in surgical stages I-II serous and clear cell carcinomas and carcinosarcoma of the endometrium: a collaborative study. Int J Gynecol Cancer 21:332–336
9. Abu-Zaid A, Azzam AZ, AlOmar O, Salem H, Amin T, Al-Badawi IA (2014) Cytoreductive surgery and hyperthermicintraperitoneal chemotherapy for managing peritoneal carcinomatosis from endometrial carcinoma: a single-center experience of 6 cases. Ann Saudi Med 34(2):159–166
10. Sohaib SA, houghton SL, Meroni R, Rockall AG, Blake P, Reznekrh (2007) Recurrent endometrial cancer: patterns of recurrent disease and assess.Ment of prognosis. Clin Radiol 62(1):28–34
11. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, Sessa C (2013) ESMO guidelines working group. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(suppl_6):vi33–vi38